- Medical conditions that the sponsor felt be relevant to the adverse event of "confusion" were present in 7/30 patients: these included multiple sclerosis, hypothyroidism, sleep apnea, and previous head injury.
- 20/30 (66.7%) were over 50 years of age
- 26 such adverse events occurred during the first 60 days of treatment
- All such adverse events eventually resolved

14.5 "Confusion" In Study OMC-GHB-2

In this randomized, double-blind, placebo-controlled trial of 4 weeks' duration 10 patients receiving GHB and 1 patient receiving placebo experienced confusion

The distribution of this adverse event by dose group, based on the sponsor's table described in Section 14.4 was as follows

Dose Group	Total Number Randomized	Number of Patients with Confusion	Percentage of Patients with Confusion	Number (%) Permanently Discontinuing Treatment On Account Of Confusion
Placebo	34	1	2.9%	0 (0%)
3 g/day	34	3	8.8%	0 (0%)
6 g/day	33	1	3.0%	1 (3.0%)
9 g/day	35	6	17.1%	1 (2.9%)

The sponsor has drawn attention to the following:

- The highest incidence of confusion was at the 9 g/day dose
- 6/10 GHB-treated patients (4/6 patients treated with 9 g/day) developed confusion during the first week of drug exposure
- 7/10 GHB-treated patients with confusion were > 50 years of age

The sponsor attributes the high incidence of confusion in this short trial to the assignment of patients to fixed doses of GHB without titration.

14.6 Narratives For Patients With Confusion As A Serious Adverse Event

I have read the sponsor's narratives and supplemented them with Case Report Forms when needed.

14.6.1 Patient 0207 (Initials —

This 53 year old woman participating in OMC-GHB-2 had a past medical history of narcolepsy with cataplexy, and fibromyalgia. Several close family members had died shortly prior to her entering the Scharf trial. The patient's father was reportedly a manic-depressive. Concomitant medications included imipramine, estrogen and testosterone, progestin, methylphenidate and a laxative.

She received Xyrem® 6 g daily. On Day 4 of treatment she developed nausea. Beginning Day 5 she became very talkative with pressured speech, and the next day was noted to be disoriented, agitated and to sleep poorly. She was seen at an emergency room where neurological examination was remarkable for hyperreflexia. Xyrem® was discontinued, the patient was treated with haloperidol and by the next day her confusion had resolved. An EEG was normal and a CT scan of the head showed minor temporal lobe asymmetry. The study drug was permanently discontinued.

14.6.2 Patient 0231 (Initials —

This patient's narrative is also reproduced in Section 18.2

This 67 year old man was enrolled in Study OMC-SXB-6. His past medical history was remarkable for a stomach ulcer, gastroesophageal reflux disease, and a cholecystectomy. Concomitant medications at study entry included clomipramine, methylphenidate, paroxetine, imipramine and modafinil.

He took Xyrem® in a dose of 4.5 g/day for 12 days and 9 g/day for 106 days. After having been on a stable dose of 9 g/day for 106 days he awoke about 1 hour after his second nightly dose feeling dizzy and confused. On getting out of bed he felt nauseated and vomited after reaching the bathroom. He felt a sensation of "shut down" and difficulty breathing, crawled from the bathroom to lie down in the hallway until he felt well enough to return to bed about 1 ½ hours after the episode began. Frequent cataplexy attacks apparently accompanied the episode. After returning to bed he slept soundly and awoke the next morning feeling well. The same day he contacted the Principal Investigator and withdrew from the study. He was never hospitalized or seen in an emergency room.

At the time the episode occurred his concomitant medications included a multivitamin, DGL (a herbal preparation), an unspecified medication for gastroesophageal reflux and methylphenidate.

The episode occurred on 7/27/99. A follow-up phone call from the study coordinator on 3/19/01 indicated that no further such episodes had occurred.

14.7 Narratives For Patients With Confusion As An Adverse Event Warranting Permanent Discontinuation Of GHB

I have read the sponsor's narratives supplemented by Case Report Forms when needed

14.7.1 Patient 0207 (Initials —

See Section 14.6.1

14.7.2 Patient 0231 (Initials —)

See Section 14.6.2

14.7.3 Patient # 0702 (Initials . —

This 59 year old woman participated in Study OMC-GHB-2. She had a past history of narcolepsy with cataplexy, cirrhosis and a left facial palsy. Concomitant medications included ipratropium bromide and albuterol.

She received OMC-GHB-2 in a dose of 9 g/day. 20 days later she began experiencing confusion, hallucinations and forgetfulness followed in the next 2 days by nausea and paranoia. Study medication was discontinued when these symptoms began and her symptoms resolved 5 days later.

14.8 Reviewer's Comments

- As records for contemporaneous formal mental status examinations for patients with "confusion" are unavailable it is unclear if all patients coded as having this adverse event were really confused, as the term is conventionally understood. Investigator terms suggest that at least some patients may not have been confused
- Nevertheless, the information available does suggest that GHB is capable, at therapeutic doses, of causing a confusional state which may be accompanied by psychotic symptoms. The incidence and seriousness of such adverse events may be slightly more pronounced at higher doses, and especially if higher doses are administered without titration. However a confusional state also appears to be capable of occurring at lower and even sub-therapeutic

(e.g., 3 g/day) doses of GHB, and after maintenance treatment for several months.

- The presence of true confusion in patients taking GHB could lead to their taking GHB in a manner other than as prescribed.
- The symptoms that have been subsumed under the COSTART term "confusion" are not surprising for a sedative drug.

15. Neuropsychiatric Adverse Events In Integrated Clinical Trials

15.1 Background

At the Division's request neuropsychiatric adverse events in the updated Integrated Clinical Trials database (including the 120-Day Safety Update) were characterized further by the sponsor. The cut-off date for the 120-Day Safety Update was 9/30/00.

The sponsor's methods were as follows:

- Adverse events coded under the following preferred terms were selected from the above: overdose, coma, death, depression, hallucinations, intentional overdose, manic depressive reaction, overdose, paranoid reaction, personality disorder, psychosis, stupor, suicide, and suicide attempt.
- Source documents, Case Report Forms and data listings were reviewed for the above patients
- Tabular and narrative summaries of events were then constructed. Narratives were prepared for deaths, serious adverse events and adverse event discontinuations.
- A review of the literature relevant to the incidence of neuropsychiatric adverse events in narcolepsy was completed
- The dosage at onset of each adverse event was determined and the start and stop dates for the adverse events recorded.

15.2 Overall Summary

50/402 (12.4%) GHB-treated patients had at least one adverse event coded under one or more of the neuropsychiatric adverse event terms outlined in Section 15.1. Their distribution by dose and severity is displayed in the following table which I have copied from the submission.

Possible Neuropsychiatric AEs	Total[a]	Placebo[b]	Xyrem Oral Solution Dosage (g/d) at Onset[c]				
			3.0	4.5	6.0	7.5	9.0
Number of patients	402 (100%)	54 (100%)	97 (100%)	269 (100%)	298 (100%)	133 (100%)	229 (100%)
Patients with ≥ 1 AE	50 (12%)	1 (2%)	5 (5%)	6 (2%)	24 (8%)	4 (3%)	16 (7%)
Patients with SAEs	7 (2%)	0	0	2 (1%)	2 (1%)	0	3 (2%)
Patients with related AEs	26 (6%)	1 (2%)	1 (1%)	3 (1%)	11 (4%)	0	12 (9%)
Patients with severe AEs	8 (2%)	0	0	3 (1%)	4 (1%)	0	3 (2%)
Patients discontinued due to AEs	10 (2%)	0	0	3 (1%)	2 (1%)	0	5 (4%)
Patient deaths due to AEs	1 (1%)	0	0	0	1 (1%)	0	0

[a] Patients are counted only once in each total column.
[b] Patients were on placebo for a short time (4 weeks) relative to the long-term exposure of those treated with Xyrem.
[c] Some patients were exposed to more than 1 dosage during the trial(s), so the sum of patients exposed to specific dosages exceeds the total number of patients in the integrated clinical trials.

As the table above indicates

- 1 death was associated with a neuropsychiatric adverse event
- 7/402 (1.7%) patients had a serious neuropsychiatric adverse event
- 10/402 (2.5%) patients discontinued treatment on account of a neuropsychiatric adverse event

- Such adverse events did appear to have their highest incidence at the 9 g/day dosage

Note that 2 prominent neuropsychiatric adverse events were not included in the above table

- Patient # 14043, participating in Study OMC-SXB-7, who had obsessive compulsive disorder survived a suicide attempt. This patient was not included in the table as the suicide attempt was, based on an incorrectly entered date in a Case Report Form, mistakenly considered to have occurred about 6 weeks after treatment ended. In fact she was still a participant in the trial when the suicide attempt was made
- Patient # 0936, participating in Study OMC-SXB-7, who had a previous history of depression **died** from what was believed to be an overdose of multiple drugs. The event occurred on 2/24/01, 5 months after the cut-off date for the 120-Day Safety Update.

15.3 Distribution Of Individual Neuropsychiatric Adverse Events

The distribution of individual COSTART-coded neuropsychiatric adverse events is as illustrated in the following table

Note that patients may have had adverse events in more than one category

COSTART Term	Number Of Patients
Total	50
Depression	27
Stupor	6
Suicide Attempt (including Overdose and Intentional Overdose)	4
Paranoid Reaction	4
Coma	2
Psychosis	2
Manic Depressive Reaction	1
Personality Disorder	1

15.4 Specific Neuropsychiatric Adverse Events

15.4.1 Depression

The sponsor has provided a table summarizing all patients coded to have the COSTART preferred term "depression."

The table provides the following data: patient ID #, trial #, sex, age, dosage at onset of confusion, start and stop date for adverse event, investigator term, whether serious or not, action taken, frequency, relationship to study drug, severity and relevant medical history.

I have not reproduced the table in this review.

In regard to the table the following are noteworthy

- Verbatim investigator terms included "depression", "depressed mood", "situational depression", "down in the dumps", and "dysphoria". The sponsor points out that the COSTART term "depression" as used in this particular context is not equivalent to a psychiatric diagnosis of Major Depressive Disorder using DSM-IV criteria.
- 27 patients experienced a total of 30 adverse events coded as depression
- 26/27 patients were receiving GHB at the time of this adverse event and 1/27 placebo

- 3 patients had a recorded previous history of depression or bipolar disorder
- In none of the instances was depression considered a serious adverse event
- GHB was permanently discontinued in 2 patients and temporarily stopped in 2 additional patients
- 5 patients received antidepressant medication to control depressive symptoms
- No patient who attempted to or committed suicide is listed in the table

15.4.2 Hallucinations

The sponsor has provided a table summarizing all patients coded to have the COSTART preferred term "hallucinations."

The table provides the following data: patient ID #, trial #, sex, age, dosage at onset of confusion, start and stop date for adverse event, investigator term, whether serious or not, action taken, frequency, relationship to study drug, severity and relevant medical history.

I have not reproduced the table in this review.

In regard to the table the following are noteworthy

- 9 patients had adverse events that were coded as hallucinations. In all 9 the investigator term also indicated that they had hallucinations.
- All 9 patients were receiving GHB at the time this adverse event appeared
- In 4/9 the hallucinations, based on the investigator term used, were hypnagogic hallucinations. In a further patient the hallucinations ceased with an increased dose of GHB and were therefore presumed to be hypnagogic hallucinations.
- The hallucinations were characterized in 4 patients (these were not patients with hypnagogic hallucinations): the hallucinations were auditory in 3 and visual in 1.
- In only 1 patient were hallucinations a reason for medication discontinuation. This patient has already been described (see Section 14.7.3)

15.4.3 Stupor

The sponsor has provided a table summarizing all patients who had an adverse event coded using the preferred term stupor.

This table is below

Patient No.	Trial	Sex/Age (yr)	Dosage at Onset (g/d)	Trial Day[a] Start	Trial Day[a] Stop	Investigator Term	Serious/ Action Taken W/Study Drug	Frequency/ Relationship/ Severity	Relevant Medical History
0122	OMC-GHB-3	F/25.4	6.0	34	34	Felt drunk	No/no change	Intermittent/ unknown/mild	Narcolepsy, cataplexy [c]
0203	OMC-GHB-3	M/35.5	9.0 [b]	55	55	Intoxicated feeling	No/ temporarily stopped	Continuous/ probably related/ moderate	Narcolepsy, cataplexy [c]
0220	OMC-GHB-3	F/55.4	9.0	46	46	Like being drunk	No/no change	Continuous/ probably related/ moderate	Narcolepsy, cataplexy [c]
0227	OMC-GHB-3	F/25.7	6.0	39	39	Felt drunk after first dose	No/no change	Continuous/ possibly related/mild	Narcolepsy, cataplexy [c] Non-specific headaches
0814	OMC-GHB-3	M/55.7	4.5	56	56	Alcohol intoxication feeling	No/no change	Continuous/ possibly related/mild	Narcolepsy, cataplexy [c]
1275	OMC-GHB-3	F/49.7	6.0 [b]	66	66	Felt intoxicated	No/ temporarily stopped	Continuous/ possibly related/mild	Narcolepsy, cataplexy [c]

[a] Day relative to first dose of Xyrem in first trial in the integrated database.
[b] Dosage was carried forward from last known entry.
[c] From OMC-GHB-2 medical history; no history was taken at entry into OMC-GHB-3.

Note that

- "Stupor" occurred in 6 patients, all of whom had only 1 episode of this adverse event
- Investigator terms suggested that all 6 patients did not have "stupor" in the sense in which the term is conventionally used in the medical literature (i.e., obtunded)
- In no patient was the adverse event serious or a reason for permanent study drug discontinuation
- As the sponsor has pointed out, such an adverse event is not unexpected given the sedative properties of GHB

15.4.4 Suicide Attempt

A total of 4 GHB-treated patients attempted to commit, or successfully committed suicide. These patients are summarized in the following table.

Patient ID #	Study	Sex/Age (years)	Duration Of Treatment With GHB At Time Of Adverse Event	GHB Dose At Time Of Adverse Event	Investigator Term And Details Of Episode	Pre-Existing Psychiatric History	Action Taken
0531	OMC-SXB-7	F/46.5	394 days	6 g/day	Death (suicide)	Bipolar Disorder	Not applicable
0936	OMC-SXB-7	F/52	18 months	6 g/day	Death from multiple drug overdose (suicide)	None recorded at time of study entry. During study was diagnosed to have bipolar disorder	Not applicable
1131	OMC-SXB-7	F/46.2	280 days	9 g/day	Conscious overdose (suicide attempt)	Depression, previous suicide attempt	Study drug discontinued
14043	OMC-SXB-7	F/26	11 years	9 g/day	Overdose (suicide attempt)	Obsessive-compulsive disorder	Study drug discontinued

The nature of the overdose in the case of the above patients was as follows

Patient ID #	Nature Of Overdose
0531	Multiple drugs including, possibly, GHB
0936	Multiple drugs including GHB
1131	GHB only
14043	Buspirone

The sponsor points out that neither of the above fatalities was due to an overdose of GHB alone

15.4.5 Paranoia

The sponsor has provided a table summarizing all patients coded to have the COSTART preferred term "paranoia."

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

Patient No.	Trial	Sex/ Age (yr)	Dosage at Onset (g/d)	Trial Day* Start	Trial Day* Stop	Investigator Term	Serious/ Action Taken W/Study Drug	Frequency/ Relationship/ Severity	Relevant Medical History
0212	OMC-GHB-3	F/ 62.7	6.0	431	433	Mild paranoia due to hypnagogic hallucinations	No/no change	Intermittent/ unknown/mild	Narcolepsy, cataplexy [b]
	OMC-GHB-3	F/ 62.7	6.0	444		Complained of "feeling paranoid" [a]	No/no change	Intermittent/ possibly related/mild	Narcolepsy, cataplexy [b]
0232	OMC-SXB-7	F/ 44.4	9.0	476	486	Acute paranoid delusional psychosis	Yes/ discontinued	Continuous/ probably related/ severe	Narcolepsy, cataplexy, headache and migraine
0219	OMC-SXB-6	F/33.1	4.5	19	35	Feeling paranoid	No/no change	Continuous/ not related/ moderate	Narcolepsy, cataplexy Depression, anxiety,
0004	OMC-GHB-2	F/49.7	9.0	22	24	Paranoia	No/ discontinued	Intermittent/ probably related/mild	Narcolepsy, cataplexy, headache thyroid surgery; cold nodule removed Known replacement thyroid anemia

[a] Day relative to first dose of Xyrem in first trial in the integrated database.
[b] From OMC-GHB-2 medical history; no history was taken at entry into OMC-GHB-3.
[c] This AE was also recorded at trial entry for OMC-SXB-7.

As is evident from the above table

- 4/402 (1%) of patients experienced paranoia as an adverse event: in each instance the COSTART term matched the investigator term
- In only 1 patient was this adverse event serious and sufficient to lead to treatment discontinuation
- A previous history of depression and anxiety was present in one patient

15.4.6 Coma

The 2 patients who were coded as having this adverse event are summarized in the following table which I have copied from the submission

Patient			Dosage at Onset	Trial Day*		Investigator	Serious/ Action Taken W/Study Drug	Frequency/ Relationship/	Relevant Medical
No.	Trial	Sex/Age	(g/d)	Start	Stop	Term	With Study Drug Yes/ discontinued	Severity Continuous/ probably related/ severe	History Narcolepsy, cataplexy
0238	OMC-SXB-6	M/64.3	4.5	170	170	Non-responsive			
2830	OMC-SXB-6	F/41.9	6.0	106	106	Knocked out	No/no change	Isolated/ possibly related/ severe	Narcolepsy Depressi'n
	OMC-SXB-6	F/41.9	6.0	173	173	Knocked out	No/no change	Isolated/ possibly related/ severe	See history above

* Day relative to first dose of Xyrem in first trial in the integrated database.

The following additional observations can be made

- Only one 1 patient was this adverse event serious and sufficient to lead to GHB discontinuation
- Patient # 2830 is described as falling repeatedly due to cataplexy, striking her head against an object and losing consciousness

The sponsor points out that neither of these adverse events could be considered a neuropsychiatric adverse event

15.4.7 Psychosis

The 2 patients for whom the COSTART term "psychosis" was used are summarized in the following table which is copied from the submission

Table 5.3.7 Patients Who Experienced Possible Treatment-Emergent Neuropsychiatric Events of COSTART Preferred Term "Psychosis" - Integrated Clinical Trials

Patient No.	Trial	Sex/Age (yr)	Dosage at Onset (g/d)	Trial Day* Start	Trial Day* Stop	Investigator Term	Serious/ Action Taken W/Study Drug	Frequency/ Relationship/ Severity	Relevant Medical History
1101	OMC-GHB 3	M/39.4	4.5	156		Acute psychosis	No/ discontinued	Continuous/ possibly related/ moderate	Narcolepsy, cataplexy, Congenital exotropia, Headaches, Bizarre dreams, Poor concentration and attention [c] schizophrenia [c]
2030	OMC-SXB-7	M/18.3	9.0 [b]	202	202	Brief reactive psychosis	No/no change	Intermittent/ definitely related/ moderate	Narcolepsy
	OMC-SXB-7	M/18.3	9.0 [b]	207	214	Brief reactive psychosis	Yes/ discontinued	Continuous/ possibly related/ severe	Narcolepsy

* Day relative to first dose of Xyrem in first trial in the integrated database.
[b] Dosage was carried forward from last known entry.
[c] From OMC-GHB-2 medical history; no history was taken at entry into OMC-GHB-3.
[d] Not disclosed at screening.

As the table indicates

- The COSTART term matched the investigator term in each instance
- Both patients discontinued GHB on account of this adverse event; in one patient the adverse event was considered serious
- One patient had a pre-existing history of schizophrenia

15.4.8 Manic Depressive Reaction

The single patient who had this adverse is summarized in the next table

Patient No.	Trial	Sex/Age (yr)	Dosage at Onset (g/d)	Trial Day* Start	Trial Day* Stop	Investigator Term	Serious/ Action Taken w/Study Drug	Frequency/ Relationship/ Severity	Relevant Medical History
0931	OMC-SXB-7	F/28.9	4.5	284	400	Bipolar affective disorder	Yes/ discontinued	Continuous/ not related/ severe	Narcolepsy Migraine [b] Depression [c]

* Day relative to first dose of Xyrem in first trial in the integrated database.
[b] From OMC-SXB-6 medical history.
[c] Not disclosed at screening.

Note that this patient had a prior history of depression

15.4.9 Personality Disorder

The patient outlined in the next table experienced a prolonged grief reaction (coded using the COSTART term of "personality disorder") following the death of a relative. The event appears to have resolved without cessation of study medication.

Patient No.	Trial	Sex/Age (yr)	Dosage at Onset (g/d)	Trial Day* Start	Trial Day* Stop	Investigator Term	Serious/ Action Taken w/Study Drug	Frequency/ Relationship/ Severity	Relevant Medical History
1570 [b]	OMC-SXB-6	F/25.1	6.0	139	430	Grief reaction	No/no change	Intermittent/ not related/mild	Narcolepsy, cataplexy, Skin hurts (in random patches)

* Day relative to first dose of Xyrem in first trial in the integrated database.
[b] This AE was also recorded (as COSTART preferred term depression) at trial entry for OMC-SXB-7.

15.5 Narratives For Deaths Associated With Neuropsychiatric Adverse Events, Serious Neuropsychiatric Adverse Events, and Discontinuations Due To Neuropsychiatric Adverse Events

These narratives are below

15.5.1 Patient # 0932 (Initials ——)

This 24 year old woman who participated in OMC-SXB-6 had a history of depression dating back to 1994. Her dose of Xyrem® was increased from 4.5 g daily to 6 g daily. On Day 84 she experienced auditory hallucinations for which she was hospitalized and treated with olanzapine. Her dose of Xyrem® was then reduced to 4.5 g daily. Her hallucinations resolved and she was discharged after 14 days continuing with GHB for the remainder of the trial. Hospital discharge records indicated to her investigator that for the previous 5 years she had experienced repeated auditory hallucinations and had 2 psychiatric hospitalizations

15.5.2 Patient # 0531 (Initials ——)

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

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

On 7/4/00 she asked friends to leave a gathering at her home as she felt unwell. After a friend was unable to contact her, emergency personnel entered her home and found her dead the following day. A post-mortem toxicology screen was positive for opiates, acetaminophen and benzodiazepines. Quantitative testing showed toxic levels of multiple drugs including hydrocodone, oxycodone, morphine, hydromorphone,

nordiazepam and zolpidem. It was presumed that she had committed suicide by taking an overdose of multiple drugs. The death certificate listed multiple drug toxicity as the cause of her death with atherosclerotic cardiovascular disease also being listed as a significant factor.

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

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

15.5.3 Patient # 0936 (Initials —

This 52 year old woman participated first in Study OMC-SXB-6, and then in OMC-SXB-7. She has a past medical history of narcolepsy with cataplexy, surgery for obesity and depression.

She received Xyrem® for a total of about 18 months. About 3 days before her death she saw a psychiatrist who diagnosed a possible bipolar disorder and prescribed lithium and paroxetine.

She was found dead in her home. Based on what remained of her supply of GHB she was believed to have consumed about 600 mL over 3 days. Prescription bottles for lithium (which should have contained about 60 tablets of uncertain strength), paroxetine (which should have contained about 45 tablets of uncertain strength) and oxycodone-acetaminophen were found to be empty. A full medical examiners report is pending but she was felt by the investigator to have died of an overdose of multiple drugs.

Earlier during the study she had been hospitalized twice on account of kidney stones. Other medications prescribed during the study were cephalexin and iron supplements

15.5.4 Patient # 1131 (Initials —

This 46 year old man was begun on Xyrem® on 4/30/99. At study entry he did not disclose that he had a past history of depression and a previous suicide attempt. Concomitant medications at study entry included modafinil 400 mg/day, ibuprofen, an aspirin-acetaminophen-caffeine combination pill, dextroamphetamine and bupropion (for smoking cessation).

His regular dose of Xyrem® at the time of the serious adverse event described below was 9 g/day.

He took an overdose of Xyrem® (subsequently estimated at 150 g) on 2/2/00. His wife found him unresponsive and incontinent of urine and feces that day. He was initially unresponsive with apneic spells, but with normal arterial blood gases. He later became combative and finally awoke, at which time he was observed to be depressed. He reported multiple major sources of stress. He required psychiatric hospitalization and did not resume Xyrem®.

15.5.5 Patient # 14043 (Initials —

This 26 year old woman had previously participated in the Scharf trial and had received GHB since 7/5/89. She entered the OMC-SXB-7 trial on 8/30/99. Her past medical history was remarkable for obsessive compulsive disorder. Concomitant medications during the OMC-SXB-7 trial include fluvoxamine, buspirone and methylphenidate.

On 4/2/00 she took her usual dose of Xyrem® (7.5 g/day) and then attempted suicide by taking 56 tablets of buspirone 5 mg. She immediately told her father what had happened, was taken to an emergency room

where she was treated and released. She reported being increasingly self-critical from January 2000 onward after beginning methylphenidate. After discontinuing Xyrem® (last dose on 4/4/00) she became more negative in outlook and noted an increase in cataplexy and in sleepiness.

15.5.6 Patient # 0232 (Initials ——

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

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

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

15.5.7 Patient # 0238 (Initials (——

This 65 year old man, participating in OMC-SXB-6, had been taking Xyrem® 4.5 g daily for 5 months. He had a background history of hypertension.

Immediately after his wife heard a loud noise around midnight, he was found comatose, flaccid, incontinent, bradycardic and hypoventilating. No convulsive movements had been witnessed. He required intubation and artificial ventilation. However the same day he awoke, was extubated and returned home. An EEG was normal; an echocardiogram showed ventricular hypertrophy with posterolateral wall hypokinesia, but with a satisfactory ejection fraction. A "cardiac event" was proposed as a cause for his symptoms by the hospital staff caring for him. However the Principal Investigator, after reviewing his hospital records considered the possibility that an inadvertent overdose with GHB was responsible for the episode was responsible for the episode. Study medication was permanently discontinued. Further information is not available.

15.5.8 Patient # 2030 (Initials ——)

This 18 year old man began taking Xyrem® on 5/28/99 and was maintained on a stable dose of 9 g/day thereafter. Concomitant medications included zolpidem, protriptyline, modafinil (200 mg/day), fluoxetine 20 mg/day, methylphenidate 40-45 mg/day. He reported no previous psychiatric history.

On 12/15/99 he began experiencing paranoia, confusion and hallucinations. He reported increasing his dose of methylphenidate earlier while preparing for examinations. He was hospitalized and treated with multiple medications. Xyrem® was stopped on 12/22/99. He improved and his psychosis was attributed to methylphenidate overuse and to sleep deprivation.

15.5.9 Patient # 0931 (Initials——

This 29 year old woman had taken Xyrem® from 7/5/99 until she developed the serious adverse event listed in the table above in April 2000. At screening, she did not disclose that she had a past history of depression.

Her dose of Xyrem® at the time of the adverse event was 4.5 g/day. She was also receiving modafinil 600 mg/day.

On 4/27/00 the study coordinator was informed that the patient had been hallucinating and had lost her job owing to a diminished ability to function at work. On 4/29/00 the patient was found to be unarousable in her car by emergency personnel: on being awakened she became violently agitated, but was also slow in

responding to questions. She was hospitalized and treated with multiple medications for agitation. Her urine drug screen was positive for benzodiazepines. The patient later reported that on 4/29/00 she pulled off the road to sleep at which time she took both nightly doses of Xyrem® together without dilution. She was diagnosed to have a bipolar disorder.

She did not take any Xyrem® after 4/29/00 and at a follow-up visit on 6/14/00 appeared mentally well.

15.5.10 Patient # 0204 (Initials —)

This 60 year old woman received GHB in OMC-GHB-3. At the time of her entry into the study, and prior to receiving GHB she was irritable, depressed and had difficulty awaking. Her only concomitant medication included acetaminophen.

During her participation in the trial she reported continued depression and insomnia. She received GHB initially in a dose of 6.0 g/day and later in a dose of 9 g/day. 19 days after first entering the study she discontinued participation on account of a lack of efficacy

15.5.11 Patient # 0213 (Initials —)

This 60 year old man participated in OMC-GHB-3 prior to which he had received GHB for about 4 months. He did not have a past medical history of depression.

He entered the OMC-GHB-3 study on a dose of 6 g/day. While in this study his dose was increased to 9 g/day; it was later reduced to 3 g/day on account of a depressed mood and excessive tiredness. After temporary interruptions of treatment to see if he improved, he eventually discontinued taking the drug permanently following which these adverse events resolved

15.5.12 Patient # 0702 (Initials —)

This 59 year old woman participated in Study OMC-GHB-2. She had a past history of narcolepsy with cataplexy, cirrhosis and a left facial palsy. Concomitant medications included ipratropium bromide and albuterol.

She received OMC-GHB-2 in a dose of 9 g/day. 20 days later she began experiencing confusion, hallucinations and forgetfulness, followed in the next 2 days by nausea and paranoia. Study medication was discontinued when these symptoms began and her symptoms resolved 5 days later.

15.5.13 Patient # 1101 (Initials —)

This 39 year old man participated in Study OMC-GHB-3. At the time of entry into the study he was receiving dextroamphetamine and methylphenidate, both of which had been taken for about a year.

He received GHB for about 6 months, last in a dose of 4.5 g/day. After 6 months of treatment he developed an "acute psychosis" leading to discontinuation of all stimulant drugs. About 2 months prior to that, methylphenidate had been discontinued and amphetamine-dextroamphetamine substituted. GHB was discontinued 2 weeks later.

4 years later the patient remained psychotic.

15.6 Experience With Neuropsychiatric Adverse Events In Controlled Clinical Trial OMC-GHB-2

This section was created by the reviewer and is not part of the sponsor's presentation.

As noted earlier this was a 4-week randomized, double-blind, placebo-controlled, parallel-arm study comparing 3 doses of GHB with placebo. I have chosen this study as it constitutes the only parallel-arm

Adverse events that could be considered neuropsychiatric are summarized in the following table. Percentages are in parentheses. As the table indicates the number of neuropsychiatric adverse events seen in this study was too small, and without a clear overall pattern in relation to study drug/dose, to draw inferences.

Adverse Event	Treatment Group			
(COSTART term)	Placebo	GHB 3 g	GHB 6 g	GHB 9 g
	(n =34)	(n = 34)	(n = 33)	(n = 35)
Any	24 (70.6)	25 (73.5)	25 (75.8)	26 (74.3)
Anxiety	1 (2.9)	1 (2.9)	0	2 (5.7)
Dream Abnormal	0	0	3 (9.1)	1 (2.9)
Thinking Abnormal	0	1 (2.9)	0	2 (5.7)
Insomnia	1 (2.9)	0	0	0
Depression	0	1 (2.9)	0	0
Nervousness	3 (8.8)	1 (2.9)	2 (6.1)	3 (8.6)
Paranoid Reaction	0	0	0	1 (2.9)
Hostility	0	0	1 (3.0)	0
Hallucinations	0	0	1 (3.0)	1 (2.9)
Emotional Lability	2 (5.9)	2	0	0
Euphoria	0	0	1 (3.0)	0

Adverse events that could be considered neuropsychiatric and led to treatment discontinuation are summarized in the next table

Patient ID #	Patient Age and Gender	Treatment Group	Adverse Event (COSTART Term)	Duration of Treatment at Onset of Adverse Event	Outcome
818	53 F	Placebo	Insomnia	3 weeks	Resolved
605	20 M	GHB 9 g	Somnolence, thinking abnormal	8 days	Resolved
702	59 F	GHB 9 g	Confusion, hallucinations, amnesia, nausea and paranoid reaction	19 days	Resolved

15.7 Psychopathology In Narcolepsy

The sponsor has reviewed medical publications that describe the association between narcolepsy and neuropsychiatric symptoms.

Based on these publications the sponsor has drawn attention to the following

- A higher incidence of psychopathology, including depression, may be present in narcoleptic patients than in controls, based on retrospective case-control studies. Depressive symptoms have been reported to be present in about 50% of narcoleptics
- Psychiatric morbidity in narcoleptics may also be related to high-dose stimulant therapy.

The sponsor considers that in patients with narcolepsy, patient status (i.e., psychiatric status) is a "complicated and dynamic representation" of the following

- Disease-associated psychosocial morbidity.
- Stimulant-induced personality changes.
- Stress variations in daily life.

- Treatment-related co-morbidities.

15.8 Reviewer's Comments

- I agree that in the majority of patients who developed neuropsychiatric adverse events while taking GHB in Integrated Clinical Trials it is not possible to attribute causality for the adverse event to GHB. Pre-existing psychiatric illness, and concomitant medications such as stimulants, as well as other factors, could be contributory. Even in patients in whom there was no recorded premorbid history of psychiatric illness the extent to which they were screened for such illness is not clear.
- However the occurrence of neuropsychiatric adverse events in patients taking GHB, even if not directly caused by the drug, could place them at risk of intentional or accidental overdose, as is suggested by the narratives above.

16. Adverse Events Coded As "Convulsions" In Integrated Clinical Trials

16.1 Background

The following request was made to the sponsor by the Division
10 patients are listed as having had "convulsions" (preferred term) in the Integrated Clinical Trials
Please identify these patients
What were the investigator terms used in these instances?
What additional information is available about these episodes?

In response to the above request the sponsor has performed an analysis of convulsions as follows:

- All patients who had adverse events with the COSTART preferred term of "convulsion" or "convulsions" in the 5 Integrated Clinical Trials (OMC-GHB-2, OMC-GHB-3, Scrima, OMC-SXB-6 and OMC-SXB-7) were included in the analysis; the cut-off date for inclusion was 9/30/00 which was also the cut-off date for the 120-Day Safety Update
- For each patient with such an adverse event the following were determined
  - Dosage of GHB at the onset of each adverse event
  - Start and stop date for each adverse event calculated from the date of the first dose of trial medication in his or her first trial with GHB
  - Investigator terms used

16.2 Results Of Analysis

16.2.1 Number And Distribution Of Patients With "Convulsion(s)"

14 out of 402 patients (3%) were recorded as having an adverse event that was coded as a "convulsion" or "convulsions." All occurred during treatment with GHB

Their distribution according to dose and severity is noted in the following table which I have copied from the submission. As the table indicates none of these instances led to death, serious adverse events or adverse event discontinuations.

			Xyrem Oral Solution Dosage (g/d) at Onset					
	Total *	Placebo	Total *	3.0	4.5	6.0	7.5	9.0
Number of patients	402 (100%)	54 (100%)	399 (100%)	97 (100%)	265 (100%)	290 (100%)	133 (100%)	129 (100%)
Patients with ≥ 1 AE of convulsion	14 (3%)	0	14 (4%)	0	3 (1%)	5 (2%)	0	6 (5%)
Patients with convulsion SAEs	0	0	0	0	0	0	0	0
Patients with related convulsion AEs	7 (2%)	0	7 (2%)	0	1 (<1%)	4 (1%)	0	2 (2%)
Patients with severe convulsion AEs	2 (<1%)	0	2 (1%)	0	1 (<1%)	1 (<1%)	0	0
Patients discontinued due to convulsion AE	0	0	0	0	0	0	0	0
Patient deaths due to convulsion AE	0	0	0	0	0	0	0	0

* Patients are counted only once in each category.

16.2.2 *Investigator Terms*

Verbatim investigator terms for all 14 patients recorded to have a "convulsion" or "convulsions" are in the following table copied from the submission.

Patient Number	COSTART Term	Verbatim Term
0221	Convulsion	Increase in major cataplexy attacks
0231	Convulsion	Increased duration of cataplectic events
0243	Convulsion	Increase partial cataplexy
0545	Convulsion	Increase in cataplexy [a]
0608	Convulsion	Increased cataplexy
0814	Convulsion	Seizures
0835	Convulsion	Increased cataplexy/ cataplexy [b]
1130	Convulsion	Cataplexy
1302	Convulsion	Increased cataplexy (significant) [a]
1306	Convulsion	Increase in cataplexy
1509	Convulsion	Multiple cataplexy attacks for 10 mins. (due to protocol violation of patient: got out of bed to use bathroom 1 and ½ hrs. after taking 1st dose of GHB)
1703	Convulsion	Bit tongue/hit temple against furniture (due to falling faster to ground: cataplexy)[c]
2936	Convulsion	Cataplexy
3937	Convulsion	Cataplexy

[a] This patient had two separate events with the same verbatim term.

[b] This patient had two separate events, one of "increased cataplexy" and one of "cataplexy"

[c] This patient had two events, one of "Bit tongue (due to falling faster to ground: cataplexy)" and one on the same day of "hit temple against furniture (due to falling faster to ground: cataplexy)"

As the table above indicates, in 13 out of 14 patients the verbatim investigator term, based on which the patient was coded as having a "convulsion" or "convulsions", indicated that the "convulsion(s)" represented cataplexy.

In the remaining patient (# 0814) the verbatim investigator term used was "seizures". A more detailed narrative for this patient is in the next section.

16.2.3 Narrative For Patient # 0814 (Initials ——

This 58 year old man had an additional medical history of esophagitis, diverticulitis, breast cancer and a penicillin allergy. Concomitant medications at study entry included tamoxifen, omeprazole, amitriptyline and promethazine.

He had narcolepsy and cataplexy for 3 years at the time of his entry into OMC-GHB-2. He later participated consecutively in OMC-GHB-3 and OMC-SXB-7. In all these studies he received a dose of 4.5 g/day of Xyrem®.

After taking GHB for 935 days he saw his neurologist (not the principal investigator) on a routine visit and reportedly described as a fugue state. Such events had occurred reportedly on Days 220 and 558 and the terms "fugue state", "patient reports being in limbo", and "trance-like state" were used to describe these episodes (the COSTART term was depersonalization). The neurologist suggested that he had seizures and treated him with phenytoin 100 mg daily; this drug was taken for slightly less than 2 months. Similar events have continued since and currently occur about once or twice a week. The investigator reportedly feels that the episodes are "consistent with mild cataplexy or memory loss." The investigator also reportedly feels that it is probable that the event termed "seizures" was cataplexy-related.

While on treatment with Xyrem® he developed congestive heart failure. He was treated with enalapril, digoxin, carvedilol and warfarin.

16.3 Reviewer's Comments

- It does appear that all but one of the 14 patients in the Integrated Clinical Trials who were listed as having "convulsion(s)" in fact had cataplexy
- The remaining patient (# 0814) was considered to have a fugue state, the etiology of which is unclear. While partial complex seizures can be the cause of such states, a primary psychiatric disorder may also be responsible. Further details of this patient's episodes are unavailable and it is therefore not possible to make a determination whether he did have partial seizures. In addition it is somewhat difficult to understand the following
  - The reason why the principal investigator felt these were episodes of cataplexy (attacks of narcolepsy can, however, be associated with automatic behavior)
  - The reason why his neurologist chose to treat him with what was almost certainly an inadequate dose of phenytoin.

17. Abnormalities Of Blood Glucose And Transaminases In Integrated Clinical Trials

17.1 Abnormalities Of Blood Glucose

17.1.1 Background And Sponsor's Methods

The Division had asked for further information with hypoglycemia and hyperglycemia depicted in a table that I have already displayed in Section 5.3.1.

The questions, all of which pertained to the Integrated Clinical Trials only, were as follows

- Patients 0810, 0815 and 0820 had exceptionally low post-baseline blood glucose estimations (ranging from 12 to 24 mg/dL).
  Are these results accurate?
  Is there an explanation for their apparent hypoglycemia?
  What were their symptoms, if any, when hypoglycemic?
- A number of patients had hyperglycemia (mainly post-baseline). Were they known diabetics or are there any other explanations for their hyperglycemia?

In responding the sponsor has discussed the instances of hypoglycemia and hyperglycemia separately.

For the 3 patients with apparent hypoglycemia, laboratory records were examined and both tabular and narrative analyses prepared.

To answer the Division's questions about hyperglycemia the sponsor identified such patients using the following criteria

- Adverse events recorded using the COSTART terms of hyperglycemia or diabetes mellitus
- Blood glucose levels ("clinically significant elevated blood glucose levels"), corresponding to the following
  Either
  A blood glucose that was > 70% higher than at baseline
  Or
  A blood glucose > 200 mg/dL

The sponsor has indicated that

- Fasting blood glucose measurements were specified for protocols OMC-GHB-2 and OMC-GHB-3, although this requirement was not always met
- "Non-fasting" blood glucose measurements were used in Protocols OMC-SXB-6 and OMC-SXB-7

Information in this amendment was supplemented by a telephone conversation with the sponsor held on 4/6/01

17.1.2 Hypoglycemia

The 3 patients with hypoglycemia are described further below

17.1.2.1 Patient # 0815 (Initials [redacted])

This 43 year old woman had no history of diabetes mellitus or any metabolic-endocrine disease and was not receiving concomitant medications capable of causing hypoglycemia.

Her fasting blood glucose levels, dates on which the respective blood samples were drawn, and concurrent Xyrem® doses are listed in the table below which I have copied from the submission

Protocol	Dose	Collection Date	Blood Glucose (Normal 60-115)
OMC-GHB-2	0	4/28/97	83
	0	5/20/97	62
	0	6/9/97	67
	9g	6/23/97	69
	9g	7/11/97	24
	9g	7/22/97	73

During the study a number of adverse events were recorded. These included disorientation, diaphoresis, unstable gait, malaise, and a smothering sensation. However these were recorded on dates when blood glucose levels were normal. On the date when she had a blood glucose of 24 mg/dL, the following adverse events were recorded: stomach cramps and diarrhea; no symptoms or physical signs consistent with hypoglycemia were recorded. The sponsor presumes that the blood glucose level of 24 mg/dL was a laboratory error.

17.1.2.2 Patient # 0820 (Initials [redacted])

This 37 year old woman had no history of diabetes mellitus or any metabolic-endocrine disease and was not receiving concomitant medications capable of causing hypoglycemia.

Her fasting blood glucose levels, dates on which the respective blood samples were drawn, and concurrent Xyrem® dose are listed in the table below which I have copied from the submission.

Protocol	Dose	Collection Date	Blood Glucose (Normal 60-115)
OMC-GHB-2	0	7/1/97	49
	0	7/8/97	44
	0	7/29/97	42
	0	8/14/97	16
	0	8/19/97	76
OMC-GHB-3	0	8/28/97	42
	6g	3/6/98	47
	6g	6/24/98	15
Discontinued From Study			

As the table indicates all her blood glucose levels across Studies OMC-GHB-2 and OMC-GHB-3 were low, with one exception (a reading of 76 mg/dL during OMC-GHB-2). During the OMC-GHB-2 study the only adverse event recorded was malaise but the date on which this was recorded is unclear; the sponsor states that "no hypoglycemic symptomatology was reported" even in association with the blood glucose level of 16 mg/dL. It is noteworthy that during this study she received placebo.

During Study OMC-GHB-3 she continued to have low fasting blood glucose levels with the lowest being recorded on 6/24/98 (15 mg/dL): according to the sponsor "there were no symptoms suggestive of acute hypoglycemia at the time of this visit but because of a large number of reported adverse events and in the best interests of the patient she was discontinued from the study at that time."

The sponsor has supplied adverse event listings for this patient for the OMC-GHB-3 study alone. On 6/24/98 the adverse events recorded included dizziness, lightheadedness, left hand "shakey", body shaking, shakiness in legs, upset stomach, headache, hallucinations ("hearing voices"), dyspnea and lack of energy. During the entire study the patient experienced the above, as well as numerous other adverse events that included numbness (including facial numbness), "down in dumps", snoring, cessation of breathing while asleep, nightmares, leg cramps, confusion, vomiting, hand and arm pain, finger cramps, depression, malaise, listlessness, nervousness, feeling cold and muscle weakness.

The sponsor has also supplied a clinical summary by the principal investigator dated 3/25/98 on which date the patient had attended a scheduled OMC-GHB-3 follow-up visit. On the afternoon of the previous day the patient had laid down for an afternoon nap when here breathing appeared "funny" and she was not responsive; she had last taken GHB at 2AM the same day. When an ambulance crew was summoned she was found to have a "stable respiratory pattern" and to respond when catheterized. After being transferred to an emergency room she became increasingly responsive over the next 2 hours. A drug screen (urine?) was reported to show traces of GHB. Electrolytes were normal. The episode was attributed to marital stress and GHB withheld the same night.

The sponsor states that no post-study blood glucose levels were drawn.

17.1.2.3 Patient # 0810 (Initials —)

This 49 year old woman had no history of diabetes mellitus or any metabolic-endocrine disease and was not receiving concomitant medications capable of causing hypoglycemia.

Her blood glucose levels (fasting in OMC-GHB-2 and OMC-GHB-3), dates on which the respective blood samples were drawn, and concurrent Xyrem® dose are listed in the table below which I have copied from the submission.

Protocol	Dose	Collection Date	Blood Glucose (Normal 70-115)
OMC-GHB-2	0	4/4/97	58
	0	4/18/97	63
	0	4/30/97	57
	3g	5/13/97	49
	3g	5/28/97	58
OMC-GHB-3	3.6g	12/4/97	12
	4.5g	1/29/98	65
	4.5g	11/19/98	75
	4.5g	4/1/99	65
OMC-5XB-7	9.0g	11/10/99	57
	9.0g	5/10/00	77

There were reportedly no adverse events recorded on the same dates that she had blood glucose levels of 49 mg/dL and 12 mg/dL. She did have insomnia, dizziness and heart burn on 6/19/97, "sick" on 9/26/98, and a urinary tract infection in December 1998.

The sponsor presumes that her blood glucose of 12 mg/dL on 12/4/97 was a laboratory error for the following reasons

- There were no adverse events, or abnormalities of physical examination recorded on the same day
- Her blood glucose was normal 2 months later and subsequently

17.1.3 Hyperglycemia

In keeping with the sponsor's method of analysis, this phenomenon is discussed under 2 headings

17.1.3.1 Adverse Events Of Hyperglycemia Or Diabetes Mellitus

5 patients with such adverse events occurred among the 402 patients treated with Xyrem® in the Integrated Clinical Trials, through the cut-off date of 9/30/00 for the 120-Day Safety Update. Further information about these adverse events is as follows

- All such adverse events occurred during treatment with GHB; none occurred during periods of treatment with placebo (54 patients).
- None of these adverse events were serious, severe, or led to study drug discontinuation or death
- The distribution of these patients by dosage at onset was as follows

Dose	Number of Patients
3.0 g/day	0
4.5 g/day	1
6.0 g/day	2
7.5 g/day	1
9.0 g/day	1

- 2 patients were recorded to have diabetes mellitus at the time of study entry.
- The outcome of the adverse event was described as follows

Resolved	2 patients
Unresolved	1 patient

Outcome unknown 1 patient

17.1.3.2 Clinically Significant Elevated Blood Glucose Levels

Using the criteria described in Section 17.1.1 the sponsor has identified 6 patients with such blood glucose levels among the 402 enrolled in the Integrated Clinical Trials

- 7 such episodes occurred in these 6 patients
- All such episodes occurred during treatment with GHB; none occurred during periods of treatment with placebo (54 patients).
- The distribution of these patients by dosage at onset was as follows

Dose	Number of Patients
3.0 g/day	0
4.5 g/day	1
6.0 g/day	2
7.5 g/day	2
9.0 g/day	1

- 4/6 patients were recorded to have diabetes mellitus at the time of study entry.
- 2 of these patients were also recorded to have adverse events coded as hyperglycemia or diabetes mellitus

17.1.4 Teleconference With Sponsor: 4/6/01

A teleconference was held with the sponsor today to discuss the above review of hypoglycemia, and, briefly, that of hyperglycemia as well.

The following items of information were conveyed/confirmed by the sponsor

- All blood glucose levels during OMC-GHB-2 and OMC-GHB-3 were done at a single central laboratory
- All 3 patients with hypoglycemia described above were from a single center (Martha Hagaman, MD, Nashville, TN)
- The blood glucose readings of 24 mg/dL (for Patient # 0815), 16 mg/dL and 15 mg/dL (for Patient # 0820), and 12 mg/dL (for Patient # 0820) were all drawn at formal study visits. At the time of these visits, physical examinations recorded in the Case Report Forms, and Dr Hagaman's recollection of their condition as confirmed during recent telephone contacts with the sponsor, indicated that these patients were normal and not exhibiting the symptoms of hypoglycemia that would have been expected at those blood glucose levels; as a result those blood glucose values were considered laboratory errors by Dr Hagaman.
- Dr Hagaman asked Patient # 0820 to return for a follow-up visit after she discontinued taking study medication: the patient declined to do so. Dr Hagaman later confirmed with the patient's primary care physician that the patient was well; there is no evidence that the patient has been investigated for an underlying metabolic-endocrine disorder.
- In 5/9 patients with hyperglycemia there was no record of pre-existing diabetes mellitus in the entries made to the Case Report Form at the screening visit

17.1.5 Dr James Knudsen's Review Of Hypoglycemia

Dr James Knudsen of this Division's Safety Team was requested to determine if

- There were cases of GHB-associated hypoglycemia in the Adverse Events Reporting System (AERS)
- There were reports of GHB-associated hypoglycemia in the medical literature

Please refer to Dr Knudsen's review for full details of the analysis conducted by him.

17.1.5.1 GHB-Associated Hypoglycemia In AERS

Among the 301 adverse event reports of GHB-exposure in AERS no cases of hypoglycemia (defined arbitrarily as a blood glucose ≤ 2.2 mmol/L) were identified.

17.1.5.2 GHB-Associated Hypoglycemia In Medical Literature

There were no published reports of hypoglycemia associated with GHB exposure in any of the 15 databases searched.

17.1.6 Reviewer's Comments

17.1.6.1 Hypoglycemia

- Adverse events recorded on specific dates may not have occurred on those dates; therefore, attempts to correlate low blood glucose readings on specific dates with symptoms recorded on those dates could be misleading
- Patient # 0820 had a number of symptoms that were compatible with hypoglycemia during her participation in the Orphan drug trials; her blood glucose levels were almost consistently low at baseline and across her period of treatment with both placebo and GHB. While her hypoglycemia does not appear to be causally linked to GHB use, it is unlikely that a total of 7 low blood glucose readings all represented laboratory errors, and in view of her symptoms it is especially surprising that these abnormalities were investigated further while she was participating in the study. I understand, however, that efforts are underway at the present time to subject her to further medical testing in this regard.
- Patients 0810 and 0815 were not recorded to have adverse events compatible with hypoglycemia at any time during study participation despite having exceptionally low blood glucose levels (12 mg/L and 24 mg/L, respectively) which might have been expected to have been always associated with pronounced symptoms. The lack of appropriate adverse events, and the reportedly normal physical examination at or around the time the blood samples were drawn does support the sponsor's contention that these laboratory readings were erroneous; yet, erroneously low blood glucose readings, are in this reviewer's experience, quite uncommon and it is especially noteworthy that all 3 such readings were from patients at a single center.
- There are no instances of GHB-associated hypoglycemia in AERS or in the medical literature, based on Dr Knudsen's review.

17.1.6.2 Hyperglycemia

- In at least 4/9 of the instances listed by the sponsor, diabetes mellitus appears to have been present and the likely mechanism of the hyperglycemia
- In the remaining patients the explanation for the hyperglycemia is not clear, but it is conceivable that at least some of these patients did have diabetes mellitus, but that the diabetes was not documented. Even assuming that all

those with hyperglycemia had diabetes mellitus the prevalence of that condition in this population is not in excess of that in the general population.

17.2 Abnormalities Of Transaminases

17.2.1 Background

The Division had asked for further information about 4 patients who had post-baseline transaminase elevations depicted in a table that I have already displayed in Section 5.3.1: #s 0202, 0507, 1610 and 1709. The Division asked whether these abnormalities were followed up and whether they had resolved.

The sponsor states that these laboratory tests were performed centrally for these trials. The reference ranges are as in the following table

Trial	Laboratory	Reference Range	
		AST (IU/L)	ALT (IU/L)
OMC-GHB-2 OMC-GHB-3	—	2-40	2-53
OMC-SXB-7	—	9-34	6-34

17.2.2 Sponsor's Description Of Individual Cases

17.2.2.1 Patient # 0202 (Initials —)

This patient was a 62 year old woman who participated consecutively in Studies OMC-GHB-2, OMC-GHB-3 and OMC-SXB-7. Her transaminase results are tabulated below; the table is the sponsor's

Protocol	Dose	Sample Date	AST (9-34)	ALT (6-34)
OMC-GHB-2	0	2/24/97	16	17
	0	3/03/97	19	19
	0	3/17/97	27	29
	3g	3/31/97	13	15
	3g	4/14/97	12	16
OMC-GHB-3	4.5g	5/27/97	15	14
	6.0g	7/28/97	14	13
	4.5g	10/2/97	13	11
	4.5g	4/6/98	11	7
	6.0g	10/7/98	18	17
	3.0g	3/14/99	19	23
OMC-SXB-7	3g	4/20/99	19	**38**
	6g	7/20/99	19	18
	6g	10/21/99	**36**	**262**
	6g	10/26/99	21	**90**
	6g	2/17/00	19	21
	6g	5/25/00	19	19
	6g	11/16/00	23	20

The sponsor reports that accompanying the elevation in ALT on 10/21/99 the patient complained of nausea, vomiting and upper abdominal pain. As the table indicates the ALT abnormality had improved 5 days later and her transaminases remained normal for at least a further year despite continuing the same dose of GHB (dosing with this drug was never interrupted). Other liver function tests-alkaline phosphatase, LDH and total bilirubin remained normal.

17.2.2.2 Patient # 0507 (Initials —)

This 34 year man participated consecutively in Studies OMC-GHB-2, OMC-GHB-3 and OMC-SXB-7. His transaminase results are tabulated below; the table is the sponsor's

Protocol	Dose	Sample Date	AST	ALT
GHB-2	0	4/30/97	38	65
	0	5/17/97	32	56
	0	5/28/97	24	36
	0	5/31/97	25	39
	9g	6/13/97	29	37
	9g	6/27/97	24	26
OMC-GHB-3	3g	1/5/98	29	51
	3g	7/20/98	**52**	**109**
	7.5g	2/15/99	35	**67**
OMC-SXB-7	**7.5g**	**5/10/99**	**49**	**86**

As the table above indicates, this patient had a mild elevation of ALT at screening and mild elevations, mainly of ALT, during Studies OMC-GHB-3 and OMC-SXB-7. Adverse events recorded (but not necessarily present) on the same days as the elevations in ALT and AST included "flu" and "heartburn/reflux". "Malaise-generally not feeling well" was recorded on 3/2/98.

The patient discontinued after the first visit of OMC-SXB-7 and did not attend a closeout visit. No blood tests were done after 5/10/99.

17.2.2.3 Patient # 1610 (Initials . ——

This patient was a 26 year old woman who participated consecutively in Studies OMC-GHB-2, OMC-GHB-3 and OMC-SXB-7. Her transaminase results are tabulated below in a table copied from the submission

Protocol	Dose	Sample Date	AST	ALT
OMC-GHB-2	0	8/6/97	22	17
	0	9/19/97	43	119
	0	9/25/97	32	48
	0	10/3/97	28	26
	3g	10/17/97	47	49
	3g	10/31/97	34	36
OMC-GHB-3	9g	5/6/98	24	23
	9g	5/15/98	18	22
	9g	11/4/98	**76**	**248**
	9g	11/11/98	17	42
	9g	1/4/99	16	11
OMC-SXB-7	9g	3/3/99	14	9

After an isolated elevation in ALT was noted prior to receiving GHB, an elevation in ALT, AST and alkaline phosphatase was noted about 1 year after beginning GHB. All enzyme elevations resolved spontaneously without discontinuation of GHB and without any adverse events contemporary with the enzyme abnormalities being recorded

17.2.2.4 Patient # 1709 (Initials ——,

This patient was a 26 year old woman who participated consecutively in Studies OMC-GHB-2, OMC-GHB-3 and OMC-SXB-7. Her transaminase results are tabulated below in a table copied from the submission

Protocol	Dose	Sample Date	AST	ALT
OMC-GHB-2	0	10/3/97	22	15
	0	10/10/97	19	18
	0	10/22/97	27	23
	9g	11/5/97	23	24
	9g	11/19/97	24	25
OMC-GHB-3	6g	5/13/98	17	13
	3g	11/11/98	30	**76**
	4.5g	4/26/99	34	38
OMC-SXB-7	4.5g	7/15/99	24	16

This patient had a single isolated elevation in ALT which was not contemporaneous with any recorded adverse events and resolved despite continuing GHB for at least another 8 months

17.2.3 Sponsor's Comments

- In all 4 of the above instances the sponsor was unable to find an explanation for the liver function abnormalities
- In all 4 instances the sponsor believed that it was unlikely that the study drug was responsible for the abnormalities

17.2.4 Reviewer's Comments

I agree with the sponsor's contention that GHB is unlikely to have been responsible for the transaminase elevations noted above

18. Patient 0231

18.1 Background

This patient (initials —— participated in the open-label study OMC-SXB-6 and was described in some detail earlier in this reviewer's NDA Safety Review.

The sponsor was asked whether this patient was hospitalized. In this submission a complete narrative has been provided. I have summarized the narrative below

18.2 Narrative

This 67 year old man was enrolled in Study OMC-SXB-6. His past medical history was remarkable for a stomach ulcer, gastroesophageal reflux disease, and a cholecystectomy. Concomitant medications at study entry included clomipramine, methylphenidate, paroxetine, imipramine and modafinil.

He took Xyrem® in a dose of 4.5 g/day for 12 days and 9 g/day for 106 days. After having been on a stable dose of 9 g/day for 106 days he awoke about 1 hour after his second nightly dose feeling dizzy and confused. On getting out of bed he felt nauseated and vomited after reaching the bathroom. He felt a sensation of "shut down" and difficulty breathing, crawled from the bathroom to lie down in the hallway until he felt well enough to return to bed about 1 ½ hours after the episode began. Frequent cataplexy attacks apparently accompanied the episode. After returning to bed he slept soundly and awoke the next morning feeling well. The same day he contacted the Principal Investigator and withdrew from the study. He was never hospitalized or seen in an emergency room.

At the time the episode occurred his concomitant medications included a multivitamin, DGL (a herbal preparation), an unspecified medication for gastroesophageal reflux and methylphenidate.

The episode occurred on 7/27/99. A follow-up phone call from the study coordinator on 3/19/01 indicated that no further such episodes had occurred.

18.3 Reviewer's Comments

- It is clear from the above narrative that the patient was not hospitalized.
- It is possible that the episode of nausea, vomiting, dizziness and other sensations was caused by Xyrem® although it is unclear why the episode occurred after the patient had been on a stable dose for over 3 months

19. Drug-Induced Lupus In Integrated Clinical Trials

19.1 Background

A limited number of patients participating in the open-label Scharf study had antinuclear antibody testing done and a proportion of these patients had positive

tests. While there were no definite cases of drug-induced lupus in that study, the sponsor was asked to analyze the safety data for the 402 patients participating in the Integrated Clinical Trials to determine if there were any patients who had clinical symptoms and signs suggestive of drug-induced lupus.

A detailed review of the section of the Amendment dealing with this matter was performed by Dr Tarek Hammad of the Safety Team. Please refer to Dr Hammad's review for full details. The following summary is based entirely on Dr Hammad's review

19.2 Sponsor's Methods

Antinuclear antibody testing was not done in the Integrated Clinical Trials. To identify possible cases of drug-induced lupus the sponsor therefore used a symptom-based case definition that was developed in consultation with Dr _____ a rheumatologist, who was earlier consulted regarding the positive antinuclear antibody tests in the Scharf trial.

The sponsor's case definition required that a patient experience two of the nine following symptoms: arthralgia, arthritis, myalgia, joint disorder, pain, alopecia, fever, malaise and rash.

The sponsor reviewed adverse event data for all 402 patients participating in the Integrated Clinical Trials. A total of 12 patients were eventually identified who had 2 or more of the symptoms subsumed under the above case definition: 10 of these patients had these symptoms while under treatment with GHB and 2 patients had these symptoms while being treated with placebo. The 10 GHB-treated patients who met the case definition are summarized in the following table which I have copied from Dr Hammad's review.

Case ID/ Study #	Sex/ age	Time to onset (d = days)	Symptoms	Outcome/ recurrence	Sodium oxybate status	Comments
1633/SXB-6	F/56 y	70 d	Myalgia, stiff & sore joints, difficulty concentrating, diarrhea, loss of taste, shortness of breath on exertion and weight gain.	Resolved after drug discontinuation/ no recurrence	Dose 9 g/night. Drug discontinued after five months of treatment due to persistent symptoms.	Patient improved within two weeks of drug discontinuation. A follow up, 14 months later, showed that symptoms disappeared completely after two months with no new medical problems.
0211/GHB-3	F/56 y	45 d	Arthralgia in three joints	Resolved/no recurrence	Dose 6 g/night. Treatment continued.	History of arthritis. Miscoded as three episodes of arthralgia.
0240/SXB-6	M/59 y	18 d	Rash on arm	Resolved/no recurrence	Dose 4.5 g/ night. Treatment continued.	None
		123 d	Joint pain	Intermittent	Dose 6 g/night Treatment continued	
0608/GHB-2, GHB-3, SXB-7	F/48 y	301, 352, 397, & 508 d	Four episodes of arthralgia and/or pain	Resolved/no recurrence	Dose 4.5 g/night. Treatment continued.	History of "long-standing" fibrositis and osteoarthritis (back, hip & knees).
0815/GHB-2	F/43 y	54, 56, & 58 d	Fever and "achiness"	NA	Dose 3 g /night. Treatment continued.	History of arthritis since 1985 & chronic fatigue syndrome. The episode diagnosed as "chronic fatigue immune dysfunction syndrome."
1302/GHB-2, GHB-3, SXB-7	F/55 y	31 d	Fever	Resolved/no recurrence.	Dose 9 g/ night. Treatment continued.	History of joint and back pain for seven years and "familial ankle swelling."
		282 d	Arthritis			
		346 d	"Severe hammer toe"			

Case ID/ Study #	Sex/ age	Time to onset (d = days)	Symptoms	Outcome/ recurrence	Sodium oxybate status	Comments
		854 d	"Unspecified pain"			
1305/GHB-2, GHB-3, SXB-7	F/73 y	Four occasions between 247-324 d	Arthritic symptoms in left knee or hip	Resolved/no recurrence	NA	History of arthritis since 1980.
1603/GHB-2, SXB-7	F/48 y	268 & 318 d	Arthralgia and myalgia	Resolved/no recurrence	Dose 4.5 g/ night. Treatment continued.	Positive ANA two years prior to GHB exposure. History of fibromyalgia since 1966, chronic fatigue, abdominal & pelvic pain, and hair loss.
		581 & 645 d	Shoulder pain	NA	NA	
1608/ GHB-3	F/42 y	43,68, & 86 d	Arthralgia (wrist joint)	Resolved/no recurrence	Dose 6 g/ night. Treatment continued.	
		503, 536, & 541 d	Low back pain and myalgia			Pain started after physical activity on day 528.
1612/GHB-2, GHB-3	F/48 y	1 d	Wrist pain	Resolved/no recurrence	Dose 6 g/night. Treatment continued	History of low back, shoulder and hip pain
		101 d	Arthralgia and alopecia		Dose 7.5 g/night. Treatment continued.	
		108, 120, 128, 153, 156, 187, 374, & 481 d	Muscle or leg pain			

After reviewing each of the above cases Dr Hammad is of the opinion that only Patient # 1633 participating in OMC-SXB-6 had symptoms and signs consistent with drug-induced lupus. However in the absence of antinuclear or antihistone antibody testing the diagnosis cannot be confirmed.

19.3 Sponsor's Conclusions

"None of the 402 patients in the Integrated Clinical Trials developed systemic lupus erythematosus or was diagnosed with drug-induced lupus during, participation in any of the five trials. A systematic review of the adverse effect data collected on these 402 patients definitively excluded symptoms suggestive of drug-induced lupus in all but one patient."

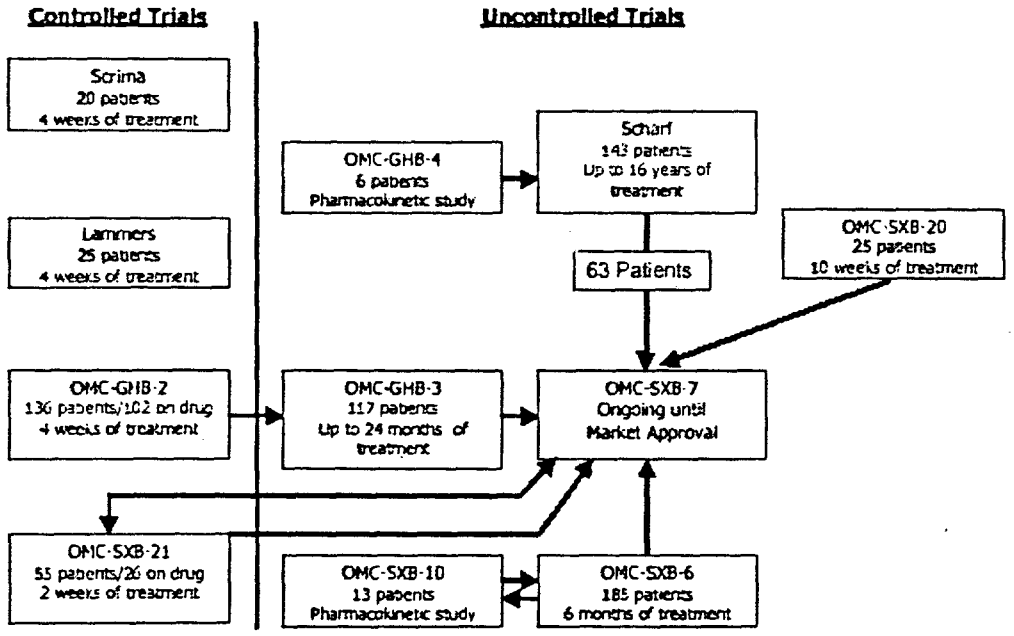
19.4 Reviewer's Comments

- I agree that there is no firm evidence that any patient participating in the Integrated Clinical trials had drug-induced lupus; however, in the absence of appropriate antibody testing, which was not performed at all in this cohort, it is hard to see how firm evidence of that diagnosis could have been obtained
- I also agree that at least one patient participating in the Integrated Clinical Trials had symptoms that may have been suggestive of drug-induced lupus.

20. Exposure Tables

20.1 Overall Schematic For Clinical Trials In Narcoleptic Patients Included In NDA

This schematic is copied from the submission and is included in this section by me for convenience.



20.2 Tables

20.2.1 Sponsor's Methods For Creating Tables

Tables were created for 2 different groups of patients

- The updated Integrated Clinical Trials database which included the following studies through the cut-off date for the 120-Day Safety Update (9/30/00): OMC-GHB-2, OMC-GHB-3, OMC-SXB-6, OMC-SXB-7 and Scrima
- All patients subsumed by the above bullet plus the Scharf study

The sponsor used the following methods for creating these tables

- Each patient dose was classified into one of 5 "standard" dose groups as in the following table

Patient Dose g/day	"Standard" Dose Group Category g/day
0 to 3.5	3
> 3.5 to 5.5	4.5
> 5.5 to 7.0	6.0
> 7.0 to 8.5	7.5
> 8.5	9.0

- Each patient's exposure to these 5 standard doses was calculated for both groups of patients and the number of patients at each dose level for each duration of exposure recorded in the tables. Assignment of patients to a dosing category was made based on continuous exposure time in that dosing category
- For the "overall duration of exposure" category each patient's time of exposure was calculated regardless of dose.
- Patients who received placebo only were not included in the tables
- Duration of exposure was calculated based on a 28-day month

- Since each patient could be represented in more than one dose category for the specified duration of exposure the overall exposure numbers do not represent arithmetical summations of the numbers in individual dose categories

20.2.2 Tables

The sponsor has presented tables for different durations of exposure

20.2.2.1 Duration of Exposure ≥ 6 Months

The sponsor's table is presented below

Patients	3.0 g/d	4.5 g/d	6.0 g/d	7.5 g/d	9.0 g/d	Overall
ISS Only	9	50	115	59	62	296
ISS + Scharf	25	87	171	83	70	360

20.2.2.2 Duration of Exposure ≥ 12 Months

The sponsor's table is presented below

Patients	3.0 g/d	4.5 g/d	6.0 g/d	7.5 g/d	9.0 g/d	Overall
ISS Only	5	27	60	26	34	223
ISS + Scharf	12	55	114	50	42	286

20.2.2.3 Duration of Exposure ≥ 24 Months

The sponsor's table is presented below

Patients	3.0 g/d	4.5 g/d	6.0 g/d	7.5 g/d	9.0 g/d	Overall
ISS Only	2	4	13	9	13	48
ISS + Scharf	6	26	66	34	23	150

20.2.2.4 Sponsor's Comments About Above Tables

The sponsor has drawn attention to the following:

- The most commonly used dose of GHB across the 3 durations of exposure was 6 g/day regardless of whether data from the long-term Scharf trial were included or excluded
- The vast majority of patients used doses ranging from 4.5 to 9 g/day, across durations of exposure. The sponsor has proposed a starting dose of 4.5 g/day with a range of 3 to 9 g/day after titration
- Even if patients from the Scharf study are excluded patient exposures are currently sufficient to meet ICH guidelines for the 6 and 12 month periods

20.3 Sponsor's Overall View Of Adequacy Of Exposure

- The sponsor has provided comparisons of the adequacy of exposure to Xyrem® with and without the Scharf study database. The following table summarizes the data presented by the sponsor

Study Pool	Integrated Clinical Trials Plus Scharf		Integrated Clinical Trials Only	
	Patients	Healthy Subjects*	Patients	Healthy Subjects*
Any Exposure	528	125	448	125
Exposure ≥ 6 Months	376	0	296	0
Exposure ≥ 12 Months	303	0	223	0
Patient-Years Of Exposure	1265	Not calculated	269	Not calculated

*Healthy subjects were exposed to single doses only

- The entire database contains sufficient patient exposure sufficient to meet the ICH guidelines at 6 months (> 300 patients) and 1 year (> 100 patients)
- "Since this is an Orphan Drug FDA has proposed a number of about 500 total subjects exposed to meet the requirement for overall exposure." The database includes over 500 subjects exposed to GHB even if the Scharf dataset is not included.

20.4 Reviewer's Comments

- The size of the Xyrem® NDA database (with the 120-Day Safety Update included) does meet ICH guidelines for drug exposure for 6 months and a minimum of 1 year if one assumes that the effective dose ranges from 3 to 9 grams/day. The ICH guidelines are met even if the Scharf study is excluded
- However, if one concludes (from the efficacy studies) that the 9 g/day dose is the only effective dose and is that to be recommended for general use the number of those exposed to Xyrem® at that dose for ≥ 6 months and ≥ 12 months does not meet ICH guidelines. If it is concluded from the efficacy studies that the effective dose of Xyrem® ranges from 6-9 g/day, the number of those exposed at that dose range for ≥ 6 months falls somewhat short of that specified in the ICH guidelines, whereas the number exposed for 12 months does not. Note that the sponsor has not supplied data for the **total** number of patients exposed for any duration (including or excluding the Scharf study) for the 6-9 g/day dose range or at the 9 g/day dose itself

Note that ICH guideline E1A (July 1997) states the following:
"The number of patients treated for 6 months at dosage levels intended for clinical use should be adequate to characterize the pattern of adverse events over time. To achieve this objective the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5% to 5%). Usually 300 to 600 patients should be adequate....

.....100 patients exposed for a minimum of 1 year is considered to be acceptable to include as part of the safety database. The data should come from prospective studies appropriately designed to provide at least one year exposure at dosage levels intended for clinical use."

- The extent of exposure to GHB in patient-years is reduced by about 79% once the Scharf study data are eliminated. Admittedly, the ICH guidelines do not specifically address the issue of desirable exposure in patient-years.
- There are no ICH guidelines that address exposure requirements for Orphan Drugs. While the sponsor's statement *that "since this is an Orphan Drug, FDA has proposed a number of about 500 total subjects exposed to meet the requirement for overall exposure"* is technically incorrect (the number was proposed by the sponsor and judged acceptable by the Division), the total number of patients exposed to Xyrem® may be appropriate for an Orphan Drug; that may be especially true if the sponsor's estimate that the number of diagnosed/treated cataplexy patients in the United States is in the range of 20,678-22,917 is correct (this estimate was conveyed to this Division at a meeting held on 2/28/01)

21. Reviewer's Summary Of "Sleepwalking"

21.1 Background

In this NDA, and especially in the Scharf Study, the term "sleepwalking" has been used as a verbatim (investigator) term for a common adverse event. The COSTART preferred term under which this entity has been coded is "sleep disorder."

The sponsor has not discussed this adverse event, either in the original NDA submission or in this Amendment. Given the frequency and potential/actual consequences of this adverse event (see below) I have chosen to discuss it further briefly

In most instances of "sleepwalking" in this NDA, a detailed description of patient behavior during that adverse event is not available.

The medical term "sleepwalking" refers to a non-REM parasomnia classified as an arousal disorder. During episodes patients exhibit complex behaviors including automatic and semi-purposeful motor activities: sitting up in bed, walking, climbing stairs, opening and closing windows and even more complex tasks, such as preparing food, may be features. Acts that are destructive or harmful may be seen, such as throwing objects, and climbing out through a window. During and immediately following episodes patients are confused; they have amnesia for the episodes. It is not at all clear that the term "sleepwalking" has a similar connotation when used in this NDA, or that it refers to a single clinical entity. In the majority of instances of sleepwalking in the Scharf study, this term appears to be derived from daily logs maintained by patients

Based on a literature search there does not appear to be an association between narcolepsy and typical sleepwalking, as defined in the paragraph above. However about 50% of narcoleptic patients have periods of automatic behavior that are described as memory lapses or blackouts; patients have amnesia for their activities during these episodes. Semi-purposeful activity is possible during such episodes which may manifest with phenomena such as walking into objects, getting lost while driving, and writing unintelligibly. Such episodes are believed to be due to micro-sleeps that intrude into wakefulness, and are most frequent in the mornings. Again there is no information supplied with the NDA that would strongly suggest that any of the "sleepwalking" episodes correspond to automatic behavior occurring as part of narcolepsy.

21.2 Incidence Of "Sleepwalking" In Xyrem® NDA

21.2.1 Controlled Clinical Trial OMC-GHB-2

The incidence of adverse events coded under the COSTART preferred term "sleep disorder" is as follows among the 4 treatment groups

Dose Group	Total Number Randomized	Number of Patients with "Sleep Disorder" (COSTART)	% of Patients with "Sleep Disorder" (COSTART)
Placebo	34	1	2.9

Dose Group	Total Number Randomized	Number of Patients with "Sleep Disorder" (COSTART)	% of Patients with "Sleep Disorder" (COSTART)
3 g/day	34	2	5.9
6 g/day	33	4	12.1
9 g/day	35	5	14.3

The sponsor has attempted to characterize the term "sleep disorder" further in the following table which I have copied from the OMC-GHB-2 clinical trial report

		GHB		
Description	**Placebo**	**3g**	**6g**	**9g**
Prolonged sleep paralysis	1	1	2	5
Sleep walking	0	0	0	2
Poor sleep maintenance/ frequent arousal	0	1	2	1
Microsleep	0	0	1	0

21.2.2 Integrated Clinical Trials

Note that OMC-GHB-2 is a component of this group of trials.

"Sleep disorder" (COSTART) occurred in 46/402 (11.4%) of patients participating in these trials. There was no dose-response seen and the sponsor has not characterized this adverse event further except in the case of those participating in OMC-GHB-2. Thus it is unclear how many patients recorded as having a "sleep disorder" (COSTART) might have been considered to have "sleepwalking"

21.2.3 Scharf Trial

Based on my review of all the Case Report Forms for this study, 45/143 (31.5%) of patients were listed as having one or more episodes of "sleepwalking." A single patient (# 01-042, initials ——) is described as having 346 episodes over a 5-year period, and many patients had multiple episodes.

The patients listed as having "sleepwalking" constitute the entire cohort of those coded under the COSTART preferred term "sleep disorder" in this study

21.3 Characterization Of "Sleepwalking" Episodes

As already indicated the sponsor has not provided more detailed descriptions of patient behavior during these episodes except in a very small number of instances.

I have not attempted to characterize the "sleepwalking" episodes in regard to patient demographics, duration, severity and seriousness of episodes, GHB dose at onset, concomitant medications and illnesses, outcome and other parameters. I currently lack both the time and resources to perform such an analysis. The sponsor should, however, be required to perform such an analysis prior to

approval. Such episodes, regardless of their etiology, have had serious consequences as outlined below.

21.4 Consequences Of "Sleepwalking" In Xyrem® NDA

Narratives are provided below for patients who were reported to have events of serious or potentially serious consequence during episodes of "sleepwalking." These consequences include taking an overdose of GHB as well as other actions. Several of these narratives are elsewhere in this review but are reproduced here for convenience. All instances occurred in the Scharf study.

21.4.1 Patient 01-215 (Initials ——

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

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

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

21.4.2 Patient 01-017 (Initials ——

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

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

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

Other significant items of information regarding this patient are as follows

- **He had many episodes of sleep walking and multiple episodes of urinary incontinence.**
- **In 2 instances episodes of sleep walking and urinary incontinence are listed in the Case Report Form as occurring on the same day although there is no evidence presented that they occurred at the same time.**
- **On the days when both incontinence and sleep walking are listed as having occurred, the patient's prescribed dose was 7.5 g/day**
- **As noted above this had multiple episodes of sleep walking that did not occur on the same days as his episodes of incontinence.**

- He also reported muscle jerks over the front of his trunk over a period of several years while taking GHB. These were stated to be most prominent when lying in bed in the morning as the last dose of GHB was wearing off; they could be controlled voluntarily and would disappear with ambulation, returning when at rest.
- He developed congestive heart failure during the study and died about 5 years after study entry. While participating in the study he underwent a thoracotomy for a right lung nodule that was confirmed to be a squamous cell carcinoma.

21.4.3 Patient 01-267 (Initials ——

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

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

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

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

21.4.4 Patient 01-206 (Initials ——

This 62 year old woman had a history of narcolepsy, hypertension and heavy smoking. She began taking GHB in a dose of 3 g/day.

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

21.5 Reviewer's Comments

- In the absence of adequate clinical descriptions in most instances it is unclear what the investigator term "sleepwalking" represents, or whether it refers to single or multiple entities.
- Regardless of what the term "sleepwalking" means in the context of this NDA, it is clear that such episodes are common; almost one-third of patients participating in the long-term Scharf safety study did have one or more such occurrences, and a single patient is recorded as having as many as 346

episodes. The incidence of this adverse event in the entire Integrated Clinical Trials grouping is unknown (except for a single study, OMC-GHB-2)

- The few clinical descriptions of this adverse event that are available in this NDA suggest that during "sleepwalking" episodes patients may be confused and may act in a manner that could be prejudicial to their own safety and that of others.
- The sponsor has not, so far, attempted to analyze this adverse event as an entity
- The fairly high incidence and potential consequences of such episodes make it essential that the sponsor should be asked to better characterize the instances of sleepwalking in this NDA prior to the drug being approved for marketing.
- In this reviewer's opinion (and on a largely speculative basis) it is possible that the term "sleepwalking" as used in this entity could be describing one or more of the following entities
  - An acute confusional state induced by GHB
  - Automatic behavior of narcolepsy
  - Partial complex seizures (these are unlikely to be caused by GHB)
  - Prolonged absence seizures (such seizures have been reported to be induced by other drugs in the past)
  - An arousal disorder akin to true sleepwalking
- It is certainly possible that some instances of "sleepwalking" in patients taking GHB are not very different in their manifestations from the episodes of "confusion" or "fugue states" or reported in others

22. Scharf Study Re-Inspection

A further inspection of the Scharf study site was conducted from 5/7/01 to 5/11/01. This second inspection was intended to validate the data presented in the Major Amendment of 3/23/01, using source documents. A sample of 31 patient records were inspected; all 31 were patients who did not enter the OMC-SXB-21 study through the cut-off date of 5/31/99. Based on discussions that I had with Dr Constance Lewin, of the Division of Scientific Investigations, who conducted the second inspection, and on her report (Clinical Inspection Summary dated 6/11/01), it did appear that, in this sample, the data presented in the Amendment were supported by the source documents in all but 6 patients in whom significant discrepancies were noted.

Overall, however, Dr Lewin recommended that the data from the Scharf Study were unacceptable on account of many deficiencies including missing drug accountability records. She recommended that the study not be used in support of the NDA.

23. Overall Comments

- The manner in which data for the Scharf study have been collected, recorded, and presented in this submission cannot be said to be ideal.
- Of the 80 patients who participated in the Scharf study and did not enter the currently ongoing Orphan Medical Treatment IND study OMC-SXB-7, 64

patients might be stated to have be "accounted for" although the basis for doing so is less-than-optimal in a significant number. Further efforts need to be made by the sponsor to account fully for 11 of the remaining 16 (unsuccessful recent efforts have been made to contact 5 patients out of those 16). The 11 patients are listed below. Adverse events that were ongoing at the time of discontinuation are reasons for obtaining further follow-up in at least some of these 11 patients

01-004/
01-027/
01-054/
01-065/
01-228/
01-240/
01-262/
01-269/
01-283/
01-268/
01-256/

- None of the "adverse events" in the "unevaluable" category that occurred in the Scharf study appear to be attributable to GHB
- Urinary and fecal incontinence both appear to be unusually common adverse events in patients taking GHB and the key issues are whether such episodes are accompaniments of unrecognized convulsions, and whether GHB is capable of causing convulsions at therapeutic doses. Currently the evidence that the vast majority of episodes of incontinence in the entire NDA are related to unrecognized convulsions is weak. There does appear to be at least 1 patient in the Scharf study in whom incontinence clearly accompanied a true convulsion.
- While there are clearly a few patients (n = 2) in the entire NDA safety database who experienced, or may have experienced, convulsions while taking GHB, the presence of confounding factors (e.g., possible benzodiazepine withdrawal) makes it difficult to link the convulsions causally to GHB. Whether GHB is capable of causing other types of seizures, e.g., absence or partial complex, is even less clear
- In this NDA, and especially in the Scharf Study, the term "sleepwalking" has been used as a verbatim (investigator) term for a common adverse event. Detailed clinical descriptions of such episodes are not available for the majority of patients and their mechanism has not been delineated. A separate analysis of these episodes has not been performed by the sponsor and it is not clear how common they are in the Integrated Clinical Trials grouping, but such episodes have been associated with serious consequences (e.g., overdose, pyrogenesis, consuming toxic chemicals) in patients enrolled in the Scharf study
- The information available in this NDA does suggest that GHB is capable, at therapeutic doses, of causing a confusional state (which may be accompanied by psychotic symptoms). The incidence and seriousness of such adverse events may be slightly more pronounced at higher doses, and especially if higher doses are administered without titration. However a confusional state also appears to be capable of occurring at lower and even

sub-therapeutic doses of GHB, and after maintenance treatment for several months. The presence of true confusion in patients taking GHB could lead to their taking GHB in a manner other than as prescribed. The symptoms that have been subsumed under the COSTART term "confusion" are not unusual for a sedative-hypnotic drug.

- In the majority of patients who developed "neuropsychiatric" adverse events (e.g., paranoia, hallucinations, anxiety, stupor, etc) while taking GHB in Integrated Clinical Trials it is not possible to attribute causality for the adverse event to GHB. Pre-existing psychiatric illness, and concomitant medications such as stimulants, as well as other factors, could be contributory. Even in patients in whom there was no recorded premorbid history of psychiatric illness the extent to which they were screened for such illness is not clear. However the occurrence of neuropsychiatric adverse events in patients taking GHB, even if not directly caused by the drug, could place them at risk of intentional or accidental overdose, as is suggested by the narratives in this review
- There is no firm evidence that any patients participating in the Integrated Clinical Trials had drug-induced lupus. However antinuclear antibody and antihistone antibody testing was not performed for patients participating in this study
- There is no evidence suggesting a causal link to GHB for the small number of hypoglycemic an hyperglycemic blood test readings in the NDA; several of the apparently hypoglycemic readings could in fact have represented laboratory errors. Neither is there firm evidence in AERS or in the medical literature that GHB is capable of causing hypoglycemia.
- GHB is unlikely to have been the cause of transaminase elevations seen in a few patients in the Integrated Clinical Trials.
- As noted above the manner in which the Scharf study was conducted was deficient in many ways. Of particular concern was the lack of systematic active surveillance for adverse events and missing drug accountability records. As also noted earlier in this review (see Section 22) the Center's Division of Scientific Investigations is of the opinion that the Scharf Study data are unacceptable and has recommended that this study not be used in support of the application. From this reviewer's perspective the best that can be said about this study is that the vast majority of those enrolled have been "accounted" for in the sense that it is unlikely that they have suffered any catastrophic events that this Agency is unaware of. I would, therefore, recommend that this study not be used in estimates of the adequacy of exposure to Xyrem® in the safety database (see next bullet)
- The total number of patients exposed to GHB in the NDA Safety Database minus the Scharf study appears sufficient to meet ICH guidelines at the 6-month and 1-year levels but not in regard to the total number of patients exposed; however allowance can be given for GHB being designated as an orphan drug and the total number exposed may therefore be acceptable.

Note that the extent of exposure to GHB in patient-years is reduced by about 79% once the Scharf study data are eliminated. Admittedly, the ICH

guidelines do not specifically address the issue of desirable exposure in patient-years.

Further if one concludes (from the efficacy studies) that the 9 g/day dose is the only effective dose and is that to be recommended for general use the number of those exposed to Xyrem® at that dose for ≥ 6 months and ≥ 12 months does not meet ICH guidelines. If it is concluded from the efficacy studies that the effective dose of Xyrem® ranges from 6-9 g/day, the number of those exposed at that dose range for ≥ 6 months falls somewhat short of that specified in the ICH guidelines, whereas the number exposed for 12 months does not. Note that the sponsor has not supplied data for the **total** number of patients exposed for any duration (including or excluding the Scharf study) for the 6-9 g/day dose range or at the 9 g/day dose itself

Note that ICH guideline E1A (July 1997) states the following:
"The number of patients treated for 6 months at dosage levels intended for clinical use should be adequate to characterize the pattern of adverse events over time. To achieve this objective the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5% to 5%). Usually 300 to 600 patients should be adequate....

.....100 patients exposed for a minimum of 1 year is considered to be acceptable to include as part of the safety database. The data should come from prospective studies appropriately designed to provide at least one year exposure at dosage levels intended for clinical use."

24. Conclusions

See Efficacy and Safety Reviews

25. Recommendations

See Efficacy and Safety Reviews

Ranjit B. Mani, M.D.
Medical Reviewer

J. Feeney, M.D. _____

rbm 6/14/01
cc:
HFD-120
NDA 21196
Homonnay

Consultative Review and Evaluation of Clinical Data

NDA	**21-196**
Sponsor:	**Orphan Medical, Inc.**
Drug:	**Xyrem (sodium oxybate)**
Material Submitted:	**Sponsor evaluation of Xyrem and Drug-induced Lupus**
Date Review Completed:	**4/16/01**
Reviewer:	**Tarek A Hammad, M.D., Ph.D., M.Sc., M.S.**

This document examines the association of Xyrem (sodium oxybate) with drug-induced lupus (DIL) among 402 patients in five trials. For your convenience in reviewing the document, it is organized as following:

1. Background
2. Findings
3. Reviewer comments

1. Background

The Xyrem primary medical reviewer requested that Orphan Medical, Inc. evaluate the potential for DIL in all company-sponsored studies since the Scharf study had raised the concern about this adverse event. On 3/23/01, the sponsor submitted a major amendment that included the requested evaluation.

1.1 General facts about DIL syndrome

Several drugs can cause a syndrome resembling SLE. These drugs induce antinuclear antibodies (ANA) within a few months. ANA may persist for years. Between 10 and 20 percent of ANA-positive individuals develop lupus-like symptoms. Most common are systemic complaints and arthralgias; polyarthritis and pleuropericarditis occur in 25 to 50 percent. Renal and CNS diseases are rare. All patients have ANA and most have antibodies to histones, but antibodies to double-stranded DNA and hypocomplementemia are rare --a helpful point in distinguishing drug-induced from idiopathic lupus. Anemia, leukopenia, thrombocytopenia, rheumatoid factors, false-positive VDRL, and positive direct Coombs' tests can occur. The initial therapeutic approach is to withdraw the offending drug; most patients improve in a few weeks. Symptoms rarely persist more than 6 months. Most lupus-inducing drugs can be used safely in patients with idiopathic SLE (Ref: Harrison's Online, part 12, chapter 312, McGrow Hill).

2. Findings

2.1 Sponsor submission

The sponsor reviewed their Integrated Clinical Trials database, which included five trials in the Xyrem NDA, namely GHB-2, GHB-3, SXB-6, SXB-7 and Scrima. Together, these five trials comprised 402 patients, many of whom participated in two or more of these

trials sequentially. The protocols did not include measurement of antinuclear antibody (ANA), therefore the sponsor had to develop a case definition to allow them to identify patients who may have developed DIL. Their case definition required that a patient experience two of nine possible DIL symptoms, which included arthralgia, arthritis, myalgia, joint disorder, pain, alopecia, fever, malaise and rash. The sponsor based the selection of these symptoms on a review article by Dr. [redacted] [reference provided in NDA] and a phone discussion with Dr. [redacted] on 3/12/01.

The sponsor identified 19 patients who displayed two or more of the symptoms listed above at any time while participating in one or more of the five trials. Seven of these 19 patients reported only one of the selected symptoms on multiple occasions. This included patients' numbers 0501 (myalgia x2), 0701 (joint disorder x2), 0814 (fever x2), 0815 (fever x3), 0820 (malaise x3), 2230 (myalgia x4), and 3533 (rash x2). The sponsor omitted those seven patients from his evaluation.

The document narrated the details of 12 patients. Two patients were in a placebo group. This reviewer summarizes the remaining ten patients in table-1.

Table-1:

Case ID/ Study ID	Sex/ age	Time to onset	Symptoms	Outcome/ recurrence	Sodium oxybate status	Comments
1633/SXB-6	F/56 y	70 d	Myalgia, stiff & sore joints, difficulty concentrating, diarrhea, loss of taste, shortness of breath on exertion and weight gain.	Resolved after drug discontinuation/ no recurrence	Dose 9 g/night. Drug discontinued after five months of treatment due to persistent symptoms.	Patient improved within two weeks of drug discontinuation. A follow up, 14 months later, showed that symptoms disappeared completely after two months with no new medical problems.
0211/GHB-3	F/56 y	45 d	Arthralgia in three joints	Resolved/no recurrence	Dose 6 g/night. Treatment continued.	History of arthritis. Miscoded as three episodes of arthralgia.
0240/SXB-6	M/59 y	18 d	Rash on arm	Resolved/no recurrence	Dose 4.5 g/ night. Treatment continued.	
		123 d	Joint pain	Intermittent	Dose 6 g/night Treatment continued	
0608/GHB-2, GHB-3, SXB-7	F/48 y	301, 352, 397, & 508 d	Four episodes of arthralgia and/or pain	Resolved/no recurrence	Dose 4.5 g/night. Treatment continued.	History of "long-standing" fibrositis and osteoarthritis (back, hip & knees).
0815/GHB-2	F/43 y	54, 56, & 58 d	Fever and "achiness"	NA	Dose 3 g /night. Treatment continued.	History of arthritis since 1985 & chronic fatigue syndrome. The episode diagnosed as "chronic fatigue immune dysfunction syndrome."
1302/GHB-2, GHB-3, SXB-7	F/55 y	31 d	Fever	Resolved/no recurrence.	Dose 9 g/ night. Treatment continued.	History of joint and back pain for seven years and "familial ankle swelling."
		282 d	Arthritis			
		346 d	"Severe hammer toe"			
		854 d	"Unspecified pain"			

Case ID/ Study ID	Sex/ age	Time to onset	Symptoms	Outcome/ recurrence	Sodium oxybate status	Comments
1305/GHB-2, GHB-3, SXB-7	F/73 y	Four occasions between 247-324 d	Arthritic symptoms in left knee or hip	Resolved/no recurrence	NA	History of arthritis since 1980.
1603/GHB-2, SXB-7	F/48 y	268 & 318 d	Arthralgia and myalgia	Resolved/no recurrence	Dose 4.5 g/ night. Treatment continued.	Positive ANA two years prior to GHB exposure. History of fibromyalgia since 1966, chronic fatigue, abdominal & pelvic pain, and hair loss.
		581 & 645 d	Shoulder pain	NA	NA	
1608/ GHB-3	F/42 y	43,68, & 86 d	Arthralgia (wrist joint)	Resolved/no recurrence	Dose 6 g/ night. Treatment continued.	
		503, 536, & 541 d	Low back pain and myalgia			Pain started after physical activity on day 528.
1612/GHB-2, GHB-3	F/48 y	1 d	Wrist pain	Resolved/no recurrence	Dose 6 g/night. Treatment continued	History of low back, shoulder and hip pain
		101 d	Artharlgia and alopecia		Dose 7.5 g/night. Treatment continued.	
		108, 120, 128, 153, 156, 187, 374, & 481 d	Muscle or leg pain			

2.2 Sponsor conclusion

"None of the 402 patients in the Integrated Clinical Trials developed Systemic Lupus Erythematosus or was diagnosed with drug-induced lupus during, participation in any of the five trials. A systematic review of the adverse effect data collected on these 402 patients definitively excluded symptoms suggestive of drug-induced lupus in all but one patient."

3. Reviewer comments

There is only one patient (# 1633/SXB-6) with a clinical picture that suggests the possibility of DIL. However, a firm diagnosis can not be made due to lack of ANA and anti-histones measurements. In the remainder of the patients, many had a history of arthritis or other musculoskeletal conditions. Although there were patients with some isolated symptoms, treatment with sodium oxybate continued with no recurrence of such symptoms.

Tarek A Hammad, M.D., Ph.D., M.Sc., M.S.
Medical Officer

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/s/

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