Patient No.	Pt Initials	Sex	Age at Trial Entry (yrs)	Date Started GHB Treatment	Date of Last Dose	Reason for Discontinuation	Comments
01-029		M	41	7/12/1987	7/30/1989	Adverse Event	Attempted suicide by GHB overdose
01-064		F	13	6/16/1987	5/00/89	Adverse Event	Increased Seizure Activity
01-066		F	44	3/25/1985	4/20/1991	Adverse Event	High ANA Titer/Possible Drug-Induced Lupus
01-238		M	45	11/30/1983	10/20/1985	Adverse Event	Decrease in short-term memory (COSTART term "amnesia")
01-244		F	55	6/21/1988	5/3/1989	Adverse Event	High ANA Titer/Possible Drug-Induced Lupus
01-247		F	33	7/25/1989	4/30/1990	Adverse Event	Seizure
01-254		F	61	5/2/1988	6/26/1989	Adverse Event	Possible pulmonary toxicity
01-259		F	41	6/3/1987	7/15/1987	Adverse Event	Depersonalization, emotional lability, hypertonia, and pain chest
01-270		F	24	1/16/1994	4/22/1999	Adverse Event	Patient became Pregnant
01-271		M	46	10/24/1994	4/30/1995	Adverse Event	Swelling of ankles and feet
01-273		F	55	11/6/1994	5/30/1995	Adverse Event	Weight loss
01-005		F	45	11/16/1987	7/12/1992	Adverse Event	Increased difficulty sleeping
01-006		M	14	7/24/1985	12/31/1992	Adverse Event	Stimulant-induced rage

Note that in the original NDA 12 patients were listed as having discontinued treatment on account of non-fatal adverse events. Patient #01-243 was listed in the original NDA as having discontinued treatment on account of weight loss; he is not listed in the above table but is listed in the table in Section 7.4.1 since he died 4 months after study drug discontinuation reportedly from a myocardial infarction. Patients 01-006 and 01-270 were not in the original table.

7.5 Review Of Individual Narratives And Case Report Forms

I have reviewed the narratives and individual Case Report Forms for all 80 Scharf study patients who did not enter the treatment IND. I have also reviewed the Case Report Forms for the 63 patients in the Scharf study who subsequently entered the treatment IND.

The information contained in the narratives and Case Report Forms is discussed under the following headings.

7.5.1 Source Of Case Report Forms

The Case Report Forms for the Scharf study were created by , a contract organization hired by the sponsor for that purpose as well as for data management, statistical analysis and report writing. The Case Report Forms were created from the available source documents generated over the preceding 15 years over which the study had been conducted.

7.5.2 Structure Of Case Report Forms

The Case Report Forms were composed of the following separate entry items

- Demographics
- Date of diagnosis of narcolepsy
- Date of pre-treatment polysomnogram
- Mean latency on Multiple Sleep Latency Test

- Date of commencement of GHB
- Daily dose of GHB at commencement
- Previous narcolepsy medications
- Concomitant medications at study entry
- Medical history
- Physical examination
- Dosing record
- Results of hematology, clinical chemistry, urinalysis and electrocardiogram testing done during study
- Adverse events
- Medications used to treat serious adverse events
- Disposition data: assessment date, whether patient was still enrolled in study, if discontinued→ date of last dose, and reason for discontinuation

7.5.3 Deficiencies In Structure Of Case Report Forms And Additional Related Concerns

After reviewing all Case Report Forms for the Scharf study the following items were identified that rendered the review of the data contained in the forms problematical

- The sheets on which entries are made and even entries on individual sheets (i.e., listings of adverse events) are not arranged in chronological order making review difficult. Neither are the sheets grouped by category.
- A clear distinction is not always made between the screening history and physical examination, e.g., symptoms are sometimes entered instead of abnormalities of physical examination
- There are no entries for any follow-up visits to either the study center in Cincinnati or to any physicians located where patients were living.
- There are no entries in the Case Report Forms that would indicate that the study site regularly contacted participating patients over the telephone to ascertain their status (i.e., status of narcolepsy, adverse events, and concomitant medications). Such determinations appear to have been based largely, if not almost entirely, on patient diaries
- Dosing records appear to have been reconstructed based on patient diaries and not on the study center's records of what patients were instructed to take
- Adverse event entries appear to be based at least partly on patient diaries. It is therefore unclear to what extent adverse events that might have been captured by more active regular surveillance by the study center may have been capture
- For patients who were irregular or lacking in accuracy in making diary entries or returning their diaries, records of dosing and adverse events could be unreliable
- It is unclear how the last date of dosing was determined for patients who discontinued from the study; it appears to have been based on diary entries in a substantial number. In other instances where the last date of dosing was unknown, patients may have taken study drug for several months after the last diary-based entries were made in the Case Report Form.
- The Case Report Forms do not actually document the clinical status of patients at the time of study drug discontinuation. Indirect inferences

regarding their clinical status can be made from the last dosing change, adverse event, electrocardiogram and laboratory data in the Case Report Forms if these were sufficiently close temporally to when GHB was stopped. Such data can provide some reassurance that these patients were not gravely ill at the time of discontinuation; if they were in fact very seriously it is unlikely for them to have been able to complete their diaries. Admittedly in a number of patients who discontinued from the Scharf study, post-treatment confirmation of health status is available from attempts at follow-up

- For patients who did not enter the treatment IND but did continue in the Scharf study, no follow-up information (i.e., adverse events, laboratory and electrocardiogram data) is available after 1998-early 1999 which is when the Case Report Forms were created. The sponsor states that since these patients continued in the Scharf study no active recent attempts at follow-up were needed.
- **Many source documents (mainly in the "progress notes" category) supplied with the Case Report Forms are undated and unsigned.**
- The sponsor's narratives have in some instances, not included serious adverse events listed in the supplied Case Report Forms. The sponsor appears to have chosen only events that were considered by the investigator to be GHB-related for further description.
  For example, Patient # 01-012 (initials —') had an episode of "disorientation, stupor, and weakness" that necessitated hospitalization. This incident is not described in the sponsor's narrative

7.5.4 Deaths And Adverse Event Discontinuations

7.5.4.1 Deaths

None of the deaths listed above were causally attributable to GHB

7.5.4.2 Adverse Event Discontinuations

Narratives have been prepared by me for all individual adverse event discontinuations except Patient 01-271 (Initials —) and are contained elsewhere in this review, in the main Safety Review or both.

In the case of Patient 01-271, a source document indicates that the patient's swelling resolved within a month of discontinuing GHB.

7.5.5 Patients Discontinued From Scharf Study For Non-Compliance

7.5.5.1 Background

I have discussed these patients separately since the material that the investigator received from them (e.g., diary entries, laboratory and electrocardiogram data) is especially likely to have been deficient.

As indicated earlier, for the majority of patients in this category, material supplied with the Amendment did not contain information obtained actively by the investigator about their health status at the time of discontinuation. As I do not have direct access to the content of their diaries (except in the few instances where excerpts have been provided) and can make only indirect inferences from

adverse event listings, dosing records, and laboratory/electrocardiogram data I have chosen to rely on whatever additional information has been provided about their status at the time of discontinuation for firm confirmation of their status at the time that treatment with GHB was terminated: such information is available in source documents (when provided), narratives and to a slight degree in the Case Report Forms themselves

7.5.5.2 Summary Of Patients Who Were Discontinued From The Scharf Study For Non-Compliance

24 patients were discontinued from the Scharf study on account of non-compliance: in 22 patients non-compliance involved not submitting study diaries sufficiently regularly, and in the remaining 2 patients, failure to follow dosing instructions. The details of these patients are in the next table

Patient # Initials	Date Of Completion of Disposition Sheet* In Case Report Form	Recorded Date Of Last GHB Dose**	Date Of Start Of Last Adverse Event Recorded In Case Report Form	Date Of Last Laboratory Test	Date Of Last Electrocardiogram	Date Of Last Change In GHB Dose	Follow-Up After Discontinuation
01-048	2/3/98	2/28/89	2/7/89	11/23/88	11/23/88	2/13/89	No attempt
01-063	2/28/98	5/31/97***	4/19/91	7/1/97	7/1/97	5/1/97	Unsuccessful attempt (in March 2001) Last phone contact with patient on 8/19/97: patient had recently seen a liver specialist but outcome of assessment was uncertain
01-201	2/25/98	12/31/83	12/24/83	5/7/84	5/7/84	12/31/83	Adverse events including peripheral edema resolved after study drug was withdrawn (contacted in March 2001) A source document (progress note) dated 1/18/91 indicated that after leaving the Scharf study the patient received GHB from another physician for "some time"
01-203	2/19/98	5/14/84	5/8/84	4/17/84	4/17/84	4/21/84	Patient clarified history of suicide attempts prior to entering Scharf study (contacted in March 2001)
01-207	1/30/98	3/31/85	3/30/85	8/20/84	8/20/84	9/14/84	No attempt
01-209	2/4/98	10/2/84	7/18/84	6/18/84	6/18/84	9/30/84	No attempt
01-210	2/6/98	5/3/85	4/23/85	10/22/84	10/30/84	3/13/85	No attempt
01-212 **	5/16/86	11/16/85	8/13/85	7/23/85	7/25/85	11/17/85	No attempt
01-213 *****	2/27/98	12/23/85	12/25/85	5/28/85	5/28/85	12/24/85	No attempt
01-215	1/29/98	10/30/88	10/29/88	1/20/88	11/11/85	9/18/88	Telephone contact with patient in November 1988 indicated that patient had not received letter of discontinuation Adverse events including dizziness and other symptoms had resolved

Patient # Initials	Date Of Completion of Disposition Sheet* In Case Report Form	Recorded Date Of Last GHB Dose**	Date Of Start Of Last Adverse Event Recorded In Case Report Form	Date Of Last Laboratory Test	Date Of Last Electrocardiogram	Date Of Last Change In GHB Dose	Follow-Up After Discontinuation
							(contacted in March 2001)
01-216 ******	1/28/98	2/22/87	2/9/87	2/9/87	2/5/85	2/16/87	No attempt
01-217 *******	2/18/98	7/19/86	7/15/86	9/4/85	5/6/85	7/9/86	No attempt
01-222 ********	2/24/98	4/21/88	2/3/88	5/27/88	No record	4/18/88	No attempt but see footnote ********
01-223	2/25/98	1/24/87	12/11/86	5/29/87	6/24/86	10/5/86	Study site received letter from patient dated 3/31/87 No subsequent attempt at follow-up
01-240	2/3/98	Unknown but patient was formally withdrawn from study on 7/5/88 in a phone conversation	No adverse events recorded	1/4/88	No record	No record	No attempts at follow-up
01-246	2/11/98	4/22/87	7/14/86	1/12/87	1/12/87	7/16/86	Not attempted
01-248	2/17/98	10/13/86	10/22/86	No record of laboratory tests	6/18/86	10/10/86	Not attempted
01-251	2/27/98	11/21/86	1/31/85	7/29/87	4/11/86	11/21/86	Not attempted
01-256	2/27/98	6/30/88	Not recorded **********	3/29/88	3/29/88	3/13/88	Not attempted
1-258	2/26/98	Unknown	3/27/91	10/7/90	10/7/90	3/21/91	Study coordinator spoke with patient on 11/27/91: he was still taking GHB at that time Study coordinator spoke with patient on 1/3/92 to request logs. Unclear whether he was still taking medication at that time. Additional follow-up not attempted
01-263	2/26/98	5/31/91	3/4/91	4/22/91	12/29/89	3/6/91	Letter from patient dated on 12/19/91 stating that GHB was of benefit but that he discontinued that medication because of its bad taste
01-267	4/8/98	7/31/97	1/16/97	12/30/97	11/30/96	5/30/97	Not attempted
01-268 **********	3/4/98	Unknown	8/96	11/3/97	4/30/97	1/25/97	Not attempted
01-288	3/19/99	Unknown **********	10/23/98	7/7/98	7/298	7/2/98	Study coordinator spoke to patient on 2/11/99 to ask for study logs and to inform her that no further medications would be shipped out unless logs were received

*The date entered in the disposition sheet is designated as an "assessment date." However, there is no evidence that the "assessment" consisted of an evaluation of the patient's status. Data entered on this sheet consisted of the following

- whether the patient was still enrolled in study
- if discontinued: date of last dose, and reason for discontinuation

**The basis on which this date was determined is unclear. In addition there are inconsistencies between the source document and Case Report Form regarding the timing of the last dose

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