CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-196

MEDICAL REVIEW

Review and Evaluation of Clinical Data

NDA (Serial Number)	21196
Sponsor:	Orphan Medical Inc.
Drug:	Xyrem®
Proposed Indication:	Narcolepsy
Material Submitted:	Amendment To NDA
Correspondence Date:	5/16/02
Date Received / Agency:	5/17/02
Date Review Completed	6/13/02
Reviewer:	Ranjit B. Mani, M.D.

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1. Background

This submission, an Amendment to the sponsor's New Drug Application (NDA) for Xyrem®, is a response to a second Approvable action letter dated 4/9/02.

An earlier and initial Approvable action was taken in a letter dated 7/2/01. That Approvable action was based on the original NDA for Xyrem®, which was submitted on 9/30/00, and a Major Amendment that was submitted on 3/23/01; the original NDA was granted priority review status. The application was also discussed at a meeting of the Peripheral And Central Nervous System Drugs Advisory Committee which was held on 6/6/01. Please see the following Agency-created documents, related to those 2 applications for full details

- The efficacy and safety reviews of the original NDA
- The clinical review of the Major Amendment
- The transcript of the Advisory Committee meeting
- The text of the Approvable letter

The sponsor responded to the initial Approvable letter with a submission dated 10/5/01; this submission led to the Approvable action letter of 4/9/02. Please see my reviews of that submission, and the text of the Approvable letter of 4/9/02 for full details

The indication currently being pursued by the sponsor is as follows:

"Xyrem® (sodium oxybate) oral solution is indicated for the treatment of cataplexy in patients with narcolepsy"

Xyrem® has been developed by Orphan Medical, Inc. for the treatment of narcolepsy under IND # [redacted] and Treatment IND # [redacted]. Data obtained from individual sponsor-investigator INDs #s: [redacted] (M. Scharf) and [redacted] (L. Scrima) have also been used in support of this application.

In this review the words/phrases/acronyms "γ-hydroxybutyrate," "gammahydroxybutyrate," "GHB," "sodium oxybate," and "Xyrem®" have been used interchangeably.

Prior to reviewing the contents of the submission, it will be helpful to outline the text of the main Approvable letter of 4/9/02 and list in tables all clinical studies that have been included in this NDA.

2. Approvable Letter Of April 9, 2002

The Approvable letter was accompanied by

- Labeling
- A medication guide

- A summary of the risk management program

Only the text of the Approvable letter proper is below:

Your October 5, 2001, amendment constituted a complete response to our July 2, 2001, approvable letter.

We also acknowledge receipt of your submission dated April 3, 2002, containing the results of the completed rat carcinogenicity study.

We also refer to the April 2, 2002, meeting between you and FDA.

We have reviewed this application under the restricted distribution regulations contained in 21 CFR 314.520 of Subpart H.

We have completed the review of this application, as amended, and it is approvable. The remaining issues that you will need to address before this application may be approved are outlined below.

Assessment of Xyrem's Potential to Induce Respiratory Depression

In our July 2, 2001 Approvable Letter we asked you to perform a formal assessment of the respiratory effects of Xyrem prior to marketing. Such assessments are routinely required in the evaluation of sedative-hypnotic drug products. Subsequently, we agreed to review the results of SXB-20, an uncontrolled polysomnographic study previously performed to evaluate the effect of Xyrem on different sleep stages. You believed the results of the respiratory monitoring in SXB-20 provided enough reassurance to allow approval while formal, controlled studies could be performed post-approval.

We have reviewed the results of SXB-20 and are concerned that Xyrem may produce clinically important deleterious effects on respiratory function during sleep, especially in patients with sleep apnea. While there was marked variability in the data collected, 2 of the 4 patients with moderate-severe sleep apnea had marked elevations over baseline in the RDI (respiratory distress index) while on treatment. Absent a control group, it is impossible to distinguish between variability and a drug effect as the cause of these elevations. As discussed in our meeting of April 2, 2002, we believe that these changes may represent a clinically significant worsening of respiratory function at night related to treatment with Xyrem in at least one, and perhaps in both, patients. We acknowledge that you believe that none of the patients experienced a clinically relevant decline in respiratory function. We agreed that you may submit a comprehensive response to our stated concerns in lieu of a definitive assessment of Xyrem's effect on respiratory function in response to this letter. While it is possible that we may find your arguments convincing (if we do, you would still need to perform an adequately designed trial to definitively address this question in Phase 4), it is also possible that we will remain concerned that Xyrem may cause an important deterioration of nighttime respiratory function. If this is the outcome, you will be required to perform an adequate study addressing this issue prior to approval.

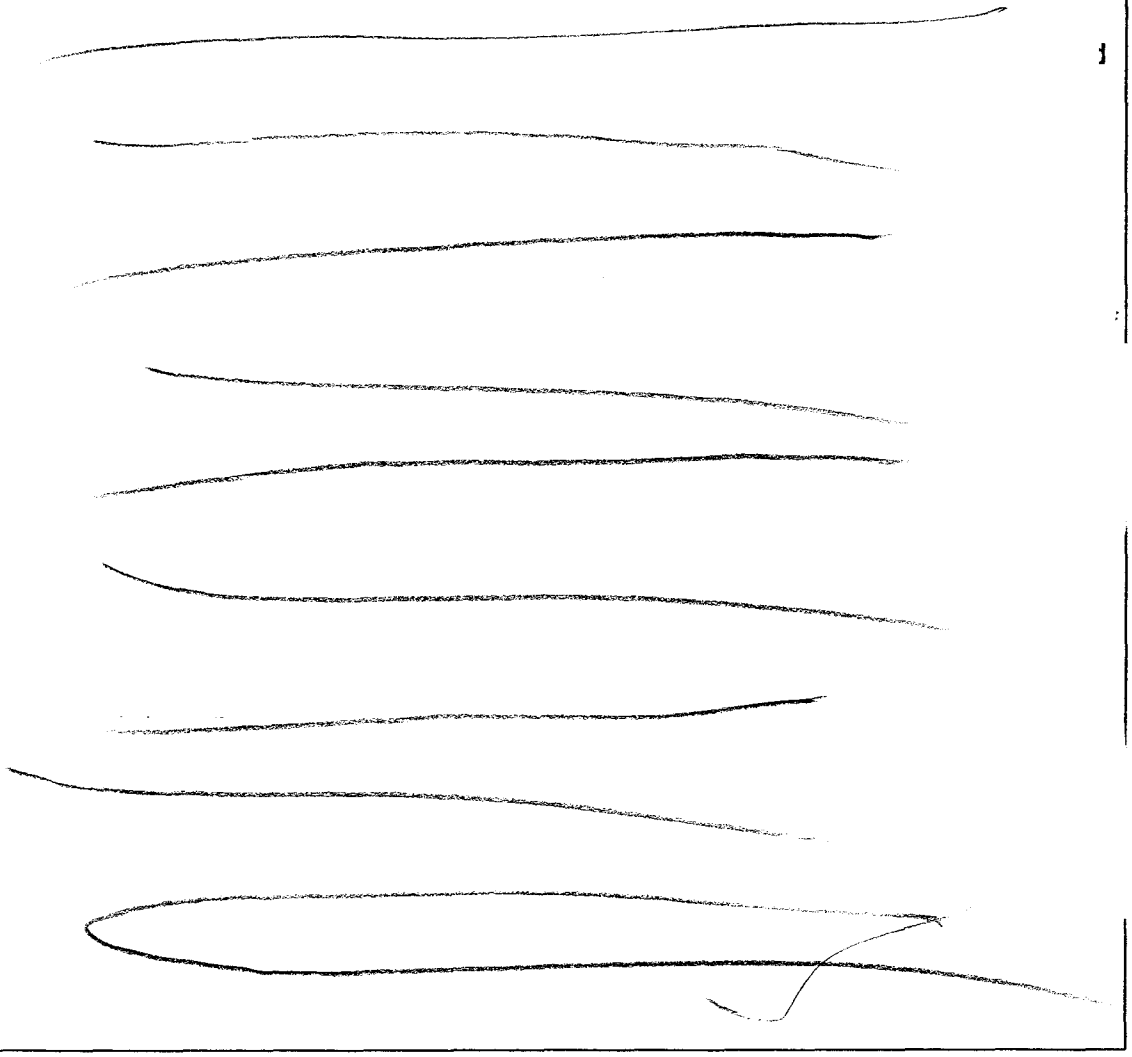
Adequacy of the Safety Database

As you know, the size of the safety database in your application is, and remains, with the Safety Update, small by the usual standard. The number of patients who reached the highest daily dose, 9gms/day, did not change appreciably with the Safety Update and is only 141, 74 of whom were treated for at least 6 months.

Given this small experience, we are particularly concerned about the results of a recent site audit, which have raised questions about the acceptability of the data generated at this site. As a result of this audit, we now believe that one or more additional site audits will be needed prior to approval. The next site audit is planned within a month.

Once the above issues are adequately addressed, we are prepared to approve Xyrem for the treatment of cataplexy in narcolepsy under Subpart H as requested in your March 12, 2002 letter. Upon initial marketing under Subpart H, the distribution of Xyrem will be regulated as described in 21 CFR 314.520. Attached to this letter are proposed labeling and an outline of a proposed risk management program that is acceptable to us. The primary component of the risk management program is a central pharmacy.

Also attached to this letter are marked up versions of the documents you plan to send to doctors and patients as part of your Physician and Patient Success Programs, including draft product labeling and a draft Medication Guide for distribution with Xyrem. All of these documents, and the specific details of the risk management program, are subject to change pending your response to this Approvable Letter, and therefore should be considered provisional at this time.



3. List of All Clinical Studies In This Application

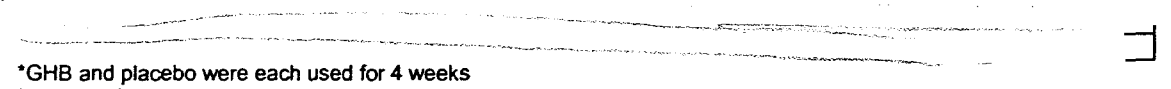
I have listed these studies in 2 categories

- Efficacy and safety studies
- Pharmacokinetic studies

3.1 Efficacy And Safety Trials

All patients enrolled in these trials had narcolepsy.

Study #	Design	Number of Patients	Duration	Status
OMC-GHB-2	Randomized, double-blind, placebo-controlled, parallel-arm	136 patients	4 weeks	Complete
OMC-GHB-3	Open-label, uncontrolled, extension study	118 patients	Up to 24 months	Complete
OMC-SXB-6	Open-label uncontrolled study	185 patients	6 months	Complete
OMC-SXB-7	Open-label uncontrolled study	268 patients	24 months or until approval	Ongoing
Scrima	Randomized, double-blind, placebo-controlled, cross-over study	20 patients	4 weeks*	Complete
Lammers	Randomized, double-blind, placebo-controlled, cross-over study	25 patients	4 weeks*	Complete
Scharf	Open-label uncontrolled study	143 patients	17 years	Complete
OMC-SXB-21	Randomized, double-blind, placebo-controlled, parallel-arm, RANDOMIZED WITHDRAWAL study after long-term open label treatment	55 patients	2 weeks**	Complete
OMC-SXB-20	Open-label, uncontrolled, dose-escalation study	27 patients	10 weeks	Complete



*GHB and placebo were each used for 4 weeks
**Period of randomized withdrawal

- The number of patients listed for ongoing studies are those enrolled as of 6/30/01.
- OMC-GHB-2 and OMC-SXB-21, as well as the Scrima and Lammers studies, were primarily intended to assess the efficacy of Xyrem® in treating cataplexy.

- OMC-SXB-20 was intended to assess the effects of 4 different doses of Xyrem® on sleep architecture

Further comments about some of the above studies are below

Study #	Comments
OMC-GHB-3	Extension to OMC-GHB-2.
OMC-SXB-6	Treatment-naïve patients (except for a single patient previously in OMC-GHB-2 and OMC-GHB-3)
OMC-SXB-7	Extension to OMC-GHB-3 (53 patients) OMC-SXB-6 (121 patients) Scharf Study (66 patients) OMC-SXB-20 (20 patients) The numbers in parentheses in this cell refer to the number of patients entering OMC-SXB-7 from each study
OMC-SXB-21	All patients enrolled in this trial were already participating in the OMC-SXB-7 trial

3.2 Pharmacokinetic Trials

125 healthy subjects and 19 narcoleptic patients participated in these trials

Study #	Number of subjects/patients
OMC-GHB-4	6*
OMC-SXB-8	36
OMC-SXB-9	13
OMC-SXB-10	13**
OMC-SXB-11	36
OMC-SXB-12	15
OMC-SXB-14	12
OMC-SXB-17	13

*The 6 narcoleptic patients participating in this study also enrolled in the Scharf study
**The 13 narcoleptic patients participating in this study also enrolled in OMC-SXB-6

4. Contents Of Submission

The submission is in electronic format. The cover letter is also available in paper.

The contents of the submission include the following separate sections

- Cover letter
- "Clarification" of respiratory data in OMC-SXB-20
- Response to labeling contained in Approvable letter of 4/9/02 (redlined/annotated and clean PDF versions; Word versions)
- Response to the following Risk Management Program elements contained in the Approvable letter of 4/9/02 (redlined/annotated and clean PDF versions; Word versions)
  - Risk Management Program proper
  - Medication Guide
  - Xyrem® Success Program (Physician and Patient)
  - Post-Marketing Evaluation Form
- Chemistry, Manufacturing, and Controls data: Stability Update supporting 36 month expiration dating.

Respiratory

A key issue identified in your approvable letter of April 9, 2002 was in relation to possible effect of Xyrem on respiratory function. Citing data from trial SXB-20, we have shown the following:

- The discussion in the attached report confirms variability in sleep disordered-breathing that is characteristic of the disease, as supported by the literature. Since there was no association between numerical changes in Respiratory Disturbance Index and oxygen desaturation in any patient in this study, these changes do not represent a safety concern.

- Although study OMC-SXB-20 was not designed as a randomized, blinded, controlled study, it does present objective measures of respiratory events, sleep architecture and oxygen saturation data. Each patient provides their own control as represented by baseline measures. Confirmation of non-oxybate effect is available from initial PSG recordings (prior to cessation of anti-cataplectic medications). Interpretation of intra-patient variability is limited by lack of randomization in this study, but is strongly supported in the literature.

- There is no dose-related effect demonstrated in the incidence of sleep-disordered breathing events that could support a pharmacologic response attributable to sodium oxybate in the dose range studied from 4.5-9g/night. There is disassociation between the numerical representations of Respiratory Disturbance Index and the effects on oxygen saturation in this study, indicating such events are brief in duration and have not led to prolonged decreases in ventilation with consequent hypoxia. Since the primary measure of respiratory function is gas exchange, the

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absence of desaturation does not represent a decline in respiratory function.

Post-Approval Safety Monitoring Study

With regards to the Post-Marketing Safety Evaluation Program, we would like to highlight two key points with respect to the enclosed materials:

1. It is our understanding from the language you placed in the letter to doctors that safety information on 1000 patients followed for six months on Xyrem therapy will fulfill our obligation for this program. Can you please confirm your agreement?

2. It is important to ensure that the post-approval safety assessment provides optimal opportunity for accurate interpretation. We agree with the changes proposed by FDA, but have added some information fields to enhance our joint ability to analyze the data captured and prevent bias. We request FDA concurrence with our proposed changes.

Labeling

Relative to the proposed package insert, there are three important issues that we wish to emphasize with this transmittal letter, listed below. We respectfully ask FDA to pay particular attention to these concerns in your review of the enclosed materials.

3. **P-Values**. We can find no evidence in any NDA correspondence between FDA and Orphan Medical that the p-values currently listed in the FDA proposed label for Trial 1 (our clinical trial OMC-GHB-2) are correct, nor can we find a source from whence they originated. In our submissions and both the advisory briefing booklets received from FDA, all p-values provided by Orphan Medical and FDA are in agreement. Yet in both the insert provided to the company in July 2001, and the most recent in April 2002, FDA has quoted p-values that differ (documents attached).

   We request adoption of the p-values agreed upon at the FDA advisory meeting for Xyrem to be placed into the package insert for Trial 1. The proposed values we have revised in the attached package insert are in agreement with the statistics we provided with our NDA, FDA's own statistics provided publicly at the advisory committee meeting, and the statistics now in the published peer-reviewed literature (article attached).

4. **Pharmacodynamics.** FDA removed all proposed language with respect to the pharmacology of oxybate. We agree with FDA in that the mechanism of action of Xyrem is unknown at this time. However, we have included language that we believe communicates factual and useful information under the heading "Pharmacodynamics". Presentation of information in this manner is consistent with other recently approved CNS drugs including Geodon® (ziprasidone HCl), Adderall® (mixed salts of amphetamines), and Ambien® (zolpidem tartrate) (professional inserts attached). We strongly support some description of known pharmacology and would seek discourse with FDA should you disagree.

5. **Black Box Warning.** Although we agree with the most of the statements proposed by FDA within the black box, the Company is concerned that a lengthy black box may not be read in its entirety by physicians. Physicians may be more likely to read and retain the most pertinent points if they appear first in a summary paragraph. In this submission, we propose a black box with language very similar that proposed by FDA. However, the sentences in the black box were reorganized so that the most important information appears in the first paragraph of the black box, with more detailed information following in subsequent paragraphs. In addition, some connecting language was omitted in order make the language more concise and decrease the length of the black box.

   As proposed in a recent E-mail, we have issues with two statements made within the black box. The first is the statement regarding plasma levels of GHB in recreational users and the second is the statement regarding the protective effects of stimulants. While we concur with all other statements made within the black box, we respectfully request that these two sentences be omitted and have proposed such with this submission.

Expiration Dating:

6. Please find enclosed evidence supporting a proposed expiry period for Xyrem of 36 months. Included in this submission are stability report summaries as well as statistical projections consistent with the FDA SAS validated protocol for predicting shelf life.

   As we can sell only product with six months or greater to expiry, the previously requested — month expiration date would necessitate destruction of approximately two-thirds of our inventory. We would greatly appreciate your advising the company of FDA's intended decision with respect to expiration dating at the earliest opportunity. The reason we request this is to facilitate our production planning operations and DEA Schedule I quota requirements for bulk drug substance which has a long lead time (estimated at 9-12 months).

7. Organization Of Review Of OMC-SXB-20 Respiratory Data Contained In Current Submission

In addition to specifically reviewing the interpretation of respiratory data contained in the current submission, I believe it will be helpful to first provide summaries of such data from this study as contained in 2 previous reviews completed by me

- My main review of the sponsor's Response to the Approvable letter of 7/2/01, which was submitted on 10/5/01. This review was completed on 3/4/02
- An addendum to my main review of the Response to the Approvable letter of 7/2/01. This review was completed on 3/29/02

I will then review the OMC-SXB-20 respiratory data clarification contained in the current submission.

8. Respiratory Data In Study OMC-SXB-20 As Contained In Earlier Review Completed 3/4/02

The summary contained in this section addressed material submitted in the earlier Response to Approvable Letter dated 10/5/01.

8.1 Background

This was an open-label study that was intended to evaluate the effects of 4 doses of Xyrem® on sleep architecture.

The final study report for OMC-SXB-20 was submitted on 12/16/00, i.e., after the original NDA submission (but within the same review cycle), and was reviewed by me along with that submission. The effects of Xyrem® on sleep architecture as derived from this study are described in my Efficacy Review of the original NDA. Safety data from this study are described in my Safety Review of the original NDA.

Arterial oxygen saturation data from all-night recordings, and data on the frequency and severity of specific respiratory-event-related measures were collected as part of the polysomnogram recordings in this study but were not included in the final study report submitted on 12/16/01.

In the Approvable letter that was issued on 7/2/01 it was noted that although GHB was a central nervous system depressant and therefore capable of producing respiratory depression, no formal assessment of its effects on respiration had been performed. It was recommended that a study be performed to assess the effects of GHB on respiration. The following was stated in the Approvable letter:

"The study should examine the effects of the recommended dosing regimen (2 doses nightly, including the highest recommended dose-9 gms divided), with both doses given in the fasted state. The study should include patients who are and who are not receiving concomitant stimulant treatment, a positive control, and

patients with concomitant illnesses that might increase their risk of respiratory depression (e.g., patients with COPD, sleep apnea, etc.)."

At a meeting with the sponsor held on 7/16/01 the Division agreed that the planned study described in the Approvable letter could be done as part of a post-marketing commitment provided that an analysis of respiratory data from OMC-SXB-20 that was to be submitted as part of the then-upcoming Amendment/Response To Approvable Letter (that was eventually submitted on 10/5/01) addressed our concerns about a potential respiratory depressant effect of Xyrem®.

The analysis of respiratory data from OMC-SXB-20 presented below is post-hoc and was not planned as part of the original protocol. The original protocol and the plan for analyzing respiratory data are summarized below

8.2 Outline Of Protocol For OMC-SXB-20 Study

8.2.1 Objectives

8.2.1.1 Primary

The primary objective of this study was to characterize the polysomnographic sleep architecture in narcoleptic patients at four GHB doses: 4.5 g, 6.0 g, 7.5 g and 9.0 g daily

8.2.1.2 Secondary

The secondary objectives of the study were to

- Assess the effect of Xyrem® on sleep as measured by the Epworth Sleepiness Scale
- Assess the effects of Xyrem® on common symptoms of narcolepsy as measured by the Narcolepsy Symptoms Assessment
- Assess EEG measures of wakefulness under soporific conditions using the Maintenance of Wakefulness Test
- Assess the safety of Xyrem®

8.2.2 Design/Summary of Investigational Plan

This was an open-label uncontrolled study divided into 2 phases. Stimulant medication was maintained at a constant level during the trial. The overall design is summarized in the following diagram

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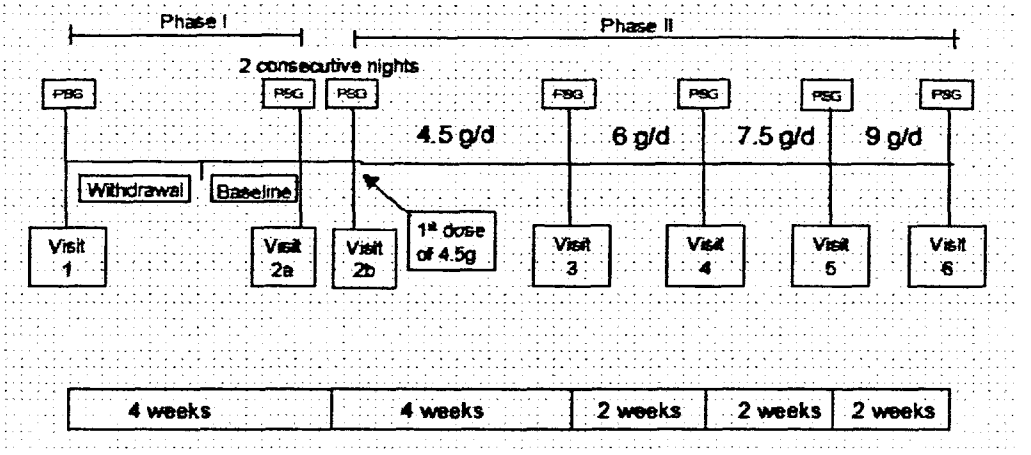


8.2.2.1 Phase I

This phase lasted 4 weeks

- In the initial 2 weeks of this phase patients were withdrawn from tricyclic antidepressants, selective serotonin re-uptake inhibitors and hypnotics
- In the last 2 weeks of this phase patients remained free of tricyclics

An overnight polysomnogram was performed at the beginning and end of this phase. The Epworth Sleepiness Scale questionnaire was administered at about the time of each polysomnogram

8.2.2.2 Phase II

This phase began with the patient receiving 4.5 g of GHB nightly for the initial 4 weeks. At the end of this period the dose was increased to 6.0 g nightly, and then further to 7.5 g nightly and 9 g nightly, at 2 week intervals. Each total nightly dose of GHB was administered in 2 equal divided doses 2.5 to 4 hours apart.

Overnight polysomnograms were performed on the night of the first dose of Xyrem® and on the last night of each dose. The Epworth Sleepiness Scale was administered at the end of each dosing period

8.2.2.3 Duration

10 weeks

8.2.3 Sample Size

20-30 planned

8.2.4 Key Inclusion Criteria

- Informed consent
- Age ≥ 18 years
- American Sleep Disorders Association criteria for narcolepsy
- Use of stable doses of tricyclic antidepressants or selective serotonin re-uptake inhibitors for narcolepsy for at least 3 weeks. If taking stimulants must have been on a stable dose for at least 3 weeks

- If female must be
  - Surgically sterile OR
  - 2 years post-menopausal OR
  - If of child-bearing potential must be using effective contraception and must continue this treatment during the study
- Adequate support for duration of trial

8.2.5 Key Exclusion Criteria

- Unstable diseases in any body system, other than narcolepsy, which would place the patient at risk or compromise the trial objectives
- Use of tricyclic antidepressants or selective serotonin re-uptake inhibitors for depression or for any indication other than narcolepsy
- History of substance abuse, as defined by DSM-IV, currently or within the past year
- History of psychiatric disorders that would preclude study participation
- Serum creatinine > 2 mg/dl; AST or ALT > 2 x upper limit of normal; serum bilirubin > 1,5 x upper limit of normal; pre-trial electrocardiogram results demonstrating a clinically significant arrhythmia or 2^{nd} or 3^{rd} degree A-V block; history of myocardial infarction within the past 6 months
- Any untreated disorder other than narcolepsy that could be considered a primary cause of excessive daytime sleepiness, including sleep apnea syndrome (criteria specified)
- Occupation requiring variable shift or routine night shift work
- Use of sodium oxybate within the preceding 30 days
- Use of any investigational drug within the preceding 30 days
- No clinically significant history of head trauma, seizure disorder or previous intracranial surgery
- Willing to not operate a car or heavy machinery if the clinical investigator feels such a restriction is warranted
- Use of medication for narcolepsy during baseline period, other than a stable dose of stimulant medication ("stable dose" defined as one without any significant change in dose for the 5 - day period just prior to the baseline period)
- Use of hypnotics, tranquilizers, antihistamines (except for the non-sedating variety of such drugs) and clonidine at the start of the baseline period.

8.2.6 Dosage

See Section 8.2.2

8.2.7 Outcome Measures

8.2.7.1 Primary Efficacy Measures

The following objective overnight polysomnogram parameters

- Wake After Sleep Onset (WASO) in minutes following the first and second dose of Xyrem and the summation
- Total Sleep Time (TST) in minutes following the first and second dose of Xyrem and the summation

- Stage 1 sleep time in minutes following the first and second dose of Xyrem and the summation
- Stage 2 sleep time in minutes following the first and second dose of Xyrem and the summation
- Stage 3 & 4 sleep time in minutes following the first and second dose of Xyrem and the summation
- Rapid Eye Movement (REM) sleep time in minutes following the first and second dose of Xyrem and the summation
- Sleep latency in minutes following the first and second dose of Xyrem
- REM sleep latency in minutes following the first and second dose of Xyrem
- Stage shifts per hour following the first and second dose of Xyrem and an average
- Total awakenings following the first and second dose of Xyrem® and the summation
- Delta power in microvolts^2/Hz following the first and second dose of Xyrem and an average

8.2.7.2 Secondary Efficacy Measures

- Epworth Sleepiness Scale
- Narcolepsy Symptoms Assessment
- Maintenance of Wakefulness Test

8.2.7.3 Safety Measures

Adverse events, safety laboratory tests, vital signs, electrocardiograms and physical examinations

8.2.8 Analysis Plan

- Demographic variables at baseline were summarized as follows
  - Gender and race were summarized by the number of patients in each category
  - Age, height and weight were summarized by descriptive statistics
- Efficacy variables were analyzed as follows
  - Inferential statistics were performed for descriptive purposes only as per the sponsor
  - Quantitative polysomnogram variables and the Epworth Sleepiness Scale were analyzed using 2-way ANOVA with patient and dosage as the main effects
  - If a statistically significant difference was found among dose groups using ANOVA, pairwise comparisons using the least significant difference test were performed. If the assumptions for the above ANOVA were not satisfied the rank changes from baseline were analyzed using the ANOVA model. The significance of the mean change from baseline (end of Phase I) in each dose group was determined using a paired t-test or a Wilcoxon signed rank test
  - For the above analysis the level of statistical significance was 0.05 (two-sided)
  - Variables for the narcolepsy symptom questionnaire measured as a change from the beginning of Phase I were presented by number and percentage of patients
- Safety analyses were performed as follows
  - Adverse events were summarized by body system using COSTART term and by relationship to treatment, dose and severity
  - Changes from the beginning of Phase 1 to the end of the study in laboratory parameters were summarized using descriptive statistics
  - Changes from the end of Phase I to the end of the study in vital signs were summarized using descriptive statistics

- Changes from the beginning of Phase I to the end of the study in electrocardiogram parameters were summarized

8.3 Instruments For Measuring Respiratory Event Data

Respiratory measurements were collected all night during overnight polysomnograms (7 studies in each patient) in all 21 patients constituting the intent-to-treat population. The following instruments were used to make these measurements

- Nasal thermistor or thermocouple measuring inspiratory and expiratory airflow
- Thoracic strain sensors measuring thoracic expansion as an index of central respiratory drive and pulmonary gas exchange
- Abdominal strain sensors which measure abdominal movement in order to allow determination of the patency of the upper airway (when interpreted together with nasal airflow and thoracic movement)
- Pulse oximetry: measuring adequacy of respiration to maintain oxygenation

8.4 Respiratory Effect Measures

These include respiratory event data and oxygen saturation data

8.4.1 Respiratory Event Measures

These are defined as follows (the definitions are standard ones)

8.4.1.1 Apnea-Hypopnea Index (AHI)

The apnea-hypopnea index is the incidence (events per hour) of apnea and hypopnea events associated with sleep, calculated separately for NREM and REM sleep

This index is calculated as follows

Number of central apneas + Number of obstructive and mixed apneas + Number of hypopneas (during REM or NREM sleep) / Number of hours of (NREM or REM) sleep

The severity of sleep apnea is defined as follows based on this index

Mild	5 to 15 events per hour
Moderate	15 to 30 events per hour
Severe	> 30 events per hour

8.4.1.2 Respiratory Disturbance Index (RDI)

The respiratory disturbance index is the incidence (events per hour) of apnea and hypopnea events associated with sleep, independent of sleep stage, represented by all sleep apnea events during the sleep period (obstructive + central + mixed) + all hypopnea events / number of hours of sleep during the study period.

It is calculated as a weighted average of AHI (NREM) and AHI (REM) with respect to the time spent in NREM and REM sleep, respectively.

The severity of sleep apnea is defined as follows based on this index

Mild	5 to 15 events per hour

Moderate	15 to 30 events per hour
Severe	> 30 events per hour

8.4.1.3 Number Of Obstructive And Mixed Apneas (OMAs)

Obstructive apnea is partial or complete upper airway obstruction during sleep. An obstructive apneic event is characterized by a transient cessation of breathing lasting > 10 seconds, in the presence of sustained respiratory effort, accompanied by oxygen desaturation of > 3% or arousal

Mixed apnea is a lack of respiratory effort during the initial apneic period followed by gradually increasing effort against an occluded upper airway. This is a variant of an obstructive apneic event during which respiratory effort is absent for several seconds after the onset of upper airway occlusion.

8.4.1.4 Number Of Central Apneas

Central apnea is defined as sleep apnea in the absence of upper airway obstruction and in the absence of inspiratory effort indicating reduced output to the muscles of inspiration from the central nervous system. A central apneic event is characterized by a cessation in airflow lasting ≥ 10 seconds, accompanied by oxygen desaturation of > 3%, or arousal, and a clear reduction in esophageal pressure swings from baseline, or absence of paradoxical respiratory effort which would indicate airway obstruction

8.4.1.5 Number of Hypopneas

Hypopnea is defined as a reduction in airflow despite ongoing inspiratory efforts. An obstructive hypopnea event is characterized by a transient reduction in breathing lasting > 10 seconds, with a clear decrease (> 50%) from baseline in the amplitude of breathing, or a decrease < 50% in the amplitude of breathing, accompanied by oxygen desaturation of > 3% or arousal.

8.4.2 Oxygen Saturation (SaO_2) Measures

These are as follows

8.4.2.1 Lowest SaO_2

The meaning of this term is self-explanatory

8.4.2.2 Continuous SaO_2

These are data collected as mean values of 5 minutes of data during the recording period

8.4.2.3 Intermittent SaO_2

These are data collected as mean values of 1 minute of data at 8 dispersed timepoints during the recording period, including lights-out (immediately after dosing), after 30, 60, 90, 120, 150, and 180 minutes, and lights-on (about 240 minutes)

8.4.2.4 Duration Of Time That Artifact-Free Sao_2 Recordings Were < 80% And < 90% Of Saturation,

This is expressed as a percentage of the 240 minutes for the study duration and as a percentage of the total time that the SaO_2 channel was artifact-free.

8.5 Methods Of Analyzing Respiratory Data

- All measurements were digitally recorded according to standardized techniques and then transferred to a central scoring location where they were analyzed using a specified software program
- For analyzing respiratory event data
  - Each patient's record consisting of 8 hours of data for each of 7 overnight tests was subdivided into 30 second epochs
  - Validated criteria were used for scoring events to obtain the respiratory event outcome measures listed above. Scoring was done by a trained and registered polysomnogram technician who was blinded to all dosage and patient information
  - The scored respiratory events were then summarized for the first and second half of each night (i.e., in relation to the first or second dose) and for the entire night. Events were also reported for NREM and REM sleep periods and for the total (REM plus NREM).
- Oxygen saturation (SaO_2) was measured continuously and was analyzed as follows
  - Each patient record was subdivided into 5-minute intervals and each interval was examined
  - Intermittent 1-minute SaO_2 at defined timepoints was also extracted and analyzed
  - The duration of periods of $SaO_2 < 80\%$ and $< 90\%$ and the lowest SaO_2 values were also analyzed
- Changes from baseline were analyzed using 2-way ANOVA. If a statistically significant difference was found among the dosage groups, then pairwise comparisons were performed. Data were tabulated and plotted for each respiratory measure by dosage group and by patient, so as to assess group and individual effects across dosages. Two-sided p-values were reported at a level of significance of 0.05.
- For uniformity the range for all SaO_2 parameters was assigned as 50% to 110% and the range for all respiratory event parameters as 1 to 200.

8.6 Results

Only the results of the respiratory effects analysis are described below

8.6.1 Patient Disposition

- 27 patients were enrolled in the study
- 25 patients were treated with GHB
- 21 patients completed the study. Of those who did not complete the study
  - 2 discontinued on account of adverse events and are described further in this review
  - 1 patient was lost to follow-up
  - 1 patient withdrew consent

21 patients were in the intent-to-treat population composed of all patients who received one dose of study medication and had at least one post-treatment evaluation.

8.6.2 Baseline And Demographic Characteristics

Baseline and demographic characteristics for all 25 treated patients are summarized below

Variable	Mean	Standard Deviation
Age (years)	52.6	8.77
Weight (kg)	84.2	16.36
Height (cm)	166.9	8.32

Gender: Males 28%; Females 72%
Race: Caucasian 92%; Black 8%

Baseline and demographic characteristics for the 21 patients in the intent-to-treat population are below

Variable	Mean	Standard Deviation
Age (years)	53.2	7.59
Weight (kg)	83.8	16.37
Height (cm)	167.6	8.66

Gender: Males 29%; Females 71%
Race: Caucasian 95%; Black 5%

8.6.3 Tricyclic Antidepressants, Selective Serotonin Re-Uptake Inhibitors And Hypnotics At Baseline

These are summarized in the next table, copied from the original full study report.

Preferred Term	Total
Number of Patients	25 (100%)
Patients Receiving Medications	22 (88%)
Clomipramine	3 (12%)
Fluoxetine	5 (20%)
Fluvoxamine	1 (4%)
Paroxetine	2 (8%)
Protriptyline	1 (4%)
Sertraline	4 (16%)
Venlafaxine	6 (24%)

TCA - Tricyclic antidepressant. SSRI - Selective serotonin reuptake inhibitors.
All medications were completed prior to the start of treatment.

Of the 21 intent-to-treat patients, 20 were taking tricyclic antidepressants, selective serotonin re-uptake inhibitors or hypnotics prior to entry into the study but these medications were withdrawn during the first 2 weeks of Phase I (withdrawal phase). The most frequent anticataplectic medications were venlafaxine (5 patients), zopiclone and fluoxetine (4 patients each) and clomipramine (3 patients)

8.6.4 Stimulant Medications

Patients were allowed to be a stable dose of stimulants throughout the trial

Of the 21 patients in the intent-to-treat population, 18 patients were taking stimulants. The stimulants used were dextroamphetamine (12 patients), methylphenidate (3 patients), modafinil (2 patients) and amfepramone (1 patient)

8.6.5 Medical History

All 21 intent-to-treat patients had a history of narcolepsy. Of these

- 3 patients had a history of asthma

- 1 patient had a history of recurring bronchitis and obstructive sleep apnea
- 1 additional patient had a history of obstructive sleep apnea which was not reported at the time of entry into the OMC-SXB-20 study

8.6.6 Protocol Deviations

These are summarized in the next table copied from the submission. The table applies to all 25 treated patients

Type of Protocol Deviation	No. of Protocol Deviations
Inclusion/exclusion criteria	6
Compliance	7
Concomitant medication	28
Study visit interval	17
Error in dosing medication	23
Efficacy measure	33
Safety measure	
Laboratory procedure	2
Other safety measure	2
Other	7
Total	125

8.6.7 Treatment Compliance

Treatment compliance at each dose level is summarized in the following table copied from the submission. Mean compliance at each dose level was high.

	Dose (g)				
Number of Patients	4.5 25	6.0 22	7.5 22	9.0 21	Total 25
Compliance (%)					
N	25	22	22	21	25
Mean	95.9	95.5	92.7	93.3	94.9
SD	11.45	9.63	9.06	13.45	7.62
Median	100.0	95.0	95.0	93.0	96.7
Minimum					
Maximum					

8.6.8 Extent Of Exposure

The mean duration of treatment was 63.3 nights (standard deviation: 21.29) for the 25 patients who received GHB.

8.6.9 Respiratory Event Data

8.6.9.1 AHI And RDI: Change From Baseline

8.6.9.1.1 Summary Statistics

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

		Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6
		Anti-cata-plexy meds (n = 21)	Baseline (Actual Value) (n = 21)	1st dose 4.5 g/d (n = 18)	4 weeks of 4.5 g/d (n = 20)	2 weeks of 6.0 g/d (n = 21)	2 weeks of 7.5 g/d (n = 20)	2 weeks of 9.0 g/d (n = 20)
AHI (NREM) (events per hour)								
1st half	Mean	1.5	5.1	-0.2	9.9	1.1	3.1 [a]	1.9
	SD	10.21	9.56	3.59	24.91	11.21	9.62	9.38
2nd half	Mean	1.5	7.1	1.1	9.0	1.4	6.5 [a,c]	1.9
	SD	14.96	12.69	8.82	21.49	9.46	13.30	11.60
Average	Mean	1.5	6.1	0.5	9.5	1.3	4.8 [a]	1.9
	SD	11.65	10.72	4.01	22.45	9.33	10.04	8.85
AHI (REM) (events per hour)								
1st half	Mean	1.7	7.5	1.9	8.1	3.7	-0.9	-0.4
	SD	18.54	11.13	12.46	25.86	14.51	16.20	10.32
2nd half	Mean	-0.4	9.5	-2.3	9.6	-3.7 [a,c]	0.5	-2.8 [c]
	SD	17.15	14.54	9.03	20.47	9.41	18.91	7.12
Average	Mean	0.7	8.5	-0.2	8.8	-0.0	-0.2	-1.6
	SD	14.93	11.92	8.97	20.41	6.69	12.49	6.90
RDI (events per hour)								
1st half	Mean	1.6	5.8	0.5	10.6 [a]	1.5	2.6	1.5
	SD	9.66	9.34	4.41	24.23	10.44	9.75	8.91
2nd half	Mean	0.3	8.2	0.1	9.0	-0.3 [a]	4.7 [a,c]	0.7
	SD	14.95	13.09	7.14	19.23	7.09	10.26	9.95
Average	Mean	0.9	7.0	0.3	9.8 [a]	0.6	3.6	1.1
	SD	11.29	10.78	3.40	20.93	7.66	8.51	7.71
		Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6
		Anti-cata-plexy meds (n = 21)	Baseline (Actual Value) (n = 21)	1st dose 4.5 g/d (n = 18)	4 weeks of 4.5 g/d (n = 20)	2 weeks of 6.0 g/d (n = 21)	2 weeks of 7.5 g/d (n = 20)	2 weeks of 9.0 g/d (n = 20)

Value for Visit 2a (baseline) is actual value; values for all other visits are change from baseline.
Within-treatment p values were analyzed by Wilcoxon signed rank test; between-treatment p values were analyzed by ANOVA on rank changes from baseline.

[a] $p \leq 0.05$ compared with baseline.
[b] $p \leq 0.01$ compared with 4.5 g/d.
[c] $p \leq 0.05$ compared with 6.0 g/d.
[d] $p \leq 0.01$ compared with baseline.
[e] $p \leq 0.05$ compared with 4.5 g/d.
[f] $p \leq 0.01$ compared with 6.0 g/d.

In the text of the submission the sponsor has summarized changes that occurred from baseline and from one post-treatment visit to another, as well as those changes that were considered statistically significant ($p < 0.05$)

From this reviewer's perspective, the following are noteworthy

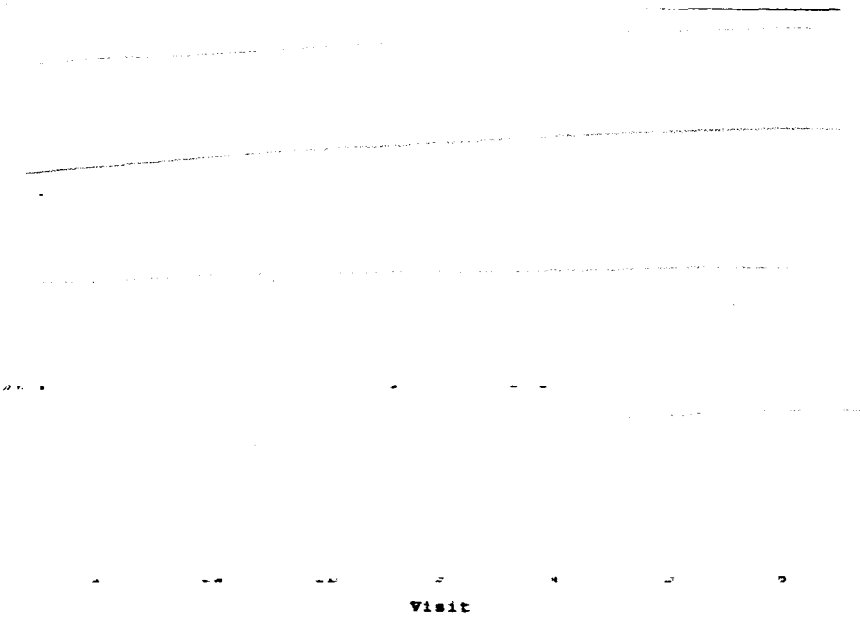
- An increase in AHI and RDI in comparison to baseline would be consistent with a worsening in indices of sleep apnea.
- There was considerable inter-patient variability in all parameters with standard deviations consistently exceeding means
- The greatest mean increases from baseline in AHI and RDI were apparent early during the study at Visit 3, after treatment with the starting dose of GHB (4.5 g/day) for 4 weeks. The only changes that were "statistically significant" ($p < 0.05$) at that timepoint were the RDI for the first half of the night, and the RDI averaged for the entire night.
- There was no clear trend to a dose response in the mean change from baseline in these parameters, when the change was an increase
- When the Visit 5 (following 2 weeks of treatment at 7.5 g/day) parameters were compared with baseline there were "statistically significant" increases in the following
  - AHI (NREM) during both halves of the night
  - AHI (NREM) averaged for the whole night
  - RDI during the second half of the night

The sponsor's view is that the changes in AHI and RDI noted during the study lacked clinical significance.

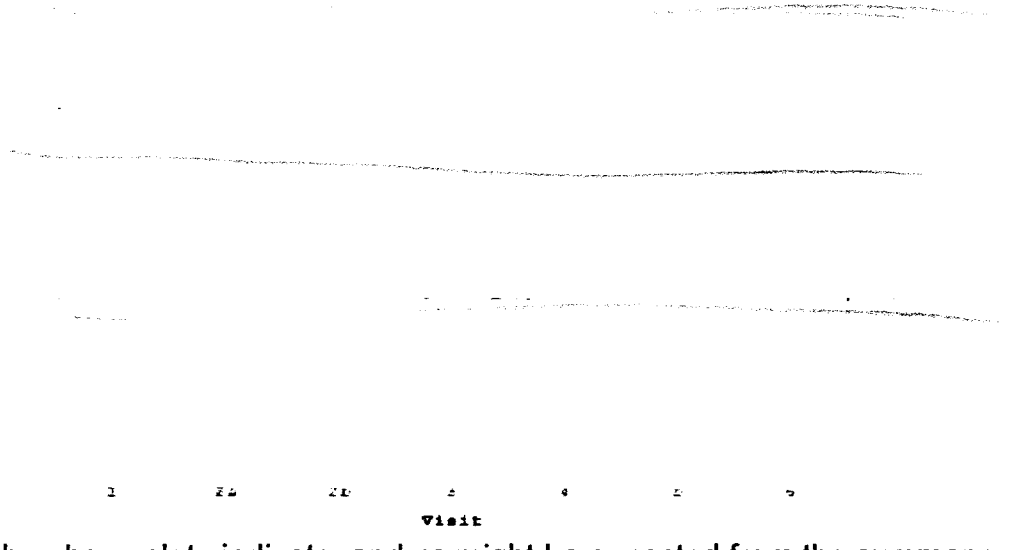
8.6.9.1.2 By-Patient Plots

8.6.9.1.2.1 RDI

By-patient by-visit plots for the first half of the night are as follows in a figure copied from the submission



By-patient by-visit plots of the second half of the night are in the next figure, again copied from the submission.



As the above plots indicate, and as might be expected from the summary statistics tabulated in Section 8.6.9.1.1, a few patients had a prominent increase in RDI at Visit 3 (after 4 weeks of treatment at 4.5 g/day)

8.6.9.1.2.2 AHI

By-patient, by-visit plots for changes in AHI, for REM and NREM sleep, and for each half of the night generally mirrored those seen for RDI, i.e., increases were most prominent at Visit 3 (after 4 weeks of treatment at 4.5 g/day).

8.6.9.2 Sleep Apnea And Hypopnea: Change From Baseline

8.6.9.2.1 Summary Statistics

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

		Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6
		Anti-cata-plexy meds (n = 21)	Baseline (Actual Value) (n = 21)	1st dose 4.5 g/d (n = 18)	4 weeks of 4.5 g/d (n = 20)	2 weeks of 6.0 g/d (n = 21)	2 weeks of 7.5 g/d (n = 20)	2 weeks of 9.0 g/d (n = 20)
Obstructive and mixed apneas (NREM)								
1st half (4 hours)	Mean	1.9	**2.9**	-0.3	10.5 *	3.7 *	3.8 *	4.0
	SD	9.09	**7.20**	2.83	29.65	10.48	9.73	13.71
2nd half (4 hours)	Mean	3.6	**3.0**	1.3	11.6	5.1	7.7 *	3.2
	SD	16.78	**6.64**	7.51	24.52	11.72	25.11	13.12
Total (Whole night)	Mean	5.5	**5.9**	1.0	22.1 *	9.8 *	11.5 *	7.2
	SD	25.57	**13.51**	5.29	50.75	20.85	33.37	26.42
Obstructive and mixed apneas (REM)								
1st half (4 hours)	Mean	0.0	**1.4**	1.7 *	2.2	2.7	1.4	0.8
	SD	4.30	**3.30**	3.25	6.56	9.21	6.36	4.20
2nd half (4 hours)	Mean	-1.2	**3.7**	-0.1	0.9	-1.6	-1.0	-1.8
	SD	7.56	**7.94**	5.43	8.69	4.71	7.50	5.78
Total (Whole night)	Mean	-1.1	**5.1**	1.7	3.1	1.1	0.4	-1.0
	SD	8.10	**10.29**	7.32	13.20	6.99	9.44	5.74
Obstructive and mixed apneas (NREM + REM)								
1st half (4 hours)	Mean	2.0	**4.3**	1.4	12.7 *	6.3	5.2 *	4.8
	SD	9.04	**10.29**	4.24	32.51	15.43	14.10	16.59
2nd half (4 hours)	Mean	2.4	**6.7**	1.3	12.5 *	3.6	6.7 *	1.5
	SD	21.78	**12.99**	4.39	26.79	9.86	19.76	8.44
Total (Whole night)	Mean	4.4	**11.0**	2.7	25.2 *	9.9	11.9	6.2
	SD	29.51	**22.94**	6.58	54.40	26.02	30.24	24.22

		Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6
		Anti-cata-plexy meds (n = 21)	Baseline (Actual Value) (n = 21)	1st dose 4.5 g/d (n = 18)	4 weeks of 4.5 g/d (n = 20)	2 weeks of 6.0 g/d (n = 21)	2 weeks of 7.5 g/d (n = 20)	2 weeks of 9.0 g/d (n = 20)
Central apneas (NREM)								
1st half (4 hours)	Mean	0.1	**3.0**	1.2	4.8	0.1	4.7	2.4
	SD	3.59	**8.84**	5.24	17.29	7.03	12.09	8.33
2nd half (4 hours)	Mean	0.0	**6.9**	1.7	8.7	0.3	4.7	3.8
	SD	16.22	**22.51**	17.13	40.11	17.99	17.99	27.27
Total (Whole night)	Mean	0.1	**9.9**	2.9	13.5	0.5	9.3	6.1
	SD	18.36	**31.11**	18.95	56.63	24.48	22.09	31.50
Central apneas (REM)								
1st half (4 hours)	Mean	-0.0	**0.4**	0.4	0.1	-0.0	0.3	-0.1
	SD	1.66	**0.81**	2.04	1.65	1.12	1.83	0.76
2nd half (4 hours)	Mean	-0.7	**2.0**	-0.1	1.2	-1.3 *	-1.4 *	-1.3 *
	SD	2.67	**3.81**	2.29	3.44	3.99	3.53	3.76
Total (Whole night)	Mean	-0.8	**2.4**	0.4	1.3	-1.3 *	-1.2 *,*	-1.4 *
	SD	2.76	**3.94**	2.20	4.51	4.03	2.46	3.62
Central apneas (NREM + REM)								
1st half (4 hours)	Mean	0.0	**3.4**	1.7	4.9	0.1	4.9	2.3
	SD	3.22	**8.84**	7.07	17.11	6.89	13.42	7.89
2nd half (4 hours)	Mean	-0.7	**8.9**	1.6	9.9	-1.0	3.3	2.5
	SD	17.65	**26.05**	17.39	38.82	20.78	19.15	29.34
Total (Whole night)	Mean	-0.6	**12.3**	3.3	14.8	-0.9	8.2	4.8
	SD	18.93	**34.64**	14.16	54.98	27.32	21.26	33.17

		Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6
		Anti-cata-plexy meds (n = 21)	Baseline (Actual Value) (n = 21)	1st dose 4.5 g/d (n = 18)	4 weeks of 4.5 g/d (n = 20)	2 weeks of 6.0 g/d (n = 21)	2 weeks of 7.5 g/d (n = 20)	2 weeks of 9.0 g/d (n = 20)
Hypopneas (NREM)								
1st half (4 hours)	Mean	1.4	6.8	-1.3	9.3	-1.2	-0.6	-0.2
	SD	19.57	14.86	5.38	27.59	13.40	16.62	16.72
2nd half (4 hours)	Mean	-1.7	5.5	-1.3	8.2	-0.3	6.8 [b]	1.0
	SD	9.56	10.06	7.03	25.20	8.43	12.66	7.80
Total (Whole night)	Mean	-0.2	12.2	-2.6	17.4	-1.6	6.2	0.9
	SD	25.37	22.55	11.13	50.16	18.22	26.83	22.62
Hypopneas (REM)								
1st half (4 hours)	Mean	-0.5	2.0	0.7	1.2	0.5	-1.4	-1.4 [a,c,d]
	SD	3.46	3.19	3.07	6.06	5.25	3.28	2.68
2nd half (4 hours)	Mean	-2.5	3.5	-2.4	-2.6 [a]	-2.3 [a]	-1.8	-1.6 [a]
	SD	6.66	6.36	6.52	6.44	4.34	7.80	2.21
Total (Whole night)	Mean	-3.4	5.6	-1.7	-1.4	-1.9	-3.2	-3.0 [a]
	SD	8.66	8.11	5.15	10.36	6.28	8.31	3.80
Hypopneas (NREM + REM)								
1st half (4 hours)	Mean	0.5	8.8	-0.6	10.4	-0.7	-2.0	-1.6
	SD	20.71	15.74	5.11	27.00	12.95	17.80	17.55
2nd half (4 hours)	Mean	-4.1	9.0	-3.7	5.6	-2.7	5.1	-0.6
	SD	15.00	15.76	13.07	21.46	7.46	13.64	8.79
Total (Whole night)	Mean	-3.6	17.8	-4.3	16.0	-3.4	3.1	-2.1
	SD	29.90	28.08	15.88	44.89	14.60	29.60	24.28

		Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6
		Anti-cata-plexy meds (n = 21)	Baseline (Actual Value) (n = 21)	1st dose 4.5 g/d (n = 18)	4 weeks of 4.5 g/d (n = 20)	2 weeks of 6.0 g/d (n = 21)	2 weeks of 7.5 g/d (n = 20)	2 weeks of 9.0 g/d (n = 20)

Value for Visit 2a (baseline) is actual value; values for all other visits are change from baseline.
Within-treatment p values were analyzed by Wilcoxon signed rank test; between-treatment p values were analyzed by ANOVA on rank changes from baseline.

[a] $p \leq 0.05$ compared with baseline.
[b] $p \leq 0.01$ compared with baseline.
[c] $p \leq 0.05$ compared with 4.5 g/d.
[d] $p \leq 0.01$ compared with 4.5 g/d.
[e] $p \leq 0.05$ compared with 6.0 g/d.

From this reviewer's perspective the following are noteworthy

- There was considerable inter-patient variability in all parameters with standard deviations consistently exceeding means
- The greatest mean increases from baseline in obstructive and mixed apneas, central apneas, and hypopneas were apparent early during the study at Visit 3, after treatment with the starting dose of GHB (4.5 g/day) for 4 weeks; these changes were seen for NREM sleep and for NREM + REM sleep (combined). The only changes that were "statistically significant" ($p < 0.05$) at that timepoint were as follows.
  - Obstructive and mixed apneas (NREM) for the first half of the night and for the whole night
  - Obstructive and mixed apneas (NREM plus REM, combined) for each half of the night and for the whole night
- There was no clear trend to a dose response in the mean change from baseline in these parameters.

8.6.9.2.2 By-Patient Plots

8.6.9.2.2.1 Obstructive And Mixed Apneas

A few patients had prominent increases at Visit 3 and at Visit 5 as illustrated below.

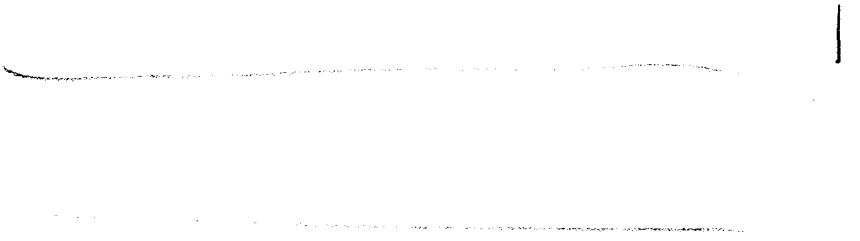
The first figure copied from the submission shows by-patient and by-visit plots for the first half of the night.

The next figure also copied from the submission shows by-patient and by-visit plots for the second half of the night.

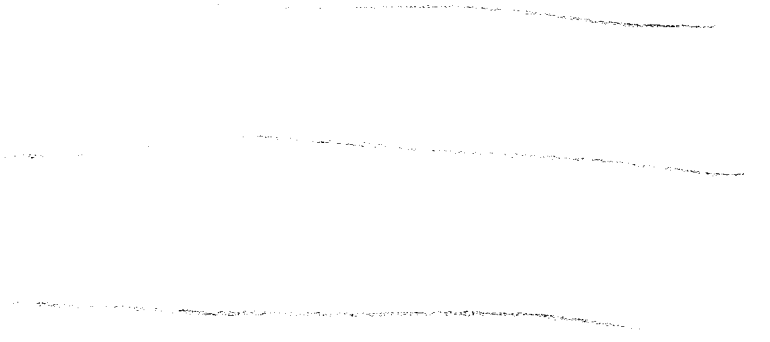
8.6.9.2.2.2 Central Apneas

The timing of prominent increases in the number of central apneas was quite variable especially for those occurring during the second half of the night, as illustrated by the following figures. However individual patients appeared to have more central apneas during the second half of the night.

The first figure copied from the submission shows by-patient and by-visit plots for the first half of the night.



The next figure also copied from the submission shows by-patient and by-visit plots for the second half of the night.

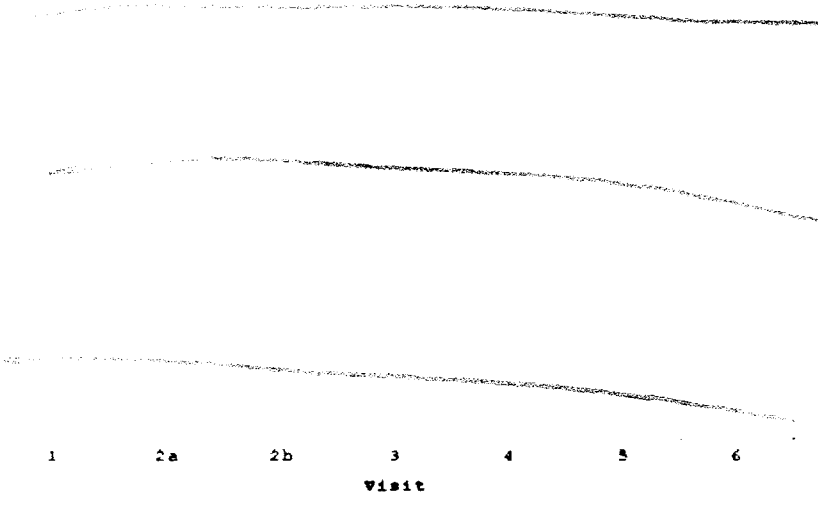


8.6.9.2.2.3 Hypopneas

The timing of prominent increases in the number of central apneas were quite variable, as illustrated by the following figures.

The first figure copied from the submission shows by-patient and by-visit plots for the first half of the night.

The next figure also copied from the submission shows by-patient and by-visit plots for the second half of the night.



8.6.9.3 Patient 017301

As noted in the by-patient plots above, this individual had a prominent increase at Visit 3, relative to baseline, in the following: obstructive and mixed apneas, hypopneas, AHI and RDI. He may have been responsible in large measure for the mean increases seen in these parameters, in the entire cohort.

This 51 year old man, had a previous history of narcolepsy, hernia, recurrent bronchitis, previous knee surgery and rosacea. He was also obese. Concomitant medications included venlafaxine, and modafinil. He was not recorded as having any adverse events during Study OMC-SXB-20 which he completed.

A polysomnogram done prior to the screening visit for this study was consistent with a diagnosis of obstructive sleep apnea syndrome.

The increase in obstructive and mixed apneas, hypopneas, AHI and RDI, seen at Visit 3 was not maintained despite further increases in dose of GHB during the remainder of the study .

This patient also had the following changes in an SaO_2 parameter, the duration of time spent with an SaO_2 less than 90%. These changes did not correlate temporally with changes in respiratory event parameters

- For measurements done during the first half of the night a steady increase was seen over the course of the trial beginning at a dose of 6 g/day.
- For measurements done during the second half of the night this parameter showed prominent fluctuations during the course of the study.

8.6.10 Oxygen Saturation Data

8.6.10.1 Summary Statistics

The following table shows summary statistics for the following parameters: continuous SaO_2 (5-minute data), duration of oxygen desaturation (time with SaO_2 < 80% and < 90%)

		Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6
		Anti-cata-plexy meds	Baseline	1st dose 4.5 g/d	4 weeks of 4.5 g/d	2 weeks of 6.0 g/d	2 weeks of 7.5 g/d	2 weeks of 9.0 g/d
Continuous SaO_2 (5-minute data; %)								
1st half	N	19	20	19	18	20	20	20
	Mean	95.8	95.5	95.1	94.7 *	95.0	95.2	95.3
	SD	1.47	1.90	1.67	1.76	2.16	2.19	2.54
2nd half	N	19	20	19	18	20	20	20
	Mean	95.9	95.5	95.3	94.7	95.0	95.3	95.5
	SD	1.49	1.88	1.94	1.87	2.26	2.12	2.41
Whole Night	N	19	20	19	18	20	20	20
	Mean	95.8	95.5	95.2	94.7 *	95.0	95.3	95.4
	SD	1.44	1.86	1.73	1.77	2.19	2.13	2.46
Duration of SaO_2 < 80% (% of 240 minutes)								
Whole Night	N	19	20	19	18	20	20	20
	Mean	0.00	0.08	0.00	0.00	0.01	0.00	0.01
	SD	0.000	0.310	0.000	0.005	0.023	0.010	0.022
Duration of SaO_2 < 90% (% of 240 minutes)								
Whole Night	N	19	20	19	18	20	20	20
	Mean	0.90	1.93	3.23	3.23	3.96	3.61	3.79
	SD	1.621	5.695	12.028	6.281	13.654	12.994	14.933

		Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6
		Anti-cata-plexy meds	Baseline	1st dose 4.5 g/d	4 weeks of 4.5 g/d	2 weeks of 6.0 g/d	2 weeks of 7.5 g/d	2 weeks of 9.0 g/d
Lowest SaO_2 (NREM) (%)								
1st half	N	19	20	17	19	21	20	20
	Mean	90.9	91.1	85.8	88.8	90.4	90.0	90.7
	SD	4.14	3.63	2.99	3.50	3.74	2.93	3.73
2nd half	N	19	20	17	18	21	20	20
	Mean	90.9	91.1	90.8	90.2	91.3	90.5	91.8
	SD	3.43	3.64	3.38	3.77	3.29	3.65	3.21
Whole Night	N	19	20	17	15	21	20	20
	Mean	89.7	90.2	88.9	89.1	89.9	89.1	90.0
	SD	3.75	3.98	3.38	3.85	3.48	3.89	3.29
Lowest SaO_2 (REM) (%)								
1st half	N	14	20	17	17	21	19	17
	Mean	89.3	90.9	87.9	90.1	90.2	90.7	90.8
	SD	3.36	4.80	4.50	4.04	4.32	4.83	4.33
2nd half	N	19	20	17	18	21	20	19
	Mean	90.9	90.5	90.8	85.9	90.0	92.0	90.7
	SD	5.17	3.6	3.34	3.11	3.79	3.69	4.45
Whole Night	N	19	20	17	19	21	20	20
	Mean	89.5	89.3	85.7	88.9	86.7	90.1	89.6
	SD	5.05	4.34	4.34	3.02	3.75	4.55	4.48

		Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6
		Anti-cata-plexy meds	Baseline	1st dose 4.5 g/d	4 weeks of 4.5 g/d	2 weeks of 6.0 g/d	2 weeks of 7.5 g/d	2 weeks of 9.0 g/d
Lowest SaO2 (NREM + REM) (%)								
1st half	N	19	20	17	19	21	20	20
	Mean	90.0	89.7	87.5	88.7	89.0	88.9	89.9
	SD	4.38	4.50	4.20	3.83	3.85	3.96	4.00
2nd half	N	19	20	17	18	21	20	20
	Mean	89.7	89.4	89.7	88.4	89.4	89.8	90.3
	SD	4.49	3.87	3.50	2.99	3.54	3.64	4.09
Whole Night	N	19	20	17	19	21	20	20
	Mean	88.5	88.3	87.3	87.5	88.0	87.9	88.6
	SD	4.53	4.35	4.07	3.33	3.45	3.73	4.17

* p ≤ 0.01 compared with baseline (t test).
* p ≤ 0.05 compared with baseline (t test).

The following are noteworthy, from the viewpoint of this reviewer

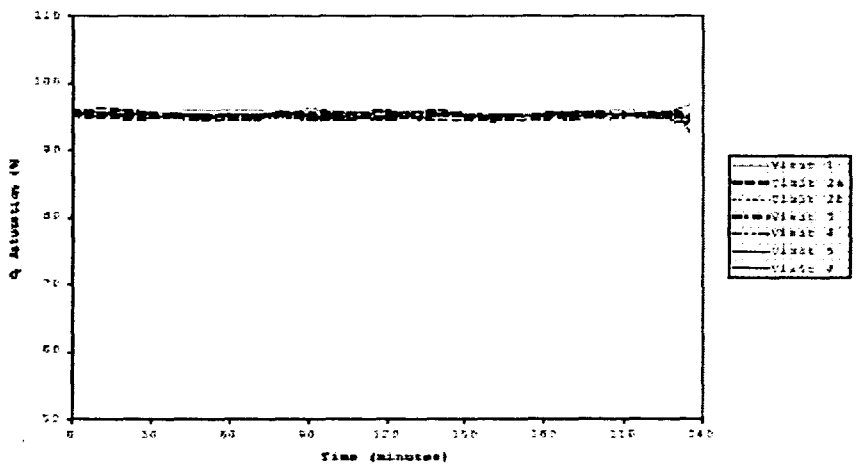
- Unlike with the respiratory event parameters, individual variability in SaO_2 was minimal
- No prominent changes were seen in any SaO_2 parameters as compared with baseline
- No dose response was apparent with any parameter
- The only "statistically significant" ($p < 0.05$), but clinically very small, change in any parameter was in continuous SaO_2 at Visit 3 for the first half of the night and for the whole night.

8.6.10.2 By-Patient Plots

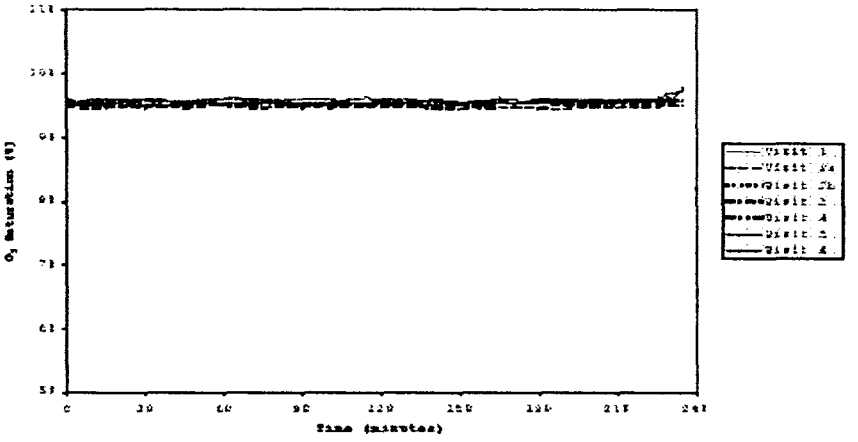
8.6.10.2.1 Continuous Oxygen Saturation

5-minute data are shown for the first half of the night and second half of night in figures copied from the submission

Mean Continuous Oxygen Saturation (5-Minute Data) vs. Time, by Visit - First Half of Night



Mean Continuous Oxygen Saturation (5-Minute Data) vs. Time, by Visit - Second Half of Night



As the above tables indicate this parameter showed no prominent changes in individual patients during the course of the study.

8.6.10.2.2 Intermittent Oxygen Saturation

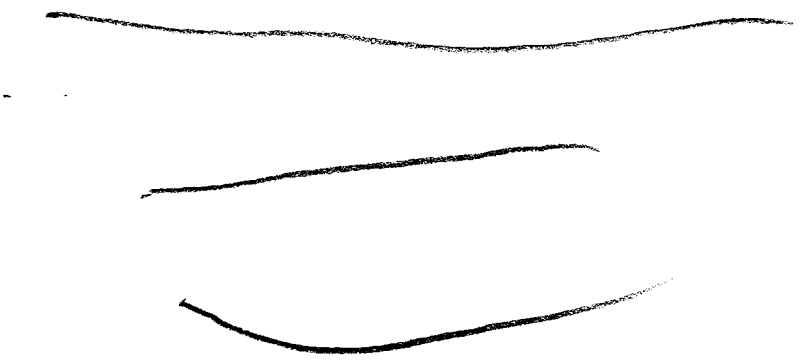
Random low SaO_2 levels were seen in a few patients without any evidence of a dose response

8.6.10.2.3 Duration Of Oxygen Desaturation Less Than 90%

This parameter was expressed a percentage of a 4-hour period.

The next figure, copied from the submission, provides a plot for this parameter for the first half of the night

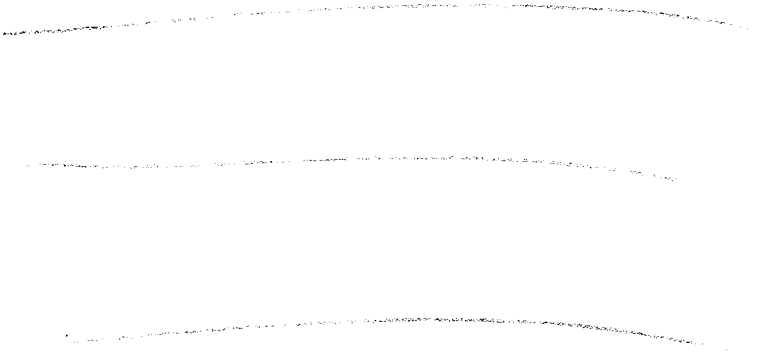
The next figure, also copied from the submission, provides a plot for this parameter for the second half of the night



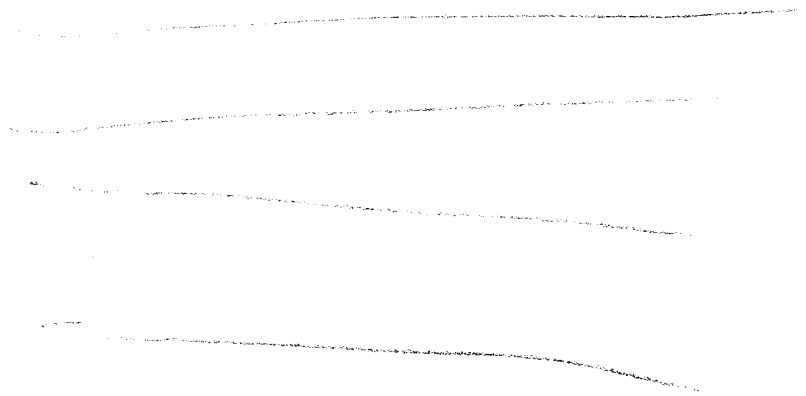
As the plots above indicate this parameter for the first half of the night increased during the course of the study for Patient 17301, and showed sharp fluctuations during the night for the same patient during the second half of the night across the course of the study.

8.6.10.2.4 Lowest SaO_2

The lowest oxygen saturation by-patient, by-visit profile for individual patients for the first half of the night is in the following figure, copied from the submission



The profile for the second half of the night is in the next figure, also copied from the submission.



The profiles for each half of the night do not show prominent changes for individual patients in this parameter.

8.6.11 Outliers For Respiratory Event And Oxygen Saturation Data

11 patients were outliers in regard to respiratory event and/or oxygen saturation data. They are summarized in the following table which I have copied from the submission.

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Patient Number	Deviation	Visit Number(s)	
		1st Half of Night	2nd Half of Night
017301	Decreased continuous SaO_2 (5-minute data)	2b, 3, 4, 5, 6	2b, 5, 6
	Decreased intermittent SaO_2 (1-minute data)	2b, 3, 4, 5, 6	2b, 5, 6
	Increased AHI (NREM) Increased AHI (REM)	3, 4, 5, 6 2a, 4, 5, 6	3, 4, 5, 6 2a, 3, 4, 6
	Increased OMAs	3, 4, 5, 6	3, 4, 5, 6
	Increased hypopneas	3, 4, 6	3, 4, 5, 6
	Increased RDI	3, 4	3, 4, 5, 6
	Increased time SaO_2 < 90%	2a, 2b, 3, 4, 5, 6	2a, 2b, 3, 4, 5, 6
017302	Increased AHI (REM)	3, 4	3, 5
	Increased hypopneas	2a, 3	2a, 3
017304	Increased AHI (NREM) Increased AHI (REM)	3, 4 3, 4	1, 3, 4 3, 4
	Increased OMAs	1, 2a, 3, 4	1, 2a, 3, 4
	Increased central apneas	3, 4	3, 4
	Increased hypopneas	3, 4	
	Increased RDI	3, 4	1, 2a, 3, 4
041300	Decreased continuous SaO_2 (nadir of 77% at 150 min)		2a
	Decreased intermittent SaO_2 (nadir of 75.89% at 150 min)		2a
041303	Increased central apneas		5, 6
041304	Increased hypopneas	3	3, 5
041307	Increased AHI (REM)	3, 5, 6	
	Increased RDI	3, 5	
041311	Decreased continuous SaO_2	1	
	Decreased intermittent SaO_2	1, 3	
042303	Decreased intermittent SaO_2 (nadir of 78.7% at lights on)		4
	Increased central apneas	1, 2a, 2b, 3, 4, 5, 6	1, 2a, 2b, 3, 4, 5, 6
	Increased RDI	1, 2a, 2b, 3, 4, 5, 6	1, 2a, 2b, 3, 4, 5, 6
042304	Increased intermittent SaO_2	1	

Patient Number	Deviation	Visit Number(s)	
		1st Half of Night	2nd Half of Night
042306	Decreased intermittent SaO_2 (nadir of 82.73% at lights-on)		2a
	Increased central apneas		6

So that the visit numbers can easily be correlated with the phases of the study, I have reproduced the sponsor's study design diagram below

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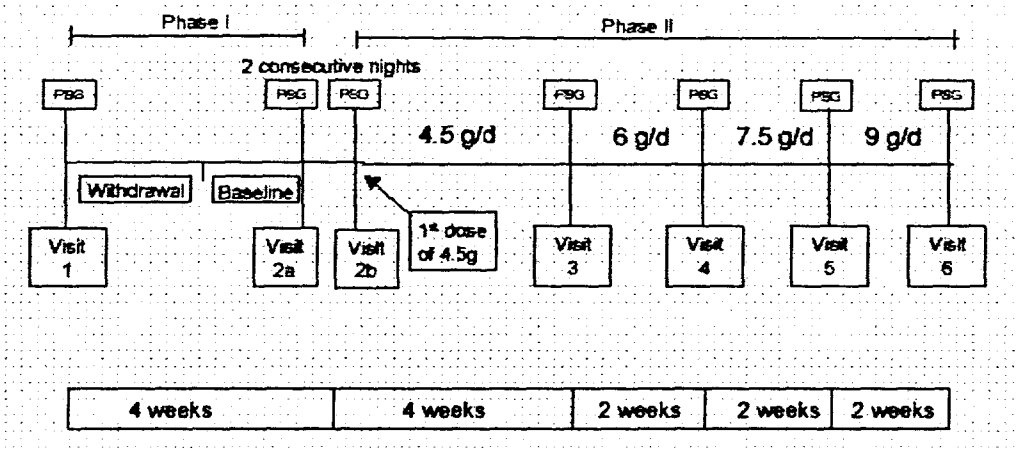


The data in the table indicate that

- Only 2 patients (#s 017301 and 017304) had a worsening with sodium oxybate across a number of respiratory event parameters
- Only 1 patient (#017301) had a clear worsening in an SaO_2 parameter – duration of SaO_2 < 90% - after being treated with sodium oxybate. For measurements done during the first half of the night a steady increase was seen over the course of the trial beginning at a dose of 6 g/day. For measurements done during the second half of the night this parameter showed prominent fluctuations during the course of the study. The changes in SaO_2 in this patient did not however correlate temporally with the changes in respiratory event parameters.

8.6.12 Discontinuations Due To Adverse Event

A single patient discontinued treatment with Xyrem® on account of a respiratory adverse event. The narrative for this patient is below; this narrative was created from the narrative and Case Report Form provided by the sponsor.

This patient (#017304) was a 67 year old woman with a known history of narcolepsy (for 25 years), tonsillectomy, breast cancer in remission (treated with lumpectomy and radiation) and obstructive sleep apnea-hypopnea syndrome (confirmed by polysomnogram done over 1 ½ years prior to her enrollment) . Concomitant medications included venlafaxine and modafinil.

At screening this patient had a false-positive urine test for benzodiazepines. After entering the OMC-SXB-20 trial she failed to attend Visit 3 (on trial date 29) and indicated a desire to discontinue medication. However she then changed her mind and attended Visit 3 on Day 36. On Day 51, a day after beginning Xyrem® in a dose of 7.5 g/day she reported being "really sensitive" and her husband noted worsening snoring, and frequent and more severe episodes of apnea. By that time she had been treated with the following doses of Xyrem®: 4.5 g/day for 35 days and 6.0 g/day for 14 days. Xyrem® was discontinued on Day 51 on account of a perceived worsening in her obstructive sleep apnea-hypopnea syndrome. The adverse event was reported to have resolved by Day 52.

Several objective parameters – AHI (NREM), OMAs and RDI – all measured during the second half of the night showed no worsening at Visits 3 and 4 as compared with Visits 1 and 2a. SaO_2 data showed no abnormalities. However the following were seen only at Visits 3 and 4

- Increased AHI (REM and NREM), central apneas, hypopneas, and RDI during the first half of the night

- Increased AHI (REM) and central apnea during the second half of the night

A further patient also discontinued treatment on account of an adverse event

This 56 year old woman (#42305) had a past history of depression with onset > 3 years prior to participating in the study. On Study Day 10 while receiving Xyrem® 4.5 g/day the patient experienced a worsening of depression; this adverse event resulted in her discontinuing Xyrem® on Day 27. Her depression reportedly resolved by Day 35

8.7 Sponsor's Conclusions

- There did not appear to be a clear relationship to dose for the changes in any of the respiratory event measures, or SaO_2, in this study. Although nominally statistically significant differences between specific doses were seen for a few parameters these changes were not consistent across increasing dose, i.e., there was no clear dose-response relationship
- In earlier human pharmacokinetic studies the C_{max} and AUC had been consistently higher after the second nightly dose of Xyrem® than after the first dose. The respiratory event parameters and SaO_2 were therefore compared between the two halves of the night, on the assumption that the first and second halves of the night would correspond to the effects of the first and second doses, respectively. There was no overall difference in these parameters between the 2 halves of the night although several individual patients appeared to have more central apneas during the second half of the night

  In addition
  - The t_{max} of Xyrem® ranges from 45-60 minutes. There was no evidence of a fall in SaO_2 corresponding to the 1-2 hour period after dosing
  - Sodium oxybate shows non-linear pharmacokinetics. An increase in total dose from 4.5 g (in two divided doses 4 hours apart) to 9 g (in two divided doses 4 hours apart) results in a 3.7-fold increase in exposure, based on AUC. [Note that Agency Biopharmaceutics reviewers are uncertain to what extent the sponsor's conclusions as stated in the previous 2 sentences are confounded by a food effect]. No increase in respiratory event data or decrease in SaO_2 was seen with an increase in dose from 4.5 g to 9 g.
- Respiratory patterns are normally different between REM and NREM sleep. Respiratory event and SaO_2 data were therefore compared between REM and NREM sleep in this study. Although there were slight but variable differences between parameters at individual visits, there were no overall differences between REM and NREM sleep, and no changes with increasing dose.
- 2 patients had respiratory effects that could be considered clinically significant
  - Patient #17304 (see Section 8.6.12) discontinued treatment on account of a subjective worsening in pre-existing sleep apnea. However several objective respiratory event measures were no worse during the second half of the night than during the first
  - Patient #17301 (see Section 8.6.9.3) had a prominent increase at Visit 3 (after a Xyrem® dose of 4.5 g/day for 4 weeks), relative to baseline, in the following:

obstructive and mixed apneas, hypopneas, AHI and RDI. The sponsor points out that this patient had pre-existing obstructive sleep apnea and obesity.

- The most prominent mean inter-visit changes for the whole cohort were seen between baseline and Visit 3 (after 4 weeks at 4.5 g/day) with increases in OMAs and hypopneas, and a decrease in continuous SaO_2 (5-minute data). While these changes were nominally statistically significant ($p < 0.05$) they were clinically minimal and the same trend did not continue at higher doses
- The respiratory event and SaO_2 measures were sensitive and these 2 categories correlated with each other

8.8 Reviewer's Comments

- It is difficult to draw any firm conclusions from this study regarding the effect of sodium oxybate on respiratory parameters; the reasons for such a view are as follows
  - The study was open-label and uncontrolled
  - The number of patients enrolled was small
  - There was considerable inter-patient variability in changes from baseline in all parameters with standard deviations consistently exceeding means
  - The study was intended to measure the effects of 4 different doses of GHB on sleep architecture and not to assess the effects of that drug on respiration.
  - The only true measures of respiratory function per se in this study were those related to arterial oxygen saturation. The "respiratory event parameters" used in this study were indices of sleep apnea and not of respiratory function, per se
- Among the numerous comparisons made in the sponsor's analysis, some were nominally statistically significant ($p < 0.05$). The clinical significance of the differences seen in most of these comparisons is however highly questionable.
- As the sponsor has also noted the most prominent mean inter-visit changes for the whole cohort were seen between baseline and Visit 3 (after 4 weeks at 4.5 g/day) with increases in obstructive and mixed apneas, and hypopneas, and a decrease in continuous SaO_2 (5-minute data). Again, although these changes were statistically significant they were clinically minimal and may have been driven largely by a single patient (#17301)
- There was no overall tendency in this cohort to a dose-response in regard to respiratory event parameters and SaO_2 (i.e., an increasing effect on respiratory event parameters and SaO_2 with increasing dose of GHB)
- The rather prominent increase in several parameters - obstructive and mixed apneas, hypopneas, apnea-hypopnea index and respiratory disturbance index – relative to baseline in a single patient (#17301) after 4 weeks of treatment with GHB at 4.5 g/day is at least somewhat noteworthy in itself. The same patient also showed a steady increase in the duration of time spent during the first half of the night at an SaO_2 less than 90%. However this patient did have pre-existing obstructive sleep apnea and there is no evidence that the changes in respiratory event parameters and SaO_2 were related to GHB; the respiratory event parameters in fact improved as the dose of GHB was increased through 6, 7.5 and 9 g/day, when it might have been expected that exposure to GHB was increasing.

- It is noteworthy that 18/21 patients who completed the study received stable doses of stimulant drugs throughout the trial. It is not inconceivable that such drugs may have led to any respiratory depressant effects of GHB becoming less apparent.
- While this study clearly had limitations it cannot be said to provide any evidence that Xyrem® has, or does not have, a respiratory depressant effect.

9. Addendum To Review Of Respiratory Data In Study OMC-SXB-20 As Contained In Earlier Review/Addendum Completed 3/29/02

The summary contained in this section also addressed material submitted in the earlier Response to Approvable Letter dated 10/5/01, and in subsequent clarifications that were requested by the Division and received prior to 4/9/02.

9.1 Background

Through the efforts of Dr John Feeney, attention was drawn to changes in respiratory event parameters in patients with pre-existing sleep apnea enrolled in the study (despite the presence of sleep apnea being an exclusion criterion) and had been considered a matter of concern. These patients will be described further in this section. The description of these patients is based upon the original submission of 10/5/01 and several subsequent responses to questions and requests for information from this Division all of which were received prior to the Approvable action of 4/9/02.

The following table lists patients who may be considered to have had at least mild sleep apnea based on an RDI > 5 at Visit 1, Visit 2a, or both, during any half of the night. Patients whose numbers are highlighted in bold type could be considered to have moderate-severe sleep apnea based on an RDI > 15 during any half of the night at Visit 1 or 2a. These patients are described further below

Patient Number	Visit	Respiratory Disturbance Index	
		First half of night	Second half of night
17301	1	7.08	3.74
	2a	14.12	32.42
17302	1	4.88	3.18
	2a	27.52	13.95
17304	1	54.36	87.09
	2a	27.39	36.02
02630*	1	10.1	2.4
	2a	3.7	2.1
42302	1	8.93	12.68
	2a	10.33	4.96
41304	1	8.13	3.25
	2a	0	1.46
41306	1	21.73	19.43
	2a	1.25	5.78
41308	1	3.08	9.59
	2a	0	0.59
41310	1	6.53	1.68
	2a	0.67	0.39
42300	1	3.13	10.14
	2a	3.01	8.65
42301	1	0.74	1.05
	2a	5.36	2.71

Patient Number	Visit	Respiratory Disturbance Index	
		First half of night	Second half of night
42303	1	32.07	20.88
	2a	24.07	45.24

*The overall all-night RDI at Visits 1 and 2a were 6.5 and 3.0, respectively

The patients with moderate-to-severe sleep apnea, and a single patient with mild sleep apnea are further described below.

9.2 Description Of Patients With Pre-Existing Moderate To Severe Sleep Apnea

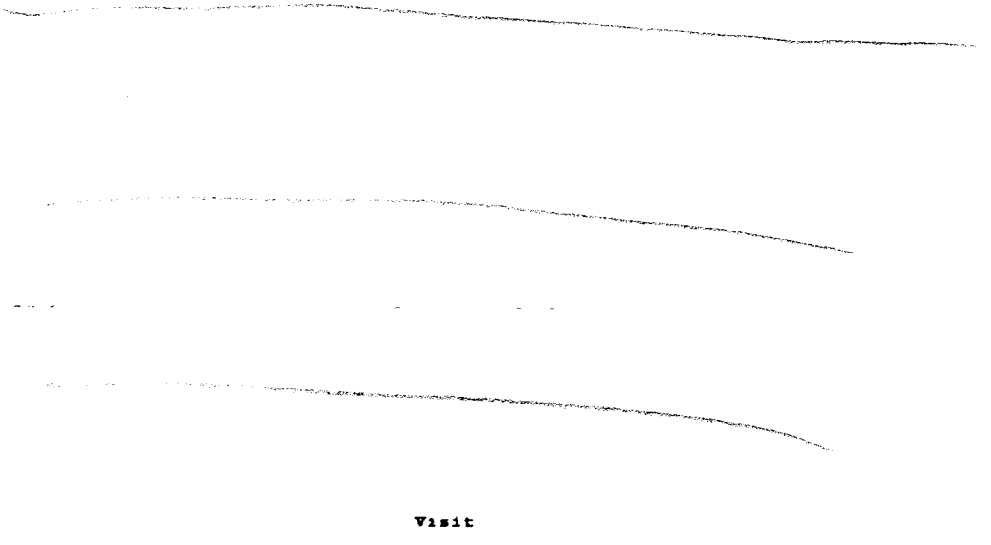
9.2.1 Patient #17301

This 51 year old man, had a previous history of narcolepsy, hernia, recurrent bronchitis, previous knee surgery and rosacea. He was also obese. Concomitant medications included venlafaxine, and modafinil. He was not recorded as having any adverse events during Study OMC-SXB-20 which he completed.

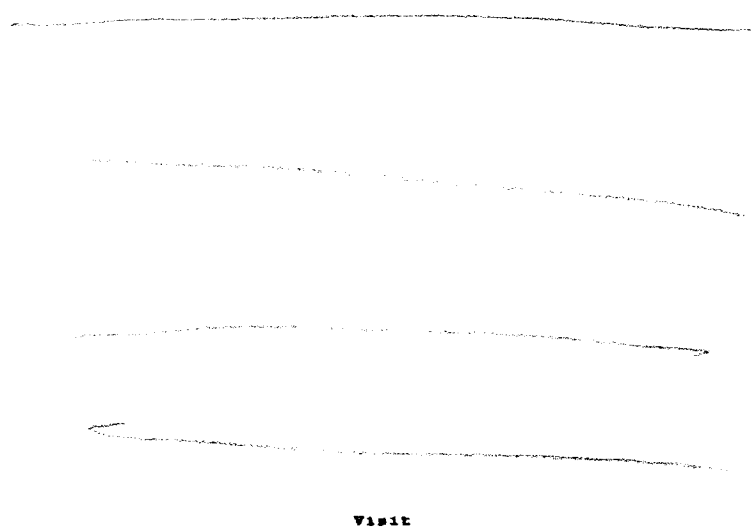
A polysomnogram done prior to the screening visit for this study was consistent with a diagnosis of obstructive sleep apnea syndrome.

As noted in the by-patient and by-visit plots below, this individual had a prominent increase at Visit 3, relative to baseline, in the following: obstructive and mixed apneas, hypopneas, AHI and RDI.

The first figure copied from the submission shows by-patient and by-visit plots for the first half of the night in RDI



The next figure also copied from the submission shows by-patient and by-visit plots for the second half of the night in RDI



Changes in RDI over the course of the study are summarized in the following table

Visit	Respiratory Disturbance Index	
	First half of night	Second half of night
1	7.08	3.74
2a	14.12	32.42
2b	7.96	21.36
3	100.9	76.36
4	39.58	39.63
5	24.67	56.88
6	31.2	42.04

The increase in obstructive and mixed apneas, hypopneas, AHI and RDI, seen at Visit 3 was not maintained despite further increases in dose of GHB during the remainder of the study .

This patient also had the following changes in a SaO_2 parameter, the duration of time spent with an SaO_2 less than 90% (see plots below). These changes did not correlate temporally with changes in respiratory event parameters

- For measurements done during the first half of the night a steady increase was seen over the course of the trial beginning at a dose of 6 g/day.
- For measurements done during the second half of the night this parameter showed prominent fluctuations during the course of the study.

The following plots taken from the study report for OMC-SXB-20 depict the duration of oxygen desaturation (percentage of each 4-hour period with SaO_2 less than 90%) by visit, for the first and second halves of each night, respectively