CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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Statistical Review and Evaluation

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NDA#:	21-196
DRUG COMPANY:	Orphan Medical, Inc.
NAME OF DRUG:	Xyrem (Sodium Oxybate)
INDICATION:	Narcolepsy
STUDIES REVIEWED:	OMC -GHB-2, Scrima, Lammers, and SXB-21
DOCUMENTS REVIEWED:	Sponsor's original NDA submission
MEDICAL REVIEWER	Ranjit Mani, M.D.

1. Introduction

Narcolepsy is a chronic neurological disorder characterized by excessive daytime sleepiness, disturbed nocturnal sleep, cataplexy, sleep paralysis, and hypnagogic hallucinations (Aldrich, 1990). The usual treatment for narcolepsy includes symptomatic treatment of daytime sleepiness with stimulants. The symptoms of cataplexy, hypnagogic hallucinations, and sleep paralysis are typically treated with tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs). The effectiveness of these treatments is limited by frequent undesirable adverse events and tolerance.

As part of the sodium oxybate development project, Orphan Medical, Inc. acquired the rights to the Scrima and Lammers data for this NDA. Results from these two trials and along with Orphan Medical's own trial OMC-GHB-2 were submitted in this NDA to form the data sets to establish the efficacy of sodium oxybate in the treatment of narcolepsy symptoms. After the submission of the NDA, another long-term efficacy trial SXB-021 was completed. Results of the study SXB-021 were later submitted to be included in this NDA.

2. Specifications and Findings of Study OMC-GHB-2

2.1 Objectives

The primary objective of this study was to evaluate and compare the efficacy of 3 doses (3g, 6g, and 9g) of GHB and placebo in the treatment of the symptoms of narcolepsy.

The secondary objective of this study was to evaluate and compare the safety of GHB and placebo when used in a narcoleptic patient population.

2.2 Study Design

This was a randomized, double blind, placebo controlled, parallel-group, multi-center study of 3 doses of GHB and placebo in the treatment of patients with narcolepsy. The study was conducted in 16 centers and a total of 136 patients were enrolled. The study was divided into 5 periods as follows:

Table 1. Study flow

Screening	Washout	Baseline	Double-blind Treatment	Follow-up
1 day - 4 wks	5 - 28 days	2 - 3 wks	4 wks	3 - 5 days
Visit 1	Visit 2	Visit 3	Visits 4, 5, 6	Visit 7
Withdrawal of TCAs	No treatment for cataplexy		Placebo or GHB 3g, 6g, or 9g	No Treatment for cataplexy

1. Screening period - lasted 1 day to 4 weeks. Tricyclic antidepressants (TCAs) or other drugs used to treat cataplexy were gradually withdrawn from patients on these drugs. Patients not on TCAs proceeded directly to the next study period if they met entry criteria. Patients were permitted to continue taking stable doses of stimulant medication throughout the study.
2. Washout period - lasted 5 - 28 days. This period allowed time to eliminate any clinical effects of TCAs, for rebound cataplexy (cataplexy that is spontaneous, unprovoked, and with greater frequency and severity than usual) to abate, and to train patients on the use of diary.
3. Baseline period - lasted 2 to 3 weeks. This period was an opportunity to assess the patients' cataplexy attacks and to establish a stable number of attacks. Eligibility for admission into the double-blind treatment period required patients to report an average of 3 or more complete and/or partial cataplexy attacks per week, during the last two weeks of the baseline period.
4. Double-blind treatment period - lasted 4 weeks. Eligible patients were randomly assigned to receive each night 3g, 6g, or 9g GHB or placebo in 2 divided doses. Patients returned approximately every 2 weeks during this period to assess safety and efficacy.
5. Follow-up period - a visit for final assessment 3 - 5 days after study medication was discontinued.

Approximately 104 patients (26 in each of the 4 treatment groups) were planned to be enrolled and 136 patients were actually enrolled and assigned to receive 4 weeks of treatment with study medication.

The study was initiated on February 7, 1997 and completed on February 9, 1998.

2.3 Main Inclusion Criteria

Patients were included in the study if they met the following criteria:

- Were 18 years of age or older;
- Had not received investigational therapy within 30 days prior to study entry;
- Had a history of excessive daytime sleepiness;
- Had a history of sudden loss of voluntary muscle control or muscle weakness (cataplexy) localizable to a specific muscle group(s) or part(s) of the body during which the patient was lucid and not experiencing an inadvertent nap or micro sleep;

- Had a valid polysomnography (PSG) within the last 5 years and a current diagnosis of narcolepsy for at least 6 months according to the following 2 items of Criteria A as established by the American Sleep Disorder Association (ASDA):
  a) Recurrent daytime naps or lapses into sleep that occur almost daily for at least 3 months;
  b) Sudden bilateral loss of postural muscle tone in association with intense emotion (Cataplexy).

In addition, a patient must have recorded an average of 3 or more complete and/or partial cataplexy attacks per week during the last 2 weeks of the baseline period to be eligible for entry into the randomized portion of the study.

2.4 Efficacy Variables

2.4.1 Primary Efficacy Variables

The primary efficacy variable for this study as defined in the protocol was the change from baseline in the total number of cataplexy attacks, which is the sum of complete and partial cataplexy attacks that occurred.

The endpoint was defined as the last 2-week period of the treatment (Visit 6) and the baseline was defined as the last 2-week period before the treatment (Visit 4).

A cataplexy attack, episode, or event was defined as a sudden loss of voluntary muscle tone usually triggered by emotions such as those associated with laughter, anger, elation, fear or surprise. These events could range from a brief experience of partial muscle weakness to an almost complete loss of muscle control lasting for several minutes and resulting in total physical collapse during which time the patient was unable to move or speak. To be classified as cataplexy for this study the patient must have been aware of the time and place during the event. The event must have been of sudden onset and localizable to a specific muscle group(s) or part of the body.

2.4.2 Secondary Efficacy Variables

Secondary measures of efficacy include following variables:

- Change in the number of complete and number of partial cataplexy attacks;
- Daytime sleepiness as measured by the Epworth Sleepiness Scale and number and duration of inadvertent naps;
- Quality of nighttime sleep as measured by number of awakenings during the nights and total amount of sleep;
- Incident of hypnagogic hallucination;
- Incident of sleep paralysis;
- Change in severity of the patients' narcolepsy symptoms as measured by the Clinical Global Impression of Change

2.5 Statistical Method

2.5.1 Primary Efficacy Analysis

The efficacy analyses were to be done on the intent-to-treat (ITT) population. The planned analyses called for an analysis of variance (ANOVA) on the change from baseline to endpoint including in the model the factors of treatment, site, and their interaction. The interaction term was then to be removed if found to be not statistically significant. In addition, an analysis of covariance (ANCOVA) was planned for the primary efficacy variable using the baseline value as a covariate. The factor of site was to be removed from this ANCOVA model, as indicated in the statistical analysis plan. An additional analysis would examine for a possible dose response relationship.

It was stated in the Statistical Analysis Plan, documented July 1997, that the method of statistical analysis implied normal distribution assumption. If the data were not normal then the most suitable data transformation method (log, square root, etc.) was to be applied. If the assumption of normality and the data transformation did not appear to be satisfied, then appropriate non-parametric methods were to be used in the analyses.

2.5.2 Analysis of Secondary Efficacy Variables

All secondary measures of efficacy except CGI-c were to be analyzed in a similar way as to the primary efficacy variable.

CGI-c was to be analyzed using Fisher's exact test and Cochran-Mantel-Haenszel (CMH) test for nonzero correlation.

2.5.3 Center Grouping

The study was to be conducted in 16 centers. In the event of any site(s) fail to reach a minimum of 8 patients, these sites were to be pooled and treated as a single site for purpose of statistical analysis.

2.5.4 Interim Analysis

No interim analyses were planned or performed for this study.

2.6 Results: Sponsor's Analysis

2.6.1 Patient Disposition

The sponsor reported that a total of 136 patients were enrolled from 16 centers. The number of patients entered by each center ranged from 1 to 21. Of the 136 patients enrolled, 16 withdrew from the study before completion. Disposition of patients is summarized in Table 2. The primary reason of withdrawal from the study was adverse

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