



**NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND
OPPORTUNITY TO EXPLAIN (NIDPOE)**

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

MAR - 1 2005

Martha H. Hagaman, M.D.
5655 Frist Boulevard, Suite 401
Medical Office Building
Hermitage, Tennessee 37076

Dear Dr. Hagaman:

Between March 11 and 14, 2002, Ms. Patricia S. Smith, Drs. Ni A. Khin and John J. Feeney, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of the following clinical investigations of the investigational drug Xyrem (sodium oxybate) also known as sodium gamma-hydroxybutyrate (GHB), performed for Orphan Medical, Inc:

Protocol [] entitled: "Long-Term, Open-Label, Multi-Center, Extension Trial of Xyrem (sodium oxybate) Oral Solution for The Treatment of Narcolepsy;"

Protocol [] entitled: "Randomized, Double-Blind, Placebo-Controlled, Multi-Center Trial to Assess The Long-Term Efficacy of Orally Administered Xyrem (sodium oxybate) When Compared to Placebo;"

Protocol [] entitled: "Open-Label, Multi-Center, Six-Month Trial of Xyrem (sodium oxybate) Oral Solution For The Treatment of Narcolepsy in Study Drug Naive Patients;" and

Protocol [] entitled: "Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Trial Comparing the Effects of Three Doses of Orally Administered Xyrem (gamma-hydroxybutyrate) with Placebo for the Treatment of Narcolepsy."

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, our personnel presented and discussed with you, your staff and Mr. [] of Orphan Medical, Inc., Form FDA 483, Inspectional Observations. We have reviewed the inspection report, the documents submitted with that report, and your written response dated March 25, 2002, addressed to FDA District Director Carl Draper, and we accept some of your response. However, we do not find your explanation acceptable in addressing the remaining matters under complaint, which are described below.

Based on our evaluation of the information obtained by the Agency, the Center for Drug Evaluation and Research (the Center) believes that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational drugs as published under Title 21, Code of Federal Regulations (CFR), Part 312 (copy enclosed), and that you have submitted false information in a required report (21 CFR 312.70).

This letter provides you with written notice of the matters under complaint and initiates an administrative proceeding, described below, to determine whether you should be disqualified from receiving investigational drugs as set forth under 21 CFR 312.70.

A list of the violations follows. The applicable provisions of Title 21, Code of Federal Regulations (21 CFR) are cited for each violation.

1. You failed to adequately supervise the above-referenced clinical studies [21 CFR 312.60].

When you signed the investigator statement (Form FDA 1572) for the above-referenced clinical studies, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities included ensuring that the studies were conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protects the rights, safety, and welfare of subjects under your care. You specifically agreed to personally conduct the clinical studies or to supervise those aspects of the studies that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, you may not delegate your responsibilities. Our inspection indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical studies were conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protects the rights, safety and welfare of human subjects.

A major factor in your failure to provide adequate supervision was your move to a location far removed from the study site in Tennessee. From June 1999 to May 2001, you resided in Bethesda, Maryland. Thus, for the three clinical studies you agreed to conduct in Nashville, Tennessee, you were not readily available to those you had delegated study tasks or to study subjects. During this two-year period, protocols [] and [] were ongoing in Nashville, Tennessee and you began enrolling subjects in protocol [] There is no documentation or other evidence to suggest that you provided adequate supervision to your staff or adequate medical coverage as required generally for any clinical trial for study subjects in your absence, although you claimed that you planned patients visits to coincide with your travel to Nashville, Tennessee from Bethesda, Maryland.

Your failure to provide adequate supervision and lack of personal involvement in the study put study subjects at risk and resulted in, or contributed to, the charges set forth below.

2. You failed to protect the rights, safety, and welfare of subjects under your care [21 CFR 312.60].

For protocols [] you failed to make adequate provision for medical coverage for emergency situations that might arise due to participation in the clinical trial, and is necessary to protect the safety and welfare of subjects under your care. The clinical studies you were conducting involved administration of investigational drug with high abuse potential, sodium oxybate or gamm-hydroxybutyrate (GHB), and significant risk of serious adverse effects such as respiratory depression.

You claimed that you had discussed plans for coverage of these studies with your institutional review board (IRB) and [] Hospital administration prior to your move to Maryland. However, there is no documentation to support your claim that the IRB reviewed your proposal and concurred, or that there were qualified individuals available to provide medical coverage for the duration of your absence. The only documentation you provided was a letter to the [] Hospital Office of Medical Affairs, dated November 4, 1999 (approximately five months after you moved to Maryland) in which you stated that [] M.D. would handle any emergency situations and that [] Psy.D., subinvestigator, (who is not a physician and is not qualified to provide medical care) would oversee any study problems. However, Dr. [] is not listed as a subinvestigator in the Forms FDA 1572 you signed for protocols [] Dr. [] signed the Form FDA 1572 to become principal investigator for protocol [] on February 15, 2001, when he replaced you as the clinical investigator after your IRB had terminated your involvement with the study.

During your absence, you claimed that you delegated oversight of non-emergency study problems to [] Psy.D., a subinvestigator for protocol [] Section 11.5 of protocol [] states that "sufficiently qualified, practicing, licensed physicians must be available to provide twenty-four hour on-call coverage during the course of clinical trials." It also states that "physical examination must be performed by an M.D. or D.O., although patients may be interviewed by a research nurse or the trained equivalent." Dr. [] is a psychologist and thus not qualified to perform the tasks that the protocol required be performed by a qualified, practicing, licensed physician, such as medical assessments, dosage changes, physical examinations, evaluation of clinical laboratory results and clinical follow-up as necessary. Available records do not indicate that there was a qualified individual available to provide medical coverage throughout your absence. You also failed to list any physician subinvestigator on Form FDA 1572 to provide on-site medical support for the long-term efficacy and safety study, protocol [] when you signed the Forms FDA 1572 on 3/17/00, 3/31/00 and 5/24/00.

During the FDA investigation, our personnel found documentation that your staff had difficulty reaching you and was also concerned about study subjects' inability to reach you.

For example, [] Psy. D., a subinvestigator who was not qualified to provide medical care, was unable to contact you when subject 0845 informed Dr. [] on December 19, 2000, about her pregnancy during her participation in protocol [] Since the informed consent for this study states that “use of Xyrem® may involve risks to the subject (and the embryo or fetus, if the subject is or becomes pregnant) which are currently unforeseeable,” you should have advised the subject to stop study drug immediately. There is no evidence that the subject was appropriately counseled about the potential risk to her fetus and about the advisability of stopping study drug. You wrote a note on January 7, 2001, that the subject had a positive pregnancy test and the last dose of study drug was taken on January 4, 2001, indicating that the subject continued taking study drug for fifteen days after she initially attempted to contact you. There were also instances under protocol [] in which abnormal laboratory results were not detected until well after the testing occurred (in some cases weeks) when the results were reviewed by the sponsor’s medical monitor, Dr. [] For three subjects in protocol [] Dr. [] felt it necessary to recommend that these subjects have follow-up visits with their primary care physicians--subjects 0831 (possible intercurrent infection), 0834 (blood glucose very high, even for a diabetic patient), and 0835 (blood glucose suggestive of diabetes).

3. You submitted false information to the sponsor or FDA [21 CFR 312.70(a)].

You submitted falsified electrocardiograms (ECGs or EKGs) for at least three subjects in Protocol [] For two subjects, #0838 and #0839, the monitor reports stated that no EKG was done at visit 1 for the subjects, but EKG tracings marked with dates that corresponded with each subjects' visit 1 were found in the subjects' files.

In two of the three cases listed below, the monitor reports stated that EKGs were not done for the subjects during their screening visits; therefore, it appears that the EKGs found in their files were altered to reflect the dates of the screening visits in order to qualify the subjects for enrollment in Protocol [] In the third case, the EKG appeared to have been altered; whether the EKG was done on the date initialed could not be verified. Failure to perform a visit 1 screening EKG is a protocol violation and potentially placed subjects at unnecessary risk. In your written response dated March 25, 2002, you claimed that, since you were not adept at reprogramming the EKG machine, you manually changed the subject names and dates. Your explanation does not provide adequate assurance of the integrity of these records and does not explain how screening EKGs that were not done at the time the study monitor examined the subjects' files subsequent to their screening visit could later be found in the same subjects' files and represent genuine screening EKGs.

For subject 0838, the monitor report dated February 10, 2000, for the monitoring visit to your site on January 5-7, 2000, stated that no EKG was done at visit 1 on 8/14/99, and that the subject had discontinued, and directed the site to write up a deviation report. No deviation report was found in the files, however, an EKG tracing allegedly from visit 1 was found in the subject's file. The EKG tracing found in subject 0838's file was originally printed by the machine on 7/21/99, but the date was marked through and the subject's initials and subject number, and the date "8/14/99" were hand-written on the tracing, along with your signature.

For subject 0839, the monitor visit notes dated February 10, 2000, also stated that no EKG was done at visit 1 on 8/30/99, and instructed the site to write "protocol departure." No protocol departure was found in the file. An EKG tracing allegedly from visit 1 was found in the subject's file. The tracing was originally printed by the machine on 1/1/94 but that date was marked through and initialed by you, and the subject's initials, subject number, and the date "8/30/99" were hand-written on the tracing.

Similarly, for subject 0845, an EKG tracing was originally dated 3/1/00; this date was marked through and changed to 3/17/00 without any initials.

4. You failed to take adequate precautions in the handling of a controlled substance [21 CFR 312.69].

At the time these studies (protocols [] were conducted, the study drug (GHB) was a controlled substance subject to the Controlled Substances Act. An investigational drug that is a controlled substance must be stored in a securely locked, substantially constructed cabinet or other enclosure, access to which is limited, to prevent diversion of the drug into illegal channels of distribution. A December 18, 2001, IRB site audit of protocol [] (study received IRB authorization to proceed on February 1, 1999) found that the study drug was stored in an unlocked cabinet.

5. You failed to maintain adequate drug accountability records [21 CFR 312.62(a)].

Drug accountability records for protocols [] appear to have been created retrospectively, as the dates of drug dispensing were not in chronological order. You admitted in your written response that there was "lack of chronological sequence for drug dispensing" for [] and []. For example, the date of dispense for subject 040- on 2/2/01, appeared after 2/14/01, for subject 0830; the date of dispense for subject 0814 on 5/2/01, appeared after 5/4/01, for subjects 0819 and 0833, according to the shipment accountability forms for protocol []. In addition, Dr. [] dictated a note to the file stating that "the number of bottles dispensed on visit dates as recorded in the source documents may not reflect the number of bottles recorded on the Investigational Drug Dispensing Record (IDDR)." In the IDDR of protocol [] Dr. [] recorded the bottle dispensed on 9/23/99, to subject 0843 was destroyed on 2/25/00; however the subject had reported that the same bottle was lost on 10/27/99. You admitted that the IDDR was signed and witnessed in error.

6. You failed to maintain adequate and accurate records [21 CFR 312.62(b)].

- a. The available progress notes for subjects 0807, 0810 and 0819 in protocol [] were inadequate and were not dictated contemporaneously. For example,
- 1) Your progress note for subject 0807 dated 10/21/99, stated that this subject presented for visit 1 on 10/21/99. You dictated in the same note about your phone conversations and dose changes which occurred 7 to 13 days after the visit 1. You

noted that the subject called you 7 days later and you increased the dose to 6 grams twice nightly. You continued dictating the same note stating that the subject called you a second time 6 days later to increase the dose to 7.5 gram twice nightly.

- 2) Your progress note for subject 0810 dated 1/7/00, contained the subject's history of present illness from visit 2 on 8/10/99; drug dosing changes made at prior visits; and the subject's symptom summary for multiple visits prior to the time you dictated your note on 1/7/00.
- 3) You dated one progress note for subject 0819 as both 8/11/99, and 11/11/99. Your progress note started with the phrase that "the patient presents today for visit two on [] and that the subject complained of anterior tibial pain. In the same note, you stated that he returned on 11/11/99, and that his anterior tibial pain lasted until 9/15/99.

b. Source data were inadequate and inaccurate, as described below.

Protocol []

- 1) It cannot be determined from your subject screening checklist whether subjects 0831, 0835, 0837, 0838, 0843, 0845 and 0846 met the inclusion/exclusion criteria for protocol [] For each of these subjects, you provided contradictory information on qualifying criteria such as diagnosis of epilepsy, substance use disorder, abnormal liver function tests, etc., as you checked both yes and no columns. These documents also contained multiple unexplained and unsubstantiated changes of these inclusion criteria.
- 2) You reported in the CRF for visit 1 on 04/10/00, that subject 0837 had an undefined history of psychiatric illness, with a date of onset of 5/22/96; however, you provided no elaboration or documentation to support your claim. When the sponsor requested clarification, you reported that the subject had a Conversion Disorder, a diagnosis that was neither listed in the source document nor suggested by the medical history.

Protocol []

- 1) The CRF indicates that a screening serum pregnancy test on 7/27/00, for subject 0845 was negative. However, there is no confirmatory laboratory report to document this.
 - 2) The diary for subject 0845 contained two different sets of handwriting, indicating that this diary was not completed solely by the subject, as required by the protocol. However, you did not document the reasons for the discrepancy.
- c. You acknowledged in your written response to the 483, dated March 25, 2002, that you did not document phone contacts with subjects enrolled in protocol [] as required by the protocol.

- d. Source documents for the physical examination of study subjects in protocols [] and Protocol [] consisted of checklists only. The signature of the individual who examined the subjects was missing. There is no documentation to indicate whether a licensed physician or otherwise qualified person performed the protocol-required physical/neurological examinations. Section 11.5 of protocol [] stated that physical examinations must be performed by an M.D. or D.O., although patients may be interviewed by a research nurse or the trained equivalent.
- e. Medical histories were inadequate in that the history forms for two subjects (0846 and 0870) in protocol [] were illegible.
- f. For protocols [] site staff signature logs and screen/enrollment logs were not maintained contemporaneously. These records were often created retrospectively, even after personnel had left your employment.

7. You failed to report adverse effects to the sponsor in accordance with 21 CFR 312.64(b).

You did not report the following adverse effects in the case report forms.

- a. The source document showed that subject 0831 (protocol []) fell against the bathtub and hit her head, shoulder and arm while she was sleepwalking. Only the sleepwalking was reported.
- b. The diary for subject 0549 (protocol []) showed that daytime sleepiness greatly increased during the study. This event was not reported.

8. You failed to obtain IRB approval [21 CFR 312.66].

Protocol []

You did not submit protocol amendments in a timely manner to your IRB for review and approval. Protocol amendment #4 dated November 17, 2000, which extended the duration of the study for an additional six months, was not submitted to the IRB for approval. Protocol amendment #5 dated August 9, 2001, which allowed for an extension of the study to a total of 54 months, was not submitted to the IRB until November 19, 2001.

9. You failed to promptly report all unanticipated problems involving risk to human subjects to the IRB [21 CFR 312.66].

Protocol []

- a. You submitted AE reports to the IRB for two subjects (0814, 0831) enrolled in this protocol several months after the events occurred. Subject 0814 was hospitalized on 8/28/00, for transient ischemic event manifested by left-sided weakness and paraesthesia. You did not report this serious adverse event to the IRB until 2/7/02. Subject 0831 had

abnormal laboratory values of creatinine 2.3 mg/dl (normal range 0.4-1.1) and BUN of 139 mg/dl (normal range 4-24) on 7/2/01. You discontinued the subject from the study on 7/28/01, based on this finding. However, you did not report this AE to the IRB until 2/7/02.

- b. There is no documentation that you notified your IRB that subject 0845 informed Dr. [] about her pregnancy on December 18, 2000, discontinued study drug on January 4, 2001, and re-enrolled in protocol [] on August 12, 2001, following delivery of her baby.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational drugs. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

On the basis of the above listed violations, the Center asserts that you have repeatedly or deliberately failed to comply with the cited regulations and that you have submitted false information to both the sponsor and the FDA. The Center proposes that you be disqualified as a clinical investigator. You may reply in writing or at an informal conference in my office to the above stated issues, including an explanation of why you should remain eligible to receive investigational products and not be disqualified as a clinical investigator. This procedure is provided for by regulation 21 CFR 312.70.

Within fifteen (15) days of receipt of this letter, write or call me at (301) 594-0020 to arrange a conference time or to indicate your intent to respond in writing. Your written response must be forwarded within thirty (30) days of receipt of this letter. Your reply should be sent to:

Joanne L. Rhoads, M.D., M.P.H.
Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room #103
Rockville, Maryland 20855

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above listed violations. You should bring all pertinent documents with you, and a representative of your choosing may accompany you. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request.

At any time during this administrative process, you may enter into a consent agreement with the Center regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and the Center.

The Center will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR 16 (enclosed) and 21 CFR 312.70. Before such a hearing, FDA will provide you notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer free from bias or prejudice and who has not participated in this matter will conduct the hearing. Such a hearing will determine whether or not you will remain entitled to receive investigational products. You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

Sincerely yours,

Joanne L Rhoads, M.D.

Joanne L. Rhoads, M.D., M.P.H.

Director

Division of Scientific Investigations, HFD-45

Office of Medical Policy

Center for Drug Evaluation and Research

Enclosures:

21 CFR 312.70

21 CFR 16

Consent agreement

cc:

[] M.D.

Chairman

[] Hospital IRB

[]
Nashville, Tennessee []

Dr. [] Chairman

[] IRB

[]
[]
Nashville, Tennessee []