ORPHAN MEDICAL

May 3, 2001

Advisors and Consultants Staff
Center for Drug Evaluation and Research, ORM
Food and Drug Administration
HFD-21, Room 1093
5630 Fishers Lane
Rockville, MD 20852
Peripheral and Central Nervous System Drugs Advisory Committee,
c/o Dr. Sandra Titus; 301-827-7001

Subject: **Xyrem® (sodium oxybate) oral solution, NDA #21-196**
USER FEE NUMBER 3,814, ORPHAN DESIGNATION NUMBER 94-858

Peripheral and Central Nervous System Drugs Advisory Committee
Briefing Booklet for June 6, 2001 Presentation

Dear Advisory Committee Member:

This briefing booklet presents data for the use of Xyrem for treatment in narcolepsy, a seriously debilitating disease. The disease is lifelong after onset, which usually occurs in the second and third decade of life. Historically, diagnosis takes an average of ten years due to low physician awareness. These factors and disease symptomatology negatively affect patients' education, employment potential and interpersonal relationships for the rest of their lives. Current treatments are unsatisfactory, and although approved therapies for daytime sleepiness exist, no therapies are approved for the auxiliary REM-related symptoms of cataplexy, hypnagogic hallucinations, and sleep paralysis. For these reasons Xyrem represents an important new therapeutic advance to meet an unmet medical need.

Narcolepsy affects an estimated 125,000 individuals in the United States, an incidence that qualifies for orphan drug designation. Excessive daytime sleepiness is diagnostic of this disease, while the REM-related symptoms affect 60-90% of patients. About 25,000 individuals have cataplexy of severity requiring pharmacologic intervention.

Limited patient availability has influenced the size of the database. Xyrem safety, efficacy, pharmacokinetics, abuse pharmacology, scheduling and risk management are summarized in this booklet from over 250 volumes of electronic and paper information which has been submitted to FDA for review.

This NDA was designated a priority by the FDA shortly after submission in recognition of the fact that narcolepsy is serious and debilitating with inadequate therapeutic options, particularly for cataplexy. The compelling medical need of narcoleptic patients for additional therapeutic options is summarized in section 2.

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The premise for approval for efficacy is based upon four double-blind controlled clinical trials, two of which were sponsored by the company and two of which were conducted by academics, one in the US and one in the Netherlands. Efficacy is summarized in section 3 of this booklet.

The company has collected data from over 400 patients during the course of its two INDs, including a treatment IND approved by FDA in 1998 (section 4). In addition, an investigator in this country has been treating a small group of patients (N=143) for up to 18 years under his IND. The company has collected information from his database that reflects over 900 patient years of clinical safety data. Information from such a database is not usually available for a new chemical entity. Questions related to this database led to the cancellation of the initial advisory committee review scheduled for March 15th. The company has now addressed these questions and our response is under review by FDA. Overall the safety data set, while not large (604 patients and subjects), supports the safe use of Xyrem for the proposed indication.

The pharmacokinetics and abuse pharmacology are included for completeness in sections 5 and 6 respectively. Also included are sections dealing with scheduling and risk management.

Public health issues related to GHB have been well recognized for over 10 years. FDA took action to remove GHB from the market in 1990 due to public health risks of abuse and its illegal promotion as a 'dietary supplement'. FDA subsequently approached Orphan Medical to develop this compound in narcolepsy in 1994. FDA again took additional action when analogues began to surface over the last 5 years. The scheduling of Xyrem was completed in 2000 following extensive public debate in Congress with advice from FDA, DEA and other stakeholders. A federal law was enacted in 2000 to create a bifurcated schedule for GHB with all illicit use falling under schedule 1 and medical use placed into schedule 3. This law, along with the 2000 World Health Organization expert working committee recommendation for schedule 4, and the HHS recommendation to Congress is included in section 7. Regrettably, these laws do not adequately address promotion of precursor chemicals as abuse alternatives to GHB.

The advisory committee has also been asked to review and discuss the risk management of Xyrem. Risk management refers to minimization of public health issues associated with a pharmaceutical product. There is no evidence that Xyrem has been diverted or used for any purpose but to evaluate its safety and efficacy in treating narcolepsy. We believe that the precautions included in the Company's post-marketing program will constrain in every way possible the risks associated with this medicine while allowing its use by patients to meet their medical needs. These precautions include mechanisms to educate physicians and patients about the proper use of Xyrem, the unique implications of the bifurcated schedule, as well as closed-loop prescription and distribution systems to restrict the opportunity for diversion or misuse. Included with this package of information from Orphan Medical is a short 8-minute video on the prescription process, along with patient and physician education materials (the two binders). The risk of diversion and abuse of Xyrem is further reduced when these post-

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marketing processes to which the Company has committed are combined with the scheduling restrictions recommended by FDA and imposed by Public Law 106-172. It should be noted that narcolepsy patients and their physicians are already very familiar with the responsible use of controlled substances since they typically manage symptoms with schedule 2 amphetamine related medications and other medications in schedule 4.

It is an unfortunate fact that illicit GHB substances, not Xyrem, represent a risk to the public health. This risk will neither be increased by approval of Xyrem, nor decreased by denial of approval due to the easy availability of analogues of GHB. While Orphan Medical has no legal responsibility for the illicit use of GHB or its precursor chemicals, we have made a moral and practical commitment to assist the FDA, DEA and other law enforcement and abuse specialists in their efforts to minimize the public health risk of illicit GHB substances.

Sodium oxybate, or gamma hydroxybutyrate, is defined as a new chemical entity since it has never been approved for human use in the United States. Products containing oxybate have been approved in Europe, as an anesthetic since the 1960s, and in Italy for use in treatment of alcoholism since 1994. We believe the data presented herein establish the medical need, efficacy and safety of Xyrem, and provide the basis for our request for approval of the following proposed indication:

> *Xyrem® (sodium oxybate) oral solution is indicated to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy.*

Should you have any questions not addressed in this briefing booklet, please let us know through Dr. Sandra Titus, the Committee's Executive Secretary.

Sincerely yours,

Dayton T. Reardan, Ph.D., RAC
Vice President of Regulatory Affairs
Phone: (952) 513-6969
FAX: (952) 541-9209
E-mail: DReardan@Orphan.com

cc: Russell Katz MD for NDA #21-196

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Xyrem® (sodium oxybate) oral solution

NDA #21-196

Briefing Booklet for the Peripheral and Central Nervous System Drugs Advisory Committee Meeting

June 6, 2001

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LIST OF ABBREVIATIONS

λ_z	elimination rate constant
5-HT	serotonin
5HIAA	5-hydoxyindolacetic acid
6-OHDA	6-hydroxydopamine
^{14}C	carbon-14
ACh	acetylcholine
NDA	New Drug Application
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AHI	Apnea Hypopnea Index
Alk phos	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ASDA	American Sleep Disorders Association
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{ext}	area under the curve from the time of the last quantified concentration to time infinity
AUC_{inf}	area under the curve from time zero to time infinity
AUC_{last}	area under the curve from time zero to the time of the last quantified concentration
AUC_{SS}	area under the curve at steady-state
A-V	atrioventricular
BDS	bulk drug substance
bpm	beats per minute
BUN	blood urea nitrogen
C	Centigrade/Celsius
C of A	Certificate of Analysis
CAS	Chemical Abstract Services
CBF	cerebral blood flow
CCA	complete cataplexy attacks
CFR	Code of Federal Regulations
CGI-c	Clinical Global Impressions of Change
CGI-s	Clinical Global Impressions of Severity
CHA	cyclohexyladenosine
CL/F	oral plasma clearance divided by absolute bioavailability
Cm	centimeter
C_{max}	observed maximum plasma concentration
CMR_{O2}	cerebral metabolic rate for oxygen
CMR_{glc}	cerebral metabolic rate for glucose
CNS	central nervous system
COSTART	coding symbols for a thesaurus of adverse reactions terms
CRA	Clinical Research Associate
CRF	case report form

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CRO	contract research organization
CSF	cerebrospinal fluid
CV	coefficient of variation
CYP2C	cytochrome P450 2C
CYP2C9	cytochrome P450 2C9
CYP2D6	cytochrome P450 2D6
CYP3A	cytochrome P450 3A
CYP3A4	cytochrome P450 3A4
DAGO	(D-Ala^2, *N*-Me-Phe^4, glycinol^5)-enkephalin
DAWN	Drug Abuse Warning Network
DDMAC	division of drug marketing, advertising and communications
DHA	dihydroalprenalol
DOPAC	dihydroxyphenylacetic acid
DP	drug product
DS	drug substance
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG	electrocardiogram
ECoG	electrocorticogram
EDS	excessive daytime sleepiness
EEG	electroencephalogram
EMG	electromyogram
ESS	Epworth Sleepiness Scale
°F	degrees Fahrenheit
F	absolute bioavailability
FDA	Food and Drug Administration
FDP	fructose 1,6 diphosphate
FFTs	first fourier transforms
g, G	gram
G6P	glucose-6-phosphate
g/d	grams per day
GABA	gamma aminobutyric acid
GABA-T	gamma aminobutyric acid transaminase
GBL	gamma butyrolactone
GCP	Good Clinical Practice
GLM	general linear model
GHB	gamma hydroxybutyrate
GMP	Good Manufacturing Practice
GTI	Global Therapeutic Impression of Change
HCT	hematocrit
HGB	hemoglobin
HH	hypnagogic hallucinations
HPLC	high pressure liquid chromatography
hr	hour
HVA	homovanillic acid
HZ	Hertz
ICH	International Conference on Harmonization
ICV	intracerebraventricular

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ID	identification
IG	intragastric
IND	investigation new drug
IP	intraperitoneal
IR	infrared
IV, iv	intravenous
IRB	Institutional Review Board
k_a	apparent first-order absorption rate constant
kg	kilogram
KF	Karl Fisher
L	liter
LD50	median lethal dose
LDH	lactate dehydrogenase
ln	natural logarithm
LOQ	limit of quantification
MAO	monoamine oxidase
MABP	mean arterial blood pressure
MAX	maximum
MES	maximal electroshock
mg	milligram
MIN	minimum
MK-801	(+)-5-methyl-10,11-dihydro-5H-dibenzo [a,d] cyclohepten-5,10-imine maleate; dizocilpine
mL, ml	milliliter
mm	millimeter
mm Hg	millimeter of mercury
MSE	mean square error
MSLT	Multiple Sleep Latency Test
MWT	maintenance of wakefulness test
n	number
NA	not available
NADDI	national association of drug diversion investigators
NaGHB	sodium gamma–hydroxybutyric acid (sodium oxybate)
NASOA	National Association of State Controlled Substance Authorities
NCS	not clinically significant
NCS-356	γ-*p*-chlorophenyl-*trans*-4-hydroxycrotonate
NCS-382	6,7,8,9-tetrahydro-5-[*H*]benzocycloheptene-5-ol-4-ylidene acetic acid
ND	not determined
NDTI	national disease and therapeutic index
NIDA	National Institute on Drug Abuse
NMDA	N-methyl-D-aspartate
NOAEL	no adverse-effect level
NREM	nonrapid eye movement
NTP	National Toxicology Program
OMI	Orphan Medical, Inc
PBO	placebo
PL	public law

PO	*per os*, oral
PCA	partial cataplexy attacks
PCP	phencyclidine
PSG	polysomnography
PTH	parathyroid hormone
QA	quality assurance
QC	quality control
QNB	quinuclinidinyl benzylate
RBC	red blood cell
REM	rapid eye movement
SAS	Statistical Analysis System
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SEM	standard error of the mean
SGOT	serum glutamic-oxalacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOREMP	sleep onset REM peroids
SqRt	square root
SSA	succinic semialdehyde
SSR	succinic semialdehyde reductase
SSRI	selective serotonin re-uptake inhibitor
SWS	slow wave sleep
SXB	sodium oxybate
$T_{1/2}$	half-life of terminal phase
TBPS	*t*-butylbicyclophosphorothionate
TCA	tricyclic antidepressant
TST	total sleep time
T_{max}	time to observed maximum plasma concentration from dosing
TNCA	total number of cataplexy attacks
V_z/F	apparent volume of distribution divided by oral bioavailability
WBC	white blood cell

DEFINITION OF TERMS

Safety for the clinical trials represented in the original NDA, and all subsequent submissions to date, is based on the following criteria set down during the first of the clinical trials represented:

Adverse Experience:
An adverse experience is any pathologic, noxious, or unintended change in anatomical, metabolic or physiologic function as dictated by physical signs, symptoms, and/or laboratory changes occurring in any phase of a clinical trial, whether or not considered related to study medication and whether associated with study medication or placebo. This includes exacerbation of a pre-existing condition or the significant failure of pharmacologic action.

Adverse experience shall be considered synonymous with the term adverse event.

Severity:
The severity of adverse experiences should be rated as mild, moderate, or severe in accordance with the following guidelines:

1. Mild:
   The adverse experience does not interfere with the patient's normal functioning, although it may be an annoyance.

2. Moderate:
   The adverse experience interferes to some extent with normal functions, but it is not hazardous to health; the event may be uncomfortable or cause embarrassment; the event may require discontinuation of drug as well as other counteractive measures.

3. Severe:
   The adverse experience interferes substantially with normal functions and presents a definite hazard to the patient's health. These experiences virtually always require discontinuation of drug and may require counteractive measures.

Causality:
The relationship between the administration of trial medication and an adverse experience is a judgment based the medical information available at the time of the assessment. The information that is usually considered in making this judgment includes but is not limited to the following.

a) The temporal sequence of the adverse experience with the administration of test medication.
b) The known characteristics of the patient/subjects' clinical state, environment, or toxic factors, or other therapy administered to the patient.

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c) The disappearance of the adverse experience on cessation of test medication or reduction in dose (dechallenge).
d) The reappearance of the adverse experience on resuming treatment with test medication (rechallenge).
e) The known response pattern of the test medication.

The relationship between trial medication and adverse experiences will be rated using the following guidelines:

1. Definitely Related:
   This category is usually chosen when the connection between administration of test medication and the adverse experience is certain, based on dechallenge and rechallenge or obviousness (e.g., pain at the site of injection).

2. Probably Related:
   This category applies when the connection between administration of test medication and the adverse experience is considered to be over 50% likely.

3. Possibly Related:
   This category applies when the connection between administration of test medication and the adverse experience is considered to be less than 50% likely.

4. Not Related:
   This category applies to those adverse experiences which are clearly due to non-trial medication causes (e.g., disease, environment).

5. Unknown:
   This category applies to those adverse experiences which after careful consideration of all other categories can not be considered definitely related, probably related, possibly related, or not related usually because of inadequate information.

Frequency:
The frequency of an event was initially rated as either continuous or intermittent. This criteria was later broadened to include the term isolated for events which resolved immediately.

Serious:
A serious adverse experience is defined as an adverse experience wherein the outcome is death, life-threatening, temporarily or permanently disabling, or which results in or prolongs inpatient hospitalization. In addition, an overdose, congenital anomaly, or the occurrence of cancer are considered to be serious adverse experiences.

SECTION 2
MEDICAL NEED

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2.0 MEDICAL NEED

2.1 Disease and Pathogenesis

Narcolepsy is among the leading causes of excessive daytime sleepiness (EDS) and is the most common neurological cause (Bassetti 1996). Narcolepsy is now recognized as a prevalent but underdiagnosed neurological disorder (Hubin 1994) that has a socio-economic impact that may be as high as that of epilepsy. The first consensus definition of narcolepsy was produced by the First International Symposium on Narcolepsy, July 1975, in France:

> "A syndrome of unknown origin that is characterized by abnormal sleep tendencies, including excessive daytime sleepiness and often disturbed nocturnal sleep, and pathological manifestations of REM sleep. The REM sleep abnormalities include sleep-onset REM periods and the disassociated REM sleep inhibitory processes, cataplexy and sleep paralysis. EDS and cataplexy and, less often, sleep paralysis and hypnagogic hallucinations are the major symptoms of the disease." (Gulleminault 1976).

Characterized by this descriptive definition, narcolepsy is not just excessive sleep, but rather an inability to maintain either wakefulness or consolidated sleep. Patients are typically excessively sleepy during daytime and insomniacs at night. In addition, narcoleptic patients experience abnormal episodes of REM sleep, such as cataplexy and sleep paralysis representing dissociated manifestations of REM sleep atonia or dream-like hallucinations occurring either in active wake, at sleep onset, or while waking from sleep (Nishino 1997).

Its classic form - narcolepsy with cataplexy - is a distinct neurologic disease with characteristic clinical and paraclinical findings. The definition of the variants of narcolepsy, however, remain a matter of controversy. The International Classification Of Sleep Disorders has defined narcolepsy as:

> "A disorder of unknown etiology, which is characterized by excessive sleepiness that typically is associated with cataplexy and other REM sleep phenomena such as sleep paralysis and hypnagogic hallucinations."

This is the definition adopted by the American Sleep Disorders Association, International Classification of Sleep Disorders, Diagnostic and Coding Manual, Diagnostic Classification Steering Committee, Thorpy MJ (Chairman) 1990.

Thus it remains a purely descriptive disease state in the absence of a defining diagnostic test or investigative measurement and can be a diagnostic challenge in the absence of cataplexy as both EDS and REM phenomena can occur in diseases other than narcolepsy. New information is now emerging as to cause, with the relationship of animal data implicating the hypocretin II receptors to the narcolepsy/cataplexy syndrome in dogs (Lin 1999) and the deficiency of the hypocretin peptide transmitters in a knockout mouse model lacking the hypocretin gene producing abnormalities of sleep control

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resembling aspects of narcolepsy (Chemelli 1999). Together these two studies implicate dysfunction of the hypocretin system, or closely related systems, to the pathophysiology of narcolepsy.

Anatomical studies determined that the sources of the hypocretin producing cells were restricted to the hypothalamus and concentrated in the perifornical nucleus and in the dorsal, lateral and posterior hypothalamus. This hypothalamic restriction applies only to the cell bodies and they have widespread neuronal projections to sites centrally related to sleep and arousal. In addition to dense hypothalamic projections, the limbic system, thalamus, subthalamic nucleus, substantia nigra, raphe, locus coeruleus, ventral tegmental area, medullary reticular formation, nucleus of the solitary tract, and other brainstem regions are innervated by these cells (Peyron 1998).

Further pathogenic support for the relationship of the hypocretins and narcolepsy has come from recent discovery of low levels of hypocretin II in the CSF of human narcoleptics (Mignot 2000) and the even more recent discovery of the significant reduction in the number of hypocretin neurons in the brains of narcoleptics (Siegel 2000, Mignot 2000).

Mutations of the hypocretic system may be responsible for some proportion of human narcolepsy cases. However, it is unlikely that most human narcoleptics have a mutation as in the canine model. Most narcoleptics have no narcoleptic relatives, ruling out the autosomal recessive mode of inheritance seen in the dogs. The typical onset of symptoms in the second decade of life or later suggests that damage has occurred to a normally functioning sleep and motor control system. Approximately 75% of the pairs of identical twins examined are discordant for the disease (Partinen 1994) suggesting that environmental factors are critical in the triggering of the disease.

More than 85% of all narcoleptic patients with cataplexy share a specific HLA allele, HLADQB1, 0602, compared with 12% to 38% of the general population (Mignot 1998). Because of the role of HLA gene products in immune regulation, in that most HLA-linked diseases are autoimmune in nature, and because of the possibility of the involvement of environmental triggers, it is speculated that narcolepsy might be an autoimmune disorder. Immune-mediated reduction in the numbers of hypocretin neurons is an exciting new hypothesis requiring research. It is certainly an attractive hypothesis implicating irreversible damage to the hypocretin neurones or to axon terminals as a plausible cause for the disorder. However, there may well be other factors "downstream" of the hypocretin system.

Even though these exciting new discoveries shed some light on the pathogenesis of the disease, treatments remain symptomatic and sodium oxybate provides new potential to favorably modify the debilitating symptom profile that defines narcolepsy.

2.2 History

Although the clinical condition was described as early as 1672 by Willis, by Schindler in 1829, Gélineau gave the first precise description of the disease and coined the term

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"narcolepsy" from the Greek meaning "seized by somnolence" in 1880. The term "cataplexy" was proposed in 1902 by Löwenfeld, and confirmed as the clinical term for the loss of muscle tone by Henneberg in 1916.

Hypnagogic hallucinations and sleep paralysis were first linked to narcolepsy in the 1920's (Bassetti 1996).

After World War II, Yoss and Daly (1957) introduced the notion of the narcolepsy "tetrad" – excessive daytime sleepiness, cataplexy, hypnagogic hallucinations and sleep paralysis. In its typical form, narcolepsy patients also experience disturbed nocturnal sleep (narcolepsy "pentad") (Nishino 1997).

Shortly after the discovery of REM sleep (Aserinsky and Kleitman 1953) the discovery that narcoleptic patients often begin their night sleep with a period of REM sleep (Vogel 1960) suggested that narcolepsy might involve abnormal REM sleep. In the same year, Rectschaffen (1963) and Takahashi (1963) independently confirmed that narcoleptic patients often have sleep onset REM periods (SOREMP's), and suggested that cataplexy, sleep paralysis and hypnagogic hallucinations were abnormal manifestations of dissociated REM sleep. This led to the generally accepted model that sleep disturbances seen in narcolepsy are divided into the two distinct categories of disturbance in the sleep/wake distribution (EDS/sleep attacks and fragmented nighttime sleep) and abnormal REM sleep related symptoms (cataplexy, hypnagogic hallucinations and sleep paralysis) (Roth 1969, Takahashi 1971). The fact that EDS and abnormal REM sleep are most often treated to date with distinct medications (stimulants for EDS and antidepressants for REM-related phenomena) also adds credence to this concept of a duality in the symptoms of narcolepsy).

2.3 Epidemiology

Narcolepsy is now recognized as a relatively prevalent but underdiagnosed neurological disorder (Hublin 1994). Following Daniel's classic review in 1934 of 147 patients with narcolepsy seen at the Mayo Clinic in Minnesota, the disease was no longer considered rare. In the same clinic, 241 cases were observed over a five year period of 1950-1954 (Yoss and Daly 1957). The exact prevalence remains unknown, with a reported variation from 0.0002% to 0.50% in different populations (Hublin 1994). The estimated prevalence for narcolepsy with cataplexy is 0.03% to 0.07% of the general adult population in whites (Dement 1973, Hublin 1994, Ohayon 1996).

Narcolepsy often remains undiagnosed or misdiagnosed for several years. In part this may occur because physicians may not include narcolepsy in the differential diagnosis of other diseases with complaints or fatigue, tiredness, problems with concentration, attention, memory and performance, and other illnesses (e.g., seizures, hallucinatory states).

Narcolepsy occurs in both sexes equally, and in all races with a lower prevalence suggested in Israeli-Jews (Wilner 1988). Rigorous clinical and paraclinical testing shows that the percentage of "true" familial narcolepsy does not exceed 4% to 7% (Goode

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1962, Billiard 1994, Parkes 1985). The risk of children of narcoleptics developing the disease is about 1% (Bassetti 1996).

2.4 Clinical Picture

2.4.1 EXCESSIVE DAYTIME SLEEPINESS (EDS)

By definition, narcolepsy can be diagnosed only in the presence of EDS, although this symptom rarely appears after the onset of other elements of the tetrad. Sleepiness is usually the most disabling symptom. It most typically mimics the feeling of sleep deprivation, but may also manifest itself as chronic tiredness or fatigue (Nishino 1997). Clinically, narcoleptic and physiologic sleepiness (i.e. after sleep deprivation) are similar in character but differ in temporal pattern and severity. In both, transition from wake to sleep is usually gradual, with increased sleep propensity in the afternoons, in situations of boredom or limited physical activity, post-prandial, and in a warm environment. Narcoleptic sleepiness, however, is usually constant, severe and only transiently and partially improved with sleep.

This continuous sleepiness fluctuates in severity and episodically becomes irresistible, with involuntary brief naps, or "sleep attacks" occurring during such unusual circumstances as talking, eating, standing, walking, driving in traffic, or even during intercourse. Honda and colleagues (1988) reported two or more sleep attacks per day in 68% of 170 patients studied. Naps are usually brief, refreshing, easily terminated by external stimuli and, in one third of cases, are associated with dream experiences (Roth 1980). The duration of the naps may be affected by situational rather than pathophysiologic differences.

Variations in the intensity of sleep attacks, the ability to resist sleep, and in the subjective awareness of sleepiness explain the differences in the phenotypical presentation of EDS. Up to 80% of patients experience fluctuations in vigilance lasting from seconds to hours, during which they can perform semipurposeful, complex acts with no recollection. The perception of the transition from wakefulness to sleep may be altered, and short, involuntary episodes of sleep or decreased vigilance (sometimes referred to as blackouts) may be experienced as paroxysmal loss of consciousness (Bassetti 1996).

2.4.2 CATAPLEXY

Cataplexy is defined as a sudden episode of muscle weakness triggered by emotions, most typically laughter, elation and joy but also anger, annoyance, embarrassment, grief, surprise, and even sexual intercourse. It is normally associated with normal consciousness, is bilateral, and lasts less than a few minutes.

Cataplexy is clinically an extremely variable symptom (Gelb 1994), and only certain muscle groups may be involved. Most often it is mild and occurs as a simple buckling of the knees, head dropping, sagging of the jaw or weakness of the arms. Slurred speech or mutism is also frequently associated. In other cases, it escalates to episodes of muscle paralysis and collapse that may last up to a few minutes. Most often the patient

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will have time to seek support or sit down. Long episodes of cataplexy occasionally blend into sleep and may be associated with hypnagogic hallucinations. Its duration exceeded twenty minutes in 2% of a series of 130 patients (Honda 1988). Rare episodes lasting longer than thirty minutes, termed status cataplecticus, can be precipitated by the abrupt discontinuation of antidepressant drugs (Hishikawa 1976) and can render the patient virtually helpless.

2.4.3 SLEEP PARALYSIS

Whereas EDS and cataplexy are cardinal symptoms of narcolepsy, sleep paralysis occurs frequently as an isolated phenomenon affecting 5% to 40% of the narcoleptic population (Dahlitz 1993). Sleep paralysis is best described as a brief inability to perform voluntary movements at the onset of sleep, or upon awakening during the night or in the morning. The patient is unable to perform even a small movement, and the episode may last a few minutes. Sleep paralysis is easily interrupted by noise or other external stimuli. It is present in 20% to 50% of narcoleptic subjects. Episodes are more common with stress, with irregular sleep or sleep deprivation, and frequency varies widely from a few life events to almost daily episodes.

2.4.4 HYPNAGOGIC HALLUCINATIONS

Abnormal visual (most often) or auditory perceptions that occur while falling asleep (hypnagogic) or upon waking up (hypnopompic) are observed frequently in narcoleptic subjects (15% to 66%), and in up to 50% of cases, they occur at least once weekly (Honda 1988). Hypnagogic hallucinations are the expression of a changing state of consciousness in which, as opposed to dreaming, elements of the normal awake mentation are still present, and they may involve one or more senses. Unlike psychotic hallucinations, subjects usually are aware of the unreal nature of the hallucination. The intensity and the accompanying fear and anxiety are sometimes the most distressing symptoms of narcolepsy.

2.4.5 OTHER SYMPTOMS

Disrupted nighttime sleep with frequent awakenings is reported by 60% to 80% of patients with narcolepsy (Billard 1985, Montplaisir 1978). Patients often complain of difficulties with concentration, visual disturbances, problems with memory and perceptual disturbances. Frequently associated problems are periodic leg movements, REM behavior disorder, and other parasomnias.

2.5 Evolution of Narcolepsy

Narcolepsy usually starts around adolescence, occasionally very abruptly, but most often insidiously. Its peak onset is in the second decade of life, with a smaller peak in the third decade. A few cases are recognized in a pediatric context, manifesting as early as five to six years of age (Challamel 1994). In most cases, however, the diagnosis of narcolepsy is made several years after the onset of the clinical condition.

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Sleepiness is usually the first symptom to appear, followed by cataplexy, hypnagogic hallucinations, and sleep paralysis. In approximately one-half of the cases, the onset of cataplexy is simultaneous with the appearance of daytime somnolence and within five years in approximately two-thirds of the cases (Honda 1988, Roth 1962). The mean time of the onset of sleep paralysis and hypnagogic hallucinations is also two to seven years later than that of sleepiness.

Sleepiness almost invariable persists over time, although a late decline in severity is not rare, and even short remissions are possible. Conversely, cataplexy, sleep paralysis and hypnagogic hallucinations may disappear spontaneously in 16% to 37% of patients (Billiard 1993).

2.6 Psychosocial Impact of Narcolepsy

Despite dynamic progress in the understanding of narcolepsy, the disease continues to cause the sufferer severe negative life effects. Before and after diagnosis, narcoleptics often experience unrelenting severe psychosocial stress, with differing stresses in each decade of life. Child and adolescent narcoleptics report embarrassment, academic decline and feelings of loss of self-worth related to the symptoms of their disease. Personality characteristics may be adopted that seek to avoid social situations that would precipitate cataplexy or draw attention to the patient's degree of somnolence. More than one-half of narcoleptics believed their symptoms caused poor performances at school (Broughton 1981). Teachers often misinterpret early symptoms and the accompanying irritability, frustration and mood swings as laziness, indifference, or even malingering. Hypnagogic hallucinations may lead individuals to question their own sanity and, at times, these occurrences are mistakenly diagnosed as psychotic episodes (Douglass 1991). Although no inherent memory disturbance has been associated with the disease, somnolence and lapses of concentration (possibly micro-sleeps) may explain the commonly reported problems with memory. Misdiagnosis may result in inappropriate treatment and underestimation of an individual's potential. Denial of the condition may further delay their seeking treatment.

Adult narcoleptics face major concerns, particularly in the workplace, and with secure interpersonal relationships. The effects of sleepiness and cataplexy have major effects on personal and public safety. Broughton (1981) examined the effects on driving. Narcoleptics reported marked increases in the following (percent narcoleptics compared to percent of controls):

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	Narcoleptics	Controls
Falling asleep while driving	66%	6.2%
Cataplexy while driving	29%	0%
Sleep paralysis while driving	11.5%	0%
Frequent near accidents	67%	0%
Motor vehicle accidents	37%	5.3%
Increased insurance rates	16%	1%
Suspended drivers' licenses	6.l%	3.9%

In the workplace, narcoleptics face not only danger of accidental injury but the reality of poor performance and job loss. In the 1981 Broughton survey narcoleptics reported the following occupational effects attributed to their symptoms.

	Narcoleptics	Controls
Reduced job performance	78%	9%
Fear of losing job	49%	0%
Decreased earnings	47%	1.2%
Actual job loss	21%	0%
Loss of promotion	3.8%	0%
Disability insurance	11%	0%

Accidental injury in narcoleptics also occurs in the home. Smoking accidents due to narcoleptic symptoms were found in 49% of patients, falls 37%, burns from hot objects 15%, cuts from sharp objects 13%, and "breaking things" 10% were reported by Cohen in 1992.

Interpersonal relations also suffer. Poor self-image and social withdrawal have been mentioned. Narcoleptics frequently feel that others view them as lazy or bored. Sleep attacks during conversations can alienate others.

Marital stress is a major problem and has been reported as high as 72% (Kales 1982). Besides interpersonal problems, financial problems resulting from job loss or accidents add external pressure on the marriage. Sexual dysfunction and loss of libido are commonly reported complaints.

A body of data supports the idea that a large number of narcoleptics also carry diagnosable psychiatric disorders, in most cases thought to result from the symptomatology of the disease and its life effects. In a study by Kales et al in 1982, more than 50% of narcoleptics had a diagnosable psychiatric disorder, all assigned as variants of depression and/or personality disorders.

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The psychosocial impacts of narcolepsy disease have been thoroughly detailed in a special journal issue edited by Goswani, Polack, Cohen, Thorpy, Kovey: Psychosocial Aspects of Narcolepsy, Loss Grief Care 1992; 5,1-203.

The culmination of the deleterious effects of narcolepsy upon work, education, occupational and household safety, recreation, personality and interpersonal relations were compared with those of epilepsy and the psychosocial impact of narcolepsy was found to be higher in all categories except driving (Broughton 1984). These data support the medical need for effective treatment.

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SECTION 3
EFFICACY

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3.0 EFFICACY

Overview of efficacy clinical trials: Four controlled and 3 uncontrolled clinical trials have been performed to evaluate the efficacy of Xyrem for the treatment of narcolepsy. These trials are summarized below:

Controlled Trials: 201 patients

- *OMC-GHB-2* – 136 patients
  Placebo, 3.0, 6.0, 9.0 g/d sodium oxybate
- *Scrima Trial* – 20 patients
  Placebo, 50 mg/kg (4.2 g/d) sodium oxybate
- *Lammers Trial* – 25 patients
  Placebo, 60 mg/kg (4.7 g/d) sodium oxybate
- *OMC-SXB-21* – 55 patients
  Placebo, 3.0, 4.5, 6.0, 7.5, and 9.0 g/d sodium oxybate

Uncontrolled Trials: 323 patients

- *OMC-GHB-3* – 117 patients
  3.0, 4.5, 6.0, 7.5, and 9.0 g/d sodium oxybate
- *OMC-SXB-6* – 185 patients
  3.0, 4.5, 6.0, 7.5, and 9.0 g/d sodium oxybate
- *OMC-SXB-20* – 21 patients
  4.5, 6.0, 7.5, and 9.0 g/d sodium oxybate

3.1 Controlled Studies

3.1.1 OMC-GHB-2

In initial discussions with the FDA in 1995, the Agency indicated that adequate prospective studies to ascertain the appropriate therapeutic dose range of sodium oxybate had not been conducted. This trial was designed to provide that information. The study was designed as a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial with three doses of sodium oxybate and placebo in narcoleptic patients meeting specific American Sleep Disorders Association (ASDA) criteria for narcolepsy. The objectives of the trial were to evaluate and compare the efficacy and safety of three doses (3g, 6g and 9g) of sodium oxybate and placebo in the treatment of the symptoms of narcolepsy. A rating of the change in the severity of the patient's narcolepsy symptoms as measured by the Clinical Global Impression of Change was provided by the investigator at the end of the four-week treatment period, compared to the rating of Clinical Global Impression of Severity of Disease at the end of the baseline period.

Patients who completed this study and continued to meet all other entry criteria except for the minimum number of cataplexy attacks, were eligible to enter a long-term, open label study (OMC-GHB-3) if they desired and if the physician responsible for their care concurred.

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3.1.1.1 Study Objectives

Primary Objective: To evaluate and compare the efficacy of three doses (3g, 6g, and 9g) of sodium oxybate and placebo in the treatment of the symptoms of narcolepsy.

Secondary Objective: To evaluate and compare the safety of sodium oxybate and placebo when used in a narcoleptic patient population.

3.1.1.2 Investigational Plan

The study was conducted at sixteen centers, and a total of 136 patients were enrolled. The study was divided into five periods as follows:

Table 3.1 Time Periods of OMC-GHB-2 Trial

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

Screening Period: Lasted one day to four weeks. For patients taking tricyclic antidepressants (TCAs) or other drugs used to treat cataplexy, these were gradually withdrawn. 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.

Washout Period: Lasted five to twenty-eight days. This period allowed time to eliminate any clinical effects of TCAs, for rebound cataplexy (cataplexy that with greater frequency and severity than usual) to abate, and to train patients on the use of the diary. The duration of this period was determined by considering the prior anticataplectic medication, and was five times the half-life of that medication, with a minimum of five days for diary training and a maximum of twenty-eight days.

Baseline Period: Lasted two to three weeks. This period was an opportunity to assess the patients' attacks of cataplexy and to establish a stable number of attacks. Eligibility for admission into the double-blind treatment period required patients to report an average of three or more complete and/or partial cataplexy attacks per week, during the last two weeks of the baseline period.

Double-Blind Treatment Period: Lasted four weeks. Eligible patients were randomly assigned to receive each night 3g, 6g, or 9g GHB or placebo in two divided doses. Patients returned approximately every two weeks during this period for assessment of safety and efficacy.

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Follow-up Period: A visit for final assessment three to five days after study medication was discontinued.

Entry criteria included adult patients with a diagnosis of narcolepsy, a history of excessive daytime sleepiness and an average of three or more cataplexy attacks per week during the baseline period. Patients with a diagnosis of sleep apnea, women of child bearing potential (unless using an accepted form of birth control), patients taking hypnotics, tranquilizers, or sedating antihistamines, and patients with a history of seizures or head trauma were excluded from the study.

Approximately 104 patients (26 in each of the four treatment groups) were planned to be enrolled in this study. One hundred and thirty-six patients were actually enrolled and randomly assigned to receive four weeks of treatment with study medication. Additional patients were enrolled to ensure that a sufficient number of evaluable patients completed the study. Medication was packaged in foil pouches and mixed with water. One dose was taken at bedtime, and the second dose was taken 2.5 to 4 hours later. A third party dispenser was employed at each site so that the investigator and the study coordinator did not handle the medication and the integrity of the blind was maintained.

The primary efficacy variable was the change from baseline in the total number of cataplexy attacks (complete + partial) recorded by patients on their diary (the change was calculated from baseline): last two weeks before study medication was started in a patient; to endpoint (the last two weeks a patient was on study medication). Other efficacy variables included the number of complete cataplexy attacks, the number of partial cataplexy attacks, changes in daytime sleepiness, changes in the number and duration of inadvertent naps/sleep attacks, changes in the number of awakenings during the night, change in the total amount of sleep, changes in the incidence of hypnagogic hallucinations, changes in the incidence of sleep paralysis, and the clinical global impressions of change.

3.1.1.3 Discussion of Study Design

Patients naïve to GHB were selected. Patients with a history of excessive daytime sleepiness, cataplexy, a current diagnosis of narcolepsy for at least six months according to Criteria A of the American Sleep Disorders Association were included. Patients were excluded if they had a diagnosis of sleep apnea syndrome or any other cause of daytime sleepiness. Patients were excluded if they were taking hypnotics, tranquilizers, antihistamines (except for non-sedating antihistamines), or clonidine at the start of the baseline period. Patients taking tricyclic antidepressants or other medication to treat cataplexy were withdrawn from those treatments gradually. The list of tricyclic antidepressants and other anticataplexy medication included: protriptyline, imipramine, clomipramine, desipramine, viloxazine, fluoxetine, paroxetine, sertraline or other serotonin reuptake inhibitors or other tricyclic or heterocyclic antidepressants. Patients taking anticonvulsants were not eligible to participate in the study. Patients were allowed to continue taking stimulant medication to include amphetamine, methamphetamine, methylphenidate, or pemoline for the treatment of daytime

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sleepiness. Patients were advised not to consume alcoholic beverages during the entire course of the trial and also to use caution in the use of any opioid analgesics or skeletal muscle relaxants. Patients were otherwise free of medication for narcolepsy during the trial. The screening, washout, and baseline periods were variable lengths of time, determined by the investigator within defined limits.

A screening period of one day to four weeks was added to the design for safety purposes. The screening period enabled investigators to gradually withdraw patients from tricyclic antidepressants or other anticataplexy medication. These medications are commonly associated with rebound cataplexy on withdrawal. The rebound cataplexy was perceived to be of sufficient magnitude to constitute a safety concern. The importance of having a companion or other support system available during the screening, washout and baseline periods was stressed to each patient. Patients were instructed to begin keeping daily diaries at the screening period in order to train them on its use prior to the baseline period.

A washout period of five to twenty-eight days was added to the design to eliminate any clinical effects of tricyclic antidepressant or other anticataplexy medication prior to baseline. The washout period started when the last dose of a tricyclic antidepressant or other anticataplexy medication was taken by the patient. The length of the washout period was determined by the investigator by considering the pharmacokinetic and pharmacodynamic profile of the tricyclic antidepressant or other anticataplexy medication being used by the patient during the screening. A minimum of five days of washout was required for patients not taking anticataplexy mediation for the purpose of insuring adequate training on the patient diary. The investigators were required to employ a washout period equivalent to a minimum of five times the half-life of the anticataplexy medication in use (for a maximum of twenty days). The investigators were provided with a list of the drugs typically used to treat cataplexy along with their half-lives and a suggested time for washout for each.

A baseline period of two to three weeks enabled the investigator to assess the patient's cataplexy incidence in the absence of anticataplectic medications, and daily dairy recording habits. The patients qualified for admission to the treatment phase by reporting an average $\geq$ three cataplexy attacks per week during the last two weeks of the baseline period.

The treatment period was four weeks in length with a clinic visit at two weeks. The treatment period was confined to four weeks because it was not ethically sound to continue a symptomatic patient randomized to placebo for a longer period. The investigators contacted each patient on the morning following the first dose of test medication to assess the patient's tolerance of the test medicine. Thereafter patients were contacted at least three times weekly for assessments of compliance, diary completion, and adverse events.

After four weeks of treatment the patients were withdrawn from test medication. The appearance of any rebound cataplexy and other adverse events were noted at a follow-up visit scheduled three to five days following the end of treatment visit.

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3.1.1.4 Assignment of Patients to Treatment Groups

At Visit 1, all patients were assigned a unique, four-digit, patient identification number in the order they were seen at the clinic. The first two digits identified the site number and the last two digits identified the patient number assigned sequentially starting with 01. At Visit 4, patients who met the entry criteria were sequentially assigned a unique three-digit randomization number in the order they entered treatment. The patients were dispensed medication labeled with the correct assigned randomization.

3.1.1.5 Selection and Timing of Dose

Individual patient treatment, including the dose of sodium oxybate, was determined by random allocation. No provisions were made in the protocol to permit modification of the dosage regimen. Each patient self-administered two doses of their assigned study medication each day. The first dose was taken at bedtime, and the second 2.5 to four hours later. Patients were instructed to use an alarm to insure that they awakened to take the second dose no more than four hours after the first.

3.1.1.6 Concomitant Medications

Patients were not permitted to take any of the following medications at any time during the study: hypnotics, tranquilizers, antihistamines (except nonsedating antihistamines), clonidine, tricyclic antidepressants, serotonin reuptake inhibitors, monoamine oxidase (MAO) inhibitors, tetracyclic antidepressants, or anticonvulsants. Patients were also not permitted to use alcohol during the study and were cautioned on the use of opioid analgesics and skeletal-muscle relaxants. Women of childbearing potential were permitted to use oral contraceptives. Periodic use of over-the-counter and prescription medicines for treatment of colds, flu, allergies, headaches, etc. required careful review by the investigator prior to use.

3.1.1.7 Primary Efficacy Variable

The primary efficacy variable for this study as defined in the protocol was the total number of cataplexy attacks which is the sum of complete and partial cataplexy attacks that occurred. The median of the total number of cataplexy attacks that occurred in each treatment group during the last two weeks of the baseline period was compared with the median number of events that occurred during the last two weeks of the treatment period (endpoint). Other efficacy measures such as daytime sleepiness and improvement in inadvertent naps were measured along with reduction in the number of episodes of cataplexy.

3.1.1.8 Statistical and Analytical Plans

As described in the protocol, the efficacy analyses were done on the intent-to-treat population. The planned analyses called for an analysis of variance on the change from baseline to endpoint induding 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 (change in total number of cataplexy attacks) using the baseline value as covariate.

Prior to the completion of the study and database lock, an analysis plan was written and approved that detailed performing a log transformation, if the assumptions for ANCOVA were not satisfied. It was anticipated that for many, if not all, of the efficacy variables, the log transformation would result in a more normal distribution conforming to the requirements of the ANCOVA.

At the time of analysis, each of the primary and secondary efficacy variables was assessed for normality and whether a log transformation would improve the distribution. The reassessment was based on using the Wilk-Shapiro test for normality on the residuals from the fitted model and a plot of the residuals against the predicted response, also from the fitted model. If the untransformed data indicated a non-normal distribution, based on the Wilk-Shapiro test, and if the transformed data demonstrated improvement (tending toward a more normal distribution) through both the Wilk-Shapiro test and the plot of the residuals against the predicted, the log transformation was used. Those measures that were analyzed using the log transformation included the following:

- Total number of cataplexy attacks
- Partial cataplexy attacks
- Complete cataplexy attacks
- Duration of inadvertent naps/sleep attacks/day
- Sleep paralysis (episodes/day)
- Hypnagogic hallucinations
- Number of awakenings

For each of these measures, because a 0 was possible, the value 1 was added prior to the log transformation. As a result, the variable analyzed was log (endpoint + 1) – log (baseline + 1). The ANCOVA model used to assess overall treatment group comparisons included treatment, site, and log (baseline + 1). The interaction of treatment and site and treatment with log (baseline + 1) were included in the model and then removed when found to be not statistically significant. Comparisons of GHB dose to placebo were performed using least-squares means with Dunnett's adjustment. The significance of the median change from baseline for each treatment group was assessed using a paired t-test.

Several measures did show a normal distribution without a log transformation. They included:

- Epworth Sleepiness Scale
- Total amount of sleep/night
- Number of inadvertent naps/day

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For these variables, the analysis procedures were consistent with those previously described, but were based on the untransformed values.

The Clinical Global Impressions of Change (CGI-c) was assessed by correlation analysis using Cochran-Mantel-Haenszel Test for Nonzero Correlation between the CGI-c score and treatment.

3.1.1.9 Determination of Sample Size

The required sample size for this study was calculated using the change from baseline in the total number of cataplexy attacks (primary efficacy variable) occurring in one week. Previous studies suggested than can effective dose of sodium oxybate would produce a mean reduction of at least 2 cataplexy attacks, based upon the number per week at baseline, in the number of weekly attacks with a standard deviation of 2.5. Using a power of 80% and a two-sided significance level of 0.05, 100 patients were needed, 25 per treatment group, to detect a treatment group difference of 2 with respect to change in cataplexy attacks.

3.1.1.10 Disposition of Patients

One hundred and thirty-six patients were enrolled in the study from sixteen centers, and sixteen patients withdrew from the study before completion, for the reasons shown in Table 3.2.

Table 3.2 Disposition of Patients

Disposition	All patients	Placebo	Xyrem dose (g)		
			3	6	9
Received study medication	136	34	34	33	35
Withdrew from study					
Adverse event	10	1	1	2	6
Protocol deviation	1		1		
Patient request	2		1		1
Lost to follow-up	1			1	
Lack of efficacy	2		1	1	
Total withdrawals	16	1	4	4	7
Completed the study	120	33	30	29	28

The primary reason for withdrawal from the study was the development of adverse events (10 patients). Patient withdrawals for adverse events were more frequent in the 9g GHB dose group than in the other three treatment groups. Patients who withdrew

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from the study were followed until adverse events or laboratory abnormalities resolved or were fully characterized.

3.1.1.11 Data Sets Analyzed

Since the analysis performed in this study was an intent-to-treat analysis, no patients were excluded from the analysis.

3.1.1.12 Demographic and Other Baseline Characteristics

The demographic characteristics of the 136 patients who received study medication are summarized in Table 3.3.

Table 3.3 Demographic Characteristics of Study Population

Characteristic	All Patients	Placebo	Xyrem dose (g)			p-value*
			3	6	9	
Age						0.2737
n	136	34	34	33	35	
mean (years)	43.06	40.82	47.06	43.52	43.91	
SD	15.03	14.33	16.89	14.98	13.53	
Gender						0.0027
Male	57	12	7	21	17	
Female	79	22	27	12	18	
Race						0.1379
Caucasian	124	29	33	31	31	
African American	9	4	0	1	4	
Asian	1	0	0	1	0	
Other	2	1	1	0	0	
Height						0.0283
N	131	31	33	33	34	
mean (cm)	170.91	171.97	166.7	173.1	171.9	
SD	9.53	8.18	8.78	10.39	9.64	
Weight						0.4847
N	134	34	33	33	34	
mean (kg)	82.87	83.98	78.86	85.04	83.56	
SD	17.36	18.89	15.65	15.54	19.08	

*p-value based on ANOVA (GLM)

Significant between group differences in gender and height were noted. The 6g GHB group was predominantly male, while the placebo and 3g GHB groups were predominantly female. Consistent with the large difference in distribution of males and females in the 3g GHB group, the height of this group was less than the other treatment groups.

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The severity of narcolepsy in the patient population was assessed by documenting the historical frequency of symptoms that were reported in the three months prior to screening.

Table 3.4 summarizes the narcolepsy symptom profile recorded in the patient diaries during the last two weeks of baseline, representing narcolepsy symptoms in the absence of anticataplectic or sedative/hypnotic medications, but with continued stable stimulant medication.

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Table 3.4 Summary of Baseline (Visit 4) Narcolepsy Symptoms by Treatment Group

		Xyrem Dose (g)			
Type of event	Placebo	3	6	9	p-value Kruskal-Wallis
Total cataplexy attacks/week					0.7749
N	34	33	33	35	
Mean	34.27	28.57	38.85	34.60	
Median	20.21	20.00	23.00	23.50	
SD	46.63	30.53	55.04	33.92	
Complete cataplexy attacks/week					0.5151
N	34	33	33	35	
Mean	6.86	7.08	15.26	8.61	
Median	1.12	4.50	4.85	2.00	
SD	12.37	8.50	27.53	14.01	
Partial cataplexy attacks/week					0.7289
N	34	33	33	35	
Mean	27.44	21.49	23.59	26.12	
Median	15.03	15.00	16.15	18.79	
SD	42.08	28.30	29.01	26.14	
Hypnagogic hallucinations/day					0.9766
N	34	33	33	34	
Mean	0.57	0.58	1.14	0.53	
Median	0.23	0.43	0.33	0.29	
SD	0.74	0.68	3.72	0.70	
Sleep paralysis episodes/day					0.9597
N	34	33	33	35	
Mean	0.51	0.42	0.73	0.41	
Median	0.26	0.14	0.08	0.10	
SD	0.74	0.55	1.84	0.60	
Inadvertent naps/day					0.7008
N	34	33	33	35	
Mean	1.71	1.91	1.70	1.72	
Median	1.57	1.93	1.45	1.27	
SD	0.96	1.43	1.12	1.56	

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3.1.1.13 Excessive Daytime Sleepiness

Daytime sleepiness was the subjective assessment of a patient's ability to remain alert and awake. Excessive daytime sleepiness was defined as difficulty remaining awake and was usually accompanied by rapid entrance into sleep when the patient was sedentary. This variable was assessed through the use of the Epworth Sleepiness Scale (ESS). The ESS is a subjective report of propensity to sleep, difficulty in maintaining an alert awake state, usually accompanied by a rapid entrance into sleep when the person is sedentary. The ESS was used at the end of baseline (Visit 4), at the end-of-treatment (Visit 6), and again at the last follow-up visit (Visit 7). Patients were to rate their "chance of dozing" on a scale of 0-3 (never, slight, moderate, and high chance of dozing) in each of eight possible situations:

- Sitting and reading
- Watching TV
- Sitting, inactive in a public place (i.e. a theater or a meeting)
- As a passenger in a car for an hour without a break
- Lying down to rest in the afternoon when circumstances permit
- Sitting talking to someone
- Sitting quietly after lunch without alcohol
- In a car, while stopped for a few minutes in traffic

The ESS measures sleep propensity based on the retrospective report of the subject's dozing behavior in eight everyday situations. This brief, self-administered questionnaire asks that the subject rate the chances that over the recent past (i.e. since the last prior rating) whether he or she would have dozed in each of the eight situations. The relative soporific nature of these situations has been described both for "sleepy patients" and a normal population of medical studies and are known to remain stable within individuals over a period of months (Johns 1991). The ESS score is the sum of eight individual item scores and ranges from 0 to 24. In one study ESS scores for narcoleptics averaged 16.8, general sleep disorder patients averaged 10.2, and healthy medical studies averaged 7.4 to 7.6 (Johns 1991).

Excessive daytime sleepiness at baseline as assessed by the Epworth Sleepiness Scale is presented in Table 3.5. This mean Epworth score can be considered in the moderately severe to markedly severe range, in spite of maintained stable stimulant medication.

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Table 3.5 Summary of Excessive Daytime Sleepiness at Baseline as Assessed by the Epworth Sleepiness Scale

		Xyrem Dose (g)		
Statistic	**Placebo**	**3**	**6**	**9**
N	34	34	32	35
Mean	18.47	17.06	17.28	16.66
SD	3.13	3.71	3.49	4.07

3.1.1.14 Clinical Global Impression of Severity (CGI-S)

This parameter was the investigator's assessment of the severity of a patient's narcolepsy and was recorded at Visit 4. It was made in relation to the investigator's total experience with the narcoleptic population using the following assessments:

- Not assessed
- Normal – no signs of illness
- Borderline ill
- Slightly ill
- Moderately ill
- Markedly ill
- Among the most extremely ill

The CGI-severity score is an expert clinical measure of the patient's general condition at baseline. The majority of patients were judged to be markedly or extremely ill, followed by those who were judged moderately ill and with much fewer patients in the borderline, slightly, or normal categories as seen in Table 3.6 below. There were no significant differences in the percentage of patients enrolled in any severity response category. Subsequent changes from the baseline CGIs score are captured in the Clinical Global Impression of change (CGI-c) score.

Table 3.6 Baseline Clinical Global Impression of Severity (CGI-S)

Treatment	Normal	Borderline	Slightly ill	Moderately ill	Markedly ill	Extremely ill
Placebo	0	2	2	8	12	10
3g Xyrem	0	1	1	11	17	4
6g Xyrem	1	1	0	14	11	6
9g Xyrem	0	1	2	13	15	4
Total	1	5	5	46	55	24

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3.1.1.15 Analysis of Efficacy

3.1.1.15.1 Primary Efficacy Variable

The primary efficacy variable was the change from baseline in the total number of cataplexy attacks. As shown in Table 3.7, the median and mean values for total cataplexy attacks/week were noted to be similar across dose groups. As noted in Table 3.7, there was a significant (p=0.0021) difference among treatment groups in change from baseline to endpoint in total number of cataplexy attacks/week with treatment. The change in total number of cataplexy attacks exceeded placebo, and was in the clinically meaningful range in all Xyrem treatment groups (Table 3.7 and Figure 3.1). Like most neuropharmacology studies, there was also considerable placebo response, potentially in part the consequence of the disciplined sleep hygiene imposed by the protocol and diary recording of sleep habits during the treatment period. As a result, the difference between Xyrem treatment groups compared to placebo response showed marginal significance in the 6g Xyrem group (p=0.0529), and unambiguous statistical significance in the 9g Xyrem group (p=0.0008).

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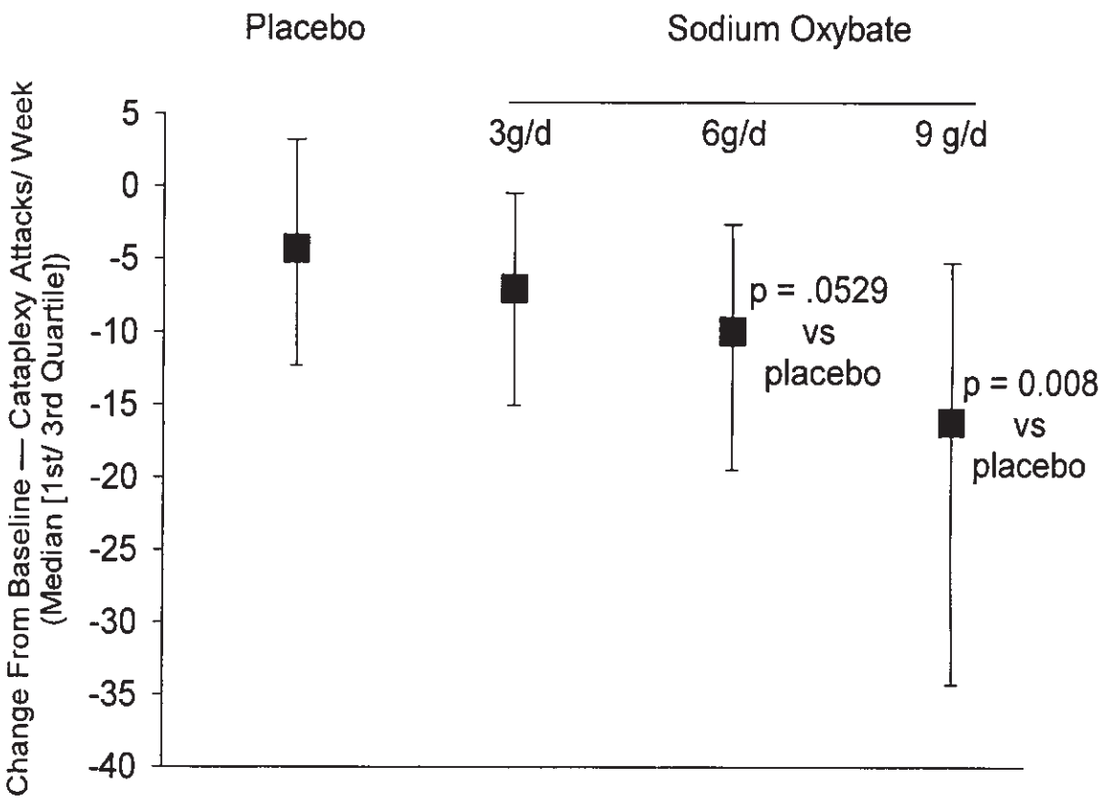
Figure 3.1 Changes in Total Number of Cataplexy Attacks (Baseline to Endpoint) — OMC-GHB-2



However, these results still indicate an important clinical response to the three dosages of sodium oxybate. The median frequency of cataplectic events at the end of four weeks of treatment shows similarity in the three dosage groups (3 g/day = 9.5, 6 g/day = 8, 9 g/day 8.7), all of which differ markedly from the median placebo response of 16.3 (see Table 3.7).

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Table 3.7 Total Number of Cataplexy Attacks

Dose group	Statistic	Observed		Change from baseline to endpoint	Comparison with placebo (p-value)
		Baseline	Endpoint		
Placebo	N	33	33	33	
	Mean	35.1	24.0	-11.1	
	Median	20.5	16.3	-4.3	
	SD	47.1	28.4	27.7	
	p-value			0.028	
3g	N	33	33	33	
	Mean	28.6	19.5	-9.1	
	Median	20.0	9.5	-7.0	0.5235
	SD	30.5	27.5	22.4	
	p-value			0.026	
6g	N	31	31	31	
	Mean	33.8	24.6	-9.2	
	Median	23.0	8.0	-9.9	0.0529
	SD	45.6	62.9	27.3	
	p-value			0.070	
9g	N	33	33	33	
	Mean	35.7	14.4	-21.3	
	Median	23.5	8.7	-16.1	0.0008
	SD	34.5	19.3	29.8	
	p-value			<0.001	

P=0.0021 for overall treatment group comparison

Interpretation of this data clinically is complicated by the fact that frequency of cataplexy attacks in this trial is not normally distributed data (incidence ranging from 2.8 cataplexy attacks/week to 249/week at baseline, with a median frequency of 21.0/week). When plots of individual patient data are considered it is possible that outlier data such as one patient in the 6 g dosage group may have represented ongoing REM rebound phenomena, directly affecting statistical interpretations. The consideration of these individual patient responses in the spaghetti plots (Figures 3.2, 3.3, 3.4, and 3.5) indicated the dose response in all dosage groups.

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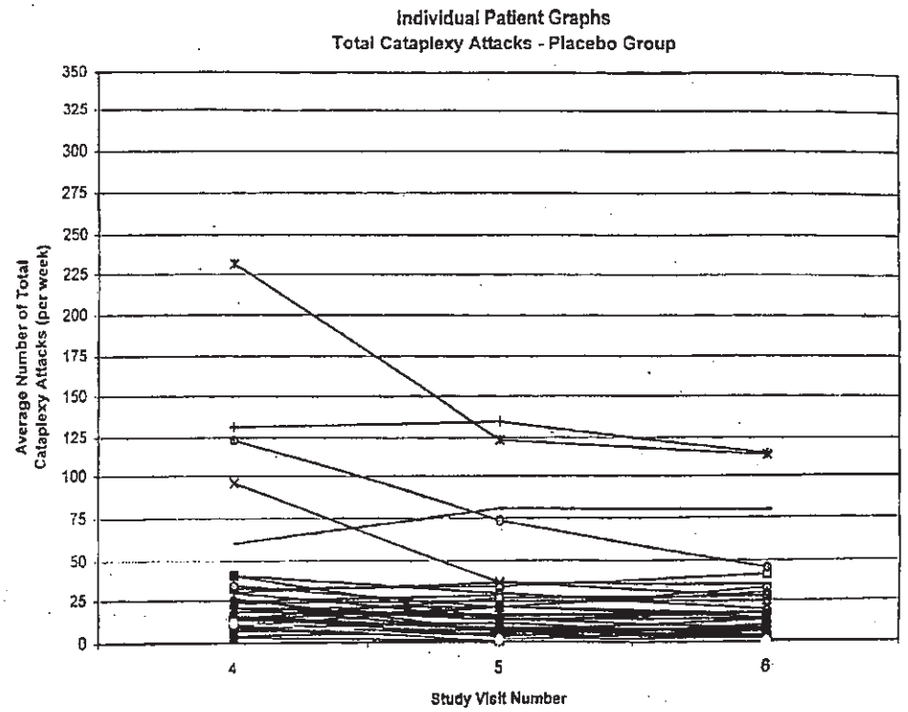
Figure 3.2



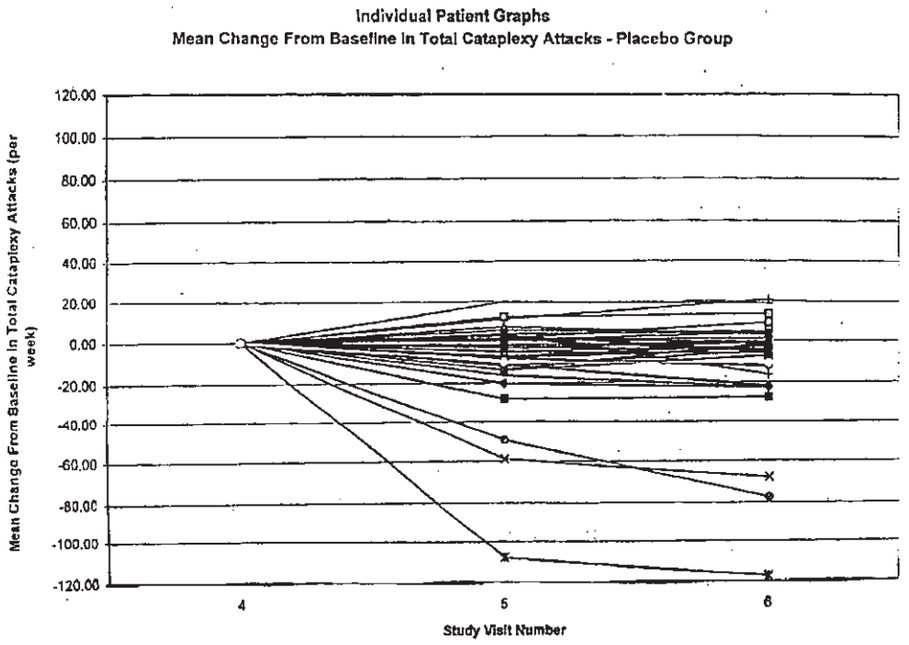


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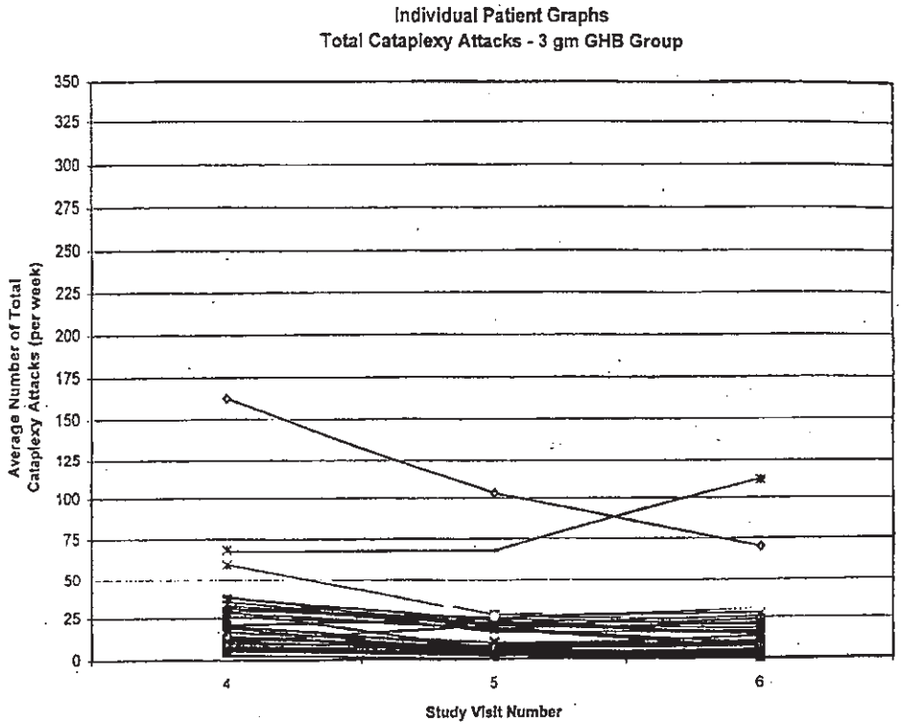
Figure 3.3


Individual Patient Graphs
Total Cataplexy Attacks - 3 gm GHB Group
Average Number of Total Cataplexy Attacks (per week)
350
325
300
275
250
225
200
175
150
125
100
75
50
25
0
4
5
6
Study Visit Number

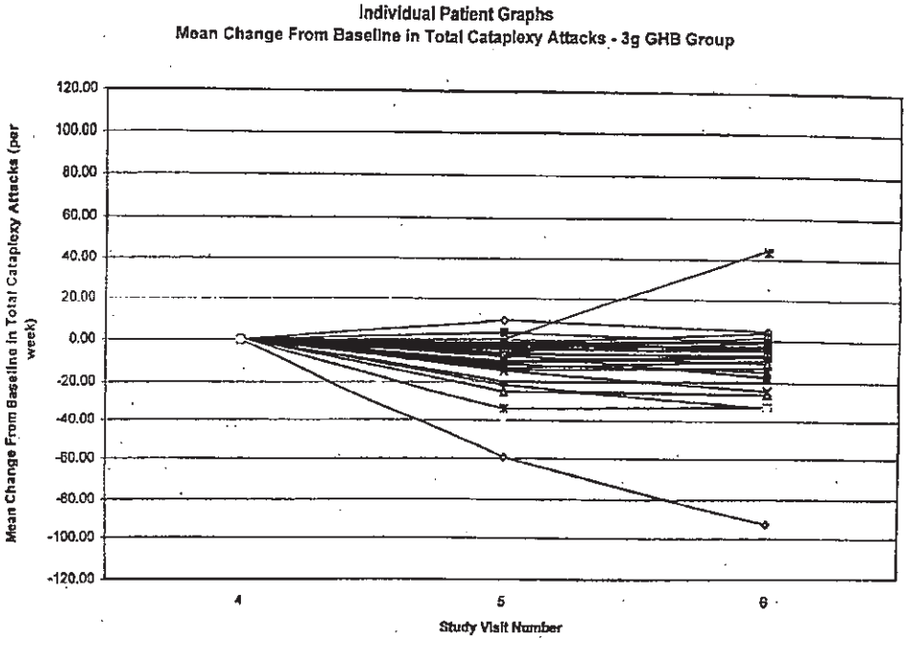
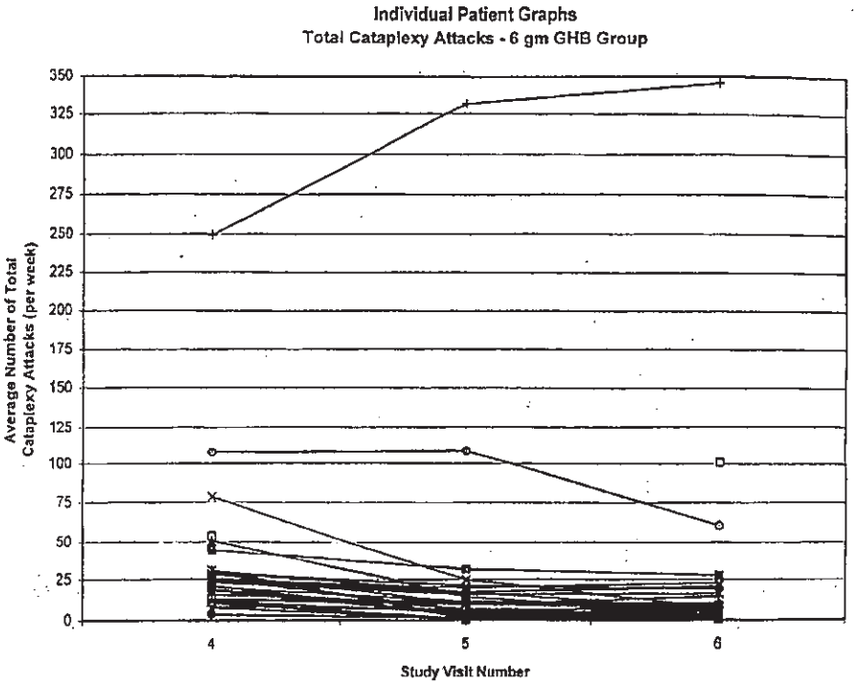

Individual Patient Graphs
Mean Change From Baseline in Total Cataplexy Attacks - 3g GHB Group
Mean Change From Baseline in Total Cataplexy Attacks (per week)
120.00
100.00
80.00
60.00
40.00
20.00
0.00
-20.00
-40.00
-60.00
-80.00
-100.00
-120.00
4
5
6
Study Visit Number

Figure 3.4



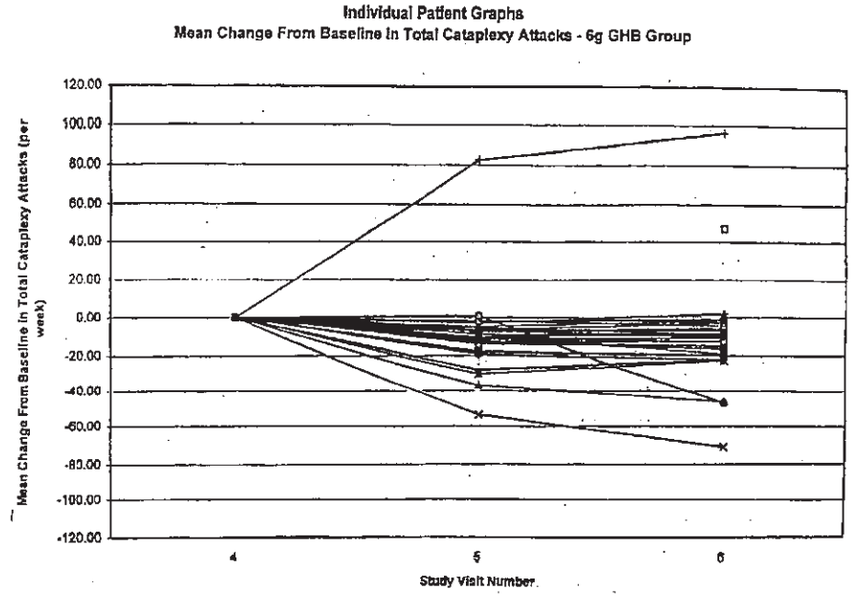


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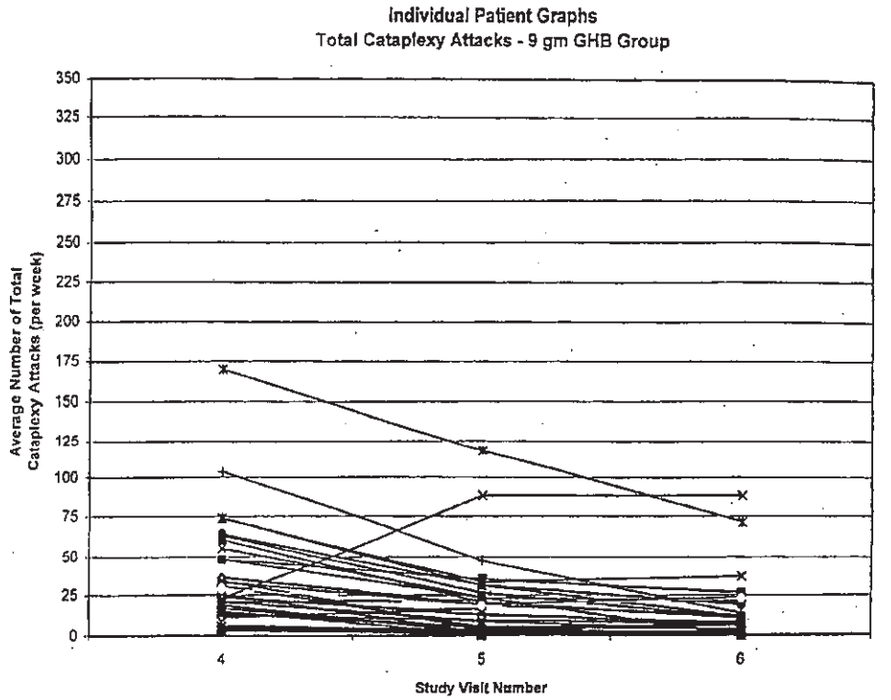
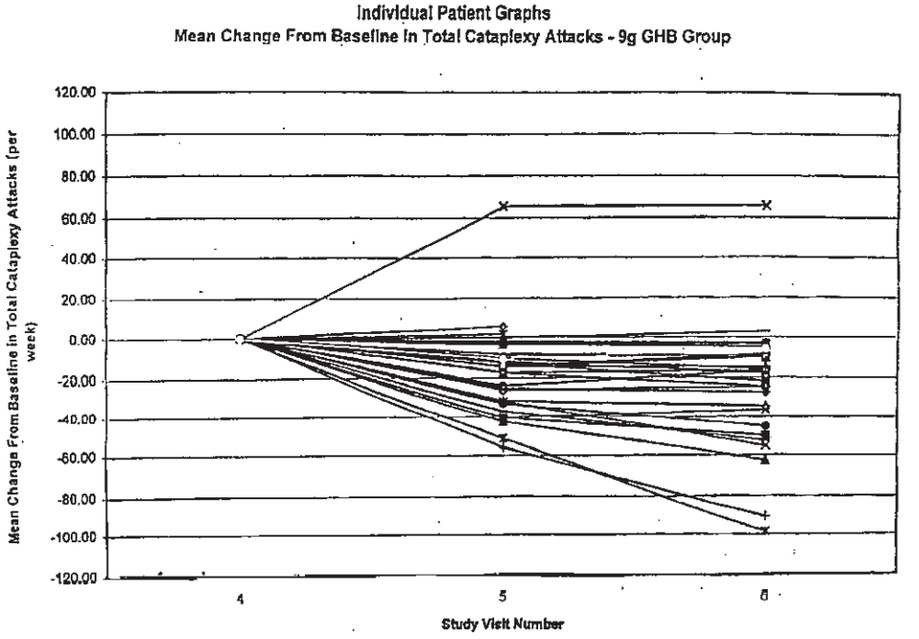
Figure 3.5





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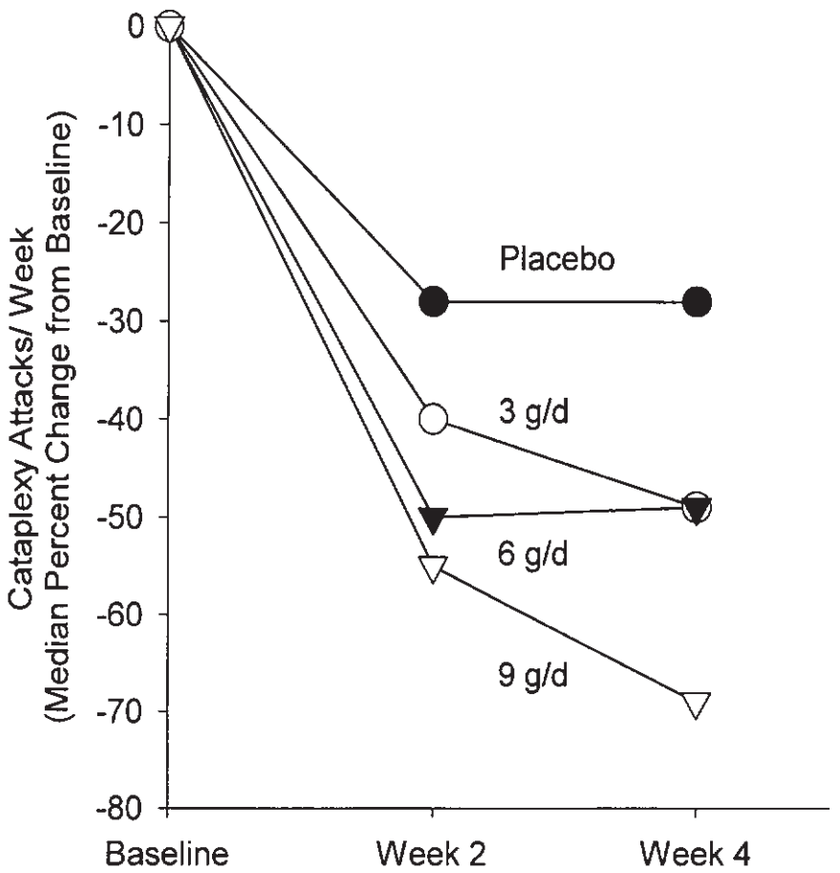
In Figure 3.6, the percentage change in the total number of cataplexy attacks from baseline (median) was calculated on the distribution of change values for each individual patient at baseline, two weeks, and four weeks of treatment. This indicates that with the exception of the 9g treatment group, the majority of the reduction in cataplexy attacks occurred during the first two weeks of treatment, as is also represented by the previous graphs of individual patients.

Figure 3.6 Changes in Number of Cataplexy Attacks by Dosage Group Over Time — OMC-GHB-2



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3.1.1.15.2 Secondary Efficacy Variables

3.1.1.15.2.1 Complete Cataplexy Attacks

As shown in Table 3.7, at baseline the median number of complete cataplexy attacks was 1.2, 4.5, 4.7, and 2.0 in the placebo, 3g, 6g and 9g treatment groups respectively. Complete cataplexy attacks were much less frequent than partial cataplexy attacks although clinically they are particularly dangerous. At endpoint the median number of complete cataplexy attacks changed by 0, -1.00, -1.62, and –1.62 in the placebo, 3g, 6g and 9g treatment groups respectively. While there appears to be a dose response, none of the decreases reached statistical significance when compared to placebo, although the pattern of changes were in a dose response manner.

3.1.1.15.2.2 Partial Cataplexy Attacks

Also shown in Table 3.7, at baseline the median number of partial cataplexy attacks was 15.05, 15.00, 15.15, and 18.79 in the place, 3g, 6g and 9g treatment groups respectively. From baseline to endpoint the median number of partial cataplexy attacks changed by –2.72, -3.69, -6.35, and –10.00 in the placebo, 3g, 6g, and 9g treatment groups respectively exhibiting a dose response relationship that was statistically significant from placebo at 9g (p=0.0009). Hence the patterns of change were similar in complete and partial cataplexy attacks although the much more frequent partial cataplexy attacks were statistically more powerful in showing the dose response.

3.1.1.15.2.3 Clinical Global Impression of Change (CGI-c)

The Clinical Global Impression of Change was an integrated clinical measure based on the investigator's overall impression of the change in the patient's condition. This measure was based on comparison of the patient's condition at the time of a comprehensive baseline interview defining the severity of patient illness at the time of entry into the study captured in the Clinical Global Impression of Severity (CGI-s). The CGI-c focused on overall clinical change in severity including all narcolepsy symptoms and effectiveness in activities of daily living and incorporating any problems in overall functioning deriving from adverse experiences.

During Visit 6 (the last treatment visit) and Visit 7, investigators rated their impressions of any change in the severity of the patient's overall condition of narcolepsy using the CGI-c rating scale as follows:

- Very much improved
- Much improved
- Minimally improved
- No change
- Minimally worse
- Much worse
- Very much worse

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As shown in Table 3.8 and Figure 3.7 below, a highly significant treatment effect was noted on the CGI-c scale. The majority of placebo patients were observed to have a modal value of *no change*, with 35% *no change*. The placebo population distributed mainly into the *no change*, *minimally improved* and *much improved* brackets with the population distribution weighted to the *no change/minimally improved* group. The majority of placebo patients fell in the combined *no change/minimally improved* brackets. A similar distribution was noted in the 3g group although with higher proportions in the *minimally improved* and *much improved* groups and a model value at the *much improved* group and half the patients in the *no change/minimally improved* brackets. In the 6g dose group, the distribution is seen to have shifted upwards with fewer *no change* and more *very much improved* patients and a majority of patients in the *minimally improved/much improved* brackets. In the 9g dose group a marked shift of distribution is seen with a large majority of patients in the *much improved* (43%) and *very much improved* (37%) brackets. Hence a global clinical assessment measure incorporating all aspects of the patient's disease strongly demonstrates the dose response trend to Xyrem.

Table 3.8 Summary of Clinical Global Impression of Change at Endpoint by Treatment Group

		Xyrem Dose (g)		
Impression	**Placebo**	**3**	**6**	**9**
Very much improved	3 (9%)	3 (10%)	5 (16%)	11 (37%)
Much improved	8 (24%)	11 (37%)	11 (35%)	13 (43%)
Minimally improved	8 (24%)	9 (30%)	9 (29%)	3 (10%)
No change	12 (35%)	6 (20%)	5 (16%)	1 (3%)
Minimally worse	0	0	0	0
Very much worse	1 (3%)	0	1 (3%)	0

P=0.0010 for overall treatment group comparison based on Cochran-Mantel-Haenzel Test for Nonzero Correlation

The CGI-c data can also be viewed in another manner as defining a responder analysis (see Table 3.9 and Figure 3.7). Given that the majority of placebo patients fall into the *no change/minimally improved* brackets, a responder was defined as a patient falling into the *much improved* or *very much improved* category. This responder definition also has the virtue of defining patients who, on face value, showed a clear clinical benefit since an experienced clinician rated them as *much improved* or *very much improved*. For this post hoc analysis, responders included the *very much improved* or *much improved* categories; and nonresponder included all other categories of CGI-c except not assessed. Patients not assessed or with missing CGI-c scores were not included in Table 3.9.

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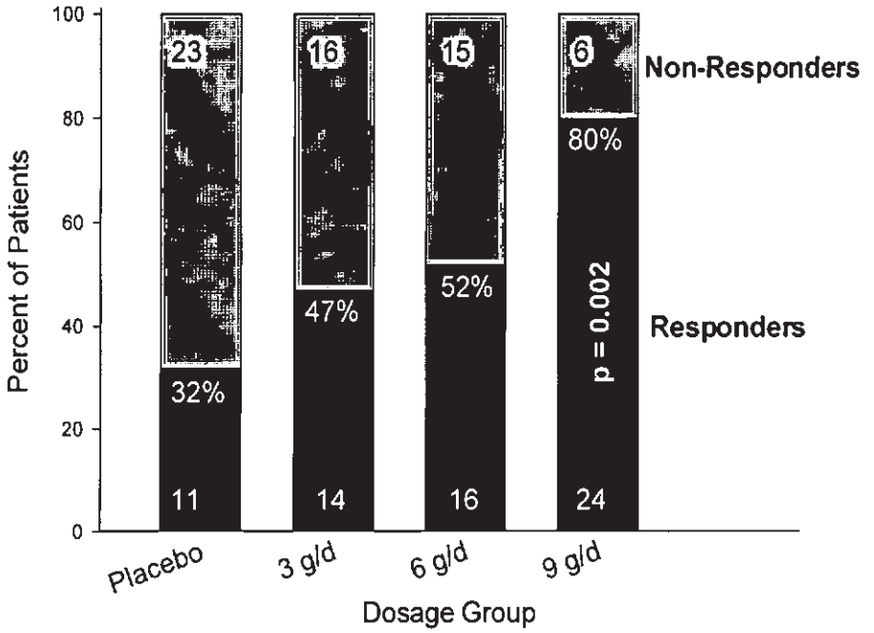
Table 3.9 Summary of Clinical Global Impression of Change to Endpoint by Treatment Group for Responders and Nonresponders

		Xyrem Dose (g)			
Category	Placebo	3	6	9	p-value* (overall comparison)
Responders	11 (32%)	14 (47%)	16 (52%)	24 (80%)	0.0014
Nonresponders	23 (68%)	16 (53%)	15 (48%)	6 (20%)	
p-value (group vs placebo)		0.3075	0.1368	0.0002	

*Based on Fisher's Exact Test

Figure 3.7 Summary of CGIc at Endpoint by Treatment Group — OMC-GHB-2



In Figure 3.7 the percentage of responders improved across the treatment groups in a dose response manner with a particularly sharp improvement to 80% in the 9g group (p=0.0002) as compared to 32% in the placebo group.

This post hoc responder analysis detects the same dose response trend evident in the inspection of the categorical analysis of the patients seen in Table 3.9.

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3.1.1.15.2.4 Excessive Daytime Sleepiness

The Epworth data provide another independent confirmation of the dose response of narcoleptic symptoms to Xyrem. The Epworth Sleepiness Scale draws on the patient's subjective assessment of their propensity to fall asleep in different circumstances. As presented in Table 3.10, Figure 3.8 below, excessive daytime sleepiness as assessed by the Epworth Sleepiness Scale improved in all Xyrem treated groups and the improvement compared with placebo was highly significant in the 9g group (p=0.0001) where the change from baseline was nearly twice that seen in the 3g and 6g groups.

Figure 3.8 Daytime Sleepiness (Baseline to Endpoint)

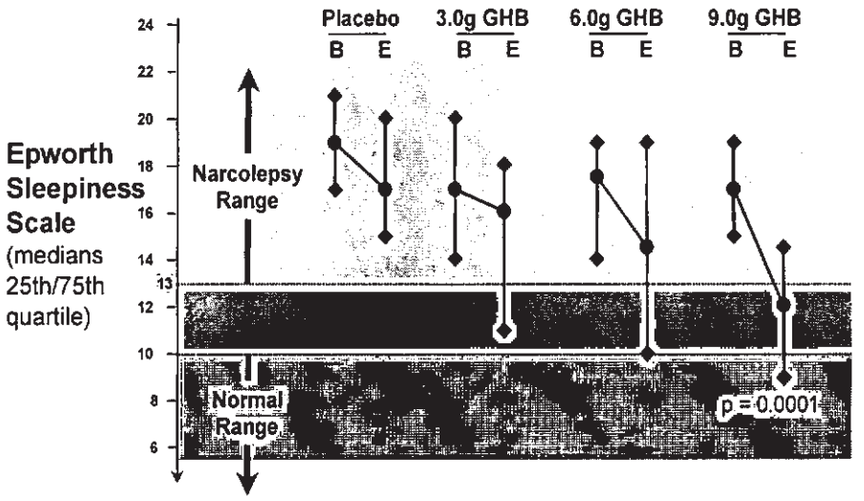

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Table 3.10 Summary of Changes from Baseline to Endpoint in Excessive Daytime Sleepiness as Assessed by Epworth Sleepiness Scale

Dose group	Statistic	Observed		Change from baseline to endpoint	Comparison with placebo (p-value)
		Baseline	Endpoint		
Placebo	N	33	31	33	
	Mean	18.4	17.3	-1.1	
	Median	19.0	17.0	-1.0	
	SD	3.2	3.6	3.1	
	p-value			0.043	
3g	N	31	31	31	
	Mean	17.1	14.6	-2.5	
	Median	17.0	16	-1.0	0.1137
	SD	3.7	5.2	3.8	
	p-value			0.001	
6g	N	30	30	30	
	Mean	16.9	14.6	-2.4	
	Median	17.0	13.5	-2.0	0.1860
	SD	3.3	4.6	3.5	
	p-value			0.001	
9g	N	28	28	28	
	Mean	16.4	11.8	-4.7	
	Median	17.0	12.0	-3.5	0.0001
	SD	3.9	4.2	4.3	
	p-value			<0.001	

P= 0.006 for overall treatment group comparison

The reduction in ESS from baseline to endpoint was observed in all treatment groups, with again a dose-response trend as with cataplexy response. This change reached statistical significance (p=0.0001) in patients in the 9g/day dosage group compared to placebo. The first and second quartile lines represent that some patients in all three treatment groups have reduced ESS scores to the extent that they no longer reach the level considered characteristic of narcolepsy (13 to 24; Johns 1991). The median score in the 9g/day dosage group was outside the narcoleptic range, and over 25% of these patients had scores that were within the "normal" range (≤ 10), indicating a highly clinically significant reduction in patients' subjective rating of somnolence, and this change was incremental beyond the status achieved with stable dosages of stimulant medications continued during the trial.

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3.1.1.15.3 Other Secondary Efficacy Measures

As presented in Figure 3.9 and Figure 3.10, compared with placebo a significant decrease in the number of inadvertent naps/sleep attacks was seen in both the 6g and 9g Xyrem groups (p=0.0497 and p=0.0122, respectively), and a significant decrease in the number of awakenings was seen in the 9g Xyrem group (p=0.0035). These data are consistent with the dose response pattern of reduced excessive daytime sleepiness reflected in the Clinical Global Impression of change and the Epworth Sleepiness Scale. No significant differences between treatments were seen in the change from baseline in the median number of hypnagogic hallucinations, sleep paralysis episodes, total amount of sleep, and duration of inadvertent naps/sleep attacks.

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Figure 3.9 Median Changes for Number of Inadvertent Naps/Sleep Attacks From Baseline to Endpoint

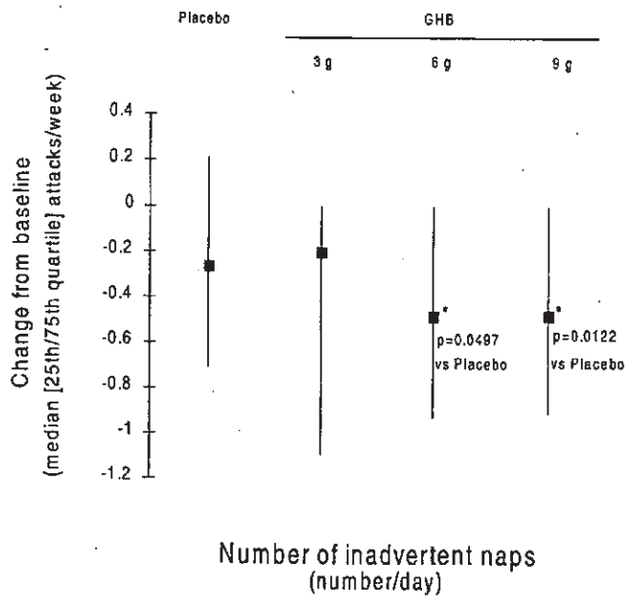
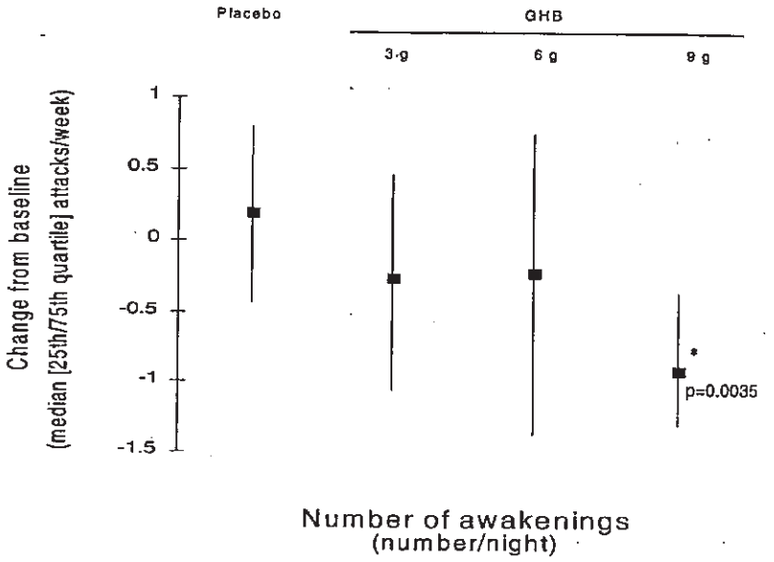


Figure 3.10 Median Changes for Number of Awakenings From Baseline to Endpoint



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An exploratory analysis was conducted of the changes from baseline to endpoint in the parameters of subjective rating of quality of sleep, level of alertness, and ability to concentrate as rated by the patients. These parameters were measured on a four-point scale: 1-excellent, 2-good, 3-fair, 4-poor. For the 6g and 9g dose groups, there was a statistically significant increase in the subjective quality of sleep (p=0.0028 and p=0.0010), level of alertness (p=0.0006 and p=0.0004), and overall reported ability to concentrate (p=0.0229 and p=0.0007).

3.1.1.15.4 Abrupt Cessation of Double-Blind Medication

The change in incidence of cataplexy attacks that occurred following discontinuation of double-blind treatment (Visit 6) through the end of the trial three to five days later (Visit 7), and from baseline to Visit 7 was calculated. Only patients for which there were data at baseline (Visit 4), Visit 6 and Visit 7 were included in this analysis.

Table 3.11 Total Cataplexy Attacks per Week by Treatment Group – Medians Change from Visit 6 to Visit 7 and from Baseline to Visit 7

					V6-V7		Baseline to V7	
Treatment Group	N	Baseline	V6	V7	Change	P-Value	Change	P-Value
Placebo	30	20.6	16.5	17.5	1.9	0.06	-3.8	0.10
3g	29	18.7	9.5	13.0	2.3	0.09	-5.4	0.07
6g	29	23.0	8.0	16.3	6.1	0.0001	-3.3	0.13
9g	27	29.2	8.0	14.0	4.7	0.0017	-11.6	0.0001

Total cataplexy attacks per week were determined by first calculating the average daily number of cataplexy attacks based on the numbers recorded in the patient diaries, then multiplying this number by seven to get Total Cataplexy Attacks per Week.

Patients discontinued sodium oxybate treatment at Visit 6 (Week 4) and were to return to the clinic for assessment of cataplexy at Visit 7, three to five days later. According to their daily diary recordings, the median number of total cataplexy attacks per week for all patients in all treatment groups trended toward their higher baseline values. A significant change from Visit 6 to Visit 7 in the median number of cataplexy attacks per week occurred in the 6g group (p=0.0001) and 9g group (p=0.0017). The 9g dose group exhibited a significantly lower median number of weekly cataplexy attacks at Visit 7 than at baseline (p=0.0001).

In all treatment groups, acute rebound cataplexy was not in evidence as the median number of attacks at Visit 7 was lower than their baseline values.

Adverse events, for the time period of up to five days prior to Visit 6 and up to five days prior to Visit 7, were compared to determine if REM rebound effects (i.e. rebound cataplexy) occur on withdrawal of Xyrem. Adverse events suggestive of REM rebound

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(sleep disturbance, hallucinations, and dream abnormal) which were present at up to five days before Visit 6 were compared with those adverse events that occurred up to five days before Visit 7. There was not an exacerbation of adverse events suggestive of REM rebound effects corresponding with the cessation of treatment with Xyrem at Visit 6. The difference in the number of events between these two periods is not statistically significant. REM rebound effects did not appear when stopping Xyrem for three to five days

3.1.1.16 Efficacy Conclusions

Table 3.12 OMC-GHB-2 Efficacy Conclusions

Parameters	Treatment	Baseline (median)	Endpoint (median)	P-value (vs. Placebo)
Total Number of Cataplexy Attacks Per Week	Placebo	20.5	16.5	--
	3g	20.0	9.5	n.s.
	6g	23.0	8.0	0.0529
	9g	23.5	8.7	0.0008
Excessive Daytime Sleepiness (Epworth Sleepiness Scale)	Placebo	19.0	17.0	--
	3g	17.0	16.0	n.s.
	6g	17.5	14.5	n.s.
	9g	17.0	12.0	0.0001
		Change in Medians		
Frequency of Inadvertent Naps/Sleep Attacks/Day	Placebo	-0.26		--
	3g	-0.20		n.s.
	6g	-0.48		0.0497
	9g	-0.48		0.0122
Number of Awakenings at Night	Placebo	+0.20		--
	3g	-0.25		n.s.
	6g	-0.21		n.s.
	9g	-0.91		0.0002
Clinical Global Impressions of Change	Placebo	32%		--
	3g	47%		0.3075
	6g	52%		0.1368
	9g	80%		0.0002

- In study OMC-GHB-2, a statistically significant greater (compared to placebo) reduction from baseline to endpoint in the total number of cataplexy attacks ($p = 0.0008$) was seen among patients in the 9.0 g/d dosage group compared to placebo-treated group, and a reduction in the number of cataplexy attacks ($p = 0.0529$) also was seen among patients in the 6.0 g/d dosage group.

- A reduction in Epworth Sleepiness Scale from baseline to endpoint was observed in all treatment groups (including placebo) with a dose-response trend similar to that seen for cataplexy; this change reached statistical significance ($p = 0.0001$) in patients in the 9 g/d dosage group compared to placebo.

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- The number of inadvertent naps or sleep attacks occurring during a day, an index of excessive daytime sleepiness, was reduced by a statistically significant amount from baseline to endpoint (compared to placebo) in the 6 g/d ($p = 0.0497$) and 9 g/d ($p = 0.0122$) dosage groups.

- The clinical investigator's assessment of change in overall disease severity, the (Clinical Global Impression of change [CGI-c]) shows a clear improvement, with the 80% responder rate in the 9.0 g/d group being significantly different from the 32% responder rate in the placebo group ($p = 0.0002$). Patients in the 3.0 g/d and 6.0 g/d dosage groups showed a dose-response trend in level of improvement.

- No significant differences between treatments were seen in the change from baseline in the median number of hypnagogic hallucinations, sleep paralysis episodes, total amount of sleep, and duration of inadvertent naps/sleep attacks.

- Following cessation of treatment at Visit 6, there was no exacerbation of cataplexy or other adverse events above baseline, suggesting that REM rebound does not occur.

3.1.2 SCRIMA TRIAL

3.1.2.1 Design

The Scrima trial (US) was a Phase II, randomized, double-blind, placebo-controlled, 2-way crossover (balanced for sequence group and gender), single-center trial comparing the efficacy of 50 mg/kg (mean 4.2 g) of sodium oxybate with placebo for the treatment of narcolepsy. The total nightly dose of trial medication was taken in 2 equal doses: at bedtime, and again approximately 3-4 hours later. Each dose was administered orally in Syrup of Orange (25 mL) and distilled water (to 100 mL). The trial design is summarized in Table 3.13.

Table 3.13 Scrima Trial Design

Baseline	Treatment 1	Washout	Treatment 2	Washout
14 Days	29 Days	6 Days	29 Days	6 Days
X	Sodium Oxybate (50 mg/kg)	X	Placebo	X
	Placebo	X	Sodium Oxybate (50 mg/kg)	X

The trial consisted of a screening period during which anticataleptic medications were withdrawn, a 14-day baseline period, two 29-day treatment periods separated by a 6-day washout period, and a washout/follow-up period of at least 5 days. In each of the treatment periods, patients took randomly assigned trial medication (50 mg/kg [mean 4.2 g] sodium oxybate) or a similar volume of diluted Syrup of Orange as placebo. A total of 10 men and 10 women were treated and all completed the trial.

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To enter the trial, patients were required to have a history of narcolepsy and cataplexy diagnosed by an accredited clinical polysomnographer, sleep onset REM periods ≥ 2 on the diagnostic Multiple Sleep Latency Test (MSLT), and a sleepiness index* ≥ 75 on the diagnostic MSLT. In addition, to continue into the randomized portion of the trial, following the withdrawal of other anticataplectic medications a patient was required to have a minimum of 10 cataplexy attacks subjectively reported during a 14-day baseline period.

Patients with moderate to severe cataplexy (averaging 20 attacks per week) were enrolled into the trial, and other anti-cataplectic treatment was withdrawn prior to baseline.

3.1.2.2 Objectives

The objectives of the trial were:

- To evaluate as primary variables the average daily number of cataplexy attacks and objective daytime sleepiness (using the sleepiness index determined by the MSLT) in narcolepsy patients during treatment with sodium oxybate as compared to placebo and baseline
- To evaluate as secondary variables the average number of sleep attacks per day, average number of awakenings per night, dosing requirements of methylphenidate, feelings on awakening, mood in the morning and evening, sleep patterns identified on the PSG, and average number of REM onsets determined by the MSLT during treatment with sodium oxybate as compared to placebo and baseline

Safety variables included the incidence of adverse events and changes in laboratory values.

3.1.2.3 Statistical Analysis

Age, weight, age at diagnosis, and the number of sleep and cataplexy attacks were analyzed using a 2-factor ANOVA (analysis of variance). The effects in the model were sequence group, gender, and the interaction of gender and sequence group. The distribution of patients with/without histories of hypnagogic hallucinations or sleep paralysis was tested for independence from gender and sequence group using contingency table methods. All patients enrolled in the study were included. (n = 20). Only patients with baseline data who were included in the post-treatment analysis were analyzed for baseline comparability. A 2-factor ANOVA was performed. The effects in the model were sequence group, gender, and the interaction of gender and sequence group.

Repeated measures ANOVA was performed on the observed data. There were 2 between-patient factors, sequence group and gender, and the 2 within-patient factors,

* Sleepiness Index = 100-(5X total sleep latency minutes/number of naps); abnormal >75, borderline 50-75, normal <50

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treatment and week. Since week was frequently significant, either as a main effect or as part of an interaction, further repeated measures analysis for the individual weeks were performed to support the overall analysis. If indicated, supportive analyses on ranks were to be performed.

Only the diary data documented the patient's status prior to treatment in Treatment Period 2. Thus, comparison to the patient's status prior to treatment in Treatment Period 1 and the return to this level was restricted to diary data. A repeated measures ANOVA was performed on the change from baseline data. This analysis was a single within-patient factor, days, and 2 between-patient factors, sequence group and gender. Separate univariate supportive analyses for washout days 1 to 5 were performed, with sequence group, gender, and their interaction as factors. The intercept was tested in each model to identify departure from baseline.

Washout from treatment in Period 1 and 2 (follow-up) was compared for the variables in the diary. A repeated measures ANOVA was performed on the change from baseline data. There were 2 between-patient factors, sequence group and gender, and the 2 within-patient factors, Day 1 to 5 of washout and follow-up.

3.1.2.4 Efficacy Results

Table 3.13a summarized the mean number of cataplexy attacks per day by treatment.

Table 3.13a Mean Number of Cataplexy Attacks Per Day

Treatment Group	Pre-Treatment Baseline (SE)	Treatment Phase Week 1 (SE)	Week 2 (SE)	Week 3 (SE)	Week 4 (SE)	Overall (SE)	Baseline to Endpoint
GHB	2.9 (0.5)	1.4 (0.2)	1.4 (0.2)	0.9 (0.2)	0.9 (0.2)	1.2 (0.2)	2.9 to 1.2 (p=0.007)
Placebo		1.5 (0.2)	2.0 (0.3)	2.1 (0.4)	1.9 (0.3)	1.9 (0.3)	2.9 to 1.9 (p=0.117)
p-value between treatments	—	n.s.	n.s.	0.005	0.004	0.013	—

n.s. - not significant

During active treatment periods over 4 weeks, a mean of 1.2 cataplexy attacks per day was reported by patients receiving sodium oxybate treatment compared to 1.9 cataplexy attacks per day by patients receiving placebo treatment, representing a mean decrease from baseline of 1.6 for sodium oxybate treatment ($p = 0.007$) and of 1.0 for placebo treatment ($p = 0.117$).

By Week 4, treatment with sodium oxybate was superior to placebo for 84% (16/19) of patients, with a mean of 0.9 cataplexy events per day after treatment with sodium oxybate compared to 1.9 per day after treatment with placebo. No cataplexy events

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were reported for 21% (4/19) of patients during Week 4 of sodium oxybate treatment compared to 5% (1/19) of patients on placebo. Nine patients (47%) reported an average of at least one fewer cataplexy attacks per day while taking sodium oxybate than while taking placebo (1/19 patients taking placebo averaged at least one less attack than while taking sodium oxybate).

There were also significantly fewer ($p = 0.013$) cataplexy attacks per day during sodium oxybate treatment overall compared to placebo. However, the data suggest an interaction, ie, there was very little difference between treatments at Week 1 ($p = 0.735$, sodium oxybate = 1.4, placebo = 1.5) and a greater difference at Week 2 ($p = 0.073$, sodium oxybate = 1.4, placebo = 2.0). At Weeks 3 and 4, significant differences were detected ($p = 0.005$, sodium oxybate = 0.9, placebo = 2.1; and $p = 0.004$, sodium oxybate = 0.9, placebo = 1.9, respectively). No other significant main effects or interactions were identified, in particular sequence group ($p=0.775$), or treatment x sequence group interaction ($p=0.713$). Thus, no evidence of carryover effect was detected (PLC:GHB-GHB:PLC for PLC-GHB=0.2 with 95% interval-0.9 to 1.3).

The mean number of cataplexy attacks decreased from Week 2 to Week 3 or Week 4 during sodium oxybate treatment and remained lower at Week 4 than Week 1. In contrast, the mean number of a cataplexy attacks increased from Week 1 to Week 2 during placebo treatment and remained higher than Week 1 at Week 4. The crossover design shows no carry-over effect of any variable, indicating that a 5-day washout was sufficient.

The number of cataplexy attacks per week by treatment group for the Scrima trial are presented in Figure 3.11 as mean cataplexy attacks/week ± SEM.

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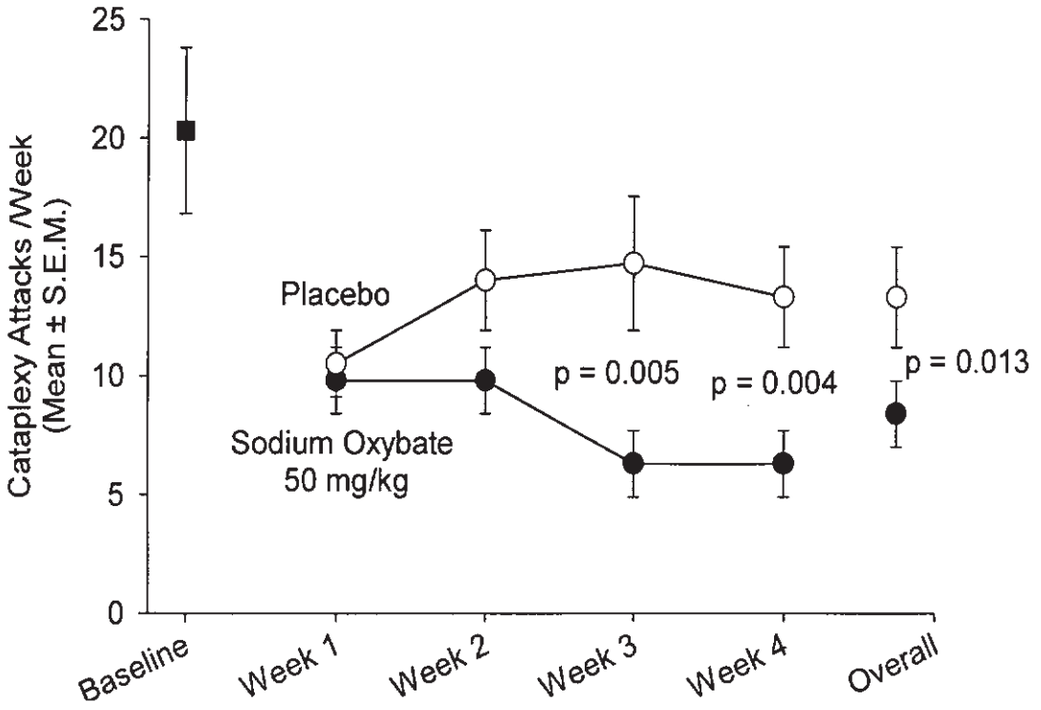
Figure 3.11 Number of Cataplexy Attacks by Treatment Group — Scrima Trial



Data Source: Scrima Trial Report

No significant treatment effects were detected overall for the MSLT sleepiness index [sleepiness index = 100-(5X total sleep latency in minutes/number of naps); abnormal >75, borderline 50-75, normal <50)], although the mean sleepiness index was less during sodium oxybate treatment (87.2) than placebo (90.3).

The mean number of sleep attacks per day during the 4 weeks of treatment decreased significantly from baseline for both sodium oxybate ($p = 0.002$) and placebo ($p = 0.007$), but differences between treatments were not significant. There was no significant difference compared to baseline in the mean number of subjective awakenings at night for either sodium oxybate or placebo, but significantly ($p = 0.042$) fewer awakenings occurred during sodium oxybate treatment versus placebo. There were no significant differences between sodium oxybate or placebo treatments versus baseline or between sodium oxybate and placebo in amount of methylphenidate taken, how patients felt upon awakening, or average morning mood.

For objective PSG studies (Table 3.14), there were statistically significant overall between treatment differences in sleep efficiency ($p = 0.023$), sleep latency ($p = 0.028$),

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percentages of Stage 1 and 3 sleep (p = 0.042 and 0.003, respectively), stage shifts (p = 0.006), and number of objective awakenings (p = 0.012), following 50 mg/kg sodium oxybate in the Scrima trial. Hence, the polysomnography data demonstrated that the continuity (increased sleep efficiency and reduced number of awakenings) and depth of sleep (decrease in Stage 1 light sleep and increase in Stage 3 deep sleep) were improved.

Table 3.14 Overnight Sleep in Narcolepsy Patients During GHB vs. Placebo Treatment: Means ± SD for 10 Males and 10 Females

		Placebo		GHB	
	Baseline	Day 1	Day 29	Day 1	Day 29
Sleep measures					
PSG time (min)	475.9 ± 13.5	472.6 ± 29.4	473.9 ± 26.2	474.7 ± 19.3	480.8 ± 3.5
Total sleep (min)	397.4 ± 46.7	413.6 ± 46.5	416.5 ± 41.3	397.2 ± 59.1	409.1 ± 41.7
Stage 0 (min)[a]	78.5 ± 45.5*	58.9 ± 39.2*	57.4 ± 38.6	77.5 ± 50.5	71.6 ± 40.7
No. of wakes[b]	27.2 ± 9.6	25.4 ± 10.2	29.4 ± 11.7	20.6 ± 6.4	23.0 ± 6.2
Sleep efficiency	83.5 ± 9.5*	87.5 ± 8.1*	88.0 ± 7.9	83.5 ± 11.1	85.1 ± 8.5
Sleep stages (%)					
Stage 1[a]	28.8 ± 11.0	26.8 ± 8.7	29.3 ± 10.8	22.4 ± 11.6	24.1 ± 8.4
Stage 2	40.6 ± 8.5*	44.6 ± 8.8*	44.0 ± 10.8	46.4 ± 10.7	44.6 ± 6.3
Stage 3[b]	3.4 ± 3.4	3.1 ± 3.6	2.3 ± 2.6	4.0 ± 4.2	5.8 ± 5.3
Stage 4	4.2 ± 6.6	3.5 ± 6.2	4.4 ± 5.8	5.3 ± 6.7	4.6 ± 4.8
Non-REM	77.0 ± 4.6	77.9 ± 5.1	80.1 ± 5.5	78.1 ± 5.7	79.1 ± 5.3
Delta[a]	7.6 ± 9.5	6.6 ± 9.4	6.8 ± 7.2	9.3 ± 9.3	10.4 ± 9.1
REM sleep	23.0 ± 4.6	22.1 ± 5.1	19.9 ± 5.5	21.9 ± 5.7	20.9 ± 5.3
No. of REM epochs	14.2 ± 6.4	13.6 ± 4.6	12.0 ± 4.7	12.1 ± 5.4	10.8 ± 4.5
Stage shifts[b]	123.4 ± 23.8	127.0 ± 25.6	132.2 ± 32.2	101.9 ± 24.8	114.8 ± 29.2
Latency to					
Sleep[a]	4.2 ± 4.6†	2.4 ± 1.6†	2.4 ± 2.1	3.5 ± 2.9	3.2 ± 2.5
Stage 2	11.0 ± 12.2	10.8 ± 12.4	8.1 ± 12.5	18.0 ± 21.3	11.4 ± 14.1
Delta sleep	39.0 ± 22.3	36.6 ± 17.2	37.7 ± 18.0	67.8 ± 67.4	47.4 ± 52.2
REM sleep	48.5 ± 78.2	31.6 ± 31.1	46.1 ± 47.4	29.8 ± 49.1	23.7 ± 27.5
First 6 h					
Stage 0 (min)	60.0 ± 41.8	44.5 ± 30.9	37.6 ± 25.2	48.0 ± 40.2	42.3 ± 23.5
Sleep efficiency	83.3 ± 11.6	87.6 ± 8.6	89.6 ± 7.0	86.7 ± 11.2	88.3 ± 6.5
Last 2 h					
Stage 0 (min)[a]	18.5 ± 12.7	15.2 ± 12.4	19.9 ± 18.2	29.4 ± 22.0	29.3 ± 23.7
Sleep efficiency	84.1 ± 10.3	87.3 ± 10.2	81.5 ± 15.5	71.7 ± 24.4	75.4 ± 20.4

Repeated-measures ANOVA of treatment differences from baseline: GHB (day 1 and 29) vs. placebo (day 1 and 29): [a]$p < 0.05$, [b]$p < 0.01$.
Baseline vs. placebo day 1: *paired-t: $p < 0.05$, †paired-t: $p < 0.10$.

Source: Scrima L, Hartman PG, Johnson FH, Thomas EE, Hiller FC. The effects of γ-hydroxybutyrate on sleep of narcolepsy patients: a double-blind study. Sleep 1990; 13(6):479-490.

3.1.2.5 Conclusions

Compared to placebo, sodium oxybate, given as a nightly divided dose of 50mg/kg (mean 4.2 g) for 4 weeks, significantly reduced the frequency of cataplexy attacks in a population of chronic narcolepsy patients. The reduction in cataplexy was greater during the last 2 weeks of sodium oxybate treatment than during the first 2 weeks. As assessed by the MLST sleep index, daytime sleepiness was not significantly reduced by this dosage or duration of sodium oxybate treatment. Polysomnography data demonstrated that sodium oxybate significantly enhanced both the continuity and the depth of nocturnal sleep as shown by a reduction in the number of awakenings, a

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decrease in the percentage of Stage 1 (light) sleep, and an increase in the percentage of Stage 3 (deep) sleep. Sodium oxybate was generally well-tolerated.

3.1.3 OMC-SXB-21

3.1.3.1 Rationale for OMC-SXB-21

In January 2000, the FDA indicated a requirement for a trial to assess the long-term efficacy of Xyrem in narcoleptic patients. Conventional controlled clinical trial designs to assess long-term efficacy require patients to be randomized into prolonged placebo and active treatment groups. In narcolepsy, a conventional trial would have required patients to withdraw and washout from existing anti-cataplexy medications, [narcoleptics are typically treated with tricyclic antidepressants (TCAs) or serotonin selective reuptake inhibitors (SSRIs)] followed by establishment of baseline levels of cataplexy prior to being randomized into treatment groups. A trial using this conventional design would have presented several difficulties. First, participation would have caused severe hardship for the patients in the placebo group, who would have been without any treatment for cataplexy for the duration of the trial. Second, the potential of not receiving long-term therapy for cataplexy would have resulted in substantial difficulties in the recruitment of sufficient numbers of patients to make the trial statistically robust. These design difficulties necessitated the development of an alternative paradigm for assessing long-term efficacy. The new study paradigm, which became the OMC-SXB-21 protocol, was an adaptation of a design suggested by the Neuropharmacology Division of the FDA. The agency provided extensive input on both study conduct and statistical analysis issues. To assess long-term efficacy, patients in the OMC-SXB-21 trial were removed from stable, long-term, open-label Xyrem therapy in a double-blinded fashion and a return of cataplexy was assessed as the primary efficacy endpoint.

3.1.3.2 Trial Objectives and Design

3.1.3.2.1 Efficacy Objective

OMC-SXB-21 was a Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial to assess the long-term efficacy of orally administered Xyrem, compared to placebo, for the treatment of narcolepsy. The primary objective of this trial was to provide evidence for the long-term efficacy of Xyrem (sodium oxybate) based on the return of cataplexy symptoms upon cessation of a minimum of 6 months of open-label treatment with sodium oxybate. The measure of efficacy was a comparison between the Xyrem and placebo groups, of the change in the number of cataplexy attacks from baseline (2-week single-blind lead-in active treatment phase) to endpoint (2-week double-blind active or placebo treatment phase).

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3.1.3.2.2 Trial Design

The trial design is summarized in Table 3.15 and discussed below.

Table 3.15 OMC-SXB-21 Trial Design

Phase I Screening	**Phase II Lead-In**	**Phase III Double-Blind Treatment**
3 to 5 Days	**14 ± 2 Days (Week 1, Week 2)**	**14 ± 2 Days (Week 1, Week 2)**
Xyrem at established dosage	Single-blind Xyrem at established dosage	Xyrem at established dosage
		Placebo
Stimulant use permitted TCA/SSRI use not permitted		

↑ Visit 1 (Randomization) ↑ Visit 2 ↑ Visit 3 ↑ Visit 4

The trial consisted of 3 phases (4 visits). During Phases I and II, patients continued Xyrem at the same dosage they were taking in OMC-SXB-7 (3, 4.5, 6, 7.5, and 9g per night in divided doses). The period from Visit 1 to Visit 2 served to screen patients for inclusion and exclusion criteria and evaluate hematology and chemistry laboratory results. Patients were randomized immediately following Visit 1. During Phase II (lead-in), patients received single-blind Xyrem for 2 weeks (Visit 2 to Visit 3). In Phase III (double-blind), half the patients received Xyrem at their established dosage, and half received placebo in identical volume to their established Xyrem dose, for 2 weeks (Visit 3 to Visit 4). During Phases II and III, patients kept diaries to record the number of daily cataplexy attacks and adverse events. Patients who received placebo during the double-blind phase were predicted to have a higher incidence of cataplexy attacks than patients who received Xyrem.

3.1.3.2.3 Patient Selection Criteria

Patients were drawn from a pool of patients participating in OMC-SXB-7 (the open-label extension to OMC-GHB-3, OMC-SXB-6, and the Scharf trial). In addition to meeting the entry criteria for participating in the OMC-SXB-7 trial, patients were also required to meet the following criteria for inclusion in OMC-SXB-21:

- Had a history of at least 5 cataplexy attacks per week, confirmed through patient query or medical history, prior to receiving initial treatment (TCAs, SSRIs, and/or Xyrem) for cataplexy.
- Had been treated continuously for the symptoms of narcolepsy with sodium oxybate for a period of 6 months to 3.5 years. The patients must have been previously enrolled in Orphan Medical clinical trials OMC-GHB-3 or OMC-SXB-6.
- Had not been taking TCAs, SSRIs, or any other anti-cataplexy medications, other than Xyrem, within the 30-day period prior to Visit 1 of this trial.
- Stimulant medications were to be maintained at constant levels throughout the trial.

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Enrollment of up to 80 patients was planned for this trial. Fifty-five (55) patients were actually treated; all completed the trial.

3.1.3.2.4 Treatments

The Xyrem trial medication was an oral aqueous solution with a concentration of 500 mg/mL of sodium oxybate. Placebo was a sodium citrate solution in equimolar concentration to the sodium in Xyrem oral solution. Placebo was shown to be similar to Xyrem in a blinded taste test (Orphan Medical Protocol OMC-SXB-16).

During the single-blind lead-in phase of the trial, each patient took the same dosage of Xyrem oral solution (3.0, 4.5, 6.0, 7.5, or 9.0 g/d in 2 divided doses) previously taken in the OMC-SXB-7 trial. During the double-blind phase of the trial, patients received either Xyrem at the same dosage as at Visit 2, or placebo at an equivalent volume to the dosage of Xyrem that the patient took during the single-blind phase.

Trial medication was self-administered. Patient compliance was calculated at Visits 2 and 3. Patients were considered non-compliant with trial medication if they missed or exceeded their prescribed doses by 30% or more.

3.1.3.2.5 Randomization and Blinding

Randomization was performed centrally and occurred following the completion of Visit 1. At the request of the FDA, the randomization code was developed to ensure that there was not dose stratification across the placebo and Xyrem treatment groups. Separate randomization code sequences were developed for the existing OMC-SXB-7 treatment doses of 4.5 (3 g/d included in this grouping), 6, 7.5, and 9g/d. Neither the Orphan Medical clinical development representatives nor the clinical site personnel knew the identity of the double-blind medication.

3.1.3.2.6 Efficacy Measurements

Patients were asked to complete a daily diary each night before bedtime during the single-blind and double-blind phases of the trial. The information captured in the diaries was the number of cataplexy attacks the patient had experienced during that day and any AEs or other relevant medical information. A cataplexy attack, episode, or event was defined as a sudden bilateral loss of voluntary muscle tone. To be classified as cataplexy for this trial, the event must have been bilateral, of sudden onset and localized to a specific muscle group(s) or part of the body, and the patient must have been aware of time and place during the event (ie, not a sleep attack or microsleep).

3.1.3.2.7 Statistical Analysis

Efficacy analyses were performed using the Intent-to-Treat Patients population, which included all patients who received 1 or more doses of double-blind trial medication, and had baseline and post-baseline cataplexy measurements.

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The primary efficacy variable was the change in the number of cataplexy attacks between baseline (2-week, single-blind lead-in phase) and endpoint (double-blind treatment phase). If fewer or greater than 14 days were available for either treatment phase, then the average number of cataplexy attacks per day was calculated and multiplied by 14.

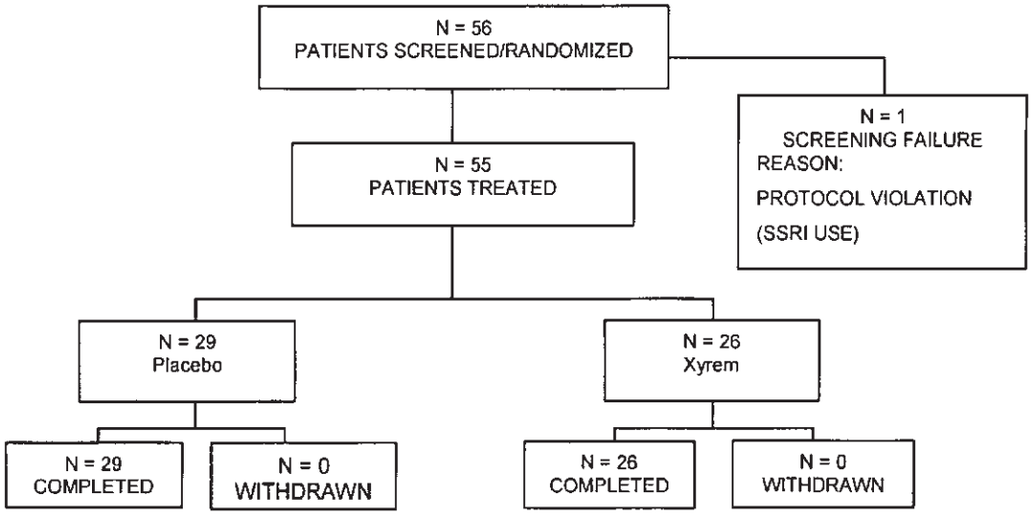
The change in the number of cataplexy attacks was analyzed using a nonparametric analysis of covariance (ANCOVA). Specifically, the baseline number of cataplexy attacks and the change from baseline in the number of cataplexy attacks were replaced by their corresponding ranks, where mean ranks were assigned in case of ties. The rank changes from baseline in the number of cataplexy attacks were analyzed using ANCOVA, including the rank baseline number of cataplexy attacks, treatment group, and baseline-by-treatment group interaction. The overall inference among treatments, placebo versus Xyrem, was presented. Two-sided p-values with a level of significance at 0.05 were used to determine statistical significance.

3.1.3.3 Patient Disposition and Demographics

3.1.3.3.1 Patient Disposition

Figure 3.12 presents the disposition of patients by treatment group. Fifty-six (56) patients were screened and randomized; 1 randomized patient failed screening due to concomitant use of an SSRI and was never treated. A total of 55 patients were treated; all completed the trial.

Figure 3.12 Disposition of Patients



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3.1.3.3.2 Patient Demographics

Patient demographic data revealed no significant differences in patient age, gender, weight, height, race, or baseline number of cataplexy attacks between the treatment groups. Table 3.16 summarizes patient demographics and current dosage at screening by treatment group. Prior to trial entry, patients had been taking Xyrem (sodium oxybate) for 7 to 44 (mean = 21) months for the treatment of narcolepsy.

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Table 3.16 Demographics and Baseline Characteristics by Treatment Group

Characteristics	Total (N=55)	Treatment Group		p-Value
		Xyrem (N=26)	Placebo (N=29)	
Age (years)				
Mean ± SD	47.7 ± 16.66	47.9 ± 17.06	47.6 ± 16.60	0.955
Range	16.3 – 82.6	19.1 – 82.6	16.3 – 70.0	
Gender (n, %)				
Male	23 (42%)	8 (31%)	15 (52%)	0.172
Female	32 (58%)	18 (69%)	14 (48%)	
Weight (kg)				
Mean ± SD	80.5 ± 20.09	83.8 ± 24.31	77.6 ± 15.22	0.250
Range	54.0 – 142.0	54.0 – 142.0	55.0 – 127.0	
Height (cm)				
Mean ± SD	170.1 ± 10.25	169.6 ± 10.42	170.6 ± 10.24	0.710
Range	152.0 – 188.0	152.0 – 188.0	155.0 – 188.0	
Race (n, %)				
Caucasian	52 (95%)	23 (88%)	29 (100%)	0.099
African-American	2 (4%)	2 (8%)	0	
Asian	0	0	0	
Hispanic	1 (2%)	1 (4%)	0	
Other	0	0	0	
Time on Xyrem (months)				
Mean ± SD	21.22 ± 12.28	23.27 ± 12.36	19.38 ± 12.13	ND
Range	7 – 44	8 – 38	7 – 44	

(continued)

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Table 3.16 Demographics and Baseline Characteristics by Treatment Group

Characteristics	Total (N=55)	Treatment Group		p-Value
		Xyrem (N=26)	Placebo (N=29)	
Cataplexy attacks (2-week baseline)				
N	55	26	29	0.436
Mean	12.6	9.0	15.7	
SD	31.75	19.25	39.88	
Median	3.0	1.9	4.0	
Minimum	0.0	0.0	0.0	
Maximum	197.0	86.8	197.0	
Daily Dosage of Xyrem at Screening (n, %)				
3.0 g/d	2 (4%)	1 (4%)	1 (3%)	ND
4.5 g/d	9 (16%)	4 (15%)	5 (17%)	
6.0 g/d	15 (27%)	7 (27%)	8 (28%)	
7.5 g/d	15 (27%)	7 (27%)	8 (28%)	
9.0 g/d	14 (25%)	7 (27%)	7 (24%)	

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3.1.3.4 Efficacy Evaluation

3.1.3.4.1 Treatment Compliance

Only 3 (5%) patients (1 placebo, 2 Xyrem) had compliance levels outside the protocol-acceptable range during one or both phases of the trial.

3.1.3.4.2 Efficacy Results

As shown in Table 3.17 and Figure 3.13, there was no change in the number of cataplexy attacks from baseline to endpoint in the Xyrem group (median change 0.0), while cataplexy attacks increased by a median of 21.0 in the placebo group. This difference was statistically significant ($p < 0.001$) when analyzed by an ANCOVA model containing rank baseline, treatment group, and baseline-by-treatment group interaction, with a median rank change from baseline of 39.0 for the placebo group and 16.5 for the Xyrem group.

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Table 3.17 Change From Baseline in Number of Cataplexy Attacks and Rank Change (Per 2 Weeks) by Treatment Group — Intent-to-Treat Patients

	Xyrem (N=26)			Placebo (N=29)		
	Phase II	Phase III	Change	Phase II[a]	Phase III	Change
Number of cataplexy attacks (per 2 weeks)						
Mean ± SD	9.0 ± 19.25	12.6 ± 30.34	3.6 ± 20.73	15.7 ± 39.88	50.4 ± 81.09	34.6 ± 55.72
Median	1.9	1.1	0.0	4.0	21.0	21.0
Minimum	0.0	0.0	-24.3	0.0	0.0	-15.0
Maximum	86.8	138.3	87.2	197.0	269.2	206.2
Rank change						
Mean ± SD			18.1 ± 12.65			36.9 ± 13.31*
Median			16.5			39.0
Minimum			1.0			3.0
Maximum			52.0			55.0

SD = standard deviation.
[a] Placebo group patients received Xyrem during Phase II.
* $p < 0.001$, from ANCOVA model containing rank baseline, treatment group, and baseline-by-treatment group interaction.

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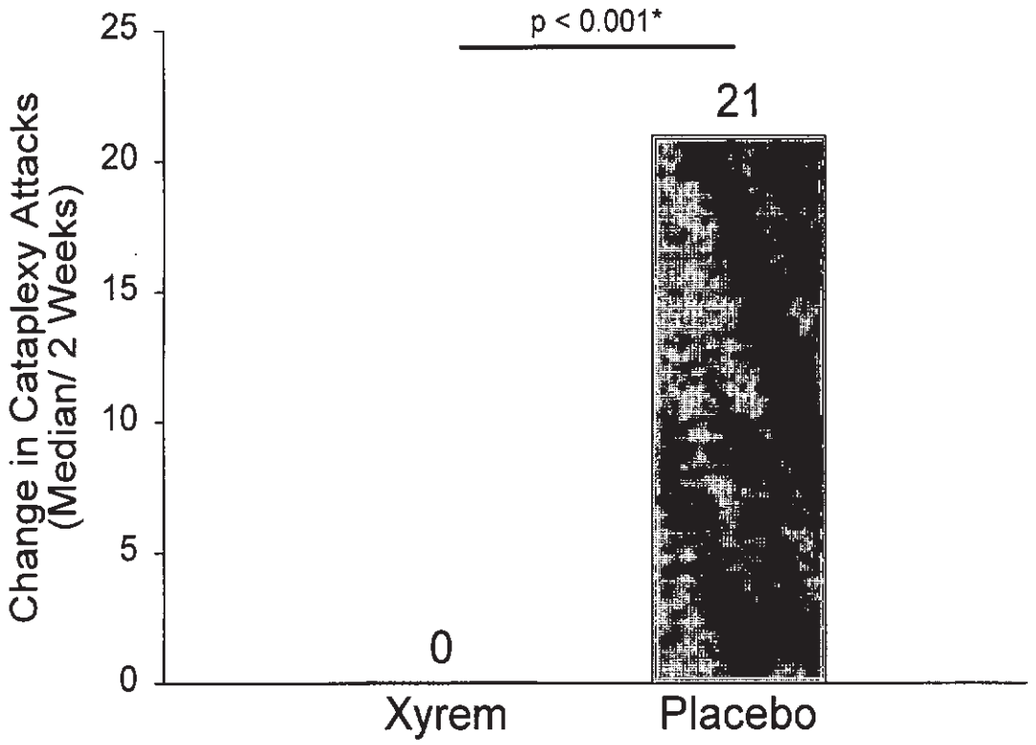
Figure 3.13 Median Change from Baseline in Number of Cataplexy Attacks



* p < 0.001, from ANCOVA model containing rank baseline, treatment group, and baseline-by-treatment group interaction.

As shown in Table 3.18 and Figure 3.14, change from baseline in the number of cataplexy attacks by week during the double-blind period mirrors the overall change from baseline: no change in the Xyrem group (median change 0.0, each week), while cataplexy attacks increased in the placebo group by a median of 4.2 in Week 1, and 11.7 in Week 2.

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Table 3.18 Change from Baseline by Week During the Double-Blind Treatment Period in the Number of Cataplexy Attacks by Treatment Group — Intent-to-Treat Patients

Number of Cataplexy Attacks	Xyrem			Placebo		
	Phase II[a]	Phase III	Change	Phase II[a]	Phase III	Change
Week 1						
Number of Patients	26	26	26	29	29	29
Mean ± SD	4.5 ± 9.62	5.3 ± 11.84	0.8 ± 7.48	7.9 ± 19.94	21.1 ± 35.13	13.2 ± 22.02
Median	0.9	1.0	0.0	2.0	7.0	4.2
Minimum	0.0	0.0	-15.4	0.0	0.0	-7.5
Maximum	43.4	50.8	25.2	98.5	126.0	87.5
Week 2						
Number of Patients	26	26	26	29	29	29
Mean ± SD	4.5 ± 9.62	7.2 ± 18.66	2.7 ± 13.74	7.9 ± 19.94	29.7 ± 47.30	21.8 ± 35.16
Median	0.9	0.5	0.0	2.0	13.0	11.7
Minimum	0.0	0.0	-10.7	0.0	0.0	-7.5
Maximum	43.4	87.5	62.0	98.5	168.0	143.5

[a] Baseline (Phase II) was determined by normalizing the total number of cataplexy attacks during the 2-week Phase II period to 7 days.

Data Source: Appendix Section 14.2.4, Summary Tables 14.2.4.1 and 14.2.4.2.

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Figure 3.14 Median Change from Baseline by Week During the Double-Blind Treatment Period in the Number of Cataplexy Attacks — Intent-to-Treat Patients

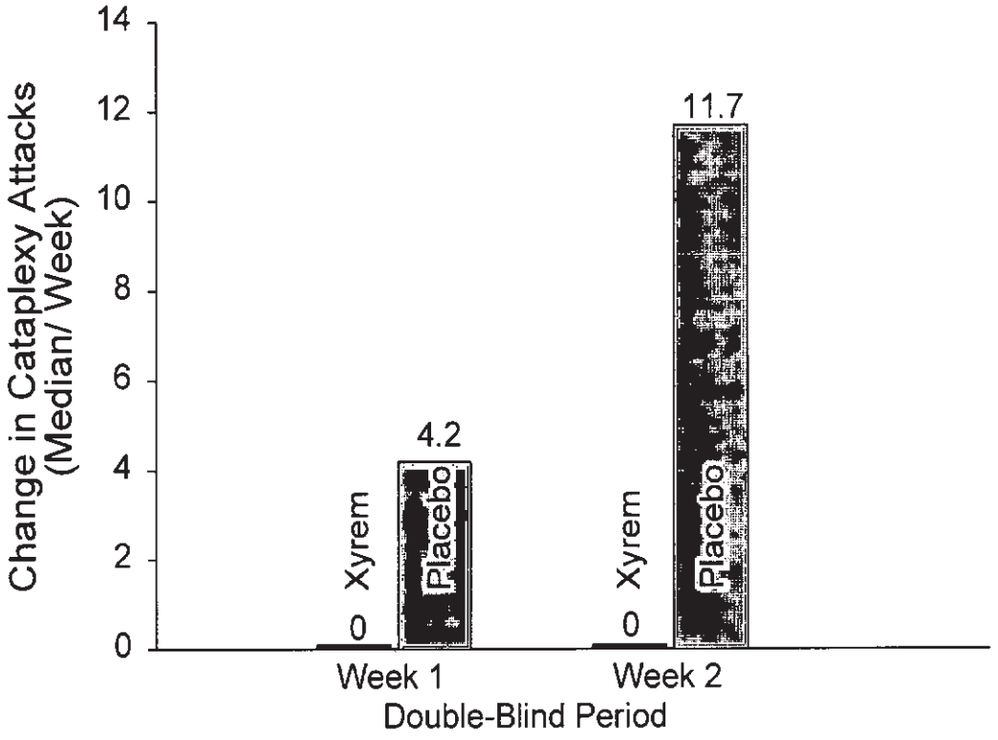

Figure 3.15 is a by-patient display of observed number of cataplexy attacks during Weeks 1 and 2 of the baseline period and during Weeks 1 and 2 of the double-blind treatment period. Solid lines are patients treated with placebo during double-blind treatment; dotted lines are patients treated with Xyrem. Because of the outliers (several patients had over 100 cataplexy attacks per week during Week 2 of the double-blind treatment period), it is difficult to discern a pattern among the data. Figure 3.16 is a by-patient display of observed number of cataplexy attacks over the course of the trial presented by treatment group. In this figure, for clarity, the 6 patients (4 placebo, 2 Xyrem) with values above 40 per week at any time are not displayed. It can be seen that patients who continued to receive Xyrem during double-blind treatment overwhelmingly maintained the low number of cataplexy attacks seen during the baseline period. In contrast, many patients who received placebo during the double-blind treatment phase showed increases at both Weeks 1 and 2, providing visual confirmation of the statistically significant increase (change from baseline) in median number of cataplexy attacks indicated by the summary statistics in Table 3.17 and Figure 3.13.

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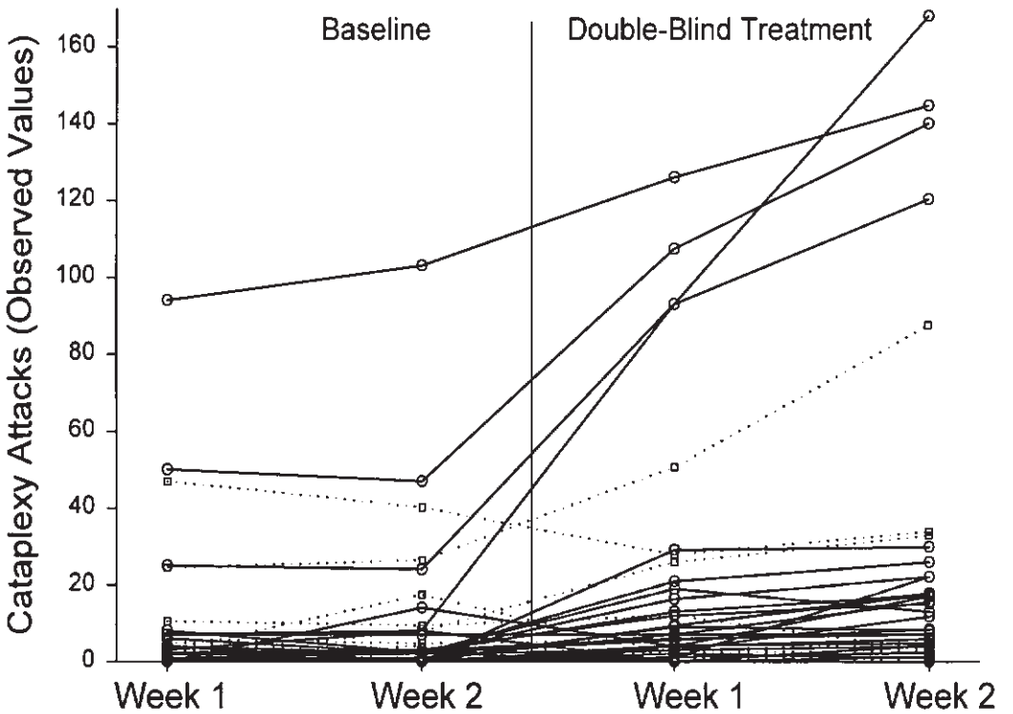
Figure 3.15 Observed Number of Cataplexy Attacks at Each Visit



Solid lines are patients treated with placebo during double-blind treatment; dotted lines are patients treated with Xyrem.

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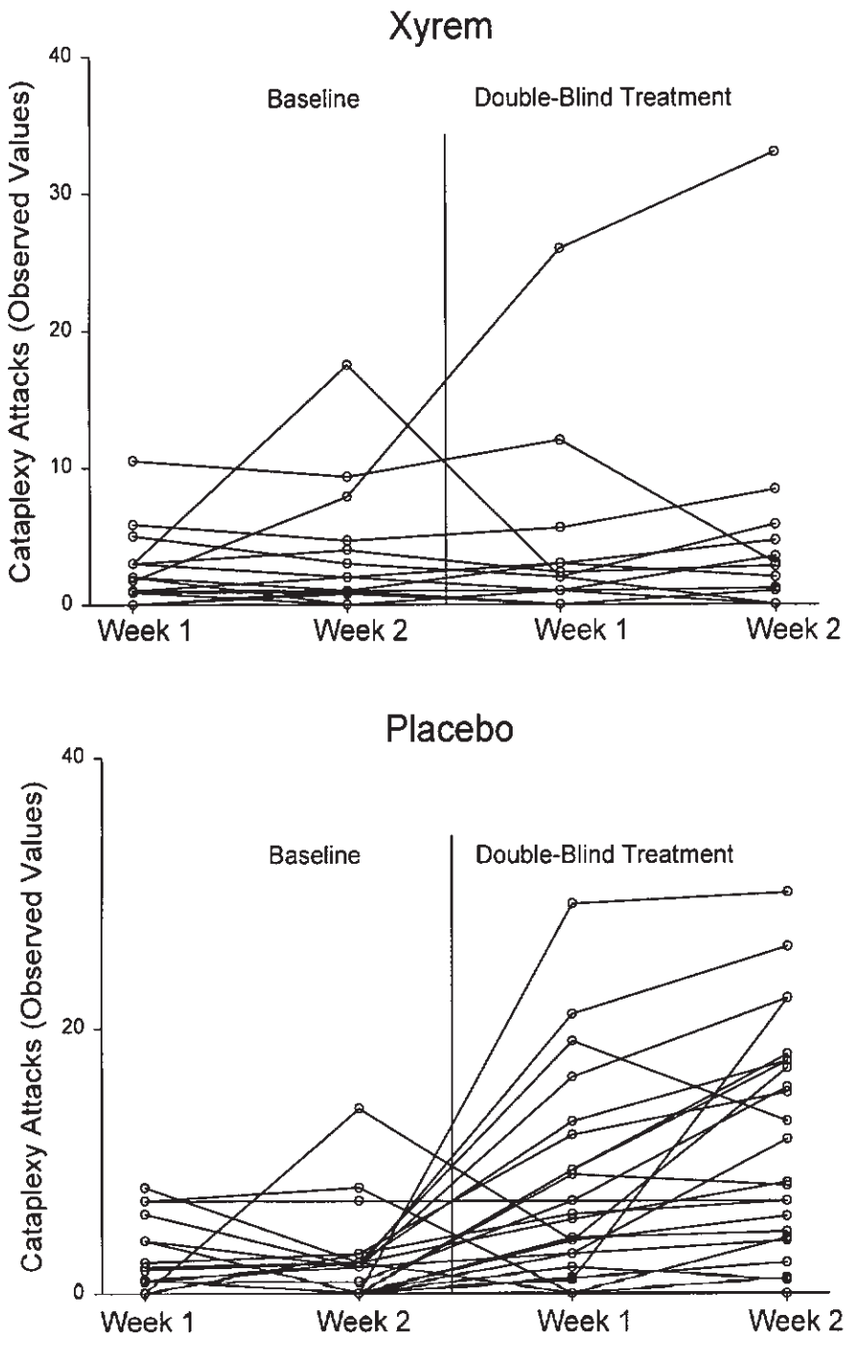
Figure 3.16 Observed Number of Cataplexy Attacks at Each Visit by Treatment Group



Six patients (4 placebo, 2 Xyrem) with values above 40 per week at any time are not displayed.

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3.1.3.4.3 Efficacy Conclusions

OMC-SXB-21 was a randomized, double-blind, placebo-controlled, parallel group, multicenter trial to assess the long-term efficacy of orally administered Xyrem when compared to placebo. Patients entering this trial were using open-label Xyrem for the treatment of narcolepsy for a period of 7 to 44 months (mean = 21 months).

During the lead-in (baseline) phase of the trial, patients continued to take Xyrem in a single-blind fashion at their established effective dosage. The frequency of cataplexy attacks was measured during the 2-week baseline period by patient entries into daily diaries. There was no statistical difference ($p = 0.436$) between treatment groups in the mean number of cataplexy attacks during this period.

Following the baseline period, patients entered the 2-week double-blind treatment phase, where the frequency of cataplexy attacks was captured in daily diaries. Patients given placebo had significantly more cataplexy attacks (median change 21.0) than did patients who continued on active Xyrem treatment (median change 0.0). When the rank change was analyzed, a statistically significant difference was seen ($p < 0.001$), with a median rank change from baseline of 39.0 for the placebo group and 16.5 for the Xyrem group. As shown in Table 3.18 and Figure 3.14, change from baseline in the number of cataplexy attacks by week during the double-blind period mirrors the overall change from baseline: no change in the Xyrem group (median change 0.0, each week), while cataplexy attacks increased in the placebo group by a median of 4.2 in Week 1, and 11.7 in Week 2.

These data strongly indicate that Xyrem is an effective long-term treatment for the control of the narcolepsy symptom of cataplexy.

3.1.4 LAMMERS TRIAL

3.1.4.1 Design

The Lammers trial (The Netherlands) was a prospective, randomized, double-blind, placebo-controlled, 2-way crossover, single-center trial comparing the efficacy of 60 mg/kg (mean 4.7 g) sodium oxybate with placebo for the treatment of narcolepsy. The total nightly dose of trial medication was taken in 2 equal doses: just before going to sleep, and again 4 hours later. Each dose was administered orally in a solution containing sugar, citric acid, crème de cacao essence, and distilled water; placebo also contained trisodium citrate, and sodium chloride. The trial design is summarized in Table 3.19.

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Table 3.19 Lammers Trial Design

Baseline 1	Treatment 1	Washout	Baseline 2	Treatment 2
1 Week	4 Weeks	3 Weeks	1 Week	4 Weeks
X	Sodium Oxybate (60 mg/kg)	X	X	Placebo
X	Placebo	X	X	Sodium Oxybate (60 mg/kg)
Continue concomitant treatment for cataplexy and EDS				

The trial consisted of two 5-week periods (1 week baseline observation, 4 weeks treatment) separated by a 3-week washout period. In each of the treatment periods, patients took randomly assigned trial medication (60 mg/kg [mean 4.7 g] sodium oxybate) or a similar placebo) in 2 divided doses at bedtime and 4 hours later as an added medication to existing therapy for narcolepsy. A total of 13 men and 12 women were treated; all completed the trial. One patient (patient 13) failed to keep his diary and was not evaluable.

To enter the trial, patients were required to have had a combination of sleep attacks during the day, and at least 1 of the "REM dissociation phenomena" (cataplexy, hynagogic hallucinations, and sleep paralysis); or, in case of clinical doubt, a positive multiple sleep latency test as recorded with a 24-hour EEG was required.

Patients were allowed to continue taking anti-cataplectic medications (TCAs/SSRIs) they had been using prior to enrollment in the trial; hence, sodium oxybate (or placebo) treatment was taken in addition to the patients' ongoing anti-cataplectic regimen (in contrast to OMC-GHB-2 and the Scrima trial, where anti-cataplectic medication was withdrawn prior to treatment with sodium oxybate). As in the OMC-GHB-2 trial and the Scrima trial, patients were allowed to continue on their stimulant medication for excessive daytime sleepiness at a constant dosage. Patients with cataplexy of relatively mild severity (approximately 5 attacks per week at baseline) were enrolled into the trial.

3.1.4.2 Objectives

Primary efficacy parameters were:

- The opinion of the patients on the benefit of the medication (global therapeutic impression [GTI])
- The opinion of the physician (global clinical impression; [GCI]) was not performed
- The number of cataplexy attacks per day

Secondary efficacy parameters were:

- The number of sleep attacks during the day
- The feeling of sleepiness during the day
- MSLT improvement of the two shortest latencies

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- The stability of alertness during the day
- The duration of the nocturnal slow wave sleep on PSG
- The number of stage-shifts at night

The tolerability and safety of the medication was assessed by interviewing the patients. Comments with respect to tolerability were recorded on the patient questionnaires.

3.1.4.3 Statistical Analysis

In the published report (Lammers *et al* [1993]) intragroup differences were analyzed using Wilcoxon's signed-rank test. As a post-hoc reanalysis, an analysis of covariance was used employing a model appropriate for a crossover design. The significance of the covariate was (also) examined. Residuals were analyzed using the Shapiro-Wilk test and non-parametric methods (Wilcoxon).

3.1.4.4 Efficacy Results

In the primary efficacy analysis reported in the publication derived from this study (Lammers *et al* [1993]), statistically significant differences between placebo and sodium oxybate-treated groups in the number of cataplexy attacks were not seen. Although the primary endpoint as analyzed according to the original statistical analysis plan did not reach statistical significance, it should be noted that patients enrolled in this trial presented with a much lower rate of cataplexy than seen in either OMC-GHB-2 or the Scrima trial (Lammers patients reported about one-fourth the rate of cataplexy attacks at baseline as did patients in either OMC-GHB-2 or the Scrima trial). In addition to this much lower rate of cataplexy, patients were allowed to continue using anti-cataplectic medication (TCAs/SSRIs) throughout the course of the trial. With such a low severity of disease at baseline, and in the presence of concomitant anti-cataplectic therapy, a robust treatment effect might prove difficult to demonstrate.

In addition, this non-significant p-value (reported in Lammers et al 1993) was obtained using a statistical model that treated each of the two drug administration periods as though they comprised two *independent* samples of patients. When these data were reanalyzed using a statistical model more appropriate for a crossover design (ANCOVA) that included treatment order, patient, period, and baseline cataplexy rate, the difference between placebo and sodium oxybate-treated groups was highly statistically significant ($p = 0.002$).

The number of cataplexy attacks/week by treatment group are presented in Figure 3.17.

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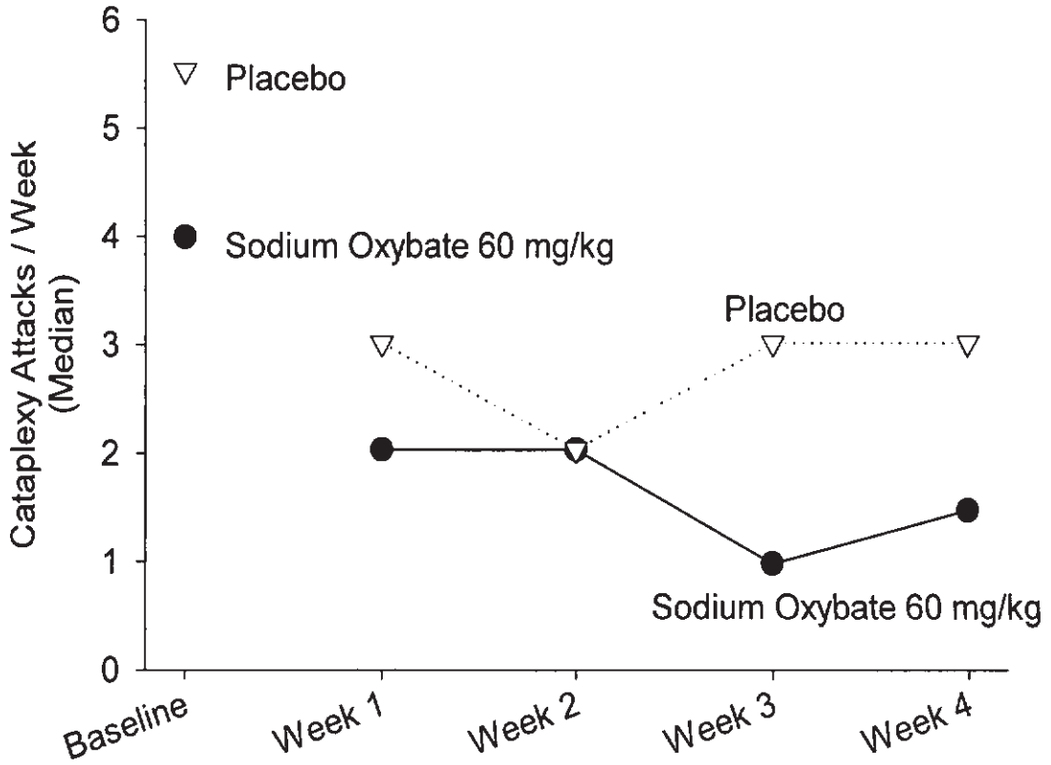
Figure 3.17 Number of Cataplexy Attacks by Treatment Group — Lammers Trial



In the Lammers trial (publication), the Global Therapeutic Impression of Change (GTI) as rated by the patients was significantly more often in favor of sodium oxybate; 15/24 (62.5%) patients reported a beneficial effect during sodium oxybate treatment compared to 2/24 (8.3%) patients during placebo treatment (p =<0.001).

Marked improvements in excessive daytime sleepiness were evident. Statistically significant between treatment reductions in daytime sleepiness (p = 0.028) (based on the patient's assessment of the feeling of sleepiness recorded on a visual analogue scale), inadvertent naps/sleep attacks (p = 0.001) (recorded on the patient diary) resulted following 60 mg/kg (mean 4.7 g) sodium oxybate.

Reanalysis of the data using a statistical model more appropriate for a crossover design also revealed a highly significant (p = 0.002) reduction in the number of cataplexy attacks.

Among polysomnographic variables, the number of awakenings during REM sleep and the percentage of wakefulness during REM sleep (p = 0.016 and 0.007, respectively) were also improved. There were also statistically significant between treatment changes in hypnagogic hallucinations (p = 0.008).

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3.1.4.5 Conclusions

The Lammers *et al* (1993) publication reported that sodium oxybate is an effective and well-tolerated treatment for symptoms of narcolepsy. Statistically significant between treatment reductions in daytime sleepiness ($p = 0.028$), inadvertent naps/sleep attacks ($p = 0.001$), and the patient GTI ($p<0.001$) following 60 mg/kg (mean 4.7 g) sodium oxybate. The number of awakenings during REM sleep, the percentage of wakefulness during REM sleep, and the frequency of hypnagogic hallucinations were also improved. Reanalysis of the data using a statistical model more appropriate for a crossover design also revealed a highly significant ($p = 0.002$) reduction in the number of cataplexy attacks.

3.2 Uncontrolled Studies

3.2.1 OMC-GHB-3

3.2.1.1 Trial Objectives and Design

3.2.1.1.1 Objectives

OMC-GHB-3 was an open-label, long-term extension of the OMC-GHB-2 double-blind trial. The primary objective of this study was to evaluate the safety of sodium oxybate when used in patients with narcolepsy for up to 24 months at doses of 3g, 4.5g, 6g, 7.5, or 9g daily. The secondary objective of this study was to evaluate the following measures of efficacy:

- Incidence of 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 the number of awakenings during the night and the total amount of sleep
- Incidence of hypnagogic hallucinations
- Incidence of sleep paralysis
- Clinical Global Impressions of Change in Severity
- Ability to Concentrate
- Quality of Sleep
- Level of Alertness

3.2.1.1.2 Trial Design

Visit 1 occurred concurrently with Visit 7 of OMC-GHB-2. Patients were not randomized to dose. All patients were to begin the study on 6g daily and investigators were required to titrate the patients to the optimum dose (3g, 4.5g, 6g, 7.5g, or 9g sodium oxybate) based on safety and efficacy. Patients made study site visits every 2 weeks during the first month of the trial, (Visits 2 and 3); one month later (Visit 4); then at 2-month

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intervals (Visits 5 – 12) for months 4 - 18; then at 3-month intervals (Visits 13 and 14) for months 21 and 24. Primary clinical endpoints were the two week intervals immediately preceding Visits 3, 4, 5, 6, 7, 8 and 9.

Efficacy information was collected using patient diaries through Month 18; for the Month 21 and 24 assessments it was collected via a patient questionnaire completed by the patient during the study site visit.

During these visits the following procedures were performed:

Visit 1

- Administration of Epworth Sleepiness Scale
- Administration of Clinical Global Impressions of Change in Severity

Visits 2 - 12

- Collection and review of all diaries
- Administration of Epworth Sleepiness Scale
- Administration of Clinical Global Impressions of Change in Severity

Visits 13 and 14

- Narcolepsy Symptom Assessment administration

3.2.1.1.3 Patient Selection Criteria

Participation was offered to all patients completing OMC-GHB-2, if they so wished and their physician concurred. They were still required to meet all the same entry criteria with the exception of a minimum incidence of cataplexy of 3 times per week. In addition, patients could not be taking medication for their disease other than a stable dose of stimulant medication.

3.2.1.1.4 Treatments

Patients entering OMC-GHB-3 were to begin the trial with 6g of sodium oxybate nightly. The total nightly dose was divided into 2 equal doses. If indicated, the sodium oxybate dose could be decreased to 3g or 4.5g per night, or increased to 7.5g or 9g per night. After the individualized dose of sodium oxybate was established, patients were to maintain that dose from Visit 2 through the completion of the trial, although dose changes after Visit 2 were permitted if clinically indicated. Patients were considered non-compliant if they missed more than 30% of their expected doses during any period between scheduled visits.

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3.2.1.1.5 Efficacy Measurements and Analysis

Patients were instructed to complete diaries on several efficacy measures. These measures included:

- Total number of cataplexy attacks
- Number of complete cataplexy attacks
- Number of partial cataplexy attacks
- Number of inadvertent naps and sleep attacks
- Number of planned naps
- Duration of planned naps
- Number of times patient woke up during the night
- Total amount of sleep
- Number of episodes of hypnagogic hallucinations
- Number of episodes of sleep paralysis
- Ability to Concentrate
- Quality of Sleep
- Level of alertness in morning

Non-diary measures of efficacy included the following:

- Epworth Sleepiness Scale
- Severity of the patient's symptoms as measured by the Clinical Global Impression of Change

The primary efficacy parameter was the change in the total number of cataplexy attacks (TNCA) from baseline (from OMC-GHB-2 trial) to endpoint. Change in TNCA was evaluated based on the weekly average of the TNCA. Since diary entries were not always completed for an assessment period (2 weeks), the completed TCNA data were normalized by calculating the daily average of the endpoint two-week interval and multiplying by 7.

Other efficacy parameters collected during the study were considered secondary measures.

3.2.1.1.6 Statistical and Analytical Plans

The following definitions were used for the planned analyses of this study:

Baseline = the Baseline period in the OMC-GHB-2 trial as defined in the protocol. Baseline for "Overall Ability to Concentrate, Quality of Sleep, and Level of Alertness", was taken from Visit 2 in OMC-GHB-3.

Endpoints = the two week intervals immediately preceding Visits 3, 4, 5, 6, 7, 8 and 9 in the 12-month OMC-GHB-3 trial. The two week intervals immediately preceding Visits 10, 11, and 12 for the 12 month follow-up period.

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Statistical analysis was performed on an intent-to-treat population. All patients who received a single dose of study medication during the trial were included. Treatment groups were developed by calculating the average dose used over the course of the study and rounding to the nearest dose category.

The average total number of cataplexy attacks was the primary efficacy measure. Overall treatment group comparison of the log mean change from baseline for TCNA was determined using analysis of covariance (ANCOVA) using the model:

log(TNCA+1) – Baseline log(TNCA+1) = Treatment + Baseline Log(TNCA+1)

No pairwise comparisons were performed. Within-group and All Patient analyses were performed using Wilcoxon Sign Rank Test.

For the secondary efficacy measures, selected statistical testing was performed. For continuous measures, ANCOVA was used to examine overall treatment effect. Within-group comparisons were performed using paired t-tests. For dichotomous secondary efficacy measures, Fisher's Exact test was utilized to examine overall treatment effect.

3.2.1.2 Patient Disposition and Demographics

3.2.1.2.1 Patient Disposition

By protocol amendment, patients could continue the study for up to 24 months, however, data were analyzed in detail only for the 12-month study duration indicated in the original protocol. Efficacy and safety were analyzed in summary for up to 18 months and 24 months, respectively.

The disposition of patients through 12 months of the study from the combined dose categories is shown in Figure 3.18. Disposition of patients through 24 months is presented in Table 3.20.

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Figure 3.18 Disposition of Patients in OMC-GHB-3 Through 12 Months

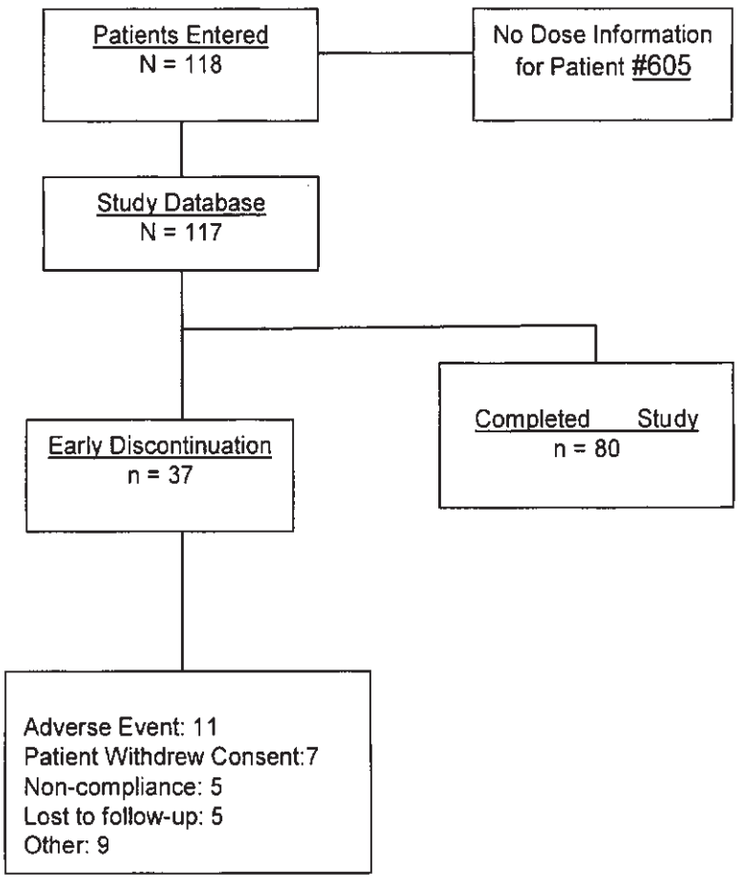

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Table 3.20 Disposition of Patients in OMC-GHB-3 Months 12 to 24

	Visit (Month)				
Reason For Withdrawal	9 (12 M)	10 (14 M)	11 (16 M)	12 (18 M)	14 (24 M)
AE	0	1	0	0	0
LOST TO FOLLOW-UP	2	1	0	0	0
NON-COMPLIANCE	2	1	2	2	0
PROTOCOL VIOLATION	0	1	0	0	0
WITHDREW CONSENT	1	1	1	0	2
OTHER	0	1	0	3	1
COMPLETED STUDY	0	2	6	7	39
TOTAL	5	8	9	12	42
Visit	9	10	11	12	14
Active Patients	76	71	63	54	42

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3.2.1.2.2 Patient Demographics

The demographic characteristics of the 117 patients who received study medication are summarized in Table 3.21 below.

Table 3.21 Baseline Demographic Characteristics of Study Population (OMC-GHB-3)

Characteristic	All Patients	GHB dose (g) 3	4.5	6	7.5	9	p-value*
	N (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Age (years)							0.262
N	117	15	20	37	25	20	
MEAN	43.4	44.9	48.7	44.3	39.5	40.2	
SD	15.1	14.1	14.7	14.5	17.0	14.1	
MIN	18.0	20.0	25.0	22.0	18.0	24.0	
MAX	79.0	73.0	71.0	67.0	79.0	65.0	
Gender							0.002
Male	51 (43.6)	1 (6.7)	7 (35.0)	15 (40.5)	15 (60.0)	13 (65.0)	
Female	66 (56.4)	14 (93.3)	13 (65.0)	22 (59.5)	10 (40.0)	7 (35.0)	
Race							1.000
Caucasian	108 (92.3)	14 (93.3)	19 (95.0)	33 (89.2)	23 (92.0)	19 (95.0)	
African-American	7 (6.0)	1 (6.7)	1 (5.0)	2 (5.4)	2 (8.0)	1 (5.0)	
Asian	1 (0.9)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	
Other	1 (0.9)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	
Height (cm)							0.017
N	99	12	16	28	24	19	
Mean	172.3	164.9	171.4	172.5	176.2	172.5	
SD	9.4	6.1	10.8	9.9	7.5	9.3	
Weight (kg)							0.003
N	106	13	17	32	24	20	
Mean	83.7	67.0	80.6	85.4	89.5	87.6	
SD	18.0	14.7	16.9	17.1	20.6	12.6	
MIN	48.5	49.4	57.2	48.5	60.8	66.2	
MAX	134.3	93.0	116.1	113.0	134.3	118.0	

*p-value: Age based on ANOVA (GLM);
Sex and Race based on Fisher's Exact Test.
Baseline = the Baseline period in Study OMC-GHB-02.

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Statistically significant differences across treatment groups were noted for sex. Additional statistically significant differences across treatment groups were noted for height and weight, consistent with the differences in distribution by sex. The majority of the 3g, 4.5g, and 6g sodium oxybate groups were female, and the majority of the 7.5g and 9g sodium oxybate groups were male.

3.2.1.3 Efficacy Evaluation

3.2.1.3.1 Treatment Compliance

At each study visit through 18 months, the overall patient population was 94% compliant with study medication through 18 months of the study.

3.2.1.3.2 Efficacy Results

By protocol amendment, patients could continue the study for up to 24 months, however, data were analyzed only for the 12-month study duration indicated in the original protocol.

For all efficacy parameters, change from baseline evaluations at specific visits represented comparison to the same measures from the OMC-GHB-2 trial end of baseline period (Visit 4).

Total number of cataplexy attacks. The results presented in Table 3.22, a summary of mean change from baseline to all endpoints for total number of cataplexy attacks per week by visit, show the significant effect produced by all combined dose groups on this primary efficacy parameter. Graphical display for cataplexy attacks per week by visit through 18 months for the median percent change from baseline, are presented in Figure 3.19. Figure 3.19 shows that that majority of the reduction in cataplexy attacks occurred during the first month of sodium oxybate treatment; there was a greater than 75% median reduction in cataplexy attacks at Visit 3 (month 2 from Baseline, month 1 of OMC-GHB-03 study treatment) and an almost 90% median reduction in cataplexy attacks at Visit 4 (month 3 from Baseline, month 2 of OMC-GHB-03 study treatment).

Graphical display for cataplexy attacks per week by dose through 12 months for the median percent change from baseline, are presented in Figure 3.20. Values were calculated from the distribution of change values for each individual. Figure 3.20 displays that there are no dose differences for change in cataplexy attacks with sodium oxybate treatment when patients are titrated to clinical effect. Greater than 90% median reduction was maintained through 18 months of study treatment (19 months from Baseline).

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Table 3.22 Change and Percent Change From Baseline to Endpoints for Total Number of Cataplexy Attacks per Week by Visit Through 18 Months (OMC-GHB-3)

	Visit Number (month)									
	3 (1 m)	4 (2 m)	5 (4 m)	6 (6 m)	7 (8 m)	8 (10 m)	9 (12 m)	10 (14 m)	11 (16 m)	12 (18 m)
Change from baseline to Visit										
N[1]	103	102	93	89	83	77	75	71	62	52
Mean[2]	-23.65	-27.50	-30.91	-32.24	-34.70	-34.51	-35.48	-36.79	-35.47	-36.14
SD	33.04	36.89	41.92	42.73	43.22	43.68	43.49	45.92	39.27	43.18
Median	-15.08	-18.25	-18.67	-19.00	-22.56	-22.17	-23.00	-23.60	-25.08	-20.08
1st Quart.	-27.00	-32.17	-34.35	-35.00	-37.83	-38.00	-38.00	-41.46	-41.00	-44.49
3rd Quart.	-5.50	-7.39	-10.00	-9.13	-11.00	-11.00	-10.50	-10.84	-11.81	-11.07
p-value*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
% Change from baseline to Visit										
Mean[2]	-61.09	-72.24	-77.93	-81.89	-86.40	-73.12	-80.05	-84.03	-85.38	-83.19
SD	60.02	46.63	35.53	29.75	25.14	79.29	42.04	30.92	22.91	25.40
Median	-76.67	-88.24	-89.53	-92.50	-96.96	-92.19	-93.08	-94.35	-95.28	-92.68
1st Quart	-93.91	-98.37	-98.00	-100.00	-100.00	-100.00	-99.73	-100.00	-100.00	-99.60
3rd Quart	-50.39	-68.07	-77.42	-80.96	-84.87	-79.03	-77.78	-83.20	-79.76	-78.61
p-value*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

[1]N reflects all patients with available data for number of cataplexy attacks at that visit.
[2]Weekly average total number of cataplexy attacks (TNCA) assessed as: (Daily average of the endpoint two week interval)*7
*p-value(Within Group) based on Wilcoxon Sign Rank test for change from baseline.

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Figure 3.19 Median Percent Change from Baseline for Total Number of Cataplexy Attacks Per Week through 18 Months (OMC-GHB-3)

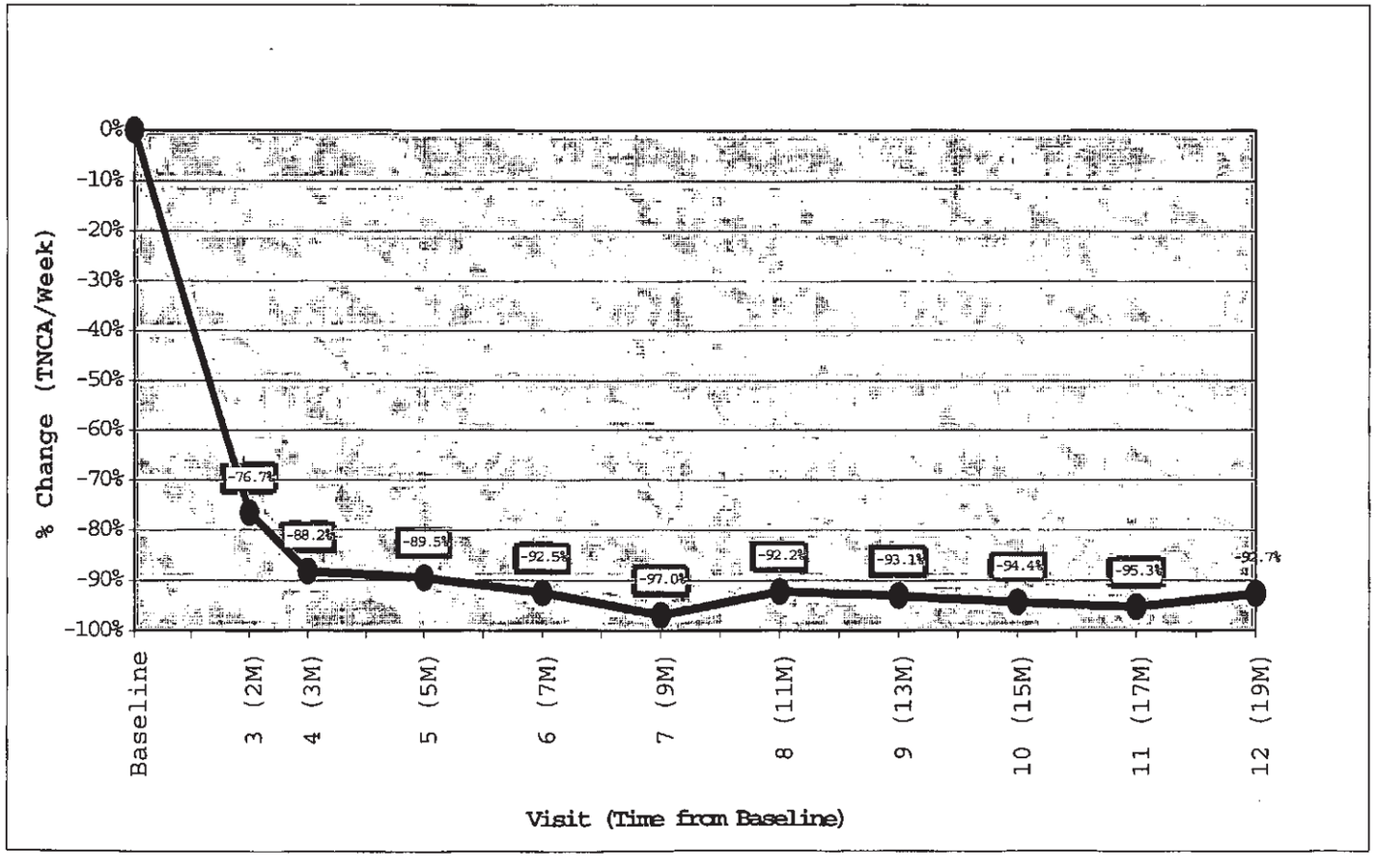

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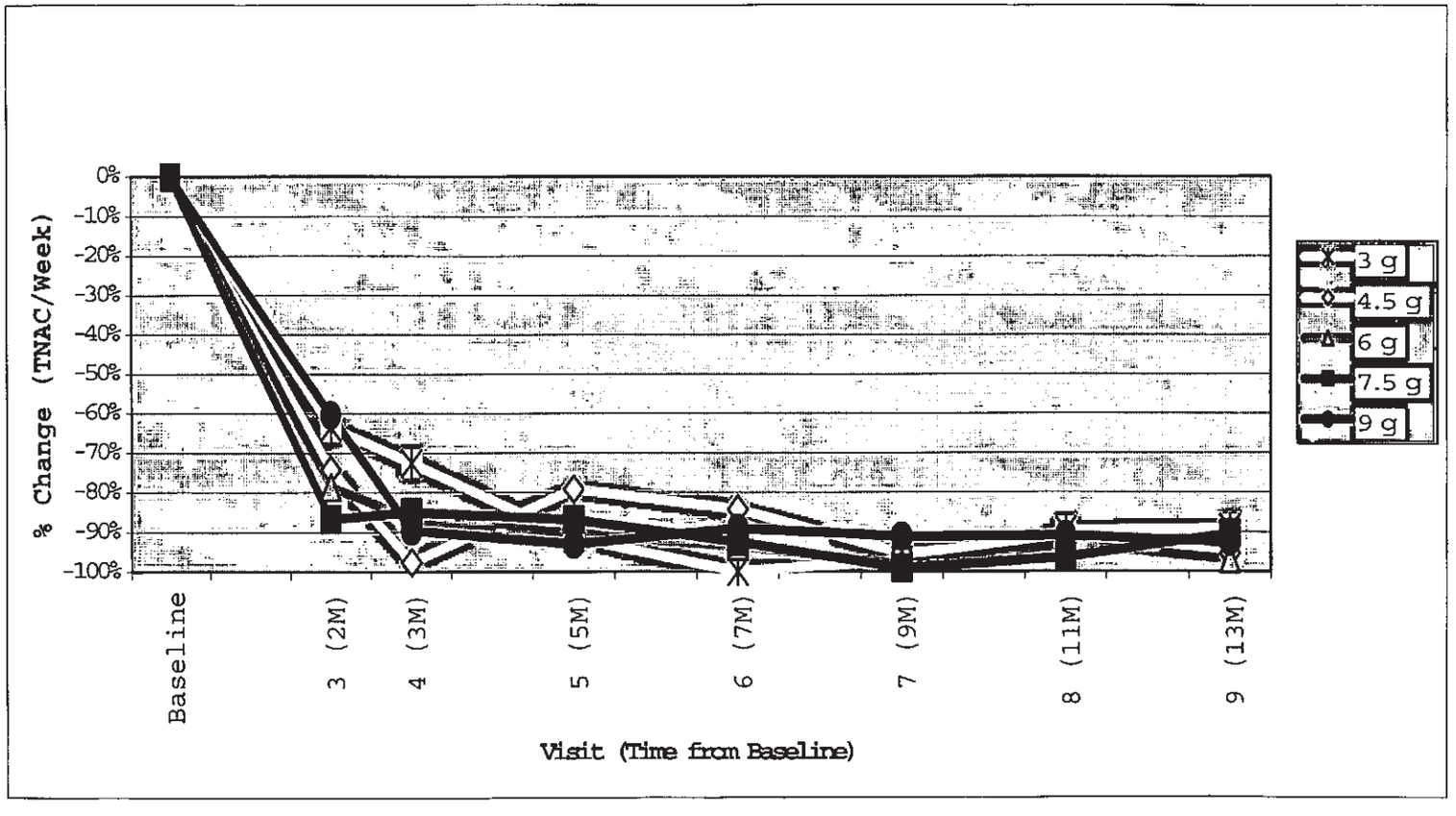
Figure 3.20 Median Percent Change from Baseline for Total Number of Cataplexy Attacks Per Week by Dose through 12 Months (OMC-GHB-3)



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Daytime Sleepiness. The results presented in Table 3.23, a summary (through 12 months of the study) of change from baseline to overall endpoints in daytime sleepiness by visit as measured by the Epworth Sleepiness Scale (ESS), show the significant effect produced by the combined dose groups on this secondary efficacy parameter. There was statistically significant improvement observed at all visits, but there was little or no change in the daytime Epworth Sleepiness Scale values with successive visits. The overall mean change from baseline was -4.47 (SD = 5.05) at Visit 3 (1 month) and -5.30 (SD = 4.57) at Visit 9 (12 months). The mean change from baseline in Epworth Daytime Sleepiness was statistically significant ($p<0.001$) at all study visits.

Table 3.23 Change from Baseline to Endpoints in Daytime Sleepiness as Measured by the Epworth Sleepiness Scale by Visit

	Visit Number						
	3 (mo.1)	4 (mo.2)	5 (mo.4)	6 (mo.6)	7 (mo.8)	8 (mo.10)	9 (mo.12)
Change from baseline* to Visit							
N[1]	106	99	91	87	83	75	74
Mean	-4.47	-5.56	-6.02	-5.76	-6.30	-5.23	-5.30
SD	5.05	5.44	5.53	4.82	5.05	4.81	4.57
Median	-3.50	-5.00	-5.00	-5.00	-6.00	-4.00	-5.00

[1]N reflects all patients with available data for Epworth Sleepiness scale at that visit.
*Baseline taken from OMC-GHB-2.

Graphical display for daytime sleepiness by visit through 18 months for the median change from baseline is presented in Figure 3.21. Visit times (months) for Figure 3.21 time intervals are measured from the Baseline (Baseline, taken from OMC-GHB-02, was 1 month prior to Visit 1 of OMC-GHB-03) rather than time since Visit 1, and, therefore, do not reflect the exact amount of time in study OMC-GHB-3. These values were calculated from the distribution of change values for each individual. The maximum effect was achieved by Visit 4 (month 3 from Baseline, month 2 of OMC-GHB-03 study treatment). The maximum decrease in daytime sleepiness was an approximate 35% median decrease in the Epworth Sleepiness scale. Clinical benefit in diminished daytime sleepiness appeared to be maintained through 18 months of study treatment (19 months from Baseline). Statistical assessment across treatment groups (3, 4.5, 6, 7.5, and 9 g/d) demonstrated that there were no significant dose differences for change in the Epworth Sleepiness Scale values.

It is important to note that the changes in EDS in response to Xyrem treatment show an identical temporal response as was seen in cataplexy, with maximum change occurring in about 8 weeks from start of treatment, and then maintained response over the remainder of the 12 months.

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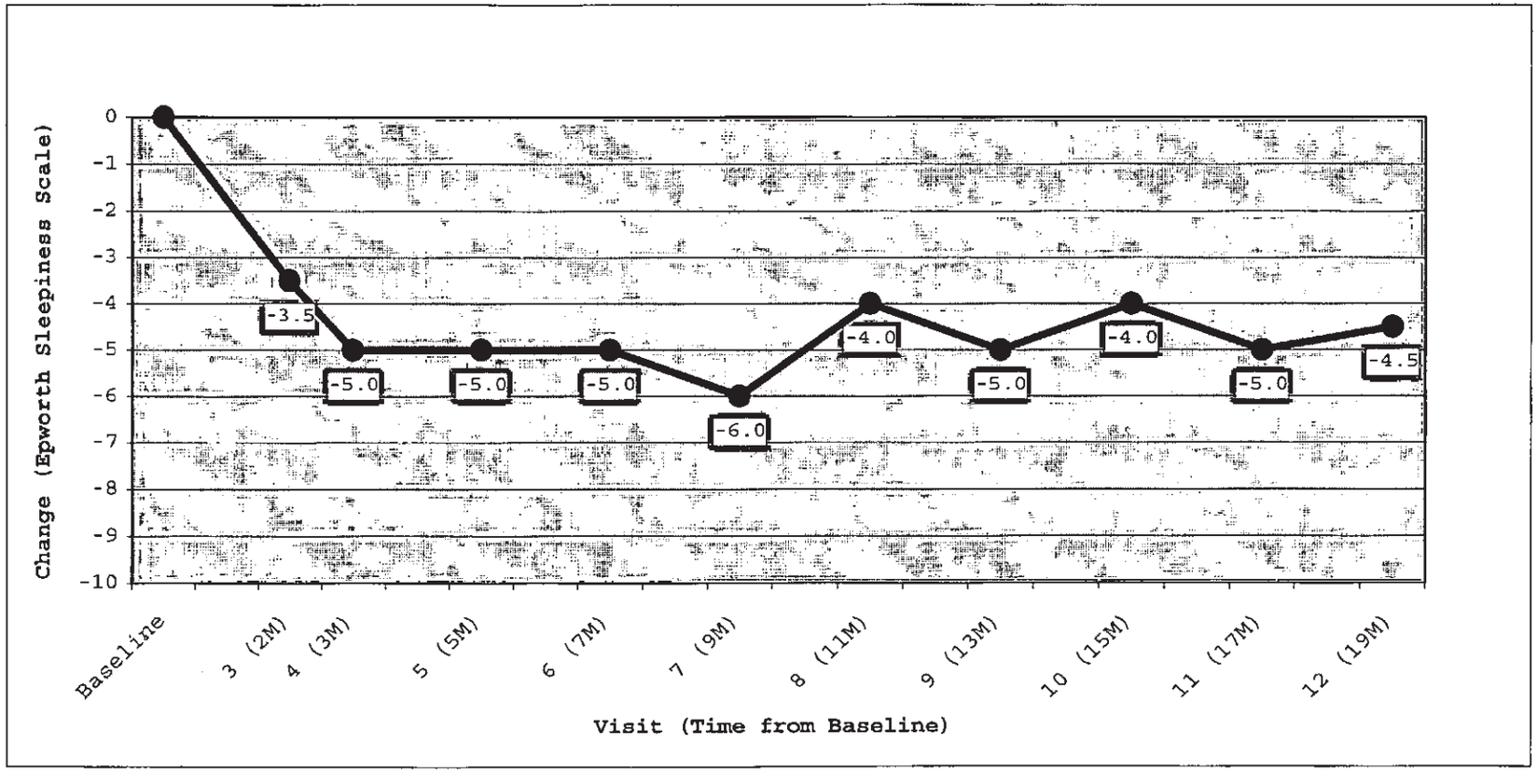
Figure 3.21 Median Change from Baseline in Daytime Sleepiness (Epworth Sleepiness Scale) through 18 Months (OMC-GHB-3)



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Inadvertent Naps/Sleep Attacks. Table 3.24 presents change from baseline to endpoints in total number and duration of inadvertent naps and sleep attacks/day by visit. These data demonstrate a slight decline (increased negative change from baseline) in the number of inadvertent naps and a general trend towards continued decline (increased negative change from baseline) in the duration of inadvertent naps with successive visits. There was no statistically significant Xyrem effect on this parameter.

Table 3.24 Change from Baseline to Endpoints in Total Number and Duration of Inadvertent Naps (Sleep Attacks/day) by Visit

	Visit Number						
	3 (mo.1)	4 (mo.2)	5 (mo.4)	6 (mo.6)	7 (mo.8)	8 (mo.10)	9 (mo.12)
Change from baseline to Visit							
Total number of inadvertent naps (sleep attacks) (N/day)							
N[1]	103	102	93	89	83	77	75
Mean	-0.77	-0.84	-0.91	-1.03	-1.04	-0.93	-1.03
SD	1.28	1.41	1.36	1.36	1.39	1.36	1.29
Median	-0.64	-0.63	-0.71	-0.85	-0.84	-0.85	-0.60
Total duration of inadvertent naps and sleep attacks (min)							
N[1]	102	101	92	88	82	77	75
Mean	-20.27	-24.29	-25.59	-26.27	-26.05	-28.35	-29.64
SD	39.00	42.45	40.60	44.32	52.21	46.26	47.74
Median	-9.96	-12.31	-11.36	-11.69	-14.32	-14.87	-10.86

[1]Patients with non-missing assessments.

Number and Duration of Planned Naps. Table 3.25 presents change from baseline to endpoints in total number and duration of planned naps by visit. These data demonstrate a decrease from baseline to Visit 3 in the number of planned naps with no change at subsequent visits and a decrease in the duration of planned naps at Visit 3 with continued improvement at successive visits. There was no statistically significant Xyrem effect on this parameter.

Table 3.25 Change From Baseline to Endpoints in Total Number and Duration of Planned Naps by Visit

	Visit Number						
	3 (mo.1)	4 (mo.2)	5 (mo.4)	6 (mo.6)	7 (mo.8)	8 (mo.10)	9 (mo.12)
Change from baseline to Visit							
Total number of planned naps (N/day)							
N[1]	102	101	93	88	82	76	74
Mean	-0.21	-0.23	-0.24	-0.29	-0.24	-0.20	-0.25
SD	0.50	0.56	0.68	0.68	0.74	0.83	0.74
Median	-0.14	-0.14	-0.10	-0.14	-0.12	-0.16	-0.15
Total duration of planned naps (min)							
N[1]	100	100	92	87	81	76	74
Mean	-12.63	-13.26	-14.94	-16.96	-15.60	-14.49	-17.17
SD	34.41	40.64	44.81	46.01	51.50	53.57	52.63
Median	-5.45	-7.77	-7.28	-12.77	-7.47	-9.74	-10.14

[1]Patients with non-missing assessments.

Nighttime sleep. Improvement in nighttime sleep was measured by collecting the number of reported awakenings during each night and the total amount of sleep each night preceding the visit to the research center. Improvement in nighttime sleep recorded in the patient diaries was evaluated and compared to the same measures from the OMC-GHB-2 trial end of baseline visit (Visit 4).

The results for the number of awakenings and total amount of sleep are shown in Table 3.26. These data demonstrate improvement from baseline at successive visits for number of awakenings per night and improvement from baseline in the total duration of sleep per night. There was little change at successive visits in the total duration of sleep per night.

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Table 3.26 Change From Baseline to Endpoints for the Number of Awakenings Each Evening and the Total Amount of Sleep by Visit

	Visit Number						
	3 (mo.1)	4 (mo.2)	5 (mo.4)	6 (mo.6)	7 (mo.8)	8 (mo.10)	9 (mo.12)
Change from baseline to Visit for:							
Number of awakenings (N/night)							
N[1]	103	102	93	89	83	77	75
Mean	-0.64	-0.71	-0.82	-0.95	-0.86	-0.95	-0.92
SD	1.51	1.62	1.66	1.59	1.58	1.65	1.60
Median	-0.48	-0.64	-0.57	-0.79	-0.71	-0.67	-0.54
Total amount of sleep (min)							
N[1]	102	101	92	88	81	76	75
Mean	18.45	14.09	21.97	18.32	26.33	22.86	19.60
SD	68.80	66.97	73.08	75.14	76.33	97.45	80.68
Median	16.39	9.75	15.31	17.50	24.07	13.60	13.72

[1]Patients with non-missing assessments.

Hypnagogic hallucinations and Sleep paralysis. Not all patients with narcolepsy report either hypnagogic hallucinations or sleep paralysis. However, in this study, 102 patients (87.2%) and 103 patients (88.0%), reported hypnagogic hallucinations or sleep paralysis symptoms, respectively, at Visit 3. The number of occurrences of these symptoms as recorded in the patient diaries were evaluated and compared to the same measures from the
OMC-GHB-2 trial end of baseline visit (GHB-2 Visit 4).

The results for the number of hypnagogic hallucinations and number of episodes of sleep paralysis are summarized in Table 3.27. A trend towards diminished symptoms was evident, at Visit 3 compared to Baseline and at subsequent visits.

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Table 3.27 Change From Baseline to Endpoints for the Number of Hypnagogic Hallucinations and Number of Episodes of Sleep Paralysis by Visit

	Visit Number						
	3 (mo.1)	4 (mo.2)	5 (mo.4)	6 (mo.6)	7 (mo.8)	8 (mo.10)	9 (mo.12)
Change from baseline to Visit for:							
Number of hypnagogic hallucinations (N/day)							
N[1]	102	101	93	88	82	76	74
Mean	-0.48	-0.58	-0.64	-0.71	-0.71	-0.78	-0.78
SD	1.83	1.89	2.07	2.17	2.23	2.36	2.38
Median	-0.18	-0.22	-0.23	-0.30	-0.28	-0.30	-0.29
Number of episodes of sleep paralysis (N/day)							
N[1]	103	102	93	89	83	77	75
Mean	-0.38	-0.43	-0.44	-0.48	-0.49	-0.54	-0.51
SD	0.95	1.11	1.16	1.21	1.23	1.30	1.29
Median	-0.07	-0.08	-0.08	-0.09	-0.14	-0.14	-0.12

[1]Patients with non-missing assessments.

Clinical Global Impression of Change (CGI-c). Table 3.28 displays the results for the CGI-c assessments for each visit by individual treatment group. For the purposes of this report, patients are categorized as "responders" or "non-responders". Approximately 80% of all patients were categorized as responders at Visit 3, however, there appeared to be a trend towards continued improvement (increased percentage of responders) at successive visits.

The response was relatively uniform across doses; there was a statistically significant difference across treatment groups at Visits 4 (p=0.017) and 6 (p=0.016) only. This difference by dose was most probably due to the variability inherent in any group with a relatively small number of patients (n = 14 for the 3g sodium oxybate dose group at Visit 4 and n = 15 for the 4.5g sodium oxybate dose group at Visit 6) and not a true reflection of a real dose-effect.

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Table 3.28 Change from Baseline to Endpoints for Clinical Global Impression of Change (CGI-c) by Visit

	Visit Number						
	3 (mo.1)	4 (mo.2)	5 (mo.4)	6 (mo.6)	7 (mo.8)	8 (mo.10)	9 (mo.12)
N[1] Total Patients	108	101	95	89	83	77	74
Change from baseline to Visit							
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Very much improved	36 (33.3)	38 (37.6)	40 (42.1)	40 (44.9)	40 (48.2)	35 (45.5)	34 (45.9)
Much improved	48 (44.4)	50 (49.5)	41 (43.2)	44 (49.4)	40 (48.2)	38 (49.4)	33 (44.6)
Minimally improved	15 (13.9)	9 (8.9)	7 (7.4)	3 (3.4)	2 (2.4)	3 (3.9)	6 (8.1)
No change	3 (2.8)	1 (1.0)	4 (4.2)	1 (1.1)	1 (1.2)	1 (1.3)	0 (0.0)
Minimally changed	5 (4.6)	3 (3.0)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Much worse	1 (0.9)	0 (0.0)	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Responder*	84 (77.8)	88 (87.1)	81 (85.3)	84 (94.4)	80 (96.4)	73 (94.8)	67 (90.5)
Non-responder	24 (22.2)	13 (12.9)	14 (14.7)	5 (5.6)	3 (3.6)	4 (5.2)	7 (9.5)

[1]N reflects all patients with available data for CGI-c scores at that visit.

*Responder = "Very much improved" or "Much improved" on CGI-c scale. Non-responder = all other categories except "Not assessed".

Ability to Concentrate, Quality of Sleep, and Level of Alertness. The efficacy measures of ability to concentrate, quality of sleep, and level of alertness are summarized in Table 3.29. The Baseline for Ability to Concentrate was Visit 2 of the OMC-GHB-3 Study; for other variables Baseline was the Baseline (Visit 4) of the OMC-GHB-2 Study. At Visit 3 all dose groups provided statistically significant improvement in the three efficacy parameters. The only exceptions were in Quality of Sleep (p=0.056) and Level of Alertness (p=0.068), both in the 4.5g treatment group. Similar statistical significance was observed for the three efficacy parameters at Visit 9. The only exception was in Level of Alertness (p=0.055), in the 3g sodium oxybate treatment group. These p-values, just above the level of statistical significance, were probably due to variability inherent in the small number of patients (n=6) in the 4.5g group, and did not reflect a true treatment failure. There were no statistically significant values across-treatments.

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Table 3.29 Change from Baseline to Endpoints for the Overall Ability to Concentrate, Quality of Sleep, and Level of Alertness by Treatment Group

	All Patients	GHB dose (g)					p-value*
		3	4.5	6	7.5	9	
Measure[1] of change from baseline[2] to visit 3							
Ability to Concentrate							
N[3]	104	14	6	55	8	21	0.719
Mean	0.66	0.81	0.56	0.66	0.76	0.56	
SD	0.59	0.69	0.37	0.58	0.58	0.61	
Median	0.69	0.93	0.41	0.69	0.79	0.44	
p-value**	<0.001	0.001	0.013	<0.001	0.007	<0.001	
Quality of Sleep							
N[3]	105	14	6	55	9	21	0.720
Mean	0.76	0.74	0.48	0.80	0.84	0.74	
SD	0.56	0.46	0.48	0.59	0.59	0.57	
Median	0.79	0.94	0.43	0.78	0.87	0.86	
p-value**	<0.001	<0.001	0.056	<0.001	0.003	<0.001	
Level of Alertness							
N[3]	105	14	6	55	9	21	0.463
Mean	0.65	0.67	0.37	0.70	0.74	0.53	
SD	0.58	0.49	0.39	0.63	0.67	0.48	
Median	0.65	0.56	0.33	0.67	0.81	0.52	
p-value**	<0.001	<0.001	0.068	<0.001	0.011	<0.001	

[1]Weighted Average of Measure (WAM) = $(1xN_{POOR} + 2xN_{FAIR} + 3xN_{GOOD} + 4xN_{EXCEL})/N$, where N_{POOR}, N_{FAIR}, N_{GOOD}, N_{EXCEL} = number of days with poor, fair, good, and excellent level of measure, respectively. $N = N_{POOR} + N_{FAIR} + N_{GOOD} + N_{EXCEL}$ = total number of days reported.

[2]Baseline for Ability to Concentrate was the Visit 2 of Study OMC-GHB-3; for other measures, Baseline was the Baseline period in Study OMC-GHB-2.

[3]Patients with non-missing assessments.

*p-value for overall treatment group based on ANOVA (GLM)

**p-value within treatment group based on paired t-test for change from baseline.

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3.2.1.4 Conclusions

Eighty-six patients (73.5%) reached dose stabilization in this open-label, long-term study. For all patients who reached dose stabilization, the mean was 3.38 weeks. As displayed in Table 3.30, there was an increased distribution of patients in the higher dose groups by last reported dose.

Table 3.30 Distribution of Patients by the Last Reported Dose (OMC-GHB-3)

	GHB dose (g)				
All Patients	**3**	**4.5**	**6**	**7.5**	**9**
	n	n	n	n	n
	(%)	(%)	(%)	(%)	(%)
117	16	11	42	13	35
	(13.7)	(9.4)	(35.9)	(11.1)	(29.9)

Overall clinical improvement, assessed as change from baseline, was evident at the earliest endpoint (Visit 3), and was maintained at all endpoints throughout the study. Patients were titrated to achieve maximum clinical benefit. In general, there appeared to be no compelling evidence of enhanced benefit with increasing dose. The data from this 12-month, open-label study demonstrate that 3g to 9g doses of sodium oxybate taken in divided doses before bedtime and 2.5-4 hours later produced significant and long-term clinical improvement in the symptoms of narcolepsy.

For the overall population, there was highly statistically significant improvement from baseline at all visits for the primary efficacy parameter, number of cataplexy attacks. There appeared to be continued improvement at successive visits; the mean change from baseline for overall treatment was a decrease of 23.65 cataplexy attacks at Visit 3 and a decrease of 35.48 cataplexy attacks at Visit 9.

Except for the 3g and 4.5g sodium oxybate dose groups at Visit 3 (p=0.122 and p=0.074, respectively), the change from baseline in number of cataplexy events was highly statistically significant for all dose groups at all visits. Statistical assessment across treatment groups demonstrated that there was no significant dose differences for change in this primary efficacy parameter. It is important to note that patients in study OMC-GHB-3 began the study on 6g daily and investigators were required to titrate the patients to an individualized dose (3g, 4.5g, 6g, 7.5g, or 9g sodium oxybate) based on safety and efficacy. Therefore, p-values for comparisons across dose groups were not expected to show statistical significance as doses represented the patients' average dose throughout the study and were not randomized groups.

Except for the 4.5g sodium oxybate dose group at Visit 3 (p=0.104) and Visit 6 (p=0.087), the decrease from baseline in daytime sleepiness as measured by the

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Epworth Sleepiness Scale was statistically significant for all dose groups at all visits. There was little or no additional improvement, however, beyond Visit 3.

A trend towards diminished symptoms was evident for all secondary efficacy parameters including: frequency and duration of inadvertent naps and sleep attacks; frequency and duration of planned naps; frequency of awakenings that occurred during the night; and frequency of hypnagogic hallucinations and episodes of sleep paralysis. However, the statistical design did not provide definitive statistical support for the clinical benefit of sodium oxybate for these secondary efficacy parameters.

For all patients the overall response to treatment, as assessed by the Clinical Global Impression of Change, was clear and positive. Responders ranged from 78.5% at Visit 3 to 96.4% at Visit 7. There was a slight trend towards a dose relationship in the CGI-c at the earlier visits, and there was no statistically significant difference across treatment groups.

3.2.2 OMC-SXB-20

3.2.2.1 Rationale

Nocturnal polysomnography provides an objective means to determine the neurological and physiological changes in response to treatment, and would provide an opportunity to obtain a broader understanding of the overall effects of Xyrem on sleep. Previous polysomnographic studies of the effects of sodium oxybate have been published in normal subjects (Lapierre 1990), non-narcoleptic depressive patients (Mamelak 1977) and in surgical patients with intravenous infusion to produce sedation (Entholzner 1995), all indicating that sodium oxybate increased delta wave sleep.

Medications used for cataplexy (TCAs and SSRIs) and for improved sleep (hypnotics and barbiturates) are known to cause a decrease in REM sleep. For example, the reductions in REM sleep have been noted for, but are not limited to, the benzodiazepine hypnotics flunitrazepam, flurazepam, and triazolam (Borbely 1985), fluvoxamine and other SSRIs (Wilson 2000, Oberndorfer 2000), the TCA imipramine (Kupfer 1989), and the imidazopyridine hypnotic Zolpidem (Brunner 1991). Since sodium oxybate has been described to produce improvement of sleep and cataplexy symptoms, it was of interest for this NDA to characterize the effects of this drug on narcoleptic sleep architecture in relation to dose.

The effects of sodium oxybate on objective measures of nocturnal sleep in narcoleptic patients have been studied in six previous clinical studies (Broughton and Mamelak 1976,1980; Scharf 1985; Bedard 1989; Scrima 1990; Lammers 1993). These six studies have examined the non-comparative effects of doses of sodium oxybate ranging from 2.25 g up to 6.75 g. In general, these previous PSG studies demonstrated that sodium oxybate produces a modest decrease in Stage 1 sleep, no changes in Stage 2 sleep, a marked increase in Stages 3 and 4 sleep (delta sleep or slow wave sleep), and a decrease in the number of awakenings. Several of the trials also documented a decrease in the number of stage shifts and a decrease in REM latency. No change in

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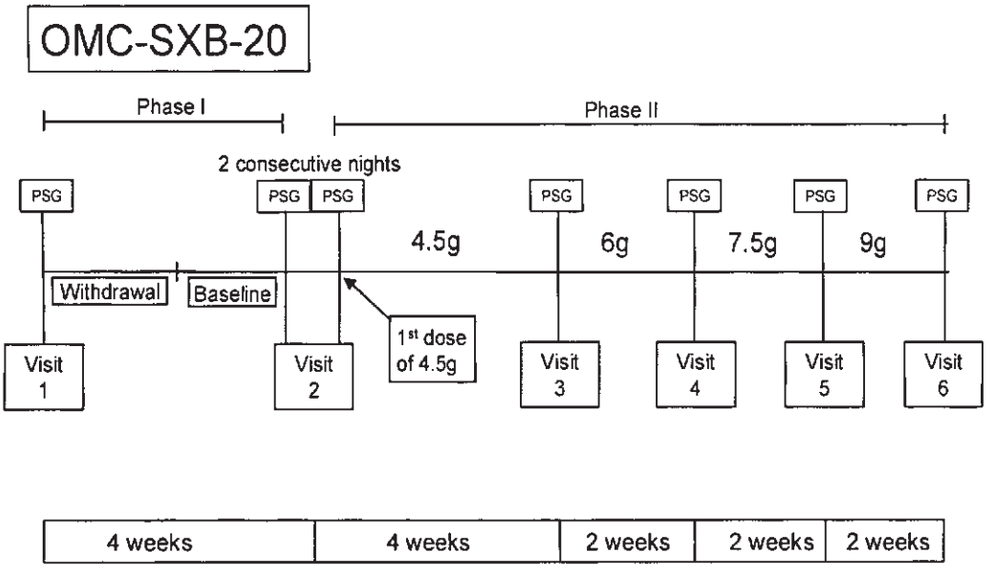
REM stage sleep duration was reported. Since the dosing regimen of sodium oxybate in these studies was different from Xyrem, it was of interest for this NDA to characterize the effects of Xyrem on the sleep architecture profile of narcoleptic patients across the doses proposed in the therapeutic regime.

3.2.2.2 Trial Objectives/Design

The primary objective of this trial design (Figure 3.22) was to characterize the polysomnographic (PSG) sleep architecture in narcoleptic patients at four escalating doses (4.5 g, 6.0 g, 7.5 g, and 9.0 g) of Xyrem, encompassing a 10-week exposure to Xyrem. In addition, parameters relating to daytime function were also evaluated for possible corresponding relationship to PSG effects.

Figure 3.22 OMC-SXB-20 Trial Design



The OMC-SXB-20 clinical trial was designed as an open-label trial using patients diagnosed with narcolepsy and with a history of cataplexy. The patients were required to be currently treated with TCAs or SSRIs, so as to be able to determine the profile of the effects of removal of these anti-cataplectic medications. The first phase of the trial was the withdrawal and washout from pre-existing medications of stable TCAs, SSRIs, and hypnotics. In the last two weeks of this phase, all patients were free of TCAs, SSRIs, and hypnotics. At the beginning of the first phase, an overnight PSG was performed to assess PSG status resulting from TCA, SSRI, and/or hypnotic therapy and again at the end of phase I (baseline, prior to first dose of Xyrem) as a baseline measure. Stimulant medication was maintained at constant dose throughout all phases of the trial.

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The second phase of the trial began with the patient receiving the first night dosing of 4.5 g Xyrem (sodium oxybate) and ended after a 10-week escalation to a final 9 g dose. An overnight PSG was performed on the night of the first dose of 4.5g Xyrem to measure any acute changes in the PSG produced by Xyrem. Each patient remained on a stable 4.5 g dose of Xyrem for 4 weeks. After the 4-week stable dosing period, another PSG was performed, and Xyrem was increased to 6.0 g, 7.5 g, and 9.0 g in successive two-week intervals (see Figure 3.22). An overnight PSG was performed on the last night of each dose of Xyrem to measure the effects of each dose of Xyrem on the PSG, and to define any dose-response on sleep architecture for each patient. For all PSG nights, Xyrem dose was administered in divided dosing just prior to lights out and again 4.0 hours later.

Subjective determinations of the effects of Xyrem on daytime sleepiness were measured by the Epworth Sleepiness Scale (ESS), and changes in common symptoms of narcolepsy were assessed by the Narcolepsy Symptoms Assessment (NSA). In addition to these subjective measures, an objective measure of the effects of Xyrem on daytime sleepiness were evaluated by the well-established procedure, the Maintenance of Wakefulness Test (MWT). The ESS Questionnaire and the NSA were administered at each visit. The Maintenance of Wakefulness Test (MWT) was administered four times: while still on TCA, SSRI, and/or hypnotics (Visit 1), after washout of these medications (Visit 2; baseline), after 4 weeks at 4.5 g Xyrem (Visit 3), and after 2 weeks at 9 g Xyrem (Visit 6).

3.2.2.2.1 Primary Measures

The primary measures consisted of a set of objective clinical PSG parameters in relation to dose of Xyrem, recorded overnight in a sleep laboratory setting. The set of objective PSG parameters for each study night included the following:

- Total Sleep Time (TST) in minutes following the first and second dose of Xyrem and a summation. Total Sleep Time is the duration of time during which the patient was recorded to be in any of the sleep stages. (Total time in bed for this trial was 8.0 hours.)
- Sleep latency in minutes following the first and second dose of Xyrem. Sleep latency is the period of time in minutes between the epoch when the lights were turned off in the room where the nocturnal PSG was being performed and the first epoch that was scored as Stage 1, 2, 3, 4 or REM.
- Stage 1 sleep time in minutes following the first and second dose of Xyrem and a summation. Stage 1 sleep time is the duration of time in minutes in which the EEG recording was scored as Stage 1 sleep. Stage 1 sleep is defined as a relatively low voltage, mixed frequency EEG without rapid eye movements (REMs).
- Stage 2 sleep time in minutes following the first and second dose of Xyrem and a summation. Stage 2 sleep time is the duration of time in minutes in which the EEG recording is scored as Stage 2 sleep. Stage 2 sleep time is defined as 12 to 14 cycles per second (cps) sleep spindles and K-complexes on a background of relatively low voltage, mixed frequency EEG activity. Sleep spindles are a spindle-shaped cluster of waves.

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- Stage 3 & 4 sleep time in minutes following the first and second dose of Xyrem and a summation. Stage 3 and 4 sleep time is the duration of time in minutes in which the EEG recording was scored as Stage 3 or Stage 4 sleep. Stage 3 sleep is defined as a form of slow wave sleep, and is used when between 20 to 50 percent of the epoch (30 seconds) is occupied by delta waves of peak-to-trough voltage equal to or greater than 75 microvolts. Stage 4 sleep is the slow wave sleep during which at least 50 percent of the epoch is occupied by delta waves of peak-to-trough voltage equal to or greater than 75 microvolts. Stage 3 and 4 sleep thus represents the slow wave sleep during which at least 20 percent of the epoch is occupied by delta waves of peak-to-trough voltage equal to or greater than 75 microvolts (Rechschaffen and Kales 1968).
- Delta power in microvolts^2/Hz following the first and second dose of Xyrem and an average. Delta power is the accumulated index of EEG signal power for frequencies between 0.5 to 4.0 Hz that occur during sleep stages 1, 2, 3, or 4 all divided by the number of fast Fourier transforms (FFTs) performed in those stages and 3.5 Hz (Guilleminault 1998).
- Rapid Eye Movement (REM) Sleep time in minutes following the first and second dose of Xyrem and a summation. REM Sleep time is the duration of time in minutes in which the EEG recording was scored as Stage REM. Stage REM sleep is defined as rapid eye movement sleep, a relatively low voltage, mixed frequency EEG in conjunction with episodic REMs and low amplitude electromyogram.
- REM sleep latency in minutes following the first and second dose of Xyrem and a summary. REM sleep latency is the duration of time in minutes between the first epoch of sleep and the first epoch scored as REM.
- Wake After Sleep Onset (WASO) in minutes following the first and second dose of Xyrem and a summation. WASO is the duration of time in minutes that the patient was wakeful (Stage W) after sleep onset had initially occurred; sleep onset was defined as the time after which a 30 second epoch scored as Stage 1, 2, 3, 4, or REM occurred. This is defined as the duration of time that is staged as awake that occurs between sleep onset and "Lights On" at the end of the sleep period.
- Stage shifts per hour following the first and second dose of Xyrem and an average. Stage shifts per hour is the number of times that an epoch (30 seconds) was scored as having a different EEG sleep stage than the previous epoch all divided by the total time between lights out and lights on.
- Total awakenings following the first and second dose of Xyrem and a summation. Awakenings is a term defined by the number of occurrences of wake epochs immediately following a sleep epoch.

3.2.2.2.2 Secondary Measures

Secondary measures consisted of both subjective and objective tools to ascertain the effects of Xyrem on daytime symptoms of narcolepsy. The set of parameters included:

- The ESS Questionnaire (Johns 1991) was used as an indication of daytime sleepiness. It was performed at each visit prior to the overnight PSG. The ESS Questionnaire instructed patients to rate their "chance of dozing" on a scale of 0-3 (never, slight, moderate, and high chance of dozing) in each of eight standard possible situations.

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- The initial NSA, at Visit 1, asked the patients to historically rate their common narcolepsy symptoms for the week prior to starting the clinical trial, while the follow-up NSA evaluations (Visits 2 – 6) rated qualitative changes in narcolepsy symptoms for the previous week in comparison to the time before entry into the trial.
- The MWT is a standardized 40-minute EEG to determine the patient's daytime wakefulness under specified soporific conditions (quiet, darkened room and semi-recumbent position) at four times during the day, spaced two hours apart (Mitler 1982, 1998). The MWT trials were used to assess average sleep latency time and to determine whether or not a sleep-onset REM Period (SOREMP) had occurred. For the MWT trials, the patient was instructed to keep to the same schedule of stimulant medications for the day of each of the MWT tests during the trial, as well as caffeine and nicotine consumption. MWT sleep latency was defined as the duration of time in minutes (up to 40-minutes) between the time when the room where the EEG was being performed was darkened and either the first epoch that was scored as Stage 2, 3, 4, or REM, or the first of 3 consecutive stages of Stage 1 sleep. For the MWT, determination of sleep latency required 10 minutes of subsequent sleep whether continuous or intermittent. The individual trial was stopped once sleep onset had been determined, or after 40 minutes if no sleep occurred.

Baseline and endpoints are defined as follows:

- Baseline consisted of the data collected on Visit 2a for PSG, ESS, and MWT; the baseline for the NSA was Visit 1. Visit 2a represents the period when patients had discontinued TCAs, continued stimulants, and was just prior to Xyrem dosing.
- Endpoints for this trial consisted of Visit 1, the first night of Xyrem administration (Visit 2b), and subsequent visits (Visit 3, 4, 5, 6)

3.2.2.3 Patient Demographics

Twenty-seven narcoleptic patients were enrolled into the trial; twenty-five patients were treated at four investigative sites; and 21 patients completed the trial. In the patient population, there was a trend towards older (average 52.6 years old),female (72%), overweight (average 84.2 kg), and Caucasian (92%) patients. It is known that age of the patient population will have an impact on sleep architecture, specifically a reduction in Stages 3 and 4 sleep are seen with increasing age. Recent literature indicates that older males exhibit markedly reduced levels of slow-wave sleep (Stage 3 and 4) (Van Cauter, 2000).

During the withdrawal period, patients withdrew from pre-existing medications of TCAs, SSRIs, and hypnotics. In the last two weeks of this phase, all patients were free of TCAs, SSRIs, and hypnotics. Stimulant medications were continued at stable dosing throughout the trial. Eighty-eight percent (88%) of patients took TCAs, SSRIs, or hypnotics prior to the start of treatment. The most frequently used medications were venlafaxine, taken by 24% of patients, fluoxetine, taken by 20% of patients, and sertraline, taken by 16% of patients.

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3.2.2.4 Efficacy Evaluation

3.2.2.4.1 Primary Variables

The primary efficacy analysis — Polysomnography Variables – (Table 3.31) provides an overall summary of total sleep time (TST), sleep latency, time in Stage 1, time in Stage 2, time in Stage 3 and 4 (also see Figure 3.23), REM sleep time, delta power, REM sleep latency, wake time after sleep onset (WASO), number of stage shifts per hour, and number of total awakenings.

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Table 3.31 Overall Summary of Changes from Baseline in Nocturnal Polysomnography Variables by Dosage — Intent-to-Treat Patients

Visit	1	2a	2b	3	4	5	6
Variable	Anti-Cataplexy Medications	Baseline[a]	1st dose 4.5 g	4.5 g	6.0 g	7.5 g	9.0 g
N	20	21	18	20	21	20	20
Stage 1 Time (min)							
Sum							
Mean (SD)	13.3 (27.63)	74.8 (31.43)	-19.8 (23.56)	-2.5 (31.61)	-6.7 (27.02)	-5.4 (39.12)	-12.2 (32.04)
P-value from baseline[b]	0.044	-	0.002	0.733	0.268	0.544	0.106
Stage 2 Time (min)							
Sum							
Mean (SD)	-1.8 (62.17)	217.8 (45.45)	-4.3 (37.40)	-0.9 (51.46)	-0.9 (62.67)	6.3 (54.05)	20.2 (58.11)
P-value from baseline[b]	0.898	-	0.636	0.938	0.947	0.607	0.137
Stage 3 and 4 Time (min)							
Sum							
Mean (SD)	0.6 (13.29)	3.5 (8.38)	5.0 (17.08)	0.6 (8.71)	5.4 (20.16)	10.7 (21.02)	23.2 (39.80)
P-value from baseline[c]	0.636	-	0.296	0.771	0.296	0.056	0.012
Delta Power (microvolts^2/Hz)							
Average							
Mean (SD)	3417.3 (31189.26)	69708.6 (19296.87)	12482.3 (10438.58)	4771.3 (13806.55)	12598.9 (25627.51)	22208.8 (17940.01)	32629.3 (27165.27)
P-value from baseline[b]	0.630	-	<0.001	0.139	0.036	<0.001	<0.001

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Table 3.31 Overall Summary of Changes from Baseline in Nocturnal Polysomnography Variables by Dosage — Intent-to-Treat Patients

Visit	1	2a	2b	3	4	5	6
Variable	Anti-Cataplexy Medications	Baseline[a]	1st dose 4.5 g	4.5 g	6.0 g	7.5 g	9.0 g
N	20	21	18	20	21	20	20
REM Sleep Time (min)							
Sum							
Mean (SD)	-37.5 (43.21)	87.2 (28.93)	16.6 (32.66)	-15.8 (30.43)	-18.1 (29.16)	-21.0 (34.07)	-33.8 (36.23)
P-value from baseline[b]	0.001	-	0.046	0.032	0.010	0.013	<0.001
REM Sleep Latency (min)							
1st half							
Mean (SD)	60.5 (98.32)	44.0 (52.21)	-18.1 (62.32)	-0.5 (70.04)	2.6 (60.69)	7.0 (83.35)	33.6 (91.71)
P-value from baseline[c]	0.010	-	0.424	0.668	0.545	0.776	0.057
2nd half							
Mean (SD)	39.3 (82.38)	47.3 (47.69)	-6.3 (40.89)	-1.2 (80.02)	-18.8 (52.36)	13.0 (75.07)	-3.3 (72.98)
P-value from baseline[c]	0.070	-	0.640	0.735	0.162	0.568	0.791
WASO (min)							
Sum							
Mean (SD)	19.2 (45.89)	79.0 (28.37)	-0.3 (34.61)	12.4 (30.70)	7.8 (42.02)	-4.4 (41.96)	-5.2 (36.79)
P-value from baseline[b]	0.078	-	0.973	0.088	0.406	0.644	0.533
TST (min)							
Sum							
Mean (SD)	-25.4 (58.19)	383.4 (29.15)	-2.5 (42.04)	-18.6 (37.79)	-20.4 (55.05)	-9.3 (51.58)	-2.6 (42.84)
P-value from baseline[b]	0.066	-	0.804	0.041	0.105	0.430	0.789

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Table 3.31 Overall Summary of Changes from Baseline in Nocturnal Polysomnography Variables by Dosage — Intent-to-Treat Patients

Visit	1	2a	2b	3	4	5	6
Variable	Anti-Cataplexy Medications	Baseline[a]	1st dose 4.5 g	4.5 g	6.0 g	7.5 g	9.0 g
N	20	21	18	20	21	20	20
Sleep Latency (min)							
1st half							
Mean (SD)	3.4 (6.39)	2.2 (2.16)	0.1 (1.89)	1.4 (2.48)	4.1 (10.76)	2.6 (3.79)	3.9 (5.35)
P-value from baseline[c]	0.022	-	0.693	0.048	0.042	0.005	0.003
2nd half							
Mean (SD)	2.7 (5.33)	2.5 (2.84)	2.4 (5.46)	3.8 (7.12)	3.8 (6.95)	6.1 (9.85)	3.9 (5.54)
P-value from baseline[c]	0.053	-	0.058	0.020	0.012	0.005	0.005
Stage Shifts Per Hour							
Average							
Mean (SD)	1.5 (5.22)	21.0 (5.28)	-3.2 (3.72)	0.3 (4.59)	-0.8 (3.92)	-3.1 (4.00)	-1.5 (4.86)
P-value from baseline[b]	0.217	-	0.002	0.792	0.364	0.002	0.185
Total Awakenings							
Sum							
Mean (SD)	4.5 (16.04)	50.2 (13.67)	-9.1 (14.22)	-0.2 (14.83)	-5.1 (14.82)	-12.9 (13.21)	-12.4 (16.34)
P-value from baseline[b]	0.230	-	0.015	0.964	0.131	<0.001	0.003

[a] Visit 2a (Baseline) is the actual value, all other visits are changes from baseline.
[b] Within treatment p-values:t-test
[c] Within treatment p-values:Wilcoxon signed rank test

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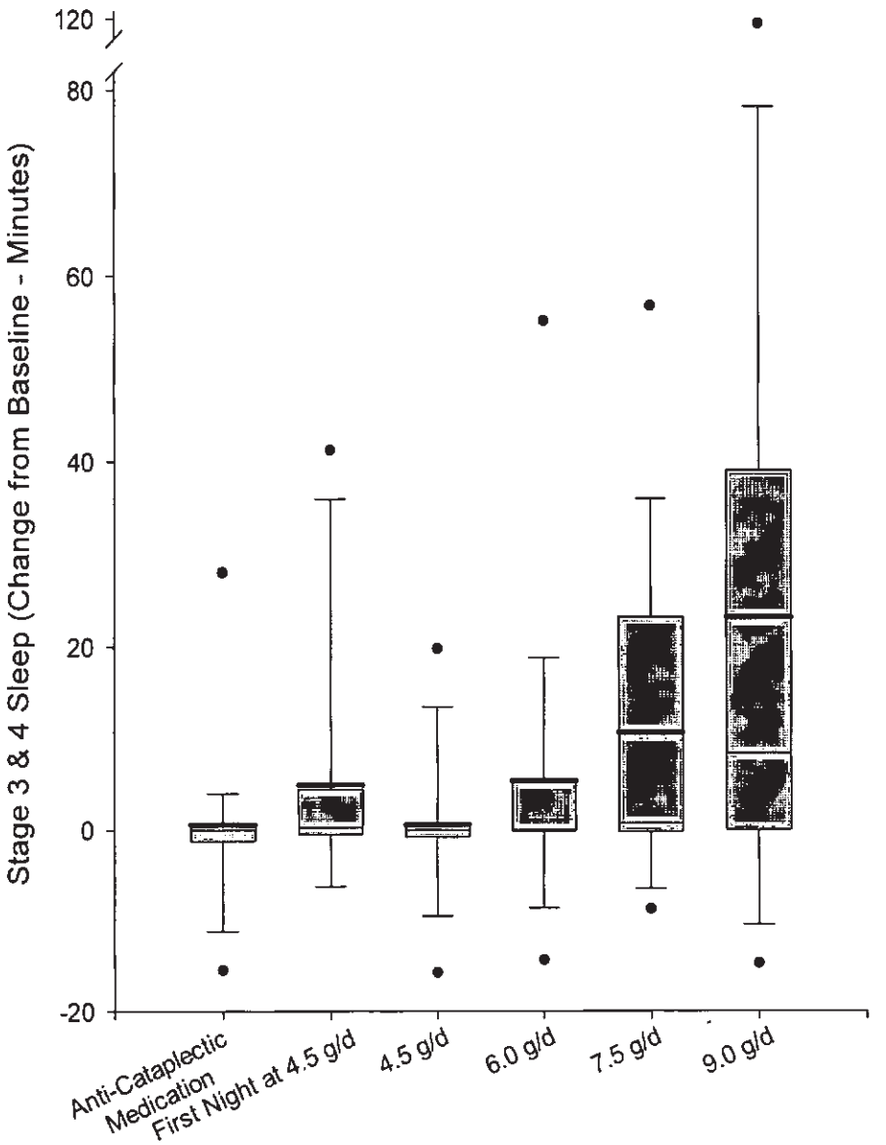
Figure 3.23 Changes in Stage 3 and 4 Sleep (From Baseline) — Intent-to-Treat Patients



In this box plot, the median is depicted by the horizontal line within the box, the mean is depicted by the bold horizontal line, the limits of the box are the 1st and 3rd quartiles, the whiskers are the 10th and 90th percentiles, and the upper and lower circular symbols denote the 95th and 5th percentiles, respectively.

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3.2.2.4.2 Secondary Variables

The secondary efficacy analysis are presented in the accompanying tables, and provides a complete, overall summary of the results from Epworth Sleepiness Score, Narcolepsy Symptoms Assessment, and Maintenance of Wakefulness Test.

Epworth Sleepiness Score (Table 3.32)
There were marked dose-related decreases in the mean ESS across all doses, incremental beyond the continued stable dosing of stimulants. These mean decreases in the ESS, a subjective measure of daytime sleepiness, also support changes seen in previous Xyrem studies (OMC-GHB-2; OMC-GHB-3). Changes in the ESS seen in the SXB-20 study are comparable to results of recent placebo-controlled stimulant studies with modafinil, a well-established stimulant for narcoleptics, in which mean ESS scores decreased 4 to 5 points in the modafinil group. A minimal decrease was observed in the placebo control (US Modafinil in Narcolepsy Study Group, 2000), indicating that ESS scores on narcoleptics in an open-label trial, such as OMC-SXB-20, may constitute real changes, as opposed to perceived changes.

Narcolepsy Symptom Assessment (Table 3.33)
There were improvements in narcolepsy symptoms of cataplexy attacks, hypnagogic hallucinations, number of sleep paralysis episodes, number of inadvertent naps/sleep attacks during the day, number of awakenings at night, and the severity of daytime sleepiness beginning with Visit 3, after 4 weeks on the 4.5 g dosage. Greater reductions in narcolepsy symptoms were seen with increasing Xyrem dosage. Quality of sleep at night, ability to concentrate, and overall condition also improved beginning with Visit 3, after 4 weeks on the 4.5 g dosage. In general, improvement in symptoms was observed with increasing doses of Xyrem, relative to the condition of the patient prior to starting the trial (when on TCA/SSRI/hypnotics).

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Table 3.32 Summary of Changes from Baseline in the Epworth Sleepiness Scale by Dosage — Intent-to-Treat Patients

Visit Condition	1 Anti-Cataplexy Medica-tions	2a Baseline	2b 1st dose 4.5 g	3 4.5 g	4 6.0 g	5 7.5 g	6 9.0 g
N	21	21	21	21	21	20	21
Mean	-1.9	19.8	0.5	-2.4	-3.8	-4.8	-5.8
SD	1.92	2.66	2.11	2.75	3.62	4.02	4.55
Median	-2.0	20.0	0.0	-2.0	-3.0	-4.0	-7.0
Minimum	-6.0	12.0	-3.0	-9.0	-12.0	-13.0	-14.0
Maximum	3.0	24.0	5.0	2.0	0.0	1.0	2.0
P-value from baseline	<0.001	-	0.341	<0.001	<0.001	<0.001	<0.001
Inference with 4.5 g	-	-	-	-	0.042	<0.001	<0.001
Inference with 6.0 g	-	-	-	-	-	0.076	0.006
Inference with 7.5 g	-	-	-	-	-	-	0.317

Visit 2a (baseline) is the actual value, all other visits are changes from baseline.
Within treatment p-values: Wilcoxon signed rank test. Between treatment p-values: ANOVA on rank changes from baseline.

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Table 3.33 Summary of Follow-up Narcolepsy Symptoms Assessment by Dosage — Intent-to-Treat Patients

Visit Condition	2a Pre-treatment	3 4.5 g	4 6.0 g	5 7.5 g	6 9.0 g
Number of Patients	**21**	**21**	**21**	**21**	**21**
Number of Cataplexy Attacks	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Increased	13 (62%)	3 (14%)	0	0	0
Decreased	0	11 (52%)	17 (81%)	18 (86%)	18 (86%)
About the same	8 (38%)	7 (33%)	4 (19%)	2 (10%)	3 (14%)
Number of Hypnagogic Hallucinations	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Increased	8 (38%)	3 (14%)	1(5%)	0	0
Decreased	0	6 (29%)	10(48%)	15 (71%)	16 (76%)
About the same	13 (62%)	12 (57%)	10(48%)	5 (24%)	5 (24%)
Number of Sleep Paralysis Episodes	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Increased	8 (38%)	1(5%)	0	0	0
Decreased	0	8 (38%)	14 (67%)	15 (71%)	16 (76%)
About the same	13 (62%)	12 (57%)	7 (33%)	5 (24%)	5 (24%)
Number of Inadvertent Naps/Sleep Attacks During the Day	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Increased	13 (62%)	1(5%)	0	0	0
Decreased	0	11 (52%)	16 (76%)	16 (76%)	16 (76%)
About the same	8 (38%)	9 (43%)	5 (24%)	4 (19%)	5 (24%)
Number of Awakenings at Night	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Increased	8 (38%)	2 (10%)	1(5%)	0	3 (14%)
Decreased	3 (14%)	11 (52%)	11 (52%)	13 (62%)	12 (57%)
About the same	10(48%)	8 (38%)	9 (43%)	7 (33%)	6 (29%)

(continued)

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Table 3.33 Summary of Follow-up Narcolepsy Symptoms Assessment by Dosage — Intent-to-Treat Patients

Visit Condition	2a Pre-treatment	3 4.5 g	4 6.0 g	5 7.5 g	6 9.0 g
Number of Patients	**21**	**21**	**21**	**21**	**21**
Severity of Daytime Sleepiness	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Increased	12 (57%)	1(5%)	1(5%)	0	0
Decreased	0	14 (67%)	14 (67%)	14 (67%)	16 (76%)
About the same	9 (43%)	6 (29%)	6 (29%)	6 (29%)	5 (24%)
Quality of Sleep at Night	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Much improved	0	4 (19%)	5 (24%)	5 (24%)	5 (24%)
Somewhat improved	3 (14%)	12 (57%)	14 (67%)	13 (62%)	12 (57%)
Unchanged	9 (43%)	4 (19%)	2 (10%)	2 (10%)	2 (10%)
Somewhat worse	4 (19%)	1(5%)	0	0	2 (10%)
Much worse	5 (24%)	0	0	0	0
Ability to Concentrate	21(100%)	21(100%)	21(100%)	21(100%)	21(100%)
Much improved	0	0	3 (14%)	3 (14%)	1 (5%)
Somewhat improved	0	9 (43%)	10 (48%)	11 (52%)	13 (62%)
Unchanged	11 (52%)	9 (43%)	7 (33%)	6 (29%)	7 (33%)
Somewhat worse	9 (43%)	3 (14%)	1 (5%)	0	0
Much worse	1 (5%)	0	0	0	0
Overall Condition	21(100%)	21(100%)	21(100%)	21(100%)	21(100%)
Much improved	0	1 (5%)	5 (24%)	7 (33%)	9 (43%)
Somewhat improved	0	16 (76%)	12 (57%)	12 (57%)	8 (38%)
Unchanged	5 (24%)	3 (14%)	4 (19%)	1 (5%)	3 (14%)
Somewhat worse	8 (38%)	1 (5%)	0	0	1 (5%)
Much worse	8 (38%)	0	0	0	0

The number of patients reported does not equal the total patients treated if data was missing.

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Maintenance of Wakefulness Test (Table 3.34)
Polysomnographic measurement of daytime wakefulness indicated a dose related increase in sleep latency. Mean (SD) sleep latency time in minutes was 4.5 (6.01) minutes at Visit 2a (baseline). Mean (SD) change at Visit 3 on 4.5 g Xyrem was 3.7 (7.68) minutes and mean change (SD) at Visit 6 on 9.0 g Xyrem was 6.1 (6.82) minutes. There were statistically significant changes from baseline at Visit 3 ($p = 0.038$), and Visit 6 ($p<0.001$).

These increases in sleep latency were incremental beyond current stimulant therapy. The magnitude of these changes for the 9 g Xyrem dose group (6.1 min) was larger than that shown for all dosages of Modafinil in recent controlled studies compared to placebo, a well-established stimulant medication for daytime sleepiness in narcoleptics. In one study, changes from baseline were only 2.1 min for 200 mg modafinil and 1.9 min for 400 mg modafinil (US Modafinil in Narcolepsy Study Group, 2000) and, in another study, changes from placebo were 4.5 min for 200 mg modafinil and 6.0 min for 400 mg modafinil (Broughton 1997).

There was a dose-related decrease in the percentage of patients with one or more sleep-onset REM period (SOREMP). At Visit 2a (baseline), 18 of 21 patients (86%) had SOREMP. At Visit 3 on 4.5 g Xyrem, 13 of 21 patients (62%) had SOREMP, and 6 of 20 patients (30%) on 9.0 g Xyrem had SOREMP. Patients on anti-cataplexy medications (Visit 1 in Table 3.34) also had decreases in SOREMPs, but not as profound as those on 9.0 g Xyrem. Prior research has shown that decreases in SOREMPs are positively associated with a reduction in cataplexy attacks (Amira 1985; Hishikawa 1995).

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Table 3.34 Summary of Maintenance of Wakefulness Test by Visit — Intent-to-Treat Patients

Visit	1	2a	3	6
	Anti-Cataplexy Medica-tions	Baseline	4.5 g	9.0 g
Number of Patients	**21**	**21**	**21**	**20**
Sleep Latency (minutes)				
N	21	21	21	20
Mean	1.0	4.5	3.7	6.1
SD	5.69	6.01	7.68	6.82
Median	0.6	2.3	1.0	3.3
Minimum	-10.8	0.5	-8.0	-5.0
Maximum	16.6	27.1	30.2	21.9
p-value from baseline	0.441	—	0.038	<0.001
Inference with Visit 3	—	—	—	0.286
SOREMP				
Yes	11 (52%)	18 (86%)	13 (62%)	6 (30%)
No	10 (48%)	3 (14%)	8 (38%)	14 (70%)

SOREMP = Sleep-onset rapid eye movement period.
Visit 2a (baseline) is the actual visit, all other visits are changes from baseline.
Within treatment p-values: t-test. Between treatment p-values: ANOVA on rank changes from baseline.
For SOREMP: Frequencies are actual counts at each visit.

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3.2.2.5 Conclusions and Discussion

3.2.2.5.1 Conclusions

With respect to the effect of four dosages of Xyrem on overnight polysomnography (PSG) recordings in narcoleptic patients, the following conclusions can be derived from the present data:

1. Xyrem treatment resulted in a dose related increase in slow wave sleep (SWS, delta sleep, Stage 3 & 4) across all 4 doses reaching significance at the 9.0 g/night regimen.
2. Delta power, a derived index of all slow wave signals, showed a dose related increase that was highly significant on the first night following 4.5 g as well as after 2 weeks of dosing at 6.0 g, 7.5 g and 9.0 g/night.
3. A dose related decrease in the number of nocturnal awakenings was recorded, which was significant at the 7.5 g and 9.0 g/night Xyrem doses.
4. Across doses a non-significant decrease in Stage 1 sleep was observed, while the amount of Stage 2 sleep remained unchanged.
5. An acute increase in REM sleep was demonstrated with the initial 4.5 g treatment, with subsequent dose related significant decreases in total REM sleep duration at all 4 doses.
6. No significant change in REM latency was observed among the 4 doses studied.
7. No dose related change in total sleep time (TST) was observed; however, a significant decrease in TST was found following 4.5 g/night dosing for 4 weeks.
8. The number of shifts in sleep stage demonstrated a decreasing trend at doses greater than 4.5 g/night but a significant decrease was recorded only following 7.5 g/ night Xyrem.
9. The total time spent awake after the onset of sleep (WASO) was not significantly altered by any of the Xyrem doses.
10. A significant dose-dependent increase in sleep latency was observed across all 4 doses.

Consistent with the objective PSG findings, the subjective report by the patients on the Narcolepsy Symptom Assessment indicated a dose related improvement in the overall quality of sleep and the perceived number of nighttime awakenings as compared to the patient's self assessment at study entry while still on their anti-cataplectic and stimulant medications. The nocturnal symptoms of hypnogogic hallucinations and sleep paralysis likewise were decreased appreciably in 16 of 21 (76%) patients.

The following are the conclusions derived from the objective and subjective measures of daytime sleepiness:

1. The administration of Xyrem produced a significant increase in sleep latency as measured by the MWT. This dose-dependant increase averaged 3.7 minutes ($p = 0.038$) after 4 weeks of 4.5 g nightly that further increased to a mean improvement of 6.1 minutes ($p < 0.001$) following the nightly 9.0 g dose. This measured response is additive to that produced by concomitant stimulant dosing.

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2. The presence of SOREMPs during MWT, which occurred in of 18 of 21 patients (86%) at baseline, decreased to 13 of 21 (62%) following 4 weeks of 4.5 g Xyrem nightly. SOREMPs further decreased to 6 of 20 patients (30%) following the 9.0 g dose.
3. The ESS total score significantly decreased in a dose-dependent manner by the nightly administration of Xyrem. The median total score of 20 at baseline improved by 2 points following the 4.5 g dose regimen ($p < 0.001$) and by 7 points after the 9.0 g dose ($p < 0.001$).
4. The patients in the current trial reported substantial improvements in subjectively determined (by NSA recording of) daytime narcolepsy symptoms including the incidence of cataplexy attacks, the number of inadvertent naps as well as decreased daytime sleepiness, and increased the ability to concentrate and a perception of overall improvement in their narcolepsy while taking nightly doses of Xyrem.

3.2.2.5.2 Discussion

This study was designed to allow descriptive comparison of standard parameters of sleep architecture in a group of narcoleptic patients initially on stimulant and anti-cataplectic medications (TCAs, SSRIs, and hypnotics) and to assess changes when these anti-cataplectic medications were discontinued (down-titration over two weeks, followed by two weeks of no medication) to provide a baseline recording with only stimulant medications continued. This allowed measurement of the PSG effects attributed to these medications and a proximate comparison with sodium oxybate effects. Dosing with Xyrem in an escalating dose regimen provided the basis for assessment of both the acute PSG effects (during first night of dosing at 4.5 g) and across the dose range from 4.5 to 9.0 g/night, representing the principal dosing regimens for Xyrem in the treatment of narcolepsy. Collection of the parameters representative of daytime sleepiness by objective (MWT) and subjective (ESS, NSA) measures allowed consideration of the relationship between nighttime sleep characteristics, Xyrem dose (or time-on-drug), and daytime clinical effect.

3.2.2.5.2.1 Stage 3 and 4 Sleep

The most important finding of this report is that of the dose-dependent increase in the restorative Stage 3 and 4 sleep time (delta sleep, slow wave sleep) following treatment with Xyrem (sodium oxybate). The increase in slow wave sleep following treatment with sodium oxybate has been repeatedly reported in the literature (Broughton 1976, 1980; Scharf 1985; Bedard 1989; Scrima 1990; Lammers 1993). The relatively small amount of slow-wave sleep recorded across the entire trial (e.g. 3.5 minutes at baseline) was attributed to the presence of strict scoring criteria which required that the slow-wave EEG amplitude be at least 75 micro-volts (peak-to-trough) (Rechtschaffen 1968), a voltage that would be expected to be low in this trial due to the high average age of the patient population (Van Cauter 2000). Slow-wave sleep for the initial polysomnograph when the patients were on TCAs, SSRIs, or hypnotics was not significantly different from baseline, confirming that these medications lack the ability to increase slow wave sleep (Borbely 1985, Kupfer 1994, Wilson 2000, Oberndorfer 2000).

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3.2.2.5.2.2 Delta Power

This increase in slow wave sleep is coincident with an increase in delta power. Delta power was determined by spectral analysis (using fast Fourier transformation) of the digital EEG signals from electronic PSG recordings so as to determine the index of all slow waves occurring during non-REM sleep between 0.5 and 4 Hz (Guilleminault 1998, Pivik 1993). As dose increases, the corresponding increase in delta power supports the increase in Stage 3 and 4 sleep. Stage 3 and 4 sleep only represents those sleep epochs containing greater than 20% and 50%, respectively, of slow waves with amplitudes of 75 microvolts or higher. Delta power differs in that it measures the total EEG signal in the delta wave range during all stages of NREM sleep. Slow wave sleep and delta wave signals in general (delta power) constitute that component of sleep that has been found to have restorative properties as demonstrated by correlation with measures of daytime performance and alertness (Jurado 1989, Schneider-Helmert 1987, Crenshaw 1999, Edinger 2000, Takahashi 1994).

3.2.2.5.2.3 REM Sleep

The effects on REM sleep time in this study were particularly interesting, and not entirely in keeping with the published literature. The expected decrease in REM sleep that was associated with TCA/SSRI/hypnotic treatment was supported by these data, with a highly significant (p=0.001) mean reduction of 37.5 minutes from the baseline mean total REM sleep time of 87.2 minutes. The acute pharmacologic response to Xyrem dosing at 4.5 g on the first night was a significant increase in total REM sleep time (p=0.046), which was followed by dose-dependent significant reductions in total REM sleep time across the 4.5, 6.0, 7.5, and 9.0 g dose groups. Previous literature had reported either no change in the proportion of REM sleep (Scrima 1990, Bedard 1989, Lammers 1993, Scharf 1985, Mamelak 1981) in narcoleptics, or a marked increase in REM sleep in the patients with depression (Broughton 1976). Further consideration of REM efficiency and REM density measures could be usefully applied to these recordings to assist in the interpretation of this unexpected data. There is a suggestion of a reciprocal relationship between REM and non-REM (NREM) sleep in humans (Merica 1998, Toussaint 1997, Uchida 1992, Takahashi 1994) and in rats (Benington 1994, Borbely 1984). Thus, the subsequent reduction in total REM sleep time beyond the pharmacologic increase produced by the initial dose of 4.5 g Xyrem may be an outcome of the drug-mediated increase in slow wave sleep.

3.2.2.5.2.4 REM Latency

Although often associated with decreases in REM latency in narcoleptics at lower doses of sodium oxybate (Broughton 1976, 1980; Scharf 1985; Bedard 1989; Scrima 1990; Lammers 1993), REM latency in the patient population in OMC-SXB-20 has not shown a decrease in REM latency, nor any dose effects. In contrast, the chronic dosing of TCA/SSRI/hypnotic medication present at the start of the trial lead to a marked increase in REM latency, relative to that recorded after their withdrawal and washout (baseline). Based on the distinctly different effects on REM latency between TCA/SSRI/hypnotic

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medications at the start of the trial and escalating Xyrem dosing, the difference in effects could represent different neuropharmacological mechanisms.

As this is a small, open-label study, definitive conclusions cannot be established from any of these independent measures. However, the uniform changes in all subjective assessments and the objective measure as provided by the MWT in daytime sleepiness provides strong support for the therapeutic response to Xyrem treatment across the range of doses studied. This provides further consistent support for the previously submitted subjective data from the OMC-GHB-2 and OMC-GHB-3 studies.

In this single-arm trial, there is a confounding of effects between time-on-drug and dose-escalation. In all findings that exhibit an increase in extent of effect across the study, a definite statement regarding the dose-dependency of these effects must be qualified by the fact that these increases in extents of effects may be caused in part by the duration of time on drug (10 weeks of exposure while escalating dose up to 9 g at Visit 6). This is an unmitigatable feature of the trial. However, the source of the effect (time and/or dose level) does not diminish the impact of the drug on PSG parameters and narcolepsy symptoms.

3.2.2.5.2.5 Maintenance of Wakefulness Test (MWT)

The incremental improvement in sleep latency for the MWT, over-and-above that which was already present with current stimulant treatment, provides an opportunity to strongly suggest that Xyrem improved daytime alertness by a large magnitude.

3.3 Efficacy Summary

Based on the results of two adequate and well-controlled studies (OMC-GHB-2 and the Scrima trial), a supporting controlled study (Lammers trial) and supportive data from 2 uncontrolled studies (OMC-GHB-3 and OMC-SXB-6), dosages of between 3 g/d and 9 g/d of sodium oxybate are effective in the treatment of narcolepsy (reducing the frequency of cataplexy attacks and excessive daytime sleepiness [reduction in the Epworth Sleepiness Scale and the number of inadvertent naps or sleep attacks] associated with narcolepsy).

The findings of OMC-GHB-2 and OMC-GHB-3 taken together support the conclusion that, while the therapeutic benefit of sodium oxybate is clearly evident within 4 weeks of nightly therapy, the full benefit is not achieved until the patient has been treated for 2 to 3 months.

A blinded, randomized trial, OMC-SXB-21, provided evidence for the long-term efficacy of Xyrem. In this trial, patients abruptly discontinued from long-term (7 to 44 months) Xyrem therapy, had a recurrence of cataplexy.

Results of the long-term open-label dose-titration studies (OMC-GHB-3 and OMC-SXB-6) also shows long-term effectiveness of dosages from 3 g/d to 9 g/d when titrated to optimal clinical effectiveness for individual patients.

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Overall, clinical improvement and benefit of sodium oxybate in the treatment of patients with narcolepsy is documented by both the physician-based (CGIc) and patient-based (Global Therapeutic Impression of Benefit) assessments.

Evidence (OMC-SXB-6) suggests that patients can safely decrease or discontinue other anti-cataplectic therapy (TCAs/SSRIs) once treatment with sodium oxybate is initiated, with continuing clinically satisfactory reduction in frequency of cataplectic attacks. There is no evidence of rebound cataplexy or other withdrawal effects (other than a return of narcolepsy symptoms) when patients are removed from sodium oxybate after 4 weeks of therapy at dosages up to 9 g/d.

In addition, sodium oxybate further improves daytime sleepiness when used adjunctively in narcoleptic patients already maintained on stimulant medications to treat their daytime sleepiness.

OMC-SXB-20 was an open-label pharmacological study that evaluated the effect of Xyrem on sleep architecture using objectively-measured nocturnal polysomnography at four escalating doses (4.5 g, 6 g, 7.5 g, 9 g) over a 10-week dosing period. The most important finding of this study is that of the increase in slow-wave sleep across all four doses of Xyrem compared to baseline in narcoleptic patients, with statistically significant increases in Stage 3&4 sleep reached at the 9.0 g per night dose as well as statistically significant increases in Delta Power at all four doses. Another important finding was the dose-related improvement in daytime sleepiness, as measured by the Maintenance of Wakefulness Test (MWT), which objectively quantifies the sleep latency of patients who are trying to remain awake while experiencing defined, soporific conditions. The increase in MWT sleep latency, relative to baseline, averaged 3.7 minutes ($p = 0.038$) after 4 weeks of 4.5 g per night of Xyrem that further increased to a mean improvement of 6.1 minutes ($p < 0.001$) following the nightly 9.0 g Xyrem dose. This vigorous response is additive to that already produced by concomitant stimulant dosing, supporting the reasons to conclude that Xyrem can be used to markedly improve daytime sleepiness in narcoleptics.

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SECTION 4
SAFETY

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4.0 SAFETY

4.1 Overview of Sodium Oxybate Trials

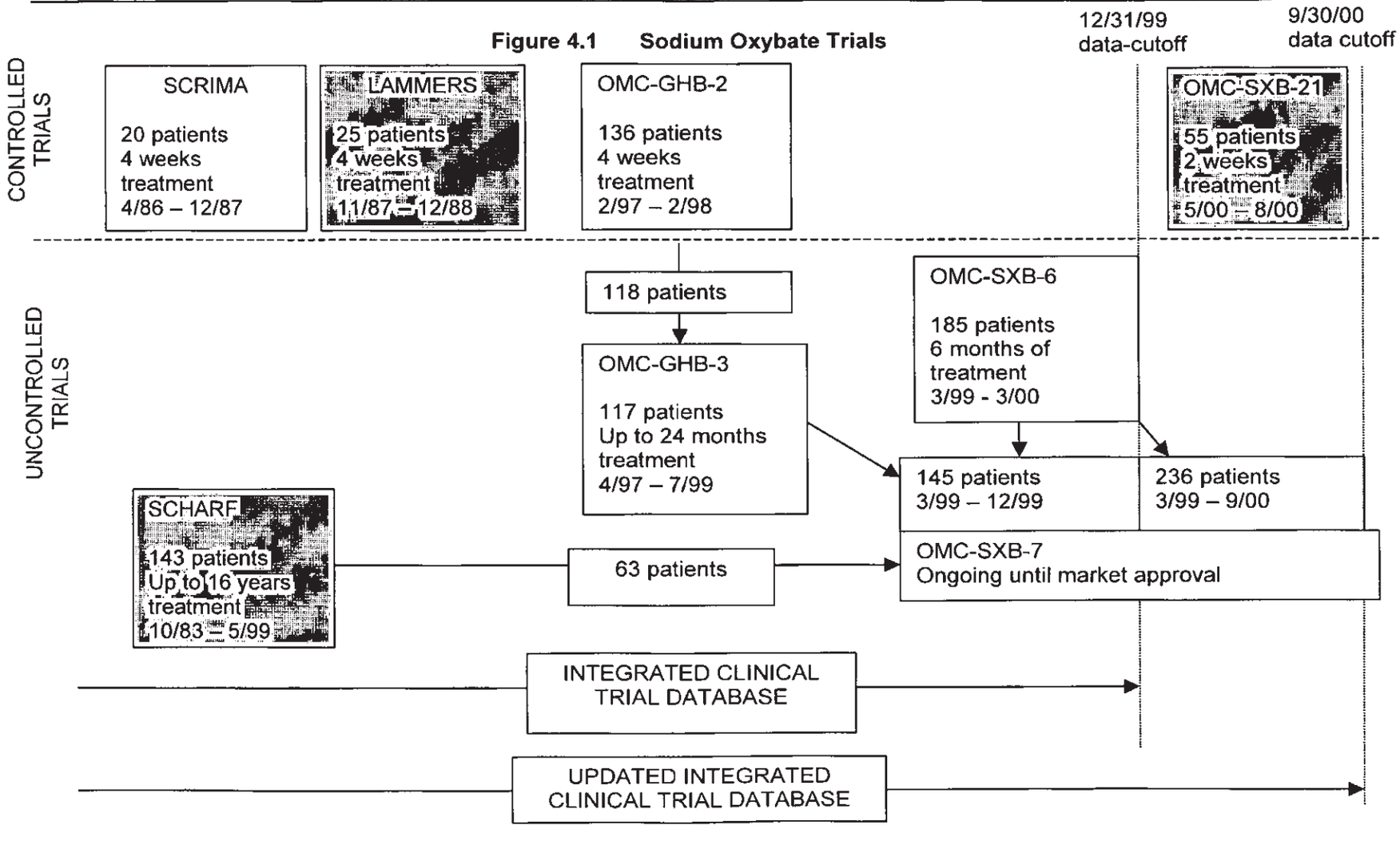
The following represents a summary of all available safety information for Xyrem (sodium oxybate). The safety data were carefully collected and reported by independent investigators conducting the clinical trials that make up the safety database in the Xyrem New Drug Application. The comprehensive database was reviewed by medical experts and summarized in individual clinical trial reports and in an Integrated Summary of Safety (submitted to FDA October 2, 2000). Safety data submitted subsequently included the Clinical Trial Report for controlled trial OMC-SXB-21 (submitted December 16, 2000) and a 4-Month Safety Update for the ongoing open-label trial (OMC-SXB-7, submitted February 2, 2001).

Four databases were used in compiling this analysis of safety:

- The updated integrated clinical trial database – this was a merge of the original integrated clinical trial database used for the Integrated Summary of Safety in the NDA and the 4-Month Safety Update database
  - The original integrated clinical trial database included two 4-week, placebo-controlled trials (Scrima and OMC-GHB-2) and 3 open-label, long-term trials (OMC-GHB-3, OMC-SXB-6, and OMC-SXB-7, the last through December 31, 1999), with a total of 402 patients, 148 of whom participated in more than 1 trial.
  - The 4-Month Safety Update database included 236 patients in the OMC-SXB-7 trial (with an additional 51 patients that transferred from OMC-SXB-6 to OMC-SXB-7 after the December 31, 1999 data cut-off).
- The Lammers trial, a 4-week, placebo-controlled trial, which was also included in the Integrated Summary of Safety as a separate database (this was not integrated in the statistical database due to its simplified method of data collection), with 25 patients
- The Scharf trial, an open-label, long-term trial, which was also included in the Integrated Summary of Safety as a separate database (this was not integrated in the statistical database due to the trial design and its history), with 143 patients, 63 of whom also participated in OMC-SXB-7 and are therefore included in the updated integrated clinical trial database
- The OMC-SXB-21 trial, a 4-week, placebo-controlled trial with 55 patients, all of whom also participated in OMC-SXB-7 (however, their safety data during OMC-SXB-21 are not included in the updated integrated clinical trial database; they were reported in the OMC-SXB-21 clinical trial report)

Figure 4.1 shows the trials included in this safety analysis. Shaded boxes represent the 3 trials (Lammers, Scharf, and OMC-SXB-21) not included in the updated integrated clinical trial database.

Figure 4.1 Sodium Oxybate Trials



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Only Adverse Events (AEs) occurring during treatment were included in the analysis of the updated integrated clinical trial database and the Scharf trial.

Of the 402 narcolepsy patients included in the updated integrated clinical trial database, 331 (82%) experienced at least 1 AE. As expected, a higher incidence (95%) was seen in the long-term clinical trial (Scharf). Related AEs were seen for 247(61%) of the 402 patients in the updated integrated clinical trial database. Severe AEs were seen for 82 (20%) of the 402 patients In the Scharf trial, severe AEs were seen for 21 (15%) of the 143 patients during the first 6 months on sodium oxybate.

Serious Adverse Events (SAEs) were experienced by 27 (7%) of the 402 patients in the updated integrated clinical trial database and 54 (38%) of the 143 patients in the Scharf trial. Two (<1%) deaths were reported in the updated integrated clinical trial database (both in the OMC-SXB-7 trial, including patient 0936, who died 5 months after the September 30, 2000, data cutoff), and 11 (8%) deaths were reported in the Scharf trial over 16 years. None of these deaths was considered related to trial medication. Fifty-three patients (13%) discontinued due to 1 or more AEs in the updated integrated clinical trial database, and 23 (16%) patients did so in the long-term (Scharf) trial. Of the discontinued patients, 42 (10%) in the updated integrated clinical trial database and 6 (4%) in the Scharf trial discontinued due to AEs considered to be related to trial medication.

For purposes of analysis, patients who had Xyrem oral solution dosages other than the protocol specified dosages were assigned a dosage according to the algorithm shown in Table 4.1.

Table 4.1 Algorithm for Assigning Dosages Other Than Those Specified by Protocol

Dosage (g/d)	Dosage Assignment(g/d)
≤ 0.00	Missing
> 0.00 to < 3.75	3.0
≥ 3.75 to < 5.25	4.5
≥ 5.25 to < 6.75	6.0
≥ 6.75 to < 8.25	7.5
≥ 8.25	9.0

4.2 Drug Exposure

In 4 of the clinical trials, patients were treated with sodium oxybate for 6 months or longer, including OMC-SXB-6 (6-month trial), OMC-GHB-3 (2-year trial), OMC-SXB-7 (2-year trial [amended to 30 months] and ongoing), and Scharf (16-year trial).

Table 4.2 provides an overview of duration of exposure for the 399 patients who received sodium oxybate in the updated integrated clinical trial database (up to September 30, 2000). Three patients received placebo in OMC-GHB-2, and did not

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continue into an open-label trial; they are therefore not included in this table. The overall patient exposure was 296 patients with ≥ 6 months, 223 patients with ≥ 1 year, and 48 patients with an exposure of ≥ 2 years.

Table 4.2 Updated Integrated Clinical Trial Database — Cumulative Duration of Sodium Oxybate Exposure, by Patient Dosage

Duration of Exposure[b]	Total	Sodium Oxybate Patient Dosage[a] (g/d)				
		3.0	4.5	6.0	7.5	9.0
Number of Patients	**399 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
≥ 6 mo (168 d)	296 (74%)	9 (9%)	50 (19%)	115 (40%)	59 (44%)	62 (48%)
≥ 1 y (336 d)	223 (56%)	5 (5%)	27 (10%)	60 (21%)	26 (20%)	34 (26%)
≥ 2 y (672 d)	48 (12%)	2 (2%)	4 (1%)	13 (4%)	9 (7%)	13 (10%)

[a] Patient Dosage: the number of patients who took the specified dosage at any time during the trial. Patients could be counted for more than 1 dosage; alternatively, patients may not have taken any 1 dosage for the specified time period but did take sodium oxybate overall for that period. Therefore, the sum of patients exposed to specific dosages does not equal the total number of patients.

[b] Duration was calculated based on a 28-day month. Duration of exposure was not calculated for the 3 patients who received placebo only.

Table 4.3 provides the duration of exposure for the 479 patients in the combined experience from the updated integrated clinical trial database and the Scharf trial. With the experience from the long-term Scharf trial included, the overall patient exposure was 360 patients with ≥ 6 months, 286 patients with ≥ 1 year, and 150 patients with an exposure of ≥ 2 years.

Table 4.3 Updated Integrated Clinical Trial Database Plus Scharf Trial — Cumulative Duration of Sodium Oxybate Exposure, by Patient Dosage

Duration of Exposure[b]	Total	Sodium Oxybate Patient Dosage[a] (g/d)				
		3.0	4.5	6.0	7.5	9.0
Number of Patients	**479 (100%)**	**198 (100%)**	**377 (100%)**	**383 (100%)**	**184 (100%)**	**159 (100%)**
≥ 6 mo (168 d)	360 (75%)	25 (13%)	87 (23%)	171 (45%)	83 (45%)	70 (44%)
≥ 1 y (336 d)	286 (60%)	12 (6%)	55 (15%)	114 (30%)	50 (27%)	42 (26%)
≥ 2 y (672 d)	150 (31%)	6 (3%)	26 (7%)	66 (17%)	34 (18%)	23 (14%)

[a] Patient Dosage: the number of patients who took the specified dosage at any time during the trial. Patients could be counted for more than 1 dosage; alternatively, patients may not have taken any 1 dosage for the specified time period but did take sodium oxybate overall for that period. Therefore, the sum of patients exposed to specific dosages does not equal the total number of patients.

[b] Duration was calculated based on a 28-day month. Duration of exposure was not calculated for the 3 patients who received placebo only.

Both with and without the experience from the Scharf trial, the most frequently administered dosage for all 3 durations of exposure (≥ 6 months, ≥ 1 year, and ≥ 2 years) was 6.0 g/d.

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Total exposure to sodium oxybate (calculated based on twelve 28-day months) was 330 patient-years in the updated integrated clinical trial database, 2 patient-years in the Lammers trial, and 996 patient-years in the Scharf trial, or a total of 1,328 patient-years.

4.3 Updated Integrated Clinical Trials

The updated integrated clinical trial database is composed of a merge of the original integrated clinical trial database used for the Integrated Summary of Safety in the NDA and the 4-Month Safety Update database.

In the OMC-GHB-3 trial, 34 patients received placebo and all but 3 of these continued into open-label trials with sodium oxybate. Since all data in the updated integrated clinical trial database are presented by last dosage, only the 3 patients who did not go on to treatment with sodium oxybate are included in the placebo group. Since the 20 patients in the Scrima trial received both placebo and sodium oxybate, they are included in the sodium oxybate group.

As shown in Table 4.4, a majority of patients in the updated integrated clinical trial database had completed treatment (48/402, 12%) or were still enrolled in OMC-SXB-7 as of the September 30, 2000, data cutoff (210/402, 52%). Of the 144 patients who discontinued treatment, 52 (13%) did so due to AEs.

Table 4.4 Patient Disposition — Updated Integrated Clinical Trial Database

Patient Disposition	Total	Placebo	Sodium Oxybate
Patients treated	402 (100%)	3 (100%)	399 (100%)
Completed treatment	48 (12%)	2 (67%)	46 (12%)
Ongoing treatment	210 (52%)	0	210 (52%)
Discontinued treatment	144 (36%)	1 (33%)	143 (36%)
AE[a]	53 (13%)	1 (33%)	52 (13%)
Patient request/withdrew consent	34 (8%)	0	34 (9%)
Patient non-compliance	19 (5%)	0	19 (5%)
Other	18 (4%)	0	18 (5%)
Lost to follow-up	11 (3%)	0	11 (3%)
Lack of efficacy	5 (1%)	0	5 (1%)
Protocol deviation/violation	4 (<1%)	0	4 (<1%)
Death[a]	2 (<1%)	0	2 (<1%)

[a] Count includes patient 0936, who died on 2/24/01, 5 months after data cutoff, but is included here for completeness.

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4.3.1 INCIDENCE OF ADVERSE EVENTS

Table 4.5 summarizes the AEs by sodium oxybate dosage at onset for the updated integrated clinical trial database.

- The majority of the 402 patients (331, 82%) experienced at least 1 AE.
- Approximately half of the patients (247, 61%) experienced related AEs.
- Severe AEs were reported for 82 patients (20%).
- Only 24 patients (6%) experienced SAEs.
- 53 patients (13%) discontinued due to AEs.
- There were 2 deaths (1%).

A higher incidence of AEs was seen with the 9.0 g/d sodium oxybate group compared with the other 4 dosage groups. This was true for:

- Patients with at least 1 AE (78% for 9.0 g/d, compared with 51% to 62% for the other 4 dosage groups)
- Patients with SAEs (6% for 9.0 g/d, vs. 1% to 3% for the other 4 dosage groups)
- Patients with related AEs (55% for 9.0 g/d, vs. 28% to 40% for the other 4 dosage groups)
- Patients with severe AEs (16% for 9.0 g/d, vs. 3% to 12% for the other 4 dosage groups)
- Discontinuations due to AEs (14% for 9.0 g/d, vs. 3% to 6% for the other 4 dosage groups)

However, the incidence for each category was lower for 7.5 g/d than for 6.0 g/d, making it difficult to infer a true dose-response relationship. Interestingly, the incidence for the placebo group was similar to that for the 9.0 g/d group for patients with at least 1 AE (70%) and patients with related AEs (50%).

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Table 4.5 AEs by Dosage at Onset — Updated Integrated Clinical Trial Database

	Total[a]	Placebo	Sodium Oxybate Dosage at Onset (g/d)					
			Total[a]	3.0	4.5	6.0	7.5	9.0
Number of patients	**402 (100%)**	**54 (100%)**	**399 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
At least 1 AE	331 (82%)	38 (70%)	326 (82%)	58 (60%)	138 (51%)	181 (62%)	72 (54%)	101 (78%)
SAEs	27 (7%)	0	27 (7%)	0	5 (2%)	11 (4%)	3 (2%)	10 (8%)
Related AEs	247 (61%)	27 (50%)	241 (60%)	37 (38%)	92 (34%)	115 (40%)	37 (28%)	71 (55%)
Severe AEs	82 (20%)	3 (6%)	80 (20%)	3 (3%)	25 (9%)	35 (12%)	6 (5%)	20 (16%)
Discontinu-ations due to AEs	53 (13%)	1 (2%)	52 (13%)	5 (5%)	15 (6%)	14 (5%)	4 (3%)	18 (14%)
Deaths	2 (1%)	0	2 (1%)	0	0	2 (1%)	0	0

[a] Patients are counted only once in each category. However, patients could have had more than 1 AE with different dosages at onset, so the sum of the patients in the dosage at onset groups may exceed the total number of patients in each event category.

Table 4.6 summarizes the incidence of AEs occurring in ≥ 5% of patients in the updated integrated clinical trial database. The most frequently reported AEs included headache (116 patients, 29%), nausea (94 patients, 23%), dizziness (76 patients, 19%), and pain (71 patients, 18%). The most frequently affected body systems were body as a whole (225 patients, 56%) and the nervous system (206 patients, 51%). There were no apparent differences in incidence of headache and pain among the 6 dosage at onset groups, including placebo and the 5 sodium oxybate groups. There was a higher incidence (23%) of nausea in the 9.0 g/d group, compared with 7% for placebo and 8% to 11% for the other 4 sodium oxybate groups. A higher incidence of dizziness was seen in the 3.0 g/d and 9.0 g/d groups (16% and 17%, respectively), compared with 4% for placebo and 6% to 12% for the other 3 sodium oxybate groups.

Approximately half of the patients (247, 61%) experienced a related AE. The great majority of these patients reported AEs that were mild (99 patients, 40% of those with related AEs, 25% of the total population) or moderate (112 patients, 45% of those with related AEs, 28% of the total population). Severe related AEs were experienced by 36 patients (15% of those with related AEs, 9% of the total population). A higher incidence of both moderate and severe AEs overall was seen in the 9.0 g/d group. Moderate AEs were seen in 28% of the 9.0 g/d group, compared with 11% for placebo and 13% to 15% for the other 4 sodium oxybate groups; severe AEs were seen in 8% of the 9.0 g/d group, vs. 2% for placebo and 1% to 4% for the other 4 sodium oxybate groups. The incidence of severe related AEs for the most frequently reported AEs listed above was 1% (5/402) for headache, 1% (3/402) for nausea, 1% (4/402) for dizziness,

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and 0 for pain. A higher incidence of mild headache was seen for placebo (11%), compared with 2% to 6% for the 5 sodium oxybate groups. No apparent differences were seen in the other AEs among the 6 groups, including placebo and the 5 sodium oxybate dosage at onset groups.

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Table 4.6 AEs Occurring in ≥ 5% of Any Group, by Body System, COSTART Preferred Term, and Dosage at Onset — Updated Integrated Clinical Trial Database

Body System COSTART Preferred Term	Total[a]	Placebo	Sodium Oxybate Dosage at Onset (g/d)					
			Total[a]	3.0	4.5	6.0	7.5	9.0
Number of patients	**402 (100%)**	**54 (100%)**	**399 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
Body as a Whole	225 (56%)	25 (46%)	221 (55%)	39 (40%)	81 (30%)	106 (37%)	41 (31%)	57 (44%)
Abdominal pain	25 (6%)	1 (2%)	24 (6%)	4 (4%)	6 (2%)	9 (3%)	3 (2%)	4 (3%)
Accidental injury	38 (9%)	0	38 (10%)	4 (4%)	6 (2%)	17 (6%)	6 (5%)	9 (7%)
Asthenia	36 (9%)	1 (2%)	35 (9%)	5 (5%)	6 (2%)	17 (6%)	5 (4%)	9 (7%)
Back pain	28 (7%)	2 (4%)	27 (7%)	2 (2%)	4 (1%)	13 (4%)	6 (5%)	8 (6%)
Chest pain	21 (5%)	0	21 (5%)	2 (2%)	4 (1%)	9 (3%)	5 (4%)	4 (3%)
Flu syndrome	41 (10%)	2 (4%)	39 (10%)	6 (6%)	7 (3%)	14 (5%)	10 (8%)	7 (5%)
Headache	116 (29%)	12 (22%)	112 (28%)	19 (20%)	40 (15%)	42 (14%)	13 (10%)	25 (19%)
Infection	42 (10%)	1 (2%)	41 (10%)	5 (5%)	2 (1%)	19 (7%)	7 (5%)	8 (6%)
Malaise	10 (2%)	3 (6%)	9 (2%)	1 (1%)	1 (<1%)	1 (<1%)	4 (3%)	3 (2%)
Pain	71 (18%)	4 (7%)	70 (18%)	12 (12%)	18 (7%)	33 (11%)	8 (6%)	16 (12%)
Viral infection	40 (10%)	0	40 (10%)	2 (2%)	6 (2%)	18 (6%)	5 (4%)	12 (9%)
Cardiovascular System	47 (12%)	2 (4%)	45 (11%)	6 (6%)	5 (2%)	17 (6%)	8 (6%)	11 (9%)
Digestive System	157 (39%)	9 (17%)	150 (38%)	23 (24%)	43 (16%)	62 (21%)	21 (16%)	42 (33%)
Diarrhea	38 (9%)	1 (2%)	37 (9%)	4 (4%)	6 (2%)	15 (5%)	7 (5%)	9 (7%)
Dyspepsia	32 (8%)	5 (9%)	27 (7%)	7 (7%)	8 (3%)	7 (2%)	2 (2%)	7 (5%)
Nausea	94 (23%)	4 (7%)	90 (23%)	9 (9%)	21 (8%)	31 (11%)	13 (10%)	30 (23%)
Vomiting	34 (8%)	1 (2%)	33 (8%)	1 (1%)	6 (2%)	14 (5%)	3 (2%)	10 (8%)
Metabolic and Nutritional System	53 (13%)	2 (4%)	53 (13%)	6 (6%)	8 (3%)	19 (7%)	14 (11%)	14 (11%)
Weight loss	12 (3%)	0	12 (3%)	0	0	4 (1%)	3 (2%)	6 (5%)

(continued)

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Table 4.6 AEs Occurring in ≥ 5% of Any Group, by Body System, COSTART Preferred Term, and Dosage at Onset — Updated Integrated Clinical Trial Database

Body System COSTART Preferred Term	Total[a]	Placebo	Sodium Oxybate Dosage at Onset (g/d)					
			Total[a]	3.0	4.5	6.0	7.5	9.0
Number of patients	**402 (100%)**	**54 (100%)**	**399 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
Musculoskeletal System	74 (18%)	2 (4%)	72 (18%)	8 (8%)	19 (7%)	33 (11%)	9 (7%)	12 (9%)
	21(5%)	2(4%)	19(5%)	2(2%)	7(3%)	10(3%)	1(1%)	2(2%)
Nervous System	206 (51%)	17 (31%)	201 (50%)	31 (32%)	66 (25%)	98 (34%)	31 (23%)	63 (49%)
Abnormal dreams	20 (5%)	0	20 (5%)	2 (2%)	8 (3%)	7 (2%)	4 (3%)	1 (1%)
Confusion	30 (7%)	1 (2%)	29 (7%)	4 (4%)	6 (2%)	11 (4%)	6 (5%)	10 (8%)
Depression	28 (7%)	1 (2%)	27 (7%)	5 (5%)	2 (1%)	12 (4%)	4 (3%)	6 (5%)
Dizziness	76 (19%)	2 (4%)	74 (19%)	16 (16%)	15 (6%)	34 (12%)	9 (7%)	22 (17%)
Emotional lability	13 (3%)	3 (6%)	10 (3%)	2 (2%)	2 (1%)	2 (1%)	1 (1%)	3 (2%)
Insomnia	25 (6%)	1 (2%)	24 (6%)	1 (1%)	8 (3%)	11 (4%)	3 (2%)	3 (2%)
Nervousness	35 (9%)	6 (11%)	31 (8%)	3 (3%)	9 (3%)	14 (5%)	3 (2%)	8 (6%)
Sleep disorder	47 (12%)	2 (4%)	45 (11%)	4 (4%)	15 (6%)	21 (7%)	5 (4%)	12 (9%)
Somnolence	60 (15%)	8 (15%)	55 (14%)	11 (11%)	14 (5%)	23 (8%)	5 (4%)	14 (11%)
Respiratory System	127 (32%)	6 (11%)	125 (31%)	16 (16%)	34 (13%)	61 (21%)	20 (15%)	18 (14%)
Cough increased	24 (6%)	2 (4%)	22 (6%)	5 (5%)	6 (2%)	10 (3%)	2 (2%)	1 (1%)
Pharyngitis	48 (12%)	3 (6%)	47 (12%)	5 (5%)	8 (3%)	23 (8%)	10 (8%)	2 (2%)
Rhinitis	36 (9%)	1 (2%)	35 (9%)	4 (4%)	12 (4%)	11 (4%)	7 (5%)	5 (4%)
Sinusitis	32 (8%)	0	32 (8%)	5 (5%)	6 (2%)	16 (6%)	4 (3%)	4 (3%)
Skin	61 (15%)	4 (7%)	58 (15%)	4 (4%)	9 (3%)	27 (9%)	5 (4%)	19 (15%)
Sweating	18 (4%)	0	18 (5%)	2 (2%)	2 (1%)	6 (2%)	1 (1%)	10 (8%)
Special Senses	52 (13%)	3 (6%)	49 (12%)	8 (8%)	10 (4%)	16 (6%)	7 (5%)	12 (9%)

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Table 4.6 AEs Occurring in ≥ 5% of Any Group, by Body System, COSTART Preferred Term, and Dosage at Onset — Updated Integrated Clinical Trial Database

Body System COSTART Preferred Term	Total[a]	Placebo	Sodium Oxybate Dosage at Onset (g/d)					
			Total[a]	3.0	4.5	6.0	7.5	9.0
Number of patients	**402 (100%)**	**54 (100%)**	**399 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
Urogenital System	94 (23%)	6 (11%)	90 (23%)	7 (7%)	18 (7%)	43 (15%)	10 (8%)	25 (19%)
Incontinence urine	8 (2%)	0	8 (2%)	0	0	2 (1%)	0	6 (5%)
Urinary incontinence	28 (7%)	0	28 (7%)	2 (2%)	8 (3%)	9 (3%)	6 (5%)	6 (5%)

[a] Patients are counted only once in each category. However, patients could have had more than 1 instance of the same AE with different dosages at onset, so the sum of the patients in the dosage at onset groups may exceed the total number of patients in each event category or body system summary.

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4.3.2 SERIOUS ADVERSE EVENTS

SAEs during treatment were experienced by 27 (7%) of the 402 patients in the updated integrated clinical trial database. Sodium oxybate dosage at onset was 3g for 1 patient 4.5 g/d for 5 patients, 6.0 g/d for 13 patients, 7.5 g/d for 2 patients, and 9.0 g/d for 8 patients (2 patients [1433 and 1630] had SAEs with different dosages at onset, and are counted twice).

Treatment-related SAEs were seen in only 11 of the 27 patients (1 in OMC-GHB-2, 1 in OMC-GHB-3, 3 in OMC-SXB-6, and 6 in OMC-SXB-7), resulting in an overall incidence of 3% (11 of 402) of SAEs possibly, probably, or definitely related to sodium oxybate treatment in the updated integrated clinical trial database.

Nine of the 11 treatment-related SAEs noted in the database resulted in inpatient hospitalization (1 SAE [23230] was originally classified as definitely related by the Investigator and upon further evaluation was determined to be not related: Therefore there are 10 treatment related SAEs.

- Patient 0207 (OMC-GHB-2) experienced confusion (severe, probably related) on Day 7 at a sodium oxybate dosage of 6.0 g/d, and was permanently discontinued from the trial. The patient recovered normal mental status following initial treatment with Haldol on the day of hospital admission. There have been no recurrences since study discontinuation.

- Patient 0232 (OMC-SXB-7) experienced acute paranoid delusional psychosis (severe, probably related) on Day 476 at a sodium oxybate dosage of 9.0 g/d, and was permanently discontinued from the trial. The SAE resolved approximately 2 months after discontinuing trial medication.

- Patient 0238 (OMC-SXB-6) fell and struck his head, proceeding to apnea, thinking abnormal, and coma (severe, probably related) on Day 170 at a sodium oxybate dosage of 4.5 g/d, and was permanently discontinued from the trial. The event resolved with no sequelae or recurrence following removal from trial medication.

- Patient 1131 (OMC-SXB-7) intentionally overdosed with Xyrem (approximately 150 g) (severe, definitely related to study medicine) on Day 280 while on a sodium oxybate maintenance dosage of 9.0 g/d, and was permanently discontinued from the trial. The patient had a history of treatment for depression and a previous suicide attempt. The patient was given psychiatric and medical referrals.

- Patient 1305 (OMC-GHB-3) experienced agitation (severe, possibly related) on Day 678 at a sodium oxybate dosage of 9.0 g/d, and trial medication was temporarily stopped. The patient later experienced an AE of "movement disorder" (Periodic Leg Movement in Sleep) and was discontinued from the trial on day 982.

- Patient 1735 (OMC-SXB-6) experienced abortion (mild, possibly related) on Day 108, previously at a sodium oxybate dosage of 6.0 g/d; however, she had been

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permanently discontinued from the trial on Day 66 when she became pregnant (protocol violation, failing the inclusion criteria).

- Patient 2030 (OMC-SXB-7) began experiencing intermittent brief reactive psychosis (severe, possibly related) on Day 207 at a sodium oxybate dosage of 9.0 g/d, and was permanently discontinued from the trial. The patient was treated with Zyprexa and Trazadone and the event resolved with no recurring psychosis.

- Patient 23230 (OMC-SXB-7) began experiencing intermittent chest pain (originally severe, and definitely related, later determined to be not related) on Day 119. The patient was hospitalized for atypical chest pain, was treated and was discharged with the diagnosis of esophageal spasms. Patient participation is ongoing in trial OMC-SXB-7.

- Patient 2536 (OMC-SXB-7) fractured her ankle (severe, possibly related) on Day 228 at a sodium oxybate dosage of 9.0 g/d, and was permanently discontinued from the trial. The patient was discharged from the hospital on day 235 and referred to the rehabilitation clinic.

The remaining 2 treatment-related SAEs did not require inpatient hospitalization:

- Patient 0231 (OMC-SXB-6) experienced dizziness, confusion, nausea, vomiting, vertigo, and asthenia (all severe, possibly related) on Day 119 at a sodium oxybate dosage of 9.0 g/d, and was permanently discontinued from the trial. All events resolved within 24 hours of occurrence.

- Patient 14043 (OMC-SXB-7) attempted suicide by buspirone overdose (severe, possibly related) on Day 216 at a sodium oxybate dosage of 7.5 g/d, and was permanently discontinued from the trial. In current follow-up, patient's family state that the patient is doing well since her release from psychiatric treatment.

4.3.3 DISCONTINUATIONS AND OTHER SIGNIFICANT ADVERSE EVENTS

Fifty-three patients in the updated integrated clinical trial database withdrew due to 1 or more AEs, including 52 patients receiving sodium oxybate and 1 patient receiving placebo (0818).

Sodium oxybate dosage at onset was 3.0 g/d for 5 patients, 4.5 g/d for 15 patients, 6.0 g/d for 14 patients, 7.5 g/d for 4 patients, and 9.0 g/d for 18 patients.

Of the 53 patients discontinued due to AEs, 42 experienced AEs considered related to trial medication by the investigator (Table 4.7).

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Table 4.7 Related AEs Causing Discontinuation — Updated Integrated Clinical Trial Database

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day[a]		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
0204	OMC-GHB-3	6.0	33	51	Insomnia	Insomnia	No	Moderate
0207	OMC-GHB-2	6.0	7	9	Acute confusional state	Confusion	Yes	Severe
0213	OMC-GHB-3	9.0	90	135	Depressed mood	Depression	No	Moderate
		9.0	90	135	Excessive tiredness	Asthenia	No	Moderate
0221	OMC-GHB-2	9.0	13	15	Dizzy	Dizziness	No	Moderate
		9.0	13	15	Increased sleepiness	Somnolence	No	Moderate
		9.0	13	15	Nauseated	Nausea	No	Moderate
		9.0	13	15	Weakness (had trouble standing)	Asthenia	No	Moderate
	OMC-GHB-3	3.0	30	108	Lethargic all day	Somnolence	No	Mild
0231	OMC-SXB-6	9.0	119	119	Dizziness	Dizziness	Yes	Severe
		9.0	119	119	Confusion	Confusion	Yes	Severe
		9.0	119	119	Nausea	Nausea	Yes	Severe
		9.0	119	119	Vomiting	Vomiting	Yes	Severe
		9.0	119	119	Vertigo	Vertigo	Yes	Severe
		9.0	119	119	Weakness	Asthenia	Yes	Severe
0232	OMC-SXB-7	9.0	476	489	Acute paranoid delusional psychosis	Paranoid reaction	Yes	Severe
0238	OMC-SXB-6	4.5	170	170	Respiratory failure	Apnea	Yes	Severe
		4.5	170	170	Non-responsive	Coma	Yes	Severe
0409	OMC-GHB-3	9.0	61		Weight loss	Weight loss	No	Mild
0509	OMC-GHB-2	6.0	1	2	Restless leg syndrome increased	Hyperkinesia	No	Severe
0533	OMC-SXB-6	4.5	10		Swelling in legs	Peripheral edema	No	Severe

(continued)

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Table 4.7 Related AEs Causing Discontinuation — Updated Integrated Clinical Trial Database

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day[a]		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
0605	OMC-GHB-2	9.0	9	12	Daytime sedation feeling; "drugged feeling"	Somnolence	No	Mild
		9.0	9	12	Poor concentration	Thinking abnormal	No	Mild
0637	OMC-SXB-6	7.5	93[b]		Restless legs	Hyperkinesia	No	Moderate
		7.5	93[b]		Anxiety	Anxiety	No	Moderate
0701	OMC-GHB-3	6.0[c]	32		Decreased sexual libido	Libido decreased	No	Moderate
		6.0[c]	32		Decreased initiative to start any activity by gradual progression	Apathy	No	Mild
0702	OMC-GHB-2	9.0	20	25	Confusion	Confusion	No	Moderate
		9.0	20	25	Forgetfulness	Amnesia	No	Moderate
		9.0	20	23	Hallucinations	Hallucinations	No	Moderate
		9.0	21	21	Nausea	Nausea	No	Mild
		9.0	22	24	Paranoia	Paranoid reaction	No	Mild
0801	OMC-GHB-3	9.0	147	178	Chest pain, patient on drug, no hospitalization, no concomitant medication	Chest pain	No	Moderate
0802	OMC-GHB-3	9.0	49	55	Nervousness	Nervousness	No	Moderate
		9.0	49	51	Metallic taste	Taste perversion	No	Mild
		9.0	49	51	Upset stomach	Dyspepsia	No	Moderate
0809	OMC-GHB-3	3.0	332	332	Inability to control body 1 hr after taking medicine	Incoordination	No	Mild
0818	OMC-GHB-2	Placebo	23		Insomnia	Insomnia	No	Moderate
0821	OMC-GHB-3	6.0	39	51	Headaches	Headache	No	Moderate
		6.0	40	51	Irritable	Nervousness	No	Moderate

(continued)

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Table 4.7 Related AEs Causing Discontinuation — Updated Integrated Clinical Trial Database

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day[a]		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
0824	OMC-GHB-2	9.0[c]	5	5	Difficulty breathing	Dyspnea	No	Severe
	OMC-GHB-3	3.0	25	29	Difficulty breathing	Dyspnea	No	Moderate
0836	OMC-SXB-6	4.5	1		Headache	Headache	No	Moderate
0844	OMC-SXB-6	4.5	1	42	Nausea	Nausea	No	Moderate
		4.5	1	42	Vomiting	Vomiting	No	Moderate
		4.5	1	42	Headaches	Headache	No	Severe
0901	OMC-GHB-2	3.0	2	18	Lethargy	Somnolence	No	Mild
		3.0	2	18	Nausea	Nausea	No	Moderate
		3.0	3	18	Chest pressure	Chest pain	No	Mild
1131	OMC-SXB-7	9.0	280	280	Conscious overdose	Intentional overdose	Yes	Severe
1134	OMC-SXB-6	4.5	3		Urinary incontinence	Urinary incontinence	No	Moderate
1142	OMC-SXB-6	7.5	31	34	Left eye exposure keratitis	Keratitis	No	Mild
1201	OMC-GHB-2	9.0	5	5	Patient lost bowel control while asleep	Incontinence, fecal	No	Moderate
14043	OMC-SXB-7	7.5	216	216	Attempted suicide	Suicide attempt	Yes	Severe
1504	OMC-GHB-2	9.0	2	2	Nausea	Nausea	No	Severe
		9.0	2	2	Vertigo	Vertigo	No	Severe
		9.0	2	2	Vomiting	Vomiting	No	Severe
1631	OMC-SXB-6	6.0	23	59	Sleepwalking	Sleep disorder	No	Moderate
		4.5	44	59	Fragmented sleep	Sleep disorder	No	Severe
		4.5	44	60	Involuntary limb movements in sleep	Sleep disorder	No	Moderate
1735	OMC-SXB-6	6.0	108[d]	108[d]	Miscarriage	Abortion	Yes	Mild
2030	OMC-SXB-7	9.0	207	214	Brief reactive psychosis	Psychosis	Yes	Severe

(continued)

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Table 4.7 Related AEs Causing Discontinuation — Updated Integrated Clinical Trial Database

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day[a]		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
2532	OMC-SXB-6	4.5	16	43	Sleepwalking	Sleep disorder	No	Mild
		4.5	16	43	Dizziness	Dizziness	No	Mild
		4.5	39	43	Arms and legs numb	Paresthesia	No	Mild
2533	OMC-SXB-6	4.5	25	81	Nausea	Nausea	No	Moderate
		6.0	74	81	Morning grogginess	Somnolence	No	Moderate
2536	OMC-SXB-7	9.0	228	228	Fractured ankle	Fractured ankle	Yes	Severe
2537	OMC-SXB-6	4.5	12		Increased headaches	Headache	No	Moderate
2633	OMC-SXB-6	4.5	2	4	Increased awakenings	Sleep disorder	No	Mild
		4.5	2	4	Tongue paresthesia	Paresthesia	No	Mild
2933	OMC-SXB-6	4.5	29		"Phlegm/knot" in throat	Pharyngitis	No	Moderate
3231	OMC-SXB-6	6.0	56		Exacerbation of colitis (Crohn's disease)	Colitis	No	Moderate
3830	OMC-SXB-6	7.5	52	62	Nausea	Nausea	No	Moderate
		7.5	58	58	Vomiting	Vomiting	No	Moderate
3831	OMC-SXB-6	3.0	12	24	Itching and swelling of extremities	Pruritus	No	Moderate
		3.0	12	24	Itching and swelling of extremities	Edema	No	Moderate
3930	OMC-SXB-6	4.5	2	3	Sleep paralysis	Sleep disorder	No	Moderate

[a] Day relative to start of treatment.
[b] Whole or partial data imputed from start of trial medication.
[c] Dosage carried forward.
[d] Patient discontinued study drug on study day 66, and the event of miscarriage occurred on day 108.

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4.3.4 DEATHS

Two deaths, both suicides (0531 and 0936), were recorded among the 402 patients in the updated integrated clinical trial database. One (0531, coded as death) was due to multiple drug toxicity that included toxic levels of 6 psychotropic drugs other than sodium oxybate. The second patient (0936) had a history of depression and a subsequent suggested diagnosis of bipolar disease. This event was officially ruled as a death due to cardiovascular disease (without autopsy by the Medical Examiner), but later evidence pointed to a possible overdose that included lithium, Paxil, and Percocet as well as sodium oxybate. This event occurred on 2/24/01, which was 5 months after the data cutoff (9/30/00), but is included here for completeness. Both deaths were considered unrelated to study drug.

4.3.5 LABORATORY RESULTS

Laboratory evaluations for the original integrated clinical trial database (laboratory results were not analyzed for the 4-Month Safety Update for OMC-SXB-7) included blood chemistry, hematology, and urinalysis. Mean changes from baseline to last observation were small and similar across all 6 groups (placebo and 5 sodium oxybate last dosage groups) for all parameters.

4.3.5.1 Blood Chemistry

Shifts in ≥ 10% of the patients were only seen for calcium and total bilirubin. A shift from normal to low calcium was seen in 14 of 132 patients (11%) in the OMC-GHB-2 and OMC-GHB-3 trials (duration of up to two years); this ranged from 0 in the placebo group (for a 4 week treatment period) and the 7.5 g/d sodium oxybate last dosage group to 25% in the 3.0 g/d sodium oxybate last dosage group (treatment duration of up to two years). A shift from normal to low total bilirubin was seen in 32 of 314 patients (10%); this ranged from 4% in the 7.5 g/d sodium oxybate last dosage group (duration of up to two years) to 33% in the placebo group (4-week treatment period).

4.3.5.2 Hematology

Shifts in ≥ 10% of the patients were only seen for basophils, with a shift from high to normal in 30 of 310 patients (10%); this ranged from 0 in the placebo group (4-week treatment period) to 20% in the 3.0 g/d sodium oxybate last dosage group (duration of up to two years).

4.3.5.3 Urinalysis

Shifts in ≥ 10% of the patients were only seen for protein, with a shift from positive to negative in 42 of 307 patients (14%); this ranged from 6% in the 4.5 g/d sodium oxybate last dosage group (duration of up to two years) to 33% in the placebo group (4-week treatment period).

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4.3.6 VITAL SIGNS AND ECG

Vital signs (pulse, respiration, blood pressure, body temperature, body weight) and ECG were analyzed for the original integrated clinical trial database (vital signs and ECG were not analyzed for the 4-Month Safety Update for OMC-SXB-7). Mean changes for all vital sign parameters were small, and were similar across all 6 groups (placebo group and 5 sodium oxybate last dosage groups).

Shifts from baseline to last observation in ECG results were analyzed. No shifts in ≥ 10% of the patients were seen overall or in any patient group for either abnormal to within normal limits or within normal limits to abnormal.

4.3.7 SAFETY SUMMARY – UPDATED INTEGRATED CLINICAL TRIALS

In dosages between 3 and 9g nightly in divided doses, sodium oxybate was generally well tolerated in the 5 trials comprising the Updated Integrated Clinical Trials. The side effects were usually mild in severity and most frequently included nausea, dizziness, and headache, and less frequently urinary incontinence (enuresis) and somnambulism (sleepwalking).

In the Updated Integrated Clinical Trials, a total of 296 patients have taken sodium oxybate for at least 6 months; of these, 223 patients have taken sodium oxybate for at least 1 year and 48 patients have taken sodium oxybate for at least 2 years. Total exposure to sodium oxybate was 329.89 patient years.

Of the 402 narcolepsy patients in this data base, 331 (82%) reported at least 1 AE. Adverse events considered to be possibly, probably, or definitely related to treatment with sodium oxybate were reported in 247 (61%) patients. Severe AEs were reported in 82 (20%) of the patients. Serious AEs were reported for a total of 27 (7%) patients, 10 whom had SAEs that were considered related to trial medication. Two deaths were reported (both suicides and both unrelated to trial medication).

Laboratory evaluations included blood chemistry, hematology, and urinalysis. The only potentially significant laboratory abnormality was hypocalcemia, which was present in 23 (17%) of 132 patients. It was a variable measure in 15 of these patients, with a return to normal during sodium oxybate treatment. In all cases, the reduction in calcium levels was minor and deemed not of clinical significance.

4.4 Lammers Trial

The Lammers trial was a double-blind, placebo-controlled, crossover trial in 25 patients to assess the effects of 60 mg/kg sodium oxybate or placebo in narcolepsy.

Sodium oxybate was well tolerated. AEs during the Lammers trial were few and mild, and were experienced by 6 (24%) of the 25 patients, as follows:

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- 2 patients during the washout period (1 patient with frequent headache, and 1 patient with severe dreaming)
- 1 patient on placebo (kidney problems, urination problems/stranguria)
- 3 patients on sodium oxybate:
  - 1 patient with severe perspiration, influenza/common cold, sore throat, headache, and frequent micturition
  - 1 patient with bladder infection, sore throat, and flickering in the eyes
  - 1 patient with terrible dreaming, dry mouth, paralysis in legs and arms, anxious, and insecure

No SAEs or deaths were reported during the trial, and no patient withdrew due to an AE.

4.5 Scharf Trial

From the time of study initiation in 1983 to the time of study closure in 2000, a total of 143 patients participated in the Scharf open-label trial. Table 4.8 summarizes the disposition of the 143 patients in the Scharf trial. As of the NDA cutoff date of May 31, 1999, 63 of these patients transferred into the Orphan Medical Treatment IND protocol OMC-SXB-7. Of the remaining 80 patients, 8 continued to participate in the Scharf open-label trial, and 71 patients had discontinued from the Scharf open-label trial prior to the cutoff date. The reasons for discontinuation were: non-compliance (24); adverse events (23); cost of study participation (13); patient request (5); lack of efficacy (4); protocol deviation and other (1 each). The patient listed as "other" for reason for discontinuation, entered Dr. Scharf's GHB fibromyalgia trial. One patient was a screen failure.

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Table 4.8 Summary of Patient Disposition in Scharf Clinical Trial

Patient Disposition	Number of Patients
Patients screened	143
Patients treated	142
Ongoing treatment (OMC-SXB-7)	63
Ongoing treatment (Scharf)	8
Discontinued treatment	71
Non-compliance	24
Failure to provide diaries	22
Failure to follow dosing instructions	2
AEs	23
Death (coded as an SAE)	10[a]
Other AE	13
Cost of medication	13
Patient request/withdrawal of consent	5
Lack of efficacy	4
Protocol deviation	1
Other (transfer to fibromyalgia study)	1

[a]In the initial Scharf Report, 11 deaths were reported, however, one patient (202)died in a boating accident seven months following discontinuation of study medication. The case report form lists patient request as the reason for discontinuation.

This open-label, long-term (up to 16 years) clinical trial was developed under the investigator's IND following consultation with the FDA in 1983. These data were collected by Dr. Scharf more as a matter of clinical record than for drug development research and, hence, there are some differences from the other trials (eg, laboratory results were generated from many different laboratories, dose titration extended to dosages as high as 12.5 g/d). These data, do, however, provide experience in long-term treatment exposure. A total of 143 patients were enrolled in this trial, with 85% (121/143), 73% (104/143), 52% (74/143), and 32% (46/143) receiving sodium oxybate for > 6 months, > 1 year, > 5 years, and > 10 years, respectively.

The FDA and Orphan Medical, Inc agreed to a compilation of the Scharf data on the premise that it would potentially provide a profile of long-term clinical experience with sodium oxybate. Orphan Medical performed a retrospective compilation of the data for all 143 patients treated for up to 16 years.

4.5.1 INCIDENCE OF ADVERSE EVENTS – SCHARF TRIAL

In the Scharf trial, Adverse Events were recorded retrospectively on CRFs from information reported by patients in daily diaries (sleep logs) and from investigator-maintained medical records. These data included any untoward events noted by the patients, including possible side effects and effects of concomitant medications, as well as intercurrent illnesses, injuries, or accidents.

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The majority of the 143 patients (136, 95.1%) experienced at least 1 AE. This is to be expected, given the unusually long duration of the trial (16 years, with 32% of patients on sodium oxybate for > 10 years). For this reason, it is difficult to compare these results with those given for the updated integrated clinical trial database, the Lammers trial, and the OMC-SXB-21 trial. To provide an easier basis for comparison, AEs over the first 6 months were analyzed for OMC-SXB-6, OMB-GHB-3, and Scharf.

Over the course of the Scharf trial, AEs reported by only 1 or 2 patients accounted for 44% of the AEs, which does not support a strong association with sodium oxybate.

Severe AEs were reported by 21 patients (14.7%) during their first 6 months in the trial. Over the course of the trial, one third of the patients (54, 37.8%) experienced SAEs, and 23 patients (16.1%) discontinued due to AEs. Eleven deaths (7.7%) were reported. No apparent differences were seen among the 5 sodium oxybate dosage of longest duration groups.

The most frequently reported AEs (nearly all of which were to be expected in a long-term trial and were associated with common intercurrent illnesses) included viral infection (56.6%), headache (52.4%), pain (48.3%), accidental injury (42.0%), nausea (40.6%), flu syndrome (38.5%), pharyngitis (37.8%), rhinitis (36.4%), increased cough (34.3%), sleep disorder (sleepwalking; 31.5%), diarrhea (28.0%), dizziness (27.3%), fever (26.6%), abdominal pain (26.6%), sinusitis (26.6%), dyspepsia (25.2%) and enuresis (23%).

Many of the most frequently reported AEs were considered not related to trial medication. During the first 6 months of treatment, the proportion of the reported AEs that were related to trial medication was 100% for sleep disorder (sleepwalking) and urinary incontinence, 48% for dizziness, 24.2% for nausea, 10.8% for pain, 7.7% for dyspepsia, and 5.9% for abdominal pain. No related AEs were seen for accidental injury, diarrhea, fever, flu syndrome, increased cough, pharyngitis, rhinitis, or sinusitis.

The frequency of cardiovascular AEs (arrhythmias and ventricular extrasystoles) appeared to be higher in the Scharf trial (26%) than in the other 2 trials (1% for OMC-SXB-6, 15% for OMC-GHB-3). This higher incidence probably reflects the higher incidence (approximately 20%) of prior history of cardiovascular disease in the Scharf trial population at baseline, and the expected age-related progression and presentation of cardiovascular morbidities in this long-term trial. Consistent with this observation is the fact that 5 of the 11 deaths in the Scharf trial were from cardiovascular causes and were unrelated to sodium oxybate treatment (as were the other 6 deaths).

4.5.1.1 Adverse Events Over the First 6 Months

To more easily compare the results from the Scharf trial with those from the other clinical trials, the incidence of AEs over the first 6 months of treatment with sodium oxybate was compared in the OMC-SXB-6, OMC-GHB-3, and Scharf trials.

The incidence of frequently occurring AEs including headache, nausea, pain, dizziness, and pharyngitis was similar in all 3 studies, except for pain (9% in OMC-SXB-6, 20% in

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OMC-GHB-3, and 26% in Scharf). The incidence of patients reporting 1 or more AEs was similar in the 3 trials (78% for OMC-SXB-6, 91% for OMC-GHB-3, and 87% for Scharf).

4.5.2 SERIOUS ADVERSE EVENTS – SCHARF TRIAL

A total of 205 SAEs were reported for 54 of the 143 patients (37.8%) in the Scharf trial. Sodium oxybate dosage at onset was 3.0 g/d for 1 patient, 4.5 g/d for 17 patients, 6.0 g/d for 21 patients, 7.5 g/d for 7 patients, and 9.0 g/d for 5 patients. Dosage at onset was unknown for 3 patients.

Only 6 of the 54 patients had SAEs considered to be related to trial medication. In addition, relationship to trial medication was missing for 7 patients with SAEs: patient 012 (disorientation, stupor, weakness), patient 047 (ulcerated colon), patient 054 (skin cancer), patient 070 (back pain), patient 241 (severe headaches), patient 273 (tumors in neck-parotid glands), and patient 277 (hospital readmission after uvulopalatopharyngoplasty surgery).

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Table 4.9 Patients with Serious Adverse Events Judged Related to the Study Medication

Patient Number	Age Sex	COSTART Term	Verbatim Term	Unexpected/ Expected	Dose[1]	Time on Drug (yr)
017[2]	68, M	Overdose	Overdose	Unexpected	18g	1.6
017	68, M	Coma	Comatose	Unexpected	18g	1.6
017	68, M	Stupor	Unresponsive	Unexpected	18g	1.6
019[3]	41, M	Suicide Attempt	Suicide Attempt	Unexpected	UNK	2.0
048[2]	27, F	Convulsion	Convulsive-like seizure	Unexpected	8.3g	5.3
048	27, F	Incontinence Urine	Urinary Incontinence	Expected	8.3g	5.3
257[2]	32, M	Reaction Unevaluable	Potential overdose	Unexpected	12g	2.6
257	32, M	Apnea	Hypoxemia	Unexpected	11.3g	8.0
267[3]	61, F	Overdose	Overdose	Unexpected	UNK	4.6
281[2]	59, M	Injury Accidental	Contusion from fall (over right eye)	Unexpected	7.5g	1.0
281	59, M	Injury Accidental	Contusion from fall (right arm)	Unexpected	7.5g	1.0
281	59, M	Injury Accidental	Head injury from fall	Unexpected	7.5g	1.0

[1]The dose listed is the dose associated with the SAE, not the patient's most common dose during the study.
[2]Patients who had more than one SAE as part of a single event except for patient 257 which represents two events.
[3]Patient reported to have taken an overdose of sodium oxybate although the exact dose is not known.

A relationship between higher dosages of trial medication and SAEs was found in this trial, although not in any other trial. Possible contributory factors affecting the frequency of SAEs include the length of the trial (16 years), the individual patients' increased age during the course of the trial (from a mean age of 45.3 years at entry to approximately 61 years at last observation), the SAEs that would be expected to occur in patients with narcolepsy, the baseline rate of cardiovascular abnormalities, and, for some patients, the continued use of TCAs.

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4.5.3 DISCONTINUATIONS AND OTHER SIGNIFICANT ADVERSE EVENTS

Twenty-three patients withdrew from the Scharf trial because of AEs. Sodium oxybate last dosage was 3.0 g/d for 5 patients, 4.5 g/d for 2 patients, 6.0 g/d for 9 patients, 7.5 g/d for 5 patients, and 9.0 g/d for 2 patients. Eight of these patients subsequently died; the reasons for discontinuation in these 8 patients were the same as the causes of death with the exception of patient 243, who withdrew from the trial because of weight loss, and died 4 months later because of a heart attack.

AEs leading to withdrawal were considered to be related to trial medication in 6 of the 23 patients:

- Patient 019 was hospitalized following a suicide attempt (SAE) using an overdose of sodium oxybate on an unspecified date. This SAE was believed to be definitely related to treatment (intentional overdose) with sodium oxybate, and the patient was discontinued from the trial. The patient was started on sodium oxybate 5.3 g/d on July 12, 1987; his last recorded dosage of sodium oxybate (9.0 g/d) was July 30, 1989.

- Patient 259 discontinued sodium oxybate due to AEs of "feeling like a zombie," stiffness in legs and chest, and excessive crying (COSTART terms delirium, hypertonia, and emotional lability). These AEs, which were considered to be probably related to trial medication, were first reported on June 6, 1987 (sodium oxybate was begun June 3,1987at a dose of 5.3g/d), at which time the dosage of sodium oxybate was decreased to 3.0 g/d. The dosage was further reduced over the next 11 days to 0.8 g/d. The problem did not resolve, and the patient was discontinued on July 15, 1987.

- Patient 271 began taking sodium oxybate (5.3 g/d) in October 1994. He reported an AE of swollen ankles and feet (COSTART term edema) on January 18, 1995. This AE was considered to be possibly related to trial medication. Initial action was to reduce salt intake, with no change in sodium oxybate dosage. The event did not resolve, and the patient discontinued the trial on April 30, 1995. The last recorded dosage of sodium oxybate was 4.3 g/d.

- Patient 066 began taking sodium oxybate on March 25, 1985. She was discontinued from 7.5g sodium oxybate treatment on 4/20/91 due to possible drug-induced lupus. The patient presented rheumatoid-like symptoms accompanied by a series of sustained high anti-nuclear antibody (ANA) titers over a period of five months preceding her discontinuation. Titers for ANA continued to be elevated for the 6 months following the discontinuation of sodium oxybate. Anti-histone antibody titer reported on 10/5/92 was negative. No symptoms consistent with lupus accompanied the elevated ANA titers and no diagnosis of drug-induced lupus or systemic lupus erythematosus was made.

- Patient 244 began taking sodium oxybate on June 21, 1988. The patient was discontinued due to high ANA titer (possible drug-induced lupus) on May 3, 1989.

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The dose at discontinuation was 2.3g. No symptoms consistent with lupus accompanied the elevated ANA titers and no diagnosis of drug-induced lupus or systemic lupus erythematosus was made. Follow-up notes of November 1992 indicated that the patient was negative for both ANA and anti-histone antibodies. The patient also informed the site that she was participating in a sodium oxybate trial under Dr. Scrima's IND. Dr. Scrima reported that the patient participated in his trial until termination in 2000 with good efficacy and no symptoms of lupus.

- Patient 254 began taking sodium oxybate on May 2, 1988. The patient discontinued due to a serious adverse event of pulmonary interstitial infiltrate, possible pulmonary toxicity on June 26, 1989. The sodium oxybate dose at discontinuation was 4.5g. The event resulted in in-patient hospitalization. The SAE report notes that the event was not related to trial medication, but source documents note that the event was "possibly related to the GHB or even the sodium load associated with GHB use". Follow-up efforts with the patient to determine if the event resolved with trial medication discontinuation were unsuccessful.

4.5.4 DEATHS – SCHARF TRIAL

Eleven patients died in the Scharf trial, including 5 deaths from cardiovascular-related causes, 5 deaths from cancer (3 lung, 1 colon, and 1 bladder), and 1 death related to a boating accident. None of the deaths was considered related to trial medication.

A significant prior history of contributory disease was present in all 5 cardiovascular-related deaths. In 2 of the 5 deaths from cancer, there was significant past history of malignancy. The medical history for 1 of the patients who developed lung cancer included persistent cold symptoms. No significant factors prior to diagnosis were identified for the remaining 2 cancer deaths.

The deaths occurred following 1.2 to 10.4 years of treatment with sodium oxybate. Of the 11 deaths reported to FDA, in only 5 cases did the date of death occur within 30 days of the last reported dose of sodium oxybate. In 4 of these cases, there was significant past medical history of disease; in the fifth case there was a history of persistent respiratory symptoms prior to the diagnosis of lung cancer.

This analysis does not reveal a pattern that could be viewed as causally related to sodium oxybate.

4.6 OMC-SXB-21 Trial

The OMC-SXB-21 clinical trial was a randomized, double blind, placebo-controlled, multicenter trial in 55 patients to assess the long-term efficacy of sodium oxybate compared with placebo. This trial was specifically designed to provide evidence of long-term efficacy of sodium oxybate based on the return of cataplexy symptoms upon cessation of a minimum of 6 months of open-label sodium oxybate treatment. A 2-week lead-in period with single-blind treatment with Xyrem at the patient's established dosage was followed by a 2-week period of double-blind treatment with either Xyrem or placebo.

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Patients randomized to placebo experienced abrupt cessation of treatment and a return of cataplexy as the definitive endpoint measure. A total of 17 patients (31%, 17/55) – 7 of 26 (27%) Xyrem patients and 10 of 29 (34%) placebo patients – experienced at least 1 AE during the trial. In the double-blind period, there were no statistically significant differences between the Xyrem and placebo groups in the incidence of patients with an AE (12% for Xyrem, 31% for placebo; p = 0.108), related AEs (4% for Xyrem, 14% for placebo; p = 0.355), or severe AEs (0 for Xyrem, 3% for placebo; p = 1.000). No deaths, discontinuations, or serious AEs occurred during the trial. The incidence and severity of AEs were low. The majority were considered to be unrelated to trial medication. During the double-blind treatment period, patients on placebo did not experience a statistically significant change in vital signs or laboratory values.

Recent literature reports (Friedman 1996, Galloway 1997) indicate that abrupt discontinuation of high-dose, chronic sodium oxybate has resulted in withdrawal symptoms, which consistently include insomnia, anxiety, and tremors. Of these, insomnia, which generally resolved within 3 days, was the most consistently described symptom. Hallucinations (Hernandez 1998) have also been reported. In the OMC-SXB-21 placebo patients, these withdrawal symptoms occurred infrequently (3 [10.3%] of 29) patients, in patients abruptly withdrawn from chronic therapeutic dosages of sodium oxybate (anxiety, 2 [7%] patients, insomnia, 1 [3%] patient). These events were considered by the investigators to be of mild severity and probably (both patients with anxiety) or possibly (the 1 patient with insomnia) related to trial medication.

Overall, the results of this study indicate that Xyrem is well tolerated. Few AEs were related to the study drug. Abrupt discontinuation of long-term Xyrem treatment at therapeutic dosages did not appear to result in an increase in AEs that would indicate the presence of a withdrawal syndrome.

4.7 Safety Summary of the Pharmacokinetic Trials

The 8 clinical pharmacokinetic trials included 6 studies done in 125 normal volunteers and 2 studies (OMC-GHB-4, OMC-SXB-10) conducted in 19 narcoleptic patients. All 8 studies involved acute dosing with either 1 or 2 doses of sodium oxybate.

Table 4.10 summarizes the AEs for the 144 subjects in the 8 integrated pharmacokinetic (PK) trials. Approximately half of the subjects (75 subjects, 52%) experienced at least 1 AE, almost all of which were considered study drug-related AEs. Only 2 subjects (1%) discontinued due to AEs. There were no SAEs and no severe AEs. Most AEs were rated as mild in severity and all AEs resolved spontaneously, with no sequelae.

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Table 4.10 Summary of Adverse Events — Integrated Pharmacokinetic Trials

	Sodium Oxybate[a]
Number of Subjects	144 (100%)
All events	
Subjects with ≥ 1 AE	75 (52%)
Subjects with SAEs	0
Subjects with related AEs	72 (50%)
Subjects with severe AEs	0
Subjects discontinuing due to AE	2 (1%)
Subject deaths	0

[a]Subjects are counted only once in each category.

The most common AEs experienced in the PK trials were nausea, dizziness, headache and vomiting. In general the frequency of AEs tended to increase with oxybate dosage but the severity and type of AE did not. In the 3 drug interaction studies, no clinically significant changes occurred in either the pattern or severity of AEs when Xyrem was administered together with protriptyline, modafinil or zolpidem. The highest incidence of AEs occurred in the fasted phase of the food effect study in which the subjects experienced 4 times as many AEs when given a 4.5g dose after an 8 hour fast as compared to the same dose given shortly after a high fat meal. The 2 subjects who discontinued due to the occurrence of AEs are detailed below.

In the dose proportionality study (OMC-SXB-9), Subject #012, a 30 year-old female, failed to return for the second dosing period after experiencing headache and nausea subsequent to the first dosing when she was administered 2 doses of 2.25g four hours apart.

In the food effect study (OMC-SXB-11), Subject #003, a 39 year-old female, was exposed to a single maximum therapeutic dose (4.5g) after a controlled 10-hour fast (overnight), with dosing at 7:00am. Initial adverse event reporting consisted of mild dizziness 30 minutes after dosing. Approximately 1 hour post-dosing, while lying supine, she developed a respiratory obstructive episode, characterized by respiratory stridor and "labored respiration". Initial repositioning did not immediately relieve the obstruction and a brief apneic event supervened. In the subsequent data analysis and report, the respiratory episode was coded with the COSTART preferred term "apnea". No positive pressure respiratory support was required since spontaneous respiratory effort followed the stimulation, and continued unassisted. Supplemental oxygen was provided via a facemask. At the time of the event, blood pressure and pulse were normal. Following the stimulation, she awoke and vomited once, after which she again fell asleep with normal respiratory rate. The duration of this entire sequence of events was approximately 2 minutes.

Again, approximately 1 hour later (that is, 2 hours post-dosing) the subject again developed a respiratory obstructive episode, beginning with respiratory stridor and proceeding to a brief pause in spontaneous respiration that resolved with stimulation and

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the placement of a facemask for supplemental oxygen. An episode of fecal incontinence accompanied this event, but the patient was arousable, responded to verbal commands and no tonic/clonic activity was part of the event. Again, blood pressure (110/64) and pulse (57/min) remained normal for the subject. The subject again responded to verbal commands to breathe deeply.

There were no other untoward events relating to medication. Two hours later the subject consumed most of the offered lunch. She remained at the study facility for the full 10 hours post-dosing, along with the other study subjects, and was discharged home with no sequelae. She chose not to return for the second dosing one week later. The plasma oxybate versus time curve for Subject #003 was not significantly different from the other 17 normal subjects dosed identically at the same time.

In addition to adverse events, vital signs (blood pressure, heart rate, respiration rate) were recorded before and at multiple time points after each dosing period in all 8 of the PK studies. No clinically significant changes in vital signs were recorded in any patient or normal volunteer in any of the 8 PK trials. Overall, the safety profile of Xyrem from the 125 healthy subjects in the PK trials was not significantly different from that of the narcoleptic patient population.

4.8 Adverse Events of Special Interest

Subsequent to the submission of the NDA, several questions were raised by the FDA regarding both the Scharf trial and the integrated clinical trials. Responses to these questions were provided to the FDA in a Major Amendment on March 23, 2001, and in an Amendment for the Scharf Trial on April 10, 2001.

The major issues are summarized here, including:

- Further description of patients with
  - AEs coded to confusion
  - AEs coded to convulsion
  - Neuropsychiatric AEs
  - AEs of hyperglycemia or diabetes mellitus
- Analysis of the potential for drug-induced lupus
- Analysis of incontinence AEs and the relationship to seizurogenesis
- Characterization of the 80 patients who did not transfer from the Scharf trial into OMC-SXB-7 as of May 31, 1999.
- Characterization of the 75 occurrences in the Scharf trial with "reaction unevaluable" AEs
- Comparison of the incidence of AEs for sodium oxybate and placebo in the controlled trials

An analysis of AEs for sodium oxybate and placebo in the 4 controlled trials is also included in this section.

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No patients in the OMC-SXB-21 trial experienced confusion, convulsions, or any neuropsychiatric event. One patient experienced hyperglycemia during the single-blind lead-in period; this was considered mild and not related to trial medication. No patients in the Lammers trial experienced any of these AEs.

4.8.1 ADVERSE EVENTS CODED AS CONFUSION

4.8.1.1 Updated Integrated Clinical Trial Database

Of the 402 patients in the updated integrated clinical trial database, 30 (7%) patients had 47 AEs with the COSTART preferred term of confusion (Table 4.11). Of these, 1 patient was in the placebo group.

Of the 30 patients who experienced confusion, 2 (<1%) had AEs considered serious by the investigator; 29 (7%) had AEs considered related (including the 1 patient on placebo); and 4 (1%) had AEs considered severe. A total of 3 patients (<1%) discontinued due to the AE of confusion. There were no deaths due to AEs of confusion. Two of the patients (0221 and 0815) had also experienced AEs of confusion prior to any treatment with Xyrem. The incidence of confusion among the 29 patients taking Xyrem does not appear to be dose-related.

Table 4.11 Summary of Patients with AE Preferred Term of Confusion by Dosage at Onset—Updated Integrated Clinical Trials

Confusion: All Events	Total[a]	Placebo	Total[a]	Xyrem Oral Solution Dosage (g/d) at Onset[b]				
				3.0	4.5	6.0	7.5	9.0
Number of Patients	**402 (100%)**	**54 (100%)**	**399 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
At least 1 AE	30 (7%)	1 (2%)	29 (7%)	4 (4%)	6 (2%)	11 (4%)	6 (5%)	10 (8%)
SAEs	2 (<1%)	0	2 (<1%)	0	0	1 (<1%)	0	1 (1%)
Related AEs	29 (7%)	1 (2%)	28 (7%)	3 (3%)	6 (2%)	10 (3%)	6 (5%)	10 (8%)
Severe AEs	4 (1%)	0	4 (1%)	0	2 (1%)	1 (<1%)	0	1 (1%)
Discontinuation due to an AE	3[c] (<1%)	0	3[c] (<1%)	0	0	1 (<1%)	0	2[c] (1%)
Deaths	0	0	0	0	0	0	0	0

[a] Patients are counted only once in the total column.

[b] Some patients were exposed to more than 1 dosage during the trial(s), so the sum of patients exposed to specific dosages exceeds the total number of patients in the updated integrated clinical trial database.

[c] Patient 2632 (9.0 g/d) discontinued due to "patient request" (confirmed by further medical review); therefore, this patient is not included here. However, the AEs of headache/confusion were contributing factors.

Of the 30 patients, 21 (70%) were women, and 20 (67%) were 50 years of age or older (range 25.7 to 73.8 years).

Most of the AEs of confusion were experienced during the first 60 days of trial: 13 patients experienced 15 AEs of confusion during Days 1 to 30; 10 patients

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experienced 11 AEs during Days 31 to 60; 5 patients experienced 5 AEs during Days 61 to 120; 7 patients experienced 13 AEs during Days 121 to 365; and 3 patients experienced 3 AEs during Days 366 to 1022. The first occurrence of confusion was during Days 1 to 30 for 13 patients; during Days 31 to 60 for 8 patients; during Days 61 to 120 for 5 patients; during Days 121 to 365 for 2 patients; and during Days 366 to 1022 for 2 patients.

Two events of confusion were not recorded as resolved:

- Patient 2539 (onset Day 74) experienced mild and intermittent "confused awakening," which was listed as ongoing in trial OMC-SXB-6, but is not listed in the patient's follow-up trial OMC-SXB-7. According to the following comment on the CRF for "action taken" for this episode, it appears that a stop date should have been entered in trial OMC-SXB-6: "Patient notes she may awaken after first dose of Xyrem but before second dose . . . she got up a few times initially but realizes she was confused. Now she intentionally goes back to sleep and avoids getting up."

- Patient 2632 experienced a moderate, probably related episode of "disorientation" on Day 267 in OMC-SXB-7 that was categorized as intermittent. On the same day this event of confusion was reported, the patient discontinued due to "patient request" (confirmed by further medical review); therefore, this patient is not listed as discontinuing due to the AE of confusion. However, the AEs of headache/confusion were contributing factors. In OMC-SXB-6, his previous trial, this patient had a similar complaint (Day 10, 9/22/99), which resolved in January 2000. Follow-up with this patient on 3/21/01 by the trial coordinator confirms that this patient's disorientation resolved soon after trial termination and the patient has had no recurrence of these symptoms.

Most of the verbatim descriptions of AEs with the COSTART preferred term of confusion included some form of the words "confusion" or "disoriented." The actual investigator terms were:

- "Confusion," "acute confusional state," or "confusion on awaking" – 15 patients with 25 events
- "Disoriented," "disoriented upon awakening," or "disorientation" – 13 patients with 15 events
- "Confusion/disorientation" – 2 patients with 2 events
- "Feeling 'drunk' after taking drug" – 3 patients with 3 events
- "Dazed feeling" – 1 patient with 1 event
- "Couldn't comprehend" – 1 patient with 1 event
- "Woozy feeling" – 1 patient with 1 event

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4.8.1.2 Analysis of Trial OMC-GHB-2

Eleven (8%) of the 136 patients in OMC-GHB-2 (including 1 patient on placebo) experienced an AE of confusion. Since this trial was only 4 weeks in duration, additional analysis was conducted.

The major difference between trial OMC-GHB-2 and the other studies is that patients were assigned dosages in a blinded, randomized manner that excluded any consideration of body weight or size, sex, or disease severity. This non-titrated dosing assignment produced the majority of occurrences of confusion in the 10 patients on active drug:

- Six patients experienced the AE at the 9.0 g/d dosage level
- Six patients experienced the AE in the first week of drug exposure, with 4 of these 6 assigned to the 9.0 g/d dosage

The emergence of these AEs, especially at the 9.0 g/d level, in the short 4 weeks of active treatment gives further support to the proposed dosing strategy, with initial dosing at the 4.5 g/d level and subsequent optimization of clinical response by dosing adjustments of 1.5 g/d every 2 weeks.

Nine of these patients continued into future trials, and only 2 had a recurrence of confusion.

4.8.1.3 Scharf Trial

All patients who had AEs with the COSTART preferred term of confusion during the Scharf trial through the data cutoff of May 31, 1999, were included in this analysis.

Of the 143 patients in the trial, 10 (7%) experienced a total of 15 AEs with the COSTART preferred term of confusion (Table 4.12). One patient experienced an SAE, 5 AEs were possibly or probably related to trial medication, 1 patient had 3 severe AEs, and no patients discontinued due to an AE of confusion.

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Table 4.12 Summary of Patients with AE Preferred Term of Confusion by Dosage at Onset – Scharf Trial

Confusion: All Events	Total[a]	Xyrem Oral Solution Dosage (g/d) at Onset[b]				
		3.0	4.5	6.0	7.5	9.0
Patients with: At least 1 AE	10[c]	0	3	3	4	0
SAEs	1	0	0	0	1	0
Related AEs	5	0	1	2	2	0
Severe AEs[c]	1	0	1[c]	0	0	0
Discontinuations due to an AE	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

[a] Patients are counted only once in each category.

[b] Dosage at onset. Dosage for patient 248 is listed as "0."

[c] Patient 027 experienced 3 events of "disoriented," all of which were considered severe.

All 15 AEs used verbatim terms including the words "confusion" or "disoriented." Five events were considered possibly or probably related to trial medication, 6 were of unknown relationship, and 4 were not related.

Of the 10 patients, 6 were men and 4 were women. For 8 of these 10 patients, the event of confusion was reported only once. Age at the time of onset ranged from 27.7 to 76.8 years. Of the 15 events, 5 occurred in the first 60 days, 4 occurred from 61 days to 1 year, 3 occurred from 1 year to 2 years, and 3 occurred at > 2 years (Days 3185, 3301, and 3314) on trial medication. The dosage at onset for these events ranged from 4.5 to 7.5 g/d.

Most events (10 of 15, 66.7%) were transient in nature, (single episodes) lasting 1 day or less. One event lasted 15 days; the remaining events (1 in each of 4 patients, 235, 248, 251, and 266) had no stop date listed. Two of these patients (248, "mental confusion", and 251, "confused") discontinued for non-compliance) on Days 89 and 218, respectively); onset of their AEs was Days 5 and 62, respectively. The other 2 patients (235, "disorientation [when awakening from sleep]," and 266 "confused sometimes [not a lot]," with onset of AEs on Days 1 and 273, respectively, transferred into OMC-SXB-7 on Days 4456 and 5623, respectively, with no confusion AEs reported in the OMC-SXB-7 trial.

Only 1 patient (012, "disoriented") experienced an SAE, which resulted in overnight hospitalization. This patient returned to study drug with no further recurrences. No patients discontinued due to AEs of confusion.

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4.8.2 ADVERSE EVENTS CODED AS CONVULSION

4.8.2.1 Updated Integrated Clinical Trial Database

Of the 402 patients in the updated integrated clinical trial database, 14 (3%) had AEs with the COSTART preferred term of convulsion(s). Thirteen (93%) of these 14 patients had investigator verbatim terms relating the event to cataplexy (Table 4.13). The single event with the investigator term of "seizures" also appeared to be cataplexy-related (see discussion below).

Table 4.13 List of COSTART and Verbatim Investigator Terms for AEs of Convulsion – Updated Integrated Clinical Trial Database

Patient Number	COSTART Term	Verbatim Term
0221	Convulsions	Increase in major cataplexy attacks
0231	Convulsion	Increased duration of cataplectic events
0243	Convulsion	Increase partial cataplexy
0545	Convulsion	Increase in cataplexy
	Convulsion	Increase in cataplexy
0608	Convulsion	Increased cataplexy
0814	Convulsion	Seizures
0835	Convulsion	Increased cataplexy
	Convulsion	Cataplexy
1130	Convulsion	Cataplexy
1302	Convulsion	Increased cataplexy (significant)
	Convulsion	Increased cataplexy (significant)
1306	Convulsion	Increase in cataplexy
1509	Convulsion	Multiple cataplexy attacks for 10 min. (due to protocol violation of patient: got out of bed to use bathroom 1½ hr. after taking 1st dose of sodium oxybate)
1703	Convulsion	Bit tongue (due to falling faster to ground: cataplexy)
	Convulsion	Hit temple against furniture (due to falling faster to ground: cataplexy)
2936	Convulsion	Cataplexy
3937	Convulsion	Cataplexy

There were 7 patients (2%) with related AEs coded as convulsion and 2 patients (<1%) with severe AEs coded as convulsion (Table 4.14). There were no SAEs, discontinuations, or deaths associated with AEs coded as convulsion. A higher incidence of AEs coded as convulsion was seen in the 9.0 g/d dosage at onset group (5%, compared with 2% for 6.0 g/d, 1% for 4.5 g/d, and 0 for 3.0 and 7.5 g/d). However, patients with the most severe cataplexy are potentially titrated to the highest dosage, which may explain the slightly higher incidence of these cataplexy related AEs, which were coded as convulsion, at 9.0 g/d.

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Table 4.14 Summary of Patients with AE Preferred Term of Convulsion, by Dosage at Onset – Updated Integrated Clinical Trials

Convulsion:			Xyrem Oral Solution Dosage (g/d) at Onset					
All Events	Total [a]	Placebo	Total [a]	3.0	4.5	6.0	7.5	9.0
Number of Patients	402 (100%)	54 (100%)	399 (100%)	97 (100%)	269 (100%)	290 (100%)	133 (100%)	129 (100%)
Patients with: ≥ 1 AE of convulsion	14 (3%)	0	14 (4%)	0	3 (1%)	5 (2%)	0	6 (5%)
Convulsion SAEs	0	0	0	0	0	0	0	0
Related convulsion AEs	7 (2%)	0	7 (2%)	0	1 (<1%)	4 (1%)	0	2 (2%)
Severe convulsion AEs	2 (<1%)	0	2 (1%)	0	1 (<1%)	1 (<1%)	0	0
Discontinued due to convulsion AE	0	0	0	0	0	0	0	0
Deaths due to convulsion AE	0	0	0	0	0	0	0	0

[a] Patients are counted only once in each category.

Of the 14 patients, 8 were women and 6 were men. Age ranged from 21.2 to 70.6 years, with 6 patients under the age of 50. Of the 17 events, 5 occurred within the first 30 days after first administration of Xyrem; 1 occurred 31 to 60 days after; 3 occurred 61 to 90 days after; 1 occurred 91 to 120 days after; 1 occurred 236 days after; 1 occurred 333 days after; 3 occurred 1 to 2 years after; and 2 occurred between 2 and 3 years after. The event termed "seizures" in patient 0814 occurred 935 days (2.6 years) after first taking Xyrem. Three of the 17 events (patients 0231, 0608, and 1302) were ongoing at last contact; however, the event for patient 1302 ("increased cataplexy, significant") was recorded as resolved on Day 38 (duration 7 days) at trial entry into OMC-GHB-3. Duration for the remaining 14 events was ≤ 1 day for 5 events, 2 to 7 days for 4 events, 8 to 14 days for 2 events, 34 and 38 days for 2 events, and 151 days for 1 event.

Of the 14 patients, 13 had events related to cataplexy; only 1 patient (0814) had a less definitive assignment of "seizures," which were considered mild, with relationship to trial medication unknown.

Patient 0814, a 58 year old male, had a history of narcolepsy for twenty years prior to the start of cataplexy. He participated in the OMC-GHB-2 trial (beginning treatment on May 28, 1997) and proceeded into OMC-GHB-3 (beginning June 30, 1997). His dose of sodium oxybate was 4.5g/day. He continued into the OMC-SXB-7 trial, beginning May 13, 1999 at the 4.5g/d dose, and remains at this dose. He had a past history of headaches, left breast cancer, and numerous falls with closed head injury due to cataplexy. He sought neurological consultation (April 15, 1999) with a two-year history of memory problems, complicated by getting lost, and a description of "losing gaps of time". Two such adverse events were reported during the study (trial days 220 and 558) with verbatim descriptive terms "fugue state; patient reports being in limbo", and "trance-like state", both of which have been COSTART coded as convulsions. It is important to

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note that this neurologic symptomatology preceded study commencement. Neurologic examination on all occasions was normal. His neurologist initiated investigation for these memory lapses, with a possible association of partial complex seizures, or possible early mild dementia or encephalopathy. MRI scan (April 15, 1999) was normal and specifically excluded metastatic disease. His EEG was normal during quiet wakefulness and stage II sleep, and during photic stimulation (hyperventilation was not done). A follow-up ambulatory, twenty-four hour EEG did indicate polyspike and wave activity that could indicate possible generalized seizure activity, but artifact could not be excluded. Overall clinical correlation was advised. A trial of Dilantin 300 mg/day was conducted over a three-month period, with no change in symptomatology. Psychiatric assessment did not contribute explanation for the confusional episodes. These events continue intermittently, and have been suggested by the principal investigator to be possibly related to the narcolepsy syndrome.

4.8.2.2 Scharf Trial

Nine patients experienced 20 AEs that coded to COSTART preferred terms of convulsion or convulsion grand mal (Table 4.15).

Table 4.15 Summary of Patients with AEs of Convulsion, by Dosage at Onset – Scharf Trial

		Sodium Oxybate Oral Solution Dosage (g/d) at Onset				
Convulsion: All Events	**Total [a]**	**3.0**	**4.5**	**6.0**	**7.5**	**9.0**
Number of convulsion AEs	20					
Patients with at least 1 AE	9	0	0	5	2	2
Convulsion SAEs	1	0	0	0	0	1
Related convulsion AEs	1	0	0	0	0	1
Severe convulsion AEs	1	0	0	0	0	1
Discontinuations due to a convulsion AE	2	0	0	1	1	0
Convulsion Deaths	0	0	0	0	0	0

[a] Patients are counted only once in each category, at the highest dosage at onset.

Table 4.16 summarizes the COSTART and verbatim terms for the 20 events in these 9 patients. Ten AEs in 4 patients included the verbatim term "seizure," including the 1 SAE and 1 related AE (same event) and 2 discontinuations. The remaining five patients reported cataplexy that was reported as convulsion.

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Table 4.16 List of COSTART and Verbatim Investigator Terms for Convulsion AEs – Scharf Trial

Patient Number	COSTART Term	Verbatim Term	Dosage at Onset (g/d)
043	Convulsion	Excessive cataplexy	6.0
048	Convulsion	Convulsive-like seizure[a]	8.3
049	Convulsion	Fall, sudden cataplexy	6.0
051	Convulsion	Fell twice, with cataplexy	6.0
064[b]	Convulsion	Seizure	7.5
	Convulsion	Seizure	6.0
	Convulsion	Seizure	6.0
	Convulsion	Seizure during the morning	6.0
	Convulsion	Seizure in the morning	6.0
	Convulsion	Another seizure in afternoon	6.0
	Convulsion	Seizure in the morning	6.0
219	Convulsion	Cataplexy	7.5
	Convulsion	Cataplexy	7.5
247[c]	Convulsion	Seizure, continuous jerking	6.0
255[d]	Convulsion Grand Mal	Brief grand mal seizure	5.3
257	Convulsion	Violent shaking and vibrations[e]	5.3
	Convulsion	Jerking during cataplexy	9.0
	Convulsion	Bad cataplexy[f]	9.0
	Convulsion	Cataplexy[f]	12.0
	Convulsion	Fall from cataplexy caused him to hit his head on furniture, increase in cataplexy resulted[f]	11.3

[a] This event was serious and determined to be possibly related to study medication.

[b] Patient 064, who had a pre-existing left frontal lobe lesion that may have contributed to the seizure activity, discontinued due to series of 7 seizures over 14-month period.

[c] Patient 247 discontinued due to the AE.

[d] Patient 255 had a history of seizures of unknown etiology at enrollment.

[e] This AE was most likely associated with fever and chills due to a severe tonsillar infection.

[f] AE was considered by the investigator to be severe.

Of the 9 patients, 6 were women and 3 were men. Age at onset ranged from 14.5 to 47.7 years, with 2 of the patients (both women) under the age of 20. Of the 20 events, 1 occurred in the first 60 days, 8 occurred from 6 months to 1 year, 5 occurred from 1 to 2 years, and 6 occurred at > 2 years (Days 1878 to 4537) following the start of trial medication. The 10 seizure-related events occurred on Days 275 to 681 (064, 7 events), day 276 (patient 247), day 310 (patient 255), and day 1931 (patient 048) of sodium oxybate treatment.

Four (043, 049, 051, and 219) of the 9 patients with AEs coding to "convulsion" had events related to cataplexy. One patient (257) had 5 events coded to convulsion,

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4 events were related to cataplexy and 1 event, verbatim term, violent shaking and vibrations, was considered to be most likely due to a concurrent infection.

Of the 4 remaining patients that had events coded to COSTART term convulsion, 2 patients (064 and 255) had events of verbatim terms seizure (064 experienced 7 separate events of unknown relationship to trial medication) and brief grand mal seizure (255), which was considered unrelated to trial medication. Patient 255 had a previous history of seizure disorders, and patient 064 had a pre-existing left frontal lobe lesion that may have contributed to the seizure activity as suggested by focal EEG changes and continuation of seizures since discontinuation of sodium oxybate study medication in May, 1989. Two patients (048 and 247) had events of verbatim terms convulsive-like seizure and seizure (continuous jerking all over body) that were possibly complicated by polypharmacy, but are considered to represent potential seizurogenesis.

4.8.3 NEUROPSYCHIATRIC ADVERSE EVENTS

Published studies indicate that symptoms of depression and other symptomatology of psychiatric illnesses are seen in 50% or more of narcolepsy patients, making it difficult to accurately characterize the reports of neuropsychiatric AEs. A review of literature concerning the incidence of psychopathology associated with narcolepsy is provided as follows:

Strong associations between neuropsychiatric pathology and sleep disorders, in particular narcolepsy, are proposed in the literature by both retrospective reviews (Sours 1963, Wilcox 1985) with comparative sex- and age-matched controls. Central mechanistic associations have been proposed to link the pathophysiology of psychosis and abnormal central sleep controls (Howland 1997, Saucerman 1997). Further psychiatric morbidity in narcoleptics on chronic high-dose stimulant therapy is well established (Pawluk 1995).

An example of the associated psychotherapy with narcolepsy was defined by John Sours in 1963 when he reviewed clinical records of patients admitted to a New York Hospital from 1932 – 1964 and coded under the categories of hypersomnia, somnolence and narcolepsy. He identified eight patients with schizoid personality disturbances and another ten patients that developed frank schizophrenic psychoses which required prolonged hospitalization. Such an association was established in the 1985 sex- and age-matched review by James Wilcox at the University of Iowa between narcolepsy and the symptoms of schizophrenia. Such associations have led to discussions as to whether psychiatric findings are epiphenomenal to, or inherent in the expression of narcolepsy.

A review of the emotional and psychosocial correlates of narcolepsy in fifty adults who had a current complaint of sleep attacks and cataplexy by Kales et al in 1982 indicated a "high level of psychopathology compared to controls". However, these authors considered this to be primarily a reaction to the disorder and its effects.

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Robert Howland (1997) established clear association between the sleep-onset REM characteristics of narcolepsy and schizophrenia, psychotic depression, and delirium tremors. He proposed this objective EEG measure as an objective surrogate of neurochemical abnormality representing a common mechanistic link.

An association between the HLA antigens related strongly to narcolepsy-cataplexy (HLA-DR2, DQ1) and its subdivision HLA-DR15, DQ6 has been suggested with schizophrenia. Douglass (1993) found that in 56 schizophrenic patients and 56 controls, the incidence of narcolepsy-associated antigens was 3.89 times higher in the schizophrenic patients. Also, that the patients with the narcolepsy-associated antigens had more hospitalizations and higher Brief Psychiatric Rating Scale scores, suggesting a severity association.

As was suggested by Kales, studies using self-report as well as traditional psychiatric measures have found significant depression among narcoleptics. People newly diagnosed with narcolepsy have reported that depression was the personality change they noted at disease onset (Broughton 1976). Recurrent episodes of depression have been reported by 51% of people with narcolepsy (Broughton 1984).

Seven hundred narcoleptics chosen randomly from the patient rolls of the American Narcolepsy Association were surveyed (response rate = 61.4%) with anonymous responses to the Center for Epidemiologic Studies Depression Scale (CES-D), indicating again that a high proportion of narcoleptics (49%) were experiencing depressive symptoms.

Patient status in narcolepsy is obviously a complicated and dynamic representation of:

- Disease-associated psychosocial morbidity.
- Stimulant-induced personality changes.
- Stress variations in daily life.
- Treatment-related co-morbidities.

It is very difficult to interpret causality of events to any single contributor.

4.8.3.1 Updated Integrated Clinical Trial Database

AE terms suggestive of neuropsychiatric events – overdose, coma, death, depression, hallucinations, intentional overdose, manic depressive reaction, overdose, paranoid reaction, personality disorder, psychosis, stupor, suicide, and suicide attempt – were analyzed for the updated integrated clinical trial database.

Of the 402 patients, 52 patients (13%) reported AEs for the specified neuropsychiatric COSTART terms. Of these, 9 patients (2%) had SAEs, 12 patients (3%) had AEs classified as severe, 27 patients (7%) had AEs considered related to trial medication, 12 patients (3%) discontinued the study due to these AEs, and 2 patients (<1%) died in association with these AEs.

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There was no clear relationship between incidence of neuropsychiatric AEs and dosage at onset.

Table 4.17 Summary of Patients with Neuropsychiatric AEs, by Dosage at Onset — Updated Integrated Clinical Trials

Neuropsychiatric AEs: All Events	Total[a]	Placebo[b]	Xyrem Oral Solution Dosage (g/d) at Onset[c]				
			3.0	4.5	6.0	7.5	9.0
Number of Patients with:	**402 (100%)**	**54 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
≥ 1 AE	52[c] (13%)	1 (2%)	5 (5%)	6 (2%)	25 (9%)	5 (4%)	14 (11%)
SAEs	9 (2%)	0	0	2 (1%)	4 (1%)	0	3 (2%)
Related AEs	27 (7%)	1 (2%)	1 (1%)	3 (1%)	12 (4%)	0	12 (9%)
Severe AEs	12 (3%)	0	0	3 (1%)	6 (2%)	0	3 (2%)
Discontinued due to AEs	12 (3%)	0	0	3 (1%)	3 (1%)	1 (1%)	5 (4%)
Patient deaths	2 (<1%)	0	0	0	2 (1%)	0	0

Note: One patient in the 6.0 g/d dosage group (0936, possible overdose) had an SAE resulting in death on 2/24/01, which was 5 months after the data cutoff (9/30/00), but is included here for completeness.

[a] Patients are counted only once in each total column.

[b] Patients were on placebo for a short time (4 weeks) relative to the long-term exposure of those treated with Xyrem.

[c] Some patients were exposed to more than 1 dosage during the trial(s), so the sum of patients exposed to specific dosages exceeds the total number of patients in any category.

Table 4.18 summarizes the neuropsychiatric AEs by COSTART preferred term.

Table 4.18 Summary of Patients with Neuropsychiatric AEs, by COSTART Preferred Term – Updated Integrated Clinical Trials

COSTART Term	Number of Patients[a]
Total	**52[b]**
Depression	27
Hallucinations	9
Stupor	6
Suicide, Suicide Attempt, and Overdose	4[b]
Paranoid Reaction	4
Coma	2
Psychosis	2
Manic Depressive Reaction	1
Personality Disorder	1

[a] Patients may have had more than 1 neuropsychiatric AE, so the sum of patients in all categories exceeds the total number of patients.

[b] One patient (0936, possible overdose) had an SAE resulting in death on 2/24/01, which was 5 months after the data cutoff (9/30/00), but is included here for completeness.

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Of the 52 patients, 31 were women and 21 were men. Age ranged from 17.7 to 68.0 years, with 31 patients (62%) under the age of 50. There was no apparent relationship between the incidence of neuropsychiatric AEs and the length of time on sodium oxybate. Of the 64 events, 10 occurred within the first 30 days after administration of Xyrem; 16 occurred 31 to 60 days after; 13 occurred 61 to 90 days after; 9 occurred 91 to 180 days after; 8 occurred 6 to 12 months after; 5 occurred 1 to 2 years after; and 2 occurred more than 2 years later (patient 1704, 2.8 years later; patient 14043. 11.7 years later). Sixteen of the 64 events were ongoing at last contact. Duration for the remaining 48 events was ≤ 1 day for 20 events, 2 to 7 days for 8 events, 8 to 14 days for 5 events, 2 to 4 weeks for 6 events, 1 to 2 months for 4 events, 2 to 3 months for 2 events, 3 to 6 months for 2 events, and 230 days for 1 event.

4.8.3.2 Scharf Trial

Of the 143 patients in the Scharf trial, 41 patients (28.7%) reported neuropsychiatric AEs (terms included overdose, suicide attempt, depersonalization, depression, emotional lability, hallucinations, hostility, neurosis, paranoid reaction, stupor, and thinking abnormal) (Table 4.19). Twelve patients (8.4%) had events that were considered definitely, probably, or possibly related to study drug, 4 patients (2.8%) had SAEs (2 of these patients experienced 2 neuropsychiatric SAEs each), 7 patients (4.9%) had AEs classified as severe (1 patient experienced 2 severe neuropsychiatric events), and 2 patients (1.4%) discontinued from the study due to these AEs.

There was no apparent dose relationship to either the frequency or severity of the selected neuropsychiatric events.

Table 4.19 Summary of Patients with Neuropsychiatric AEs, by Dosage at Onset – Scharf Trial

Neuropsychiatric AEs : All Events	Total[a]	Xyrem Oral Solution Dosage (g/d) at Onset				
		3.0	4.5	6.0	7.5	9.0
Number of Neuropsychiatric AEs	84	3	14	23	25	19
Patients with: at least 1 AE	41	1	9	12	11	8
SAEs	4	0	1	0	1	2
Related AEs	12	0	1	4	3	4
Severe AEs	7	2	2	0	2	1
Discontinuations due to an AE	2	0	0	1	0	1
Deaths	0	0	0	0	0	0

[a] Patients are counted only once in each category; patients are classified by the highest dosage at which a neuropsychiatric AE occurred.

Table 4.20 summarizes the neuropsychiatric events by COSTART preferred term, in order of decreasing frequency.

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Table 4.20 Summary of Patients with Neuropsychiatric AEs, by COSTART Preferred Term – Scharf Trial

COSTART Term	Number of Patients[a]	Number of Events
Total	41	84
Depression	22	28
Emotional lability	10	14
Thinking abnormal	9	13
Depersonalization	7	7
Hostility	6	8
Stupor	6	7
Neurosis	2	2
Overdose	2	2
Suicide attempt	1	1
Hallucinations	1	1
Paranoid reaction	1	1

[a] Patients may have had more than 1 AE.

Of the 41 patients, 23 were men and 18 were women. Age at the time of AE onset ranged from 14.2 to 76.8 years. There was no apparent relationship between the incidence of neuropsychiatric AEs and the length of time on sodium oxybate. Of the 84 events, 22 occurred in the first 60 days of sodium oxybate treatment; 6 occurred at 61 to 120 days; 21 occurred at 121 days to 12 months; 9 occurred at 1 year to 2 years; and 15 occurred at > 2 years. Eleven events had an unknown onset date.

4.8.3.3 Depression

The assignment of the COSTART term depression to verbatim terms of "depression," "depressed mood," "situational depression," "patient reports 'down in the dumps,'" and "dysphoria" (reported in the updated integrated clinical trial database) and to verbatim terms of "depression," "feels quite depressed," "very down," "not happy," or "possible depression" (reported in the Scharf trial) does not constitute a definitive psychiatric diagnosis of Major Depressive Disorder. The essential features of a Major Depressive Disorder (DSM-IV) include a period of at least 2 weeks during which there is either depressed mood or loss of interest or pleasure in nearly all activities. The individual must also experience 4 additional related symptoms. Thus, it is important to distinguish between a transient symptom of feeling depressed and depression as a major psychiatric disorder.

4.8.3.3.1 Updated Integrated Clinical Trial Database

Of the 402 patients in the updated integrated clinical trial database, 27 patients (6.7%) had 30 AEs that were coded to depression. Seventeen of the 30 events were considered not related, 1 was probably related, 8 were possibly related, and 4 were of unknown relationship to test medication administration. Of the 9 related AEs, 7 lasted longer than 2 weeks. Sixteen of the 30 events were continuous, 12 intermittent, and

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2 were unknown as to frequency. None of the events was considered serious. Two patients had a previous history of depression.

The actions taken with trial medication included no change in treatment for 26 events, temporary discontinuation of medication for 2 events, and permanent discontinuation for 2 events. Medication was initiated for management of 5 events (3 with Zoloft, 1 with Nortriptyline, and 1 with Sertraline). Depression was considered related to test medication for only 2 of these 5 events.

4.8.3.3.2 Scharf Trial

Twenty-two (15.4%) of the 143 patients participating in the Scharf open-label clinical trial for up to 16 years reported 28 AEs of depression. This included 14 men, with a mean age of 44 years (range 14.8 to 73.6 years) and 8 women, with a mean age 47.6 years (range 18.4 to 63.5 years). The mean dosage at onset was 5.6 g/d (range 2.3 to 9 g/d).

Two of the 28 depressive events were considered possibly related (218 and 238), 25 not related, and 1 of unknown relationship to trial medication. The intensity was considered severe in 5, moderate in 1, mild in 2, and not indicated in 20 of the AEs.

One patient was hospitalized for depression; the event was reported as an SAE (patient 019). This event (considered unrelated to study drug) started 217 days following the start of treatment and while the patient was receiving 6 g/d of sodium oxybate. The patient had a previous history of depression, suicidal ideation, and possible anxiety neurosis.

Three other patients reported relevant medical histories prior to treatment – patient 202 (psychiatric disorder with visual and auditory hallucinations), patient 255 (paranoia and difficulty controlling his temper), and patient 286 (depression).

Of the 2 patients with AEs coded to depression that were considered possibly related to study drug, 1 (238) lasted 2 days and 1 (218) was of unknown duration.

Six of the 28 AEs lasted 1 day, and 1 lasted 30 days. There was no reported stop date for 17 AEs; the start date for these ranged from 1 month to 14.5 years after initiation of sodium oxybate treatment, with a mean of 3.9 years. Four AEs had neither start nor stop date.

The incidence of depression reported in the Scharf trial appears to approximate that reported in the literature. Given the very long duration (over 16 years) of the trial, and the propensity of the narcoleptic population toward recurrent episodes of depression (Broughton 1984), there does not appear to be a causal relationship between depression and sodium oxybate treatment in this setting.

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4.8.3.4 Hallucinations

4.8.3.4.1 Updated Integrated Clinical Trial Database

Nine (2.2%) of the 402 patients reported hallucinations. In 3 of these patients, the hallucinations were hypnagogic in nature and are probably attributable to the narcolepsy disease state. A fourth patient experienced unspecified hallucinations that stopped when her sodium oxybate dosage was increased, indicating that these hallucinations were most likely hypnagogic in nature as well.

One patient reported an isolated event (unspecified hallucinations), which was considered possibly related to trial medication. Another patient had hallucinations (described as "colors and shapes"), which were described as continuous and lasted 1 day; this was considered to be probably related to trial medication.

One patient reported on 2 consecutive clinic visits that she experienced a total of 9 auditory hallucinations ("voices"). These occurred over the course of 55 days; they resolved spontaneously and did not recur during the remainder of the trial.

After 20 days on trial medication, another patient experienced confusion, forgetfulness, and unspecified hallucinations and her trial medication was stopped. Ten days later, she developed nausea and after an additional day, intermittent paranoia. All of her symptoms resolved 2 weeks after stopping medication.

A final patient had a previous history of mental illness, including auditory hallucinations, prior to entry in the trial (this information had been intentionally withheld by the patient). On Day 84, she developed moderately severe auditory hallucinations requiring hospitalization. Given her subsequently disclosed past psychiatric history, these symptoms were deemed unrelated to the study medication. Her symptoms subsided following therapy with antipsychotic medication.

4.8.3.4.2 Scharf Trial

One of the 143 patients reported an AE that coded to the COSTART term hallucinations. This event occurred on Day 1918 at a dosage of 9.0 g/d. The patient experienced a hypnagogic hallucination, a REM-related symptom of narcolepsy, during which he dove out of bed and jammed his head against the wall. The event was not considered serious, but did necessitate a visit to the clinic for a neck radiograph. The patient was placed in a neck collar and prescribed Naprosyn and aspirin. The event was considered to be probably related to study medication by the investigator.

4.8.3.5 Stupor

4.8.3.5.1 Updated Integrated Clinical Trial Database

Six (1.5%) of the 402 patients reported AEs that coded to stupor. The verbatim terms all included the terms "drunk" or "intoxicated." Each of the 6 patients reported this AE only

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once, with each occurrence lasting 1 day or less. All 6 patients were in OMC-GHB-3; there were 4 women and 2 men, ranging in age from 25 to 55 years. The events occurred following 34 to 66 days of sodium oxybate treatment. Dosage at onset was 4.5 g/d for 1 patient, 6.0 g/d for 3 patients, and 9.0 g/d for 2 patients. Five of the AEs were considered possibly or probably drug-related, while the relationship for the sixth was unknown.

4.8.3.5.2 Scharf Trial

Six (4.2%) of the 143 patients reported 7 AEs that coded to the COSTART term stupor. The verbatim terms used to describe 4 of these events in 3 patients include the words "drunk," "intoxicated," and "tipsy." One of these 4 events was considered probably related, 2 possibly related, and 1 of unknown relationship to trial medication. Two events had a duration of 1 day, 1 event lasted 15 days, and 1 event did not have a stop date recorded These 4 AEs occurred after 1 to 134 days of Xyrem administration, with the dosage at onset ranging from 6.0 to 7.5 g/d. None of these events was considered serious.

One additional patient (257) experienced an AE of verbatim term "acting 'like he's retarded.'" The time of the event and dosage at onset were unknown. The event was not serious and was of unknown relationship to trial medication. The patient continued in the trial through the May 31, 1999 data cutoff.

Two additional patients experienced 2 AEs that were considered serious. Patient 017 experienced an event of verbatim term "unresponsive" that was part of an overdose (see Table 4.9). The second patient (012) experienced an event with verbatim terms "disoriented," "stupor," and "weak" on Day 725 (7.5 g/d). The patient was hospitalized overnight. The patient continued the trial for an additional 8 years with no recurrence of the event.
These descriptive events do not appear to qualify as psychopathology.

4.8.3.6 Suicide Attempt, Overdose, Intentional Overdose

4.8.3.6.1 Updated Integrated Clinical Trial Database

Two suicides (0531 and 0936), 1 attempted suicide (14043), and 1 intentional overdose (1131) were recorded among the neuropsychiatric AEs in the 402 patients in the updated integrated clinical trial database.

One suicide (0531, coded as death) was due to multiple drug toxicity that included toxic levels of 6 psychotropic drugs other than sodium oxybate. The second suicide (0936) by a patient with a history of depression and a subsequent suggested diagnosis of bipolar disease, was officially ruled as a death due to cardiovascular disease (without autopsy by the Medical Examiner) but later evidence pointed to a possible overdose that included lithium, Paxil, and Percocet as well as sodium oxybate. This event occurred on 2/24/01, which was 5 months after the data cutoff (9/30/00), but is included here for completeness.

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