17 March 2011

EMA/406550/2011

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xyrem

sodium oxybate

Procedure No.: EMEA/H/C/000593/II/0026

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

An agency of the European Union

© European Medicines Agency, 2011. Reproduction is authorised provided the source is acknowledged.

Invented name/name:	Xyrem
International non-proprietary name/common name:	sodium oxybate

Indication summary (as last approved):	Treatment of cataplexy in adult patients with narcolepsy
Marketing authorisation holder:	UCB Pharma Ltd.

1. Scope of the variation and changes to the dossier

Scope of the variation:	Update of relevant sections of the SmPC to include the following information relevant to the authorised indication: contraindication in patients with major depression (4.3), information on drug-drug interactions with duloxetine, lorazepam and tramadol (4.5), pharmacokinetic results in elderly population (5.2) and safety information in relation to the clinical trials conducted in fibromyalgia patients (4.2, 4.4, 4.6 and 4.8). Information on absolute bioavailability and preclinical data were also updated in section 5.2, and 5.3, respectively. The Package Leaflet has been amended accordingly. Finally, annex II has been updated in order to delete the reference to the versions of the RMP and Pharmacovigilance system and to reflect the previously agreed yearly PSUR cycle.
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	1, 2 and 5
Product Information affected:	Summary of Product Characteristics and Package Leaflet (Attachment 1 – changes highlighted) and Annex II.

2. Steps taken for the assessment

Step	Step date
Submission date:	16 March 2010
Start of procedure:	28 March 2010
Rapporteur's assessment report circulated on:	7 June 2010
Co-Rapporteur's assessment report circulated on:	23 May 2010
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 June 2010
MAH's responses submitted to the CHMP on:	17 September 2010
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	4 November 2010
Rapporteur's updated assessment report on the MAH's responses circulated on:	15 November 2010
Follow on Request for supplementary information and extension of timetable adopted by the CHMP on:	18 November 2010
MAH's responses submitted to the CHMP on:	14 January 2011
Rapporteur's preliminary assessment report on the MAH's responses for follow on request for supplementary information circulated on:	28 February 2011
An Oral explanation to the CHMP took place on:	15 March 2011
CHMP opinion:	17 March 2011

3. Scientific discussion

3.1. Introduction

Fibromyalgia (FMS) is a common chronic disease. It affects at least 2% of the world's general population, mostly adult women.

Hallmarks of fibromyalgia are widespread pain for at least 3 months and pain in at least 11 of 18 anatomically defined tender points. In addition to pain and tenderness, patients suffer a constellation of debilitating symptoms, including fatigue, decreased ability to function in daily life, poor sleep, decreased health-related quality of life, stiffness, depression, and anxiety. Pain levels reported by patients with fibromyalgia are significant and long-lasting; reports of mean baseline pain range from 6.4 to 7.1 on 0 to 10 numerical rating scales or 0 to 10 on visual analogue scales (VAS). This pain level often persists over long periods.

There is increasing evidence that non-restorative sleep and its influence on peripheral functions promote hyperalgesia, fatigue, and bodily hypersensitivity. Early studies demonstrated that fibromyalgia-like symptoms could be induced in healthy subjects by decreasing their quality of sleep, which has since been confirmed in experimental studies using different methodologies. It was further demonstrated that a follow-up night of undisturbed sleep after rapid-eye movement (REM) or slow-wave sleep deprivation, was associated with an increase in pain-tolerance threshold.

Recently, the important role of central nervous system (CNS) hypersensitivity has been emphasized. The fragmentation of slow-wave sleep increases sensitivity to pain as well as to non-painful stimuli such as loud sounds and bright light. Fragmented sleep is a result of periodic arousal disturbances and has been demonstrated in fibromyalgia patients using polysomnography; the high index of such arousal disturbances in fibromyalgia patients is an indicator of sleep instability and is associated with unrefreshing, less efficient sleep and is correlated to the severity of clinical symptoms in fibromyalgia patients.

Varying brain functions during sleep and waking phases are involved in circadian changes in metabolic functions of the body. For example, growth hormone production occurs in the very early sleep stages and is associated with the emergence of slow-wave sleep or deep sleep. Several studies have demonstrated decreased growth hormone levels and disturbances of the hypothalamic-pituitary-adrenal axis in fibromyalgia patients. In addition, neurotransmitter functions and dysfunctions in fibromyalgia patients also contribute to hypersensitivity and disordered sleep. There is evidence suggesting sodium oxybate-induced neuromodulation of the monoaminergic, glutaminergic, cholinergic, and opioidergic systems as well as possible modification of growth hormone secretion and neurosteroids production. It has also been described that sodium oxybate reduced pain and fatigue associated with fibromyalgia, increased slow-wave sleep, and decreased alpha intrusions into non-REM slow-wave sleep (SWS).

In the European Union (EU), no drug has the approved therapeutic indication fibromyalgia, but multiple medications are used as therapy in fibromyalgia patients, like SSRIs, SNRIs, TCAs, NSAIDs and other analgesics, and anticonvulsants. In addition, non-pharmacological treatment such as cognitive therapy, acupuncture and physical training is applied on the patients.

The proposed dosing regimen initially applied for was a starting and recommended maintenance dose of 4.5 g/day sodium oxybate (divided into two equal doses) with possible increased up to 6 g/day in patients with severe symptoms based on individual patient response and tolerability.

Xyrem oral solution 500 mg/ml (sodium oxybate) is currently approved in the EU for treatment of narcolepsy with cataplexy in adult patients with a recommended starting dose is 4.5 g/day sodium oxybate (divided into two equal doses). The dose should be titrated to effect based on efficacy and tolerability up to a maximum of 9 g/day.

This type II variation was initially submitted to extend the indication as follows:

"Xyrem is indicated in adults: Treatment of moderate to severe symptoms of fibromyalgia."

On the basis of the data provided, the CHMP did not support the extension of the indication. However, as a result of the evaluation of the new data, the CHMP recommends to update the SmPC and the Package Leaflet accordingly, as described in the scientific discussion.

Information on Paediatric requirements

Not applicable

Scientific Advice

A CHMP scientific advice for sodium oxybate (EMEA/H/SA/731/1/2006) was provided on 27 July 2006 pertaining to non clinical and clinical aspects.

3.2. Non Clinical aspects

In line with the CHMP scientific advice, no further animal studies have been conducted to characterise the pharmacological and toxicity profile of sodium oxybate to support the indication initially applied for since the previously submitted non clinical data were considered sufficient.

Ecotoxicity/Environmental Risk Assessment (ERA)

In line with CHMP guideline on environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00), the company provided a justification to be exempted of the ERA requirement for the indication initially applied for due to the nature of Xyrem. Xyrem contains sodium oxybate, also known as γ-hydroxybutyric acid (GHB) which is an endogenous constituent of mammalian brain thought to be synthesised from GABA in GABAergic neurons, acting in similar way to some neurotransmitters in the mammalian brain, and therefore is not expected to impact on the environment.

3.3. Clinical aspects

3.3.1. Introduction

The development program completed to support the indication initially applied for, consisted of:

- Four Phase I studies to investigate the pharmacokinetic/pharmacodynamic effects of sodium oxybate when co-administered with fomepizole (**07-004**), duloxetine (**07-005**), lorazepam (**07-007**), tramadol (**07-008**);

- One randomised, double blind, placebo-controlled, parallel group, Phase II study (**OMC-SXB-26**) to investigate 4.5 g or 6g/night of sodium oxybate taken orally in 2 equally divided doses;
- Two randomised double blind, placebo-controlled, parallel group, 14 week, Phase III studies (**06-008** and **06-009)** to investigate 4.5g and 6g/night of sodium oxybate taken orally in 2 equally divided doses;
- An open label, 38 week study (**06-010**) designed to provide additional data on long term of safety and efficacy and to assess long term effects on quality of life (QoL).

Updated data were also provided concerning absolute bioavailability of sodium oxybate and a pharmacokinetic study **(06-015)** performed in the elderly population was submitted.

Regarding the clinical aspects, the present submission was not in line with following main recommendations from 2006 CHMP scientific advice:

- Results of the phase II study showed that point estimates for 4.5g/night for the majority of evaluated scores (+subscores) and questionnaires of the three co-primary measures and the secondary endpoints were within the range of the results of the 6g/night group. Moreover, some of the results indicate that a dose of 4.5g/night might lead to better results in terms of efficacy. Therefore the Company is advised to reconsider the proposed titration regimen also regarding endpoints not directly related to tolerability. It would have been good practice to conduct a proper dose-finding study in this population. Apparently, 3g/night was never tested in the fibromyalgia population, supposedly due to a lack of efficacy of that dose in the treatment of narcolepsy. The Company should consider the possibility that 3g/night could be effective in the fibromyalgia population and might show better tolerability. From the narcolepsy dossier it is known that the 9g/night dose gives rise to serious safety concerns and it is certainly undesirable to include it in the dose range.
- Currently no specific regulatory guidelines to develop/register a new product for the management of FMS are available. However, minimum requirements regarding study duration included in the Guideline on clinical investigation of medicinal products intended for the treatment of neuropathic pain (CHMP/EWP/252/03) should be adopted for the phase III setting in FMS. Therefore, the proposed study duration of 12 weeks after a stable dose has been achieved in all treatment groups is generally endorsed. Since FMS is a chronic disorder, it is emphasized that a 12-week duration can only support the short-term treatment of FMS. In order to support a claim for long-term treatment, the maintenance of effect and possible development of tolerance need to be investigated, e.g. in an open label study extension phase lasting 12 months. Alternatively a relapse prevention study could be envisaged. As in the narcolepsy development program, the investigation of maintenance of effect would require a sufficient number of patients being switched from the phase III (carried out in the EU) to the open label phase.
- Since fibromyalgia is a common condition and Xyrem is a drug with a number of uncertainties regarding safety, it is advisable to enlarge the database to figures closer to the recommended 1500 exposures.
- Approval for the indication "treatment of FMS" in the EU can only be sought if the proposed treatment leads to an improvement in different dimensions that are specific for FMS, minimum requirements for the claim to use Xyrem as a long-term treatment in FMS are met. Furthermore, at least one of the two proposed phase III studies and open label extensions concerning the investigation of maintenance of effect as well as safety should be conducted in the EU.

The MAH stated that the clinical trials have been conducted in accordance with Good Clinical Practice. No GCP inspections were conducted in the clinical program for fibromyalgia.

3.3.2. Pharmacokinetics

Absorption

Absolute bioavailability was not specifically studied at the time of the initial authorisation. In the literature, limited data suggested a bioavailability of 28%. This low figure was considered probably due to a high first pass metabolism. Within the present application, the MAH submitted a specific bioavailability study. An absolute bioavailability from the oral solution given as once- and twice-daily administrations of 2.25 g sodium oxybate and once-daily administration of 4.5 g sodium oxybate of about 88% was observed in reference to a 5 minute IV infusion of the same doses.

Metabolism

Studies in vitro with pooled human liver cytochromes indicated that sodium oxybate did not significantly inhibit the activities of the human isoenzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 up to the concentration of 3mM (378 µg/mL). However, these levels are considerably lower than levels achieved with therapeutic doses. Given the potential increased in human exposure with the indication initially applied for, complementary data would be required to cover a concentration range that is sufficiently high for detecting clinically relevant inhibition.

Special population

Study 06-015 (elderly)

No relevant difference in the pharmacokinetic parameters in patients <65 years and patients ≥65 years up to 3 g/d sodium oxybate were observed. As there is no information indicating relevant age-dependent changes in the major elimination pathway of sodium oxybate, no changes in the pharmacokinetics of sodium oxybate in patients ≥65 years are expected at the maximal recommended dose of 9 g/d (4.5 g twice per night) for sodium oxybate. When administering sodium oxybate at the maximally recommended doses of 9 g/d in patients ≥65 years, an impaired motor and/or cognitive function cannot be excluded.

Pharmacokinetics interaction studies

Four Phase I studies to investigate the pharmacokinetic effects of sodium oxybate when co-administered with fomepizole (**07-004**), duloxetine (**07-005**), lorazepam (**07-007**), tramadol (**07-008**);

Study 07-004 (fomepizole)

The mean plasma concentration time curves demonstrate that co-administration of fomepizole did not prolong sodium oxybate exposure. The objective, allowing a once-nightly administration of sodium oxybate via the extension of the sodium oxybate half-life by fomepizole was not met. No further detailed pharmacokinetic and pharmacodynamic analyses were therefore conducted.

Study 07-005 (duloxetine)

Co-administration of sodium oxybate (2.25g/day) and duloxetine (60mg/day) resulted in similar pharmacokinetic profiles to those observed when each of these drugs was given alone and did not appear to worsen sleepiness with an increase in VAS over the first 5 hours and a magnitude of mean

changes from predose over this time period similar for sodium oxybate alone and in combination with duloxetine.

Study 07-007(lorazepam)

Co-administration of sodium oxybate (2.25g/day) and lorazepam (2mg/day) resulted in similar pharmacokinetic profiles to those observed when each of these drugs was given alone, however it did produce sleepiness with an increased effect when sodium oxybate and lorazepam were co-administered. Attention and cognition as measured by Digit Symbol Substitution Test (DSST) were least affected when sodium oxybate was administered alone.

Study 07-008 (tramadol)

Co-administration of tramadol (100 mg/day) with sodium oxybate (2.25g/day) resulted in relative similar pharmacokinetic profiles to those observed when each of these drugs was given alone. The 90% confidence intervals (CIs) for comparison of tramadol and O-desmethyl tramadol AUC0-24 and Cmax ss with and without sodium oxybate co-administration were partially contained in the bioequivalence range, slightly exceeding the upper end. However, the results did not necessary reflect the effect in a clinical setting where tramadol is dosed twice daily or at bedtime and when Xyrem is given in much higher doses at a daily basis. Similar increases in mean sleepiness VAS were observed with sodium oxybate alone and in combination with tramadol. However this finding should be interpreted cautiously since tramadol is only administered as a single dose 11 hours before the dosing of Xyrem and tramadol alone had little impact on sleepiness.

OMC-SXB-17 (modafinil)

No pharmacokinetic interaction were observed between sodium oxybate (4.5g) and modafinil (200 mg).Sodium oxybate has been administered concomitantly with CNS stimulant agents in approximately 80% of patients in clinical studies in narcolepsy. Whether this affected respiration during the night is unknown and this has been reflected in the SmPC, considering a potential pharmacodynamic interaction cannot be ruled out since only a single dose of modafinil 200 mg was used.

Mechanism of action

GHB binds to two receptors, the gamma hydroxybutyrate receptor (GHBR) and the gamma aminobutyric acid (GABA) B-subtype (GABAB) receptor in central nervous system tissues (*Lingenhoehl et al. 1999*, *Mathivet et al. 1997*). Although the exact mechanism by which sodium oxybate reduces pain in fibromyalgia is unknown, sodium oxybate is believed to inhibit central pain (*Sherman & Gebhart 1975*) through stimulation of the GABAB receptor, which may result in inhibition of spinal neurons and/or inhibition of excitatory neurotransmitter release in the spinal cord (*Chanimov et al. 1999*, *Hosli et al. 1983*). Actions at supraspinal sites may also contribute to the clinical effects of sodium oxybate on pain (*Potes et al. 2006*). The role of the GHBR in central pain inhibition is unknown. GHB does not have activity at mu, delta, or kappa opioid receptors (*Feigenbaum & Simantov 1996*). Sodium oxybate/GHB is known to modulate the activity of noradrenergic (Szabo et al. 2004), serotonergic (*Gobaille et al. 2002*, *Waldmeier & Fehr 1978*), and dopaminergic (*Madden & Johnson 1998*, *Aghajanian & Roth 1970*) pathways in animal models and promote growth hormone secretion in humans (*Van Cauter et al. 1997*) and in animal models (*Bluet-Pajot et al. 1978*). Sodium oxybate's effects on sleep may contribute to its effects on pain reduction. In a dose-related manner, sodium oxybate decreases wake after sleep onset (WASO), increases non REM sleep, including Stage 3/4 (slow-wave sleep) and reduces sleep disruption, which is linked to decreased pain threshold, decreased inhibition of pain, and somatic symptoms of widespread pain (*Black et al. 2009*, *Mamelak et al. 2004*, *Scharf et al. 2003*, *Lapierre et al. 1990*, *Smith et al. 2007*, *Onen et al. 2001*, *Lentz et al. 1999*, *Moldofsky et al. 1975*).

Primary and Secondary Pharmacology

Pharmacodynamic effects of sodium oxybate on sleepiness; attention and cognition have been investigated in the newly submitted interaction studies in healthy volunteers. Results were previously discussed in relation to the pharmacokinetic profile of sodium oxybate.

3.3.3. Discussion on clinical pharmacology

In a specific study, the absolute bioavailability from the oral solution given as once- and twice-daily administrations of 2.25 g sodium oxybate and once-daily administration of 4.5 g sodium oxybate of about 88% was observed in reference to a 5 minute IV infusion of the same doses. The CHMP agreed to update this value in the SmPC which was originally based on limited literature data.

Elderly population was not originally studied. In a specific study conducted in a limited number of patients greater than the age of 65 years the pharmacokinetics of sodium oxybate was not different compared to patients younger than 65 years of age. This information has now been reflected in the SmPC.

Given the potential increase in human exposure with the indication initially applied for (fibromyalgia), complementary in vitro data on human liver cytochromes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP2C8, and CYP2B6) would be required by the CHMP to cover a concentration range that is sufficiently high for detecting clinically relevant inhibition.

Following the results of the new interaction studies conducted with fomepizole, duloxetine, lorazepam and tramadol, the CHMP noted that some of these studies did not include the maximal recommended doses for each drug. Following clarifications from the MAH, the CHMP concluded the following:

- No relevant information to be included in the SmPC from the study with fomepizole taking into consideration that once-nightly administration of sodium oxybate via the extension of the sodium oxybate half-life by fomepizole was not met.
- No pharmacokinetic interaction is expected at the maximal recommended daily dose of 9 g (4.5 g twice per night) for sodium oxybate and the maximal dose of 120 mg/d for duloxetine. No additional effect on sleepiness was observed when comparing single doses of sodium oxybate alone (2.25 g) and sodium oxybate (2.25 g) in combination with duloxetine (60 mg at steady state).
- An increase of symptoms of CNS depression and/or respiratory depression cannot be excluded when combining the maximally recommended daily dose of 9 g sodium oxybate (4.5 g twice per night) with lorazepam (6 mg/day) or tramadol (400 mg/day).
- In addition, the MAH performed a literature search on the available data on interaction with Xyrem up to July 2010. Non clinical data were found relevant to be added to the SmPC and were related to cross tolerance with baclofen that was clearly demonstrated in rodents. Some of the data were already reflected in the SmPC (ethanol, morphine, oxytocin, flumenazil); others referred to illicit drugs (phencyclidine, MDMA)and were considered not relevant for the therapeutic use of Xyrem and therefore not included in the SmPC. Additionally, data on interactions with ritonavir/saquinavir and salicylic acid/probenecid were also found; however these were lacking of information to be included in the SmPC.

Adequate information has been reflected in the SmPC on the basis of the above conclusion (see section 3.8).

Regarding pharmacodynamic profile of Xyrem, effects on sleepiness, attention and cognition were investigated in the pharmacokinetic interaction studies conducted in healthy volunteers.

3.3.4. Conclusion on clinical pharmacology

Overall, the MAH performed additional interaction studies relevant to the indication initially applied for (fibromyalgia). Further investigation on the metabolism (interaction with CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP2C8, and CYP2B6) would be required by the CHMP, given the potential increased in human exposure.

3.4. Clinical efficacy

The Phase II study (**OMC-SXB-26**), the 2 short term Phase III studies (**06-008** and **06-009)** and the open label long term study (**06-010**) are presented below.

3.4.1. Dose response study

Study **OMC-SXB-26** was a multicenter, randomised, double-blind, placebo-controlled, parallel-group study in subjects diagnosed with fibromyalgia according to the American College of Rheumatology (ACR, Wolfe et al, 1990). The study was conducted in the United States (US) only.

Subjects underwent screening assessments and those who met the eligibility criteria underwent a drug withdrawal and washout period during which time pain medications and any treatment for fibromyalgia were gradually withdrawn. At the end of the 2-week baseline assessment period, subjects who continued to meet inclusion/exclusion criteria and who reported an average pain score above 4 (on a VAS of 0 to 10) during the last week of the baseline period were randomised to one of three treatment groups: Xyrem 4.5 g/night, Xyrem 6 g/night, or placebo. During the double-blind treatment period subjects received Xyrem 4.5 g/night, Xyrem 6 g/night, or matching placebo in two equally divided doses each night for 8 weeks. Follow-up visits were scheduled 2, 4, and 8 weeks after initial dosing.

A total of 195 patients were randomised. Most (91.6%) randomised subjects did not consider themselves to be normal sleepers. More than half (53.1%) described their usual sleep as poor and 42.8% described their usual sleep as fair. The mean clinical global impression scores (CGIs) at baseline for the placebo, Xyrem 4.5 g/night, and Xyrem 6 g/night groups were 4.2, 4.0, and 4.1 (using a 6-point scale where 1=normal, 4=moderately ill, and 6=among the most extremely ill).

The primary efficacy parameter (Fibromyalgia Syndrome Composite Response) was a binary composite parameter for the treatment of fibromyalgia syndrome. The proportion of subjects in each treatment group that met all 3 of the following response criteria was compared to assess the efficacy of Xyrem in response to fibromyalgia syndrome.

- Pain Severity: Overall pain severity was assessed by pain VAS data recorded 3 times a day by the subject in an electronic diary (eDiary). For pain VAS, a response was defined as a reduction in average pain of 20% or greater from baseline to Week 8.
- Functionality (Fibromyalgia Impact Questionnaire [FIQ]): Change from baseline to a study visit was assessed. A response was defined as a reduction of 20% or greater in FIQ total score from baseline to Week 8.
- Patient Global Impression of Change (PGIc): The subject's perception of the overall improvement in their fibromyalgia symptoms was assessed by means of the PGIc questionnaire completed at the

Main secondary efficacy endpoints were: Severity of Pain, Fibromyalgia Impact Questionnaire (FIQ) Total Score, Patient Global Impression of Change (PGIc), Subjective and Objective Assessments of Sleep and Fatigue.

Results of the primary analysis (ITT) are summarised in Table 1.

Table 1

Analysis	Placebo (n=66)	Xyrem 4.5 g/night (n=62)	Xyrem 6 g/night (n=67)	Overall *P* value[a]
ITT Population				
LOCF Analysis	62	57	64	
Responders, n (%)	8 (12.9)	17 (29.8)	18 (28.1)	0.052
Comparison to placebo *P* value[a]		0.024	0.035	
BOCF Analysis	66	62	67	
Responders, n (%)	8 (12.1)	16 (25.8)	16 (23.9)	0.112
Comparison to placebo *P* value[a]		0.047	0.078	
Observed Data	54	52	49	
Responders, n (%)	8 (14.8)	17 (32.7)	17 (34.7)	0.041
Comparison to placebo *P* value[a]		0.030	0.019	

Secondary analysis of the primary efficacy parameter using the PP population did not show statistically significant differences between the treatment groups using LOCF, BOCF, or observed data.

An exploratory analysis of the primary efficacy parameter was performed changing the criteria for a responder to a 30% reduction in the Pain VAS and the FIQ total score. Results are shown in Table 2:

Table 2

Analysis	Placebo (n=66)	Xyrem 4.5 g/night (n=62)	Xyrem 6 g/night (n=67)	Overall *P* value[a]
LOCF Analysis	62	57	64	
Responders, n (%)	7 (11.3)	15 (26.3)	17 (26.6)	0.060
Comparison to placebo *P* value[a]		0.035	0.029	
BOCF Analysis	66	62	67	
Responders, n (%)	7 (10.6)	14 (22.6)	16 (23.9)	0.101
Comparison to placebo *P* value[a]		0.068	0.043	
Observed Data	54	52	49	
Responders, n (%)	7 (13.0)	15 (28.8)	16 (32.7)	0.046
Comparison to placebo *P* value[a]		0.044	0.017	

Effect on pain

The average change in pain scores from baseline to endpoint (Week 8) was a reduction of 16.91 and 19.47 for subjects in the 4.5 and 6 g/night groups, respectively, and a reduction of 9.60 for subjects in the placebo group using a VAS scale of 0 to 100 (where 0=no pain and 100=worst imaginable pain). Xyrem 6 g/night showed a statistically significant reduction in overall pain severity compared to placebo (p=0.006), and Xyrem 4.5 g/night showed a reduction in pain severity approaching

significance compared to placebo (p=0.051).The proportions of subjects who achieved a 30% or greater reduction in pain severity in the Xyrem 4.5 and 6 g/night groups were 41.4% and 47.6%, respectively, compared to 23.8% for subjects in the placebo group (p=0.039 and p=0.005 for 4.5 and 6g/night, respectively).

Effect on multidimensional function

The FIQ total score was significantly reduced from baseline to endpoint for both Xyrem groups compared to placebo (p=0.028 and p=0.029 for 4.5 and 6g/night, respectively). The proportions of subjects who achieved a 30% or greater reduction in the FIQ total score were 48.1% and 50.8% of subjects in the Xyrem 4.5 and 6 g/night groups, respectively, compared to 26.7% of subjects who received placebo (p=0.018 and p=0.006 for for 4.5 and 6g/night, respectively).

Effect on patient global

The Patient Global Impression of Change (PGIc) showed 40% of subjects who received Xyrem 4.5 g/night and 33.3% of subjects who received Xyrem 6 g/night rated their symptoms at endpoint (Week 8) as "very much better" or "much better" compared to 20% of subjects in the placebo group (p=0.019 and p=0.095 for 4.5 and 6g/night, respectively).

Effect on sleep

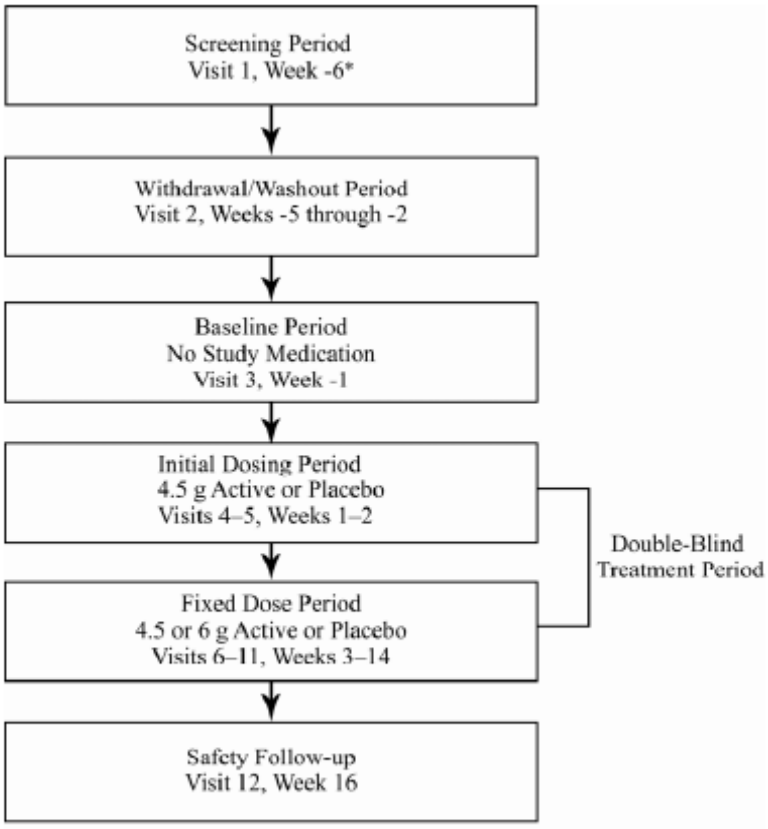
Subjective assessments of sleep showed statistically significant reductions from baseline to endpoint (Week 8) for severity of daytime sleepiness (ESS) and sleep impairment (JS), and significantly less difficulty from being sleepy or tired while performing specific activities (FOSQ) for subjects in both Xyrem groups compared to placebo (p<0.001 for all secondary measures). Subjective assessments of fatigue showed statistically significant reductions from baseline to endpoint (Week 8) for fatigue VAS scores for subjects in both Xyrem groups compared to placebo (p=0.038 and p=0.004 for 4.5 and 6g/night, respectively). Statistically significant changes in objective measures of sleep using polysomnography compared to placebo included increased Stage 2 and Stage 3 & 4 sleep (Xyrem 6 g/night), decreased REM sleep (both Xyrem groups), increased NREM sleep (Xyrem 6 g/night), and decreased wake after sleep onset (WASO) (Xyrem 6 g/night). Although both doses had increases in Stage 3 & 4 sleep, the difference from placebo was statistically significant for the Xyrem 6 g/night group only (p=0.018). Improvements in total sleep time and sleep efficiency from baseline to endpoint (Week 8) were seen for subjects who received Xyrem 6 g/night, but the changes were not statistically significant compared to placebo (p=0.071 and p=0.073, respectively).

3.4.2. Main studies

3.4.2.1. Short term studies

Two randomised multicenter, double blind, placebo-controlled, parallel group, 14 week, Phase III studies (**06-008 and 06-009**) to investigate 4.5g and 6g/night of sodium oxybate taken orally in 2 equally divided doses were conducted (see Figure 1) with a safety follow up at week 16. Study 06-008 was conducted in the US only whereas study 06-009 included European sites (France, Germany, Italy, the Netherlands, Poland, Spain and the United Kingdom).

Figure 1. Trial Flow Diagram



* The screening period was extended to 6 weeks in subjects referred for sleep apnea screening.

Study participants

Main inclusion criteria

- Subjects met the American College of Rheumatology (ACR) criteria for fibromyalgia at screening and at baseline

- Subjects had at least 5 of 7 days with 100% compliance on the VAS self-rated pain scale in the week prior to Visit 4 and had an average VAS pain score of ≥50/100 mm as recorded in the subject diary on the 100% compliant days

- Subjects were willing to discontinue opiates, benzodiazepines, muscle relaxants (cyclobenzaprine), anticonvulsants, antidepressants, dopamine agonists and/or tramadol , or any other medications, herbal remedies, and/or devices being used to treat their fibromyalgia symptoms until trial completion

- Subjects agreed to use only acetaminophen (paracetamol) as rescue pain medication and to limit the dose to a maximum of 4 g/day throughout the course of the trial. Subjects may have taken a single daily dose of ≤325 mg aspirin for cardiac protection. Any other use of aspirin was prohibited during this trial.

- Subjects were willing to discontinue the ingestion of alcohol for the duration of the trial

Main exclusion criteria

- Subjects had any of the following medical conditions: rheumatic disease in addition to fibromyalgia, such as rheumatoid arthritis, inflammatory arthritis, or systemic lupus erythematosus, symptoms of

painful osteoarthritis or symptomatic osteoarthritis (e.g., osteoarthritis associated with stiffness and muscle weakness) at screening or prior to randomization, pain from traumatic injury, uncontrolled hypo- or hyperthyroidism of any type, autoimmune disease (with the exception of inactive Hashimoto's thyroiditis), multiple sclerosis, unstable cardiovascular, endocrine, gastrointestinal, hematologic, hepatic, immunologic, metabolic, neurological, pulmonary, and/or renal disease, current or recent (i.e., no evaluable disease within the past 5 years) neoplastic disease (excluding localized basal cell carcinoma), Systemic infection, Any disease, disorder or condition that would have placed the subject at risk during, the trial, interfered with the subject's or investigator's ability to measure change on any outcome measures and/or compromised the objectives outlined in the protocol;

- Subjects had a history of myocardial infarction, transient ischemic attack, or cerebrovascular accident

- Subjects had a Major Depressive Disorder (as defined by the Mini International Neuropsychiatric Interview [MINI], was being treated for a Major Depressive Disorder, or had a history of psychotic and/or bipolar disorder. Subjects considered for discontinuation of antidepressant medication required careful evaluation as to any risks from cessation of antidepressant therapy. If, in the opinion of the investigator, a reasonable risk of resultant subject harm existed, the subject was to be excluded from study participation.

- Subjects had any other problems that, in the investigator's opinion, would preclude the subject's participation and completion of this trial or compromise reliable representation of subjective symptoms

- Subjects had a MINI suicidality module score >0 and/or answered "yes" to the suicide question (A3-g) on the Major Depressive Episode module of the MINI and/or response ≥1 on Question 9 of the Beck Depression Inventory-II

- Subjects had a current or past history of substance use disorder including alcohol abuse as defined by the Diagnostic and Statistical Manual of Mental Disorders IV, Text Revision (DSM-IV-TR)

- Subjects had a clinically significant history of seizure disorder either past or present, a history of clinically significant head trauma (i.e., concussion resulting in clinically significant loss of consciousness), chronic persistent migraine headaches, or past invasive intracranial surgery

- Subjects were experiencing clinically significant medication withdrawal symptoms after the withdrawal/washout period; fatigue and/or drowsiness/sedation in association with intake of allowed medications

- Subjects had any of the following exclusionary clinical laboratory results: Serum creatinine >2.0 mg/dL; Thyroid stimulating hormone (TSH) >6 µU/mL or <0.3 µU/mL; Abnormal liver function tests (aspartate aminotransferase [AST] or alanine; aminotransferase [ALT] more than twice the upper limit of normal); Elevated serum bilirubin more than 1.5 times the upper limit of normal; Pretrial electrocardiogram (ECG) results demonstrating clinically significant; arrhythmias or conduction delays; Positive pregnancy test at any time during the trial; Positive urine drug screen for drugs of abuse and/or positive alcohol test at screening or at the end of baseline;

- Subjects were diagnosed with sleep apnea and was not currently on stable continuous positive airway pressure (CPAP) therapy for the last 30 days prior to baseline

- Subjects had Generalized Anxiety Disorder as defined by DSM-IV-TR

Treatment, Randomisation and blinding

Xyrem (sodium oxybate) oral solution, 4.5 or 6 g/night administered in 2 divided doses, or placebo. Patients were randomised to the treatments in a 1:1:1 fashion. Randomisation took place at the baseline visit (= visit 4).

In study 06-008, the volume ingested was greater for the 6 g dose, i.e. 12 ml, than for the 4.5 g dose, i.e., 9 ml, as both solutions contented 500 mg/mL. In study 06-009, however, the concentration of sodium oxybate was different, with 500 mg/mL for the 6 g/night regimen and 375 mg/mL for the 4.5 g/night dose, in order to have the same volume for all three treatment groups (4.5g, 6 g or placebo). Half of the total dose was taken just before sleep, the other half 2.5-4 hours later.

Outcomes/Endpoints and Statistical Methods

These are presented in Table 3

Table 3

Primary and Sequential Secondary Endpoints in the Statistical Analysis Plans for US and EU Submissions

Endpoint Category	United States	European Union
Primary	Pain Severity Response (Pain VAS, binary)	Pain Severity Response (Pain VAS, binary) Functionality Response (FIQ total score, binary)
Sequential Secondary	Functionality Response (FIQ total score, binary) Fatigue VAS PGI-c Response (binary) SF-36 Physical Component (PCS) Sleep Patterns (Jenkins Sleep Scale)	Sleep Patterns (Jenkins Sleep Scale) FOSQ (total score) Fatigue VAS

VAS = visual analog scale; FIQ = Fibromyalgia Impact Questionnaire; FOSQ = Functional Outcomes of Sleep Questionnaire; PGI-c = Patient Global Assessment of Change; SF-36 = Short Form 36

The primary endpoint was pain severity response (defined as the proportion of subjects had at least a 30% reduction in overall pain VAS from baseline to Week 14). The functionality response was defined as the proportion of subjects had at least a 30% reduction in the FIQ total score from baseline to Week 14. In the EU, pain severity response and functionality response were used as co-primary endpoints.

For the Phase 3 controlled studies (06-008 and 06-009), the BOCF analyses of all efficacy endpoints were pre-specified as the primary imputation method in both the US and EU analysis plans. The LOCF and observed data analyses were also performed as sensitivity analyses.

Sample size

In each study, a sample size of 525 subjects was planned, based on data from Study OMC-SXB-26. This sample size was estimated to provide at least 81% power to detect a difference in both co-primary endpoints for one dose of Xyrem, assuming the percentages of responders in the Xyrem and placebo groups were 30% and 15%, respectively. These sample size calculations were based on chi-square tests with a significance level of 0.05.

Results

Participant flows/Analysis populations

Disposition of the subjects in short term studies are presented in Table 4.

Table 4 Disposition of Subjects in the Phase 3 Controlled Studies (06-008 and 06-009), ITT Populations

	06-008				06-009			
	Placebo n (%)	SXB 4.5 g n (%)	SXB 6 g n (%)	Total n (%)	Placebo n (%)	SXB 4.5 g n (%)	SXB 6 g n (%)	Total n (%)
No. Subjects Randomized	183	182	183	548	188	195	190	573
No. Subjects Treated	183 (100.0)	182 (100.0)	182 (99.5)	547 (99.8)	188 (100.0)	194 (99.5)	189 (99.5)	571 (99.7)
No. Subjects Completed	111 (60.7)	119 (65.4)	104 (56.8)	334 (60.9)	131 (69.7)	129 (66.2)	116 (61.1)	376 (65.6)
No. Subjects Discontinued	72 (39.3)	63 (34.6)	79 (43.2)	214 (39.1)	57 (30.3)	66 (33.8)	74 (38.9)	197 (34.4)
Adverse event(s)	20 (10.9)	35 (19.2)	42 (23.0)	97 (17.7)	11 (5.9)	30 (15.4)	40 (21.1)	81 (14.1)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal of consent	11 (6.0)	10 (5.5)	15 (8.2)	36 (6.6)	6 (3.2)	8 (4.1)	5 (2.6)	19 (3.3)
Lost to follow-up	6 (3.3)	3 (1.6)	5 (2.7)	14 (2.6)	5 (2.7)	4 (2.1)	4 (2.1)	13 (2.3)
Lack of study drug efficacy	30 (16.4)	12 (6.6)	13 (7.1)	55 (10.0)	23 (12.2)	18 (9.2)	19 (10.0)	60 (10.5)
Sponsor decision	2 (1.1)	1 (0.5)	2 (1.1)	5 (0.9)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Investigator decision	1 (0.5)	1 (0.5)	1 (0.5)	3 (0.5)	2 (1.1)	0 (0.0)	0 (0.0)	2 (0.3)
Protocol deviation/violation	2 (1.1)	1 (0.5)	1 (0.5)	4 (0.7)	9 (4.8)	4 (2.1)	4 (2.1)	17 (3.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	2 (1.1)	4 (0.7)

SXB = sodium oxybate
Note: Primary reasons for discontinuation are listed. Percentages are based on number of subjects randomized.

Recruitment

In study 06-008, patients were recruited in a number of 74 sites in the USA. In study06-009 , patients were recruited in the USA (67 sites), France (7 sites), Germany (9 sites), Italy (2 sites), the Netherlands (2 sites), Poland (6 sites), Spain (8 sites), and the UK (7 sites).

Conduct of the study

A considerable number of protocol amendments were issued, however, these were not considered to have major impact of the study outcome.

Baseline data

These are presented in Tables 5, 6 and 7.

Table 5

	All US Subjects	All EU Subjects	All Subjects Overall
Age (years)			
N	928	193	1121
Mean±SD	46.7±11.4	47.2±9.0	46.8±11.0
Median (minimum, maximum)	48.0 (18, 80)	48.0 (20, 74)	48.0 (18, 80)
Gender			
N	928	193	1121
Male, n (%)	89 (9.6)	19 (9.8)	108 (9.6)
Female, n (%)	839 (90.4)	174 (90.2)	1013 (90.4)
Weight (kg)			
N	925	193	1118
Mean±SD	77.41±15.08	70.95±13.5	76.30±14.94
Median (minimum, maximum)	76.50 (41.6, 123.4)	70.00 (47.0, 117.8)	75.05 (41.6, 123.4)
BMI (kg/m^2)			
N	925	193	1118
Mean±SD	28.39±4.70	26.28±4.41	28.02±4.72
Median (minimum, maximum)	28.30 (15.4, 42.6)	25.8 (18.1, 38.5)	27.90 (15.4, 42.6)
BMI Categories			
N	928	193	1121
<30, n (%)	566 (61.2)	155 (80.3)	721 (64.5)
≥30, n (%)	359 (38.8)	38 (19.7)	397 (35.5)
Time since first fibromyalgia symptoms (years)			
N	915	185	1100
Mean±SD	9.62±8.70	10.02±8.22	9.69±8.62
Median (minimum, maximum)	7.0 (0, 49)	8.0 (0, 51)	7.0 (0, 51)
Time since first fibromyalgia symptoms – categories			
N	915	185	1100
<5 years, n (%)	302 (33.0)	53 (28.6)	355 (32.3)
≥5 years, n (%)	613 (67.0)	132 (71.4)	745 (67.7)
Time since first fibromyalgia diagnosis- (years)			
N	928	193	1121
Mean±SD	5.68±6.54	3.99±4.01	5.39±6.21
Median (minimum, maximum)	3.0 (0, 48)	3.0 (0,24)	3.0 (0, 48)

BMI= Body Mass Index, EU=European Union, SD=standard deviation, US=United States, VAS=visual analog scale
Source: RSI Table 2.1, 2.2

Table 6

	All US Subjects N=928	All EU Subjects N=193	All Subjects Overall N=1121
Baseline characteristics for efficacy endpoints			
Use of non-pharmacologic treatment n (%)	N=928	N=193	N=1121
Yes	362 (39.0)	48 (24.9)	410 (36.6)
No	566 (61.0)	145 (75.1)	711 (63.4)
Disease severity n (%)	N=928	N=193	N=1121
Moderately ill or less severe	581 (62.7)	72 (37.3)	653 (58.3)
Markedly ill or more severe	346 (37.3)	121 (62.7)	467 (41.7)
Pain VAS	N=928	N=193	N=1121
Mean±SD	71.26±13.01	74.60±13.56	71.83±13.16
Pain VAS category n (%)	N=928	N=193	N=1121
VAS <70mm	446 (48.1)	75 (38.9)	521 (46.5)
VAS ≥70mm	482 (51.9)	118 (61.1)	600 (53.5)
Fatigue VAS	N=928	N=193	N=1121
Mean±SD	72.70±14.30	73.48±17.44	72.84±14.89
Fatigue VAS category n (%)	N=928	N=193	N=1121
VAS <70mm	386 (41.6)	68 (35.2)	454 (40.5)
VAS ≥70mm	542 (58.4)	125 (64.8)	667 (59.5)
FIQ total score	N=928	N=192	N=1120
Mean±SD	62.08±13.89	66.26±14.76	62.79±14.12
FIQ category n (%)	N=928	N=192	N=1120
FIQ <59	374 (40.3)	55 (28.6)	429 (38.3)
FIQ ≥59	554 (59.7)	137 (71.4)	691 (61.7)
FOSQ total score	N=908	N=173	N=1081
Mean±SD	13.70±3.69	13.14±3.81	13.61±3.71
FOSQ category n (%)	N=908	N=173	N=1081
FOSQ <15	554 (61.0)	114 (65.9)	668 (61.8)
FOSQ ≥15	354 (39.0)	59 (34.1)	413 (38.2)
Jenkins Sleep Scale total score	N=908	N=172	N=1080
Mean±SD	15.19±4.40	14.88±4.69	15.14±4.45
Jenkins category n (%)	N=908	N=172	N=1080
Jenkins <16	390 (43.0)	80 (46.5)	470 (43.5)
Jenkins ≥16	518 (57.0)	92 (53.5)	610 (56.5)
Depression score BDI-II	N=927	N=191	N=1118
Mean±SD	10.66±8.36	16.32±9.58	11.63±8.84

Table 7

	All US Subjects N=928	All EU Subjects N=193	All Subjects Overall N=1121
BDI-II category n (%)	N=927	N=191	N=1118
Minimal (0-13)	652 (70.3)	81 (42.4)	733 (65.6)
Mild (14-19)	149 (16.1)	50 (26.2)	199 (17.8)
Moderate (20-28)	91 (9.8)	41 (21.5)	132 (11.8)
Severe (29-63)	35 (3.8)	19 (9.9)	54 (4.8)

BDI-II=Beck's Depression Inventory, EU=European Union, FIQ=Fibromyalgia Impact Questionnaire, FOSQ=Functional Outcomes of Sleep Questionnaire, SD=standard deviation, US=United States, VAS=visual analog scale

Source: Source: RSI Table 2.1, 2.2

Number analysed

These are presented in Tables 8 and 9.

Table 8 Analysis populations for study 06-008:

Table 6. Analysis Populations, ITT Population

	Placebo n (%)	Xyrem 4.5 g n (%)	Xyrem 6 g n (%)	Total n (%)
No. Subjects in ITT Population	183	182	183	548
No. Subjects in All-Treated Population	183 (100.0)	182 (100.0)	182 (99.5)	547 (99.8)
No. Subjects in PP Population	107 (58.5)	108 (59.3)	99 (54.1)	314 (57.3)
No. Subjects Excluded from PP Population	76 (41.5)	74 (40.7)	84 (45.9)	234 (42.7)
Did not complete study per protocol	72 (39.3)	63 (34.6)	79 (43.2)	214 (39.1)
Did not receive study medication	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Did not meet eligibility criteria	2 (1.1)	3 (1.6)	2 (1.1)	7 (1.3)
Received excluded medications	4 (2.2)	4 (2.2)	4 (2.2)	12 (2.2)
Diary compliance <70%	13 (7.1)	15 (8.2)	24 (13.1)	52 (9.5)
Study medication compliance <60%	6 (3.3)	8 (4.4)	16 (8.7)	30 (5.5)

ITT=intent-to-treat, PP=per-protocol

Note: Percentages are based on number of subjects in the ITT population. A subject may be included in more than one category (reason for exclusion from PP population). Therefore, the category counts and percentages may not add up to the total counts.

Note: Category of "did not meet eligibility criteria" refers to eligibility criteria for inclusion in the PP population. Enrollment criteria and eligibility criteria for the PP population overlap, but are not identical.

Table 9 Analysis populations for study 06-009:

Table 8. Analysis Populations, ITT Population

	Placebo n (%)	Xyrem 4.5 g n (%)	Xyrem 6 g n (%)	Total n (%)
No. Subjects in ITT Population	188	195	190	573
No. Subjects in All-Treated Population	188 (100.0)	194 (99.5)	189 (99.5)	571 (99.7)
No. Subjects in PP Population	116 (61.7)	114 (58.5)	98 (51.6)	328 (57.2)
No. Subjects Excluded from PP Population	72 (38.3)	81 (41.5)	92 (48.4)	245 (42.8)
Did not complete study per protocol	57 (30.3)	66 (33.8)	74 (38.9)	197 (34.4)
Did not receive study medication	0 (0.0)	1 (0.5)	1 (0.5)	2 (0.3)
Did not meet eligibility criteria	4 (2.1)	3 (1.5)	5 (2.6)	12 (2.1)
Received excluded medications	8 (4.3)	5 (2.6)	7 (3.7)	20 (3.5)
Diary compliance <70%	18 (9.6)	17 (8.7)	19 (10.0)	54 (9.4)
Study medication compliance <60%	11 (5.9)	19 (9.7)	11 (5.8)	41 (7.2)
Cross-treated*	2 (1.1)	0 (0.0)	0 (0.0)	2 (0.3)
Received incorrect dose after run-in	4 (2.1)	5 (2.6)	6 (3.2)	15 (2.6)

ITT=intent-to-treat, PP=per-protocol

*Cross-treated were subjects who were randomized to placebo but were dispensed at least one bottle or Xyrem treatment and those randomized to Xyrem treatment who were dispensed at least one bottle of placebo.

Outcomes and estimation

Results of the co-primary endpoints together with secondary endpoints are shown in Table 10:

Table 10

	Study 06-008				Study 06-009			
Endpoint/Domain	Placebo	Xyrem 4.5 g	Xyrem 6 g	Overall p-value	Placebo	Xyrem 4.5 g	Xyrem 6 g	Overall p-value
Pain VAS using BOCF	**N=183**	**N=182**	**N=183**		**N=188**	**N=195**	**N=190**	
Responder (≥30% reduction), n (%)	50 (27.3)	84 (46.2)	72 (39.3)	<0.001	38 (20.2)	69 (35.4)	67 (35.3)	0.001
p-value vs. placebo	N/A	<0.001	0.015		N/A	<0.001	0.001	
Pain VAS using LOCF	**N=176**	**N=179**	**N=171**		**N=183**	**N=193**	**N=183**	
Responder (≥30% reduction), n (%)	62 (35.2)	97 (54.2)	100 (58.5)	<0.001	49 (26.8)	81 (42.0)	94 (51.4)	<0.001
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.002	<0.001	
FIQ total score using BOCF	**N=183**	**N=182**	**N=183**		**N=188**	**N=195**	**N=190**	
Responder (≥30% reduction), n (%)	55 (30.1)	84 (46.2)	72 (39.3)	0.007	41 (21.8)	77 (39.5)	76 (40.0)	<0.001
p-value vs. placebo	N/A	0.002	0.062		N/A	<0.001	<0.001	
FIQ total score using LOCF	**N=178**	**N=179**	**N=175**		**N=181**	**N=190**	**N=185**	
Responder (≥30% reduction), n (%)	69 (38.8)	99 (55.3)	98 (56.0)	0.001	54 (29.8)	95 (50.0)	102 (55.1)	<0.001
p-value vs. placebo	N/A	0.002	0.001		N/A	<0.001	<0.001	
Jenkins Sleep Scale using BOCF	**N=183**	**N=182**	**N=183**		**N=188**	**N=195**	**N=190**	
Change from baseline, LS Mean (SE)	-2.5 (0.43)	-4.7 (0.42)	-4.5 (0.42)	<0.001	-2.1 (0.36)	-3.4 (0.36)	-4.2 (0.36)	<0.001
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.007	<0.001	
Jenkins Sleep Scale using LOCF	**N=169**	**N=167**	**N=172**		**N=166**	**N=176**	**N=174**	
Change from baseline, LS Mean (SE)	-2.9 (0.48)	-6.1 (0.47)	-6.2 (0.46)	<0.001	-2.9 (0.42)	-4.9 (0.41)	-5.9 (0.41)	<0.001
p-value vs. placebo	N/A	<0.001	<0.001		N/A	<0.001	<0.001	
FOSQ total score using BOCF	**N=183**	**N=182**	**N=183**		**N=188**	**N=195**	**N=190**	
Change from baseline, LS Mean (SE)	1.21 (0.235)	2.00 (0.230)	1.81 (0.230)	0.038	0.70 (0.214)	1.71 (0.212)	1.54 (0.212)	0.001
p-value vs. placebo	N/A	0.015	0.060		N/A	<0.001	0.005	
FOSQ total score using LOCF	**N=166**	**N=165**	**N=164**		**N=163**	**N=173**	**N=173**	
Change from baseline, LS Mean (SE)	1.63 (0.289)	2.28 (0.281)	2.32 (0.282)	0.146	0.98 (0.276)	2.10 (0.268)	2.09 (0.268)	0.003
p-value vs. placebo	N/A	0.101	0.079		N/A	0.003	0.004	

	Study 06-008				Study 06-009			
Endpoint/Domain	Placebo	Xyrem 4.5 g	Xyrem 6 g	Overall p-value	Placebo	Xyrem 4.5 g	Xyrem 6 g	Overall p-value
Fatigue VAS using BOCF	N=183	N=182	N=183		N=188	N=195	N=190	
Change from baseline, LS Mean (SE)	-15.07 (2.053)	-24.01 (2.010)	-20.96 (2.011)	0.006	-11.86 (1.927)	-20.18 (1.934)	-19.26 (1.899)	0.004
p-value vs. placebo	N/A	0.002	0.035		N/A	0.002	0.007	
Fatigue VAS using LOCF	**N=176**	**N=179**	**N=171**		**N=183**	**N=193**	**N=183**	
Change from baseline, LS Mean (SE)	-17.57 (2.167)	-27.94 (2.084)	-30.02 (2.144)	<0.001	-13.65 (1.939)	-22.96 (1.908)	-26.22 (1.922)	<0.001
p-value vs. placebo	N/A	<0.001	<0.001		N/A	<0.001	<0.001	
PGI-c using BOCF	**N=183**	**N=182**	**N=183**		**N=188**	**N=195**	**N=190**	
Achieving "very much better" or "much better" at Week 14, n (%)	41 (22.4)	73 (40.1)	61 (33.3)	0.001	26 (13.8)	51 (26.2)	57 (30.0)	<0.001
p-value vs. placebo	N/A	<0.001	0.020		N/A	0.003	<0.001	
PGI-c using LOCF	**N=173**	**N=174**	**N=174**		**N=181**	**N=190**	**N=179**	
Achieving "very much better" or "much better" at Week 14, n (%)	47 (27.2)	84 (48.3)	79 (45.4)	<0.001	29 (16.0)	61 (32.1)	71 (39.7)	<0.001
p-value vs. placebo	N/A	<0.001	<0.001		N/A	<0.001	<0.001	
SF-36 PCS using BOCF	**N=183**	**N=182**	**N=183**		**N=188**	**N=195**	**N=190**	
Change from baseline, LS Mean (SE)	3.48 (0.611)	6.01 (0.599)	5.95 (0.599)	0.003	2.58 (0.569)	4.93 (0.564)	4.83 (0.563)	0.004
p-value vs. placebo	N/A	0.003	0.003		N/A	0.003	0.005	
SF-36 PCS using LOCF	**N=160**	**N=162**	**N=160**		**N=161**	**N=169**	**N=168**	
Change from baseline, LS Mean (SE)	4.96 (0.709)	7.81 (0.684)	8.82 (0.690)	<0.001	3.57 (0.683)	6.42 (0.667)	6.34 (0.668)	0.003
p-value vs. placebo	N/A	0.003	<0.001		N/A	0.002	0.003	

BOCF=baseline observation carried forward, FIQ= Fibromyalgia Impact Questionnaire, FOSQ=Functional Outcomes of Sleep Questionnaire, ITT=intent-to-treat, LOCF=last observation carried forward, LS=least squares, N/A=not applicable, PGI-c=Patient Global Impression of Change, SE=standard error, SF-36=Short Form-36, VAS=visual analog scale

Note: Baseline was the average of all available daily averages during the last week of the baseline period. For each post-baseline week, the average of all available daily averages for that week was used. Analysis results for the Pain VAS and FIQ response are based on chi-square tests. The p-values for the Composite Responses were obtained from a chi-square test.

Results from the PP analyses were consistent with the results from the ITT analyses: in study 06-008, results from patients with ≥ 30 % reduction from baseline to week 14 in Pain VAS are 77/108 (71.3 %) and 68/99 (68.7%), both with p<0.001. The corresponding values for FIQ total score were 75/108 (69.4%) and 68/99 (86.7%) with p=0.005 and 0.008, respectively. In study 06-009, results from patients with ≥30 % reduction from baseline to week 14 in Pain VAS were 63/114 (55.3%) and 56/98 (57.1%), both with p<0.001. The corresponding values for FIQ total score were 70/114 (61.4%) and 62/98 (63.3%), both with p<0.001.

Analysis performed across trials (pooled analyses and meta-analyses)

Effects of demographic characteristics, regions (US versus EU) and other characteristics (non-pharmacological treatment, use of rescue medication) were performed using pooled data from studies 06-008 and 06-009.

Effects of age, gender and race

Subjects ≥65 years (n=45) and subjects <65 years (n=1076) had numerically greater proportions of responders in pain VAS and FIQ total score in both of the Xyrem groups compared to the placebo group. The p-values for the <65 years subgroup were <0.001 for these data for both Xyrem groups compared to placebo.

Male subjects (n=108) and female subjects (n=1013) had numerically greater proportions of responders in pain VAS and FIQ total score in both of the Xyrem groups compared to the placebo group. The p-values for females were <0.001 for these data for both Xyrem groups compared to placebo.

Non-Caucasian subjects (n=99) had numerically greater proportions of responders in pain VAS and FIQ total score than the Caucasian subjects (n=1022) at both Xyrem doses.

Effect of the non pharmacological treatment, use of rescue medication

In both dosing groups a statistically significant difference was observed between active therapy and placebo in the response, independently if non-pharmacological treatment was used or not.

Use of rescue medication was clearly lower in patients receiving Xyrem than in patients receiving placebo in the overall phase 3 population (20-30% less).

Effect of region

This is presented in Tables 11 and 12.

Table 11

	US				EU			
	Placebo	Xyrem 4.5 g	Xyrem 6 g	Overall p-value	Placebo	Xyrem 4.5 g	Xyrem 6 g	Overall p-value
Pain VAS using BOCF, n (%)	**N=307**	**N=305**	**N=316**		**N=64**	**N=72**	**N=57**	
Responder (≥30% reduction)	73 (23.8)	131 (43.0)	121 (38.3)	<0.001	15 (23.4)	22 (30.6)	18 (31.6)	0.543
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.352	0.316	
Responder (≥50% reduction)	49 (16.0)	105 (34.4)	93 (29.4)	<0.001	7 (10.9)	14 (19.4)	13 (22.8)	0.203
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.171	0.079	
Responder (≥60% reduction)	39 (12.7)	82 (26.9)	77 (24.4)	<0.001	4 (6.3)	12 (16.7)	9 (15.8)	0.147
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.060	0.091	
Responder (≥70% reduction)	30 (9.8)	64 (21.0)	66 (20.9)	<0.001	4 (6.3)	8 (11.1)	6 (10.5)	0.581
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.318	0.394	
Pain VAS using LOCF, n (%)	**N=295**	**N=301**	**N=300**		**N=64**	**N=71**	**N=54**	
Responder (≥30% reduction)	93 (31.5)	153 (50.8)	174 (58.0)	<0.001	18 (28.1)	25 (35.2)	20 (37.0)	0.541
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.378	0.302	
Responder (≥50% reduction)	59 (20.0)	117 (38.9)	128 (42.7)	<0.001	9 (14.1)	17 (23.9)	15 (27.8)	0.167
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.146	0.065	
Responder (≥60% reduction)	46 (15.6)	91 (30.2)	106 (35.3)	<0.001	4 (6.3)	13 (18.3)	11 (20.4)	0.057
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.035	0.022	
Responder (≥70% reduction)	35 (11.9)	67 (22.3)	87 (29.0)	<0.001	4 (6.3)	9 (12.7)	7 (13.0)	0.383
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.206	0.211	

BOCF=baseline observation carried forward, ITT=intent-to-treat, LOCF=last observation carried forward, N/A=not applicable, VAS=visual analog scale
Note: Baseline is the average of all available daily averages during the last week of the baseline period. For each post-baseline week, the average of all available daily averages for that week is used. Pain VAS scale is from 0 (no pain) to 100 (worst imaginable pain). Analysis results are based on chi-square tests.
Source: ISE, Table 2.3.2

Table 12

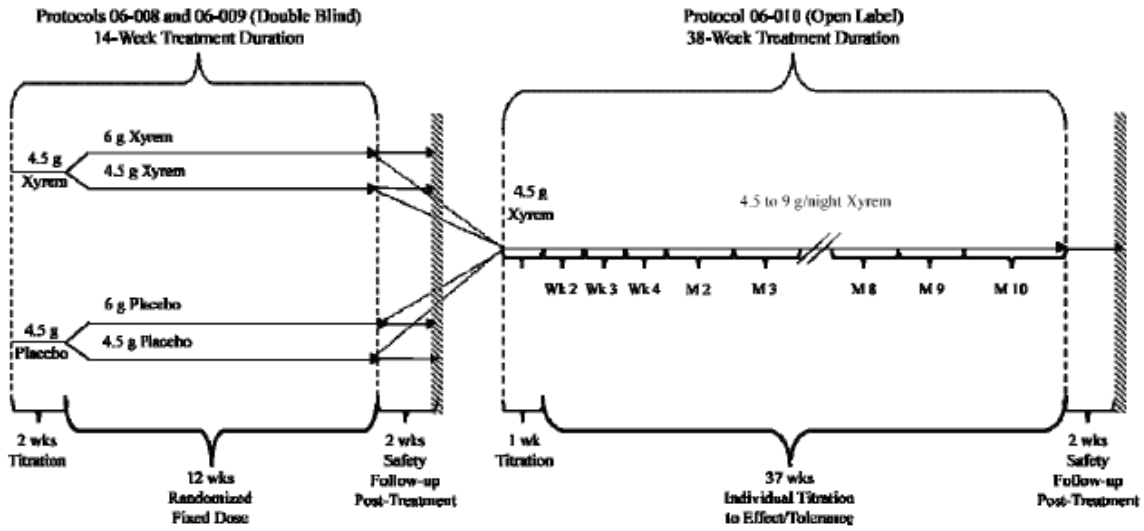
	US				EU			
	Placebo	Xyrem 4.5 g	Xyrem 6 g	Overall p-value	Placebo	Xyrem 4.5 g	Xyrem 6 g	Overall p-value
FIQ Total Score using BOCF, n (%)	**N=307**	**N=305**	**N=316**		**N=64**	**N=72**	**N=57**	
Responder (≥30% reduction)	79 (25.7)	138 (45.2)	126 (39.9)	<0.001	17 (26.6)	23 (31.9)	22 (38.6)	0.367
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.492	0.157	
Responder (≥50% reduction)	48 (15.6)	90 (29.5)	91 (28.8)	<0.001	5 (7.8)	16 (22.2)	13 (22.8)	0.042
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.020	0.021	
Responder (≥60% reduction)	37 (12.1)	73 (23.9)	74 (23.4)	<0.001	3 (4.7)	13 (18.1)	9 (15.8)	0.051
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.016	0.041	
Responder (≥70% reduction)	26 (8.5)	57 (18.7)	56 (17.7)	<0.001	1 (1.6)	12 (16.7)	6 (10.5)	0.013
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.003	0.035	
FIQ Total Score using LOCF, n (%)	**N=297**	**N=300**	**N=305**		**N=62**	**N=69**	**N=55**	
Responder (≥30% reduction)	102 (34.3)	166 (55.3)	174 (57.0)	<0.001	21 (33.9)	28 (40.6)	26 (47.3)	0.336
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.428	0.140	
Responder (≥50% reduction)	60 (20.2)	103 (34.3)	118 (38.7)	<0.001	6 (9.7)	18 (26.1)	16 (29.1)	0.020
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.015	0.007	
Responder (≥60% reduction)	45 (15.2)	83 (27.7)	97 (31.8)	<0.001	3 (4.8)	14 (20.3)	10 (18.2)	0.028
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.009	0.022	
Responder (≥70% reduction)	31 (10.4)	64 (21.3)	68 (22.3)	<0.001	1 (1.6)	13 (18.8)	6 (10.9)	0.006
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.001	0.034	

BOCF=baseline observation carried forward, FIQ=Fibromyalgia Impact Questionnaire, ITT=intent-to-treat, LOCF=last observation carried forward, N/A=not applicable
Note: Baseline is the last value collected during the baseline period. Sum of the normalized subscale scores is used, with 0 indicating no impairment and 100 indicating maximum impairment. Analysis results are based on chi-square tests.
Source: ISE, Table 3.3.2

3.4.2.1. Long term study

Study **06-010** was an open label, 38 week study designed to provide additional data on long term of safety and efficacy and to assess long term effects on quality of life (QoL). Subjects who completed one of the short term Phase III controlled studies (either Study 06-008 or 06-009) were eligible to enrol in this open-label, continuation study to assess the long-term safety and efficacy of Xyrem (see Figure 2).

Figure 2



M=month, Wk(s)=week(s)

Note: In Study 06-008, both active treatments contained sodium oxybate at the same concentration; the two doses were achieved by adjusting the volume of active drug solution administered. In Study 06-008, placebo was administered in two different volumes to match the volumes of active treatments. In Study 06-009, the two active treatments contained sodium oxybate at different concentrations, enabling administration of the two doses with the same volume of oral solution. In Study 06-009, placebo was administered in one volume, matching the two active treatments.

Note: In addition to the visits outlined for all sites in the schematic above, for sites in Germany, visits were added at Weeks 6, 10, and 14 and telephone contacts were added every 2 weeks (per Federal Institute for Drugs and Medical Devices feedback [BfArM]). For sites in France, visits were added at Weeks 6, 10, 14, 18, 22, 26, 30, and 34 to allow study drug dispensing in compliance with French law.

Study participants

Main inclusion criteria

- Subjects completed Study 06-008 or 06-009 within the past 7 days
- Subjects were able, in the opinion of the investigator, to take Xyrem for approximately 9.5 months and complete all tests and visits described in the protocol
- Subjects must have been willing to refrain from the use of any medications, herbal remedies, and/or devices being used to treat his/her fibromyalgia symptoms until trial completion. Such medications included but were not limited to: opiates, benzodiazepines, muscle relaxants, cyclobenzaprine, anticonvulsants, antidepressants, dopamine agonists, and/or tramadol.
- Subjects agreed to use only ibuprofen (up to 1200 mg/day), naproxen (up to 660 mg/day), or acetaminophen (paracetamol) (up to 4 g/day) as rescue pain medication (Simultaneous use of acetaminophen and either ibuprofen or naproxen was permitted. Simultaneous use of ibuprofen and naproxen was not allowed on the same day during the study.)
- Subjects were willing to not drink alcohol for the duration of the trial

Main exclusion criteria

- Subjects experienced any serious adverse event that was related to study drug during participation in Study 06-008 or 06-009
- Subjects in the opinion of the investigator, experienced an adverse event in Protocol 06-008 or 06-009 that may have prevented him/her from safely participating in and completing the current study
- Subjects had any new condition, physical examination finding, or laboratory test result that, in the opinion of the investigator, could have impacted subject safety, interfered with the evaluation of the subject, or affected the subject's compliance with the protocol requirements
- Subjects developed a current primary diagnosis of major depressive disorder, psychotic disorder, and/or bipolar disorder (Diagnostic and Statistical Manual of Mental Disorders IV, Text Revision [DSM-IV-TR])
- Subjects were in the opinion of the investigator, a suicidal or homicidal risk; or the subject scored ≥1 on Question 9 of the Beck Depression Inventory-II (BDI-II) at Visit 1 or any time during Study 06-008 or 06-009
- Subjects had a positive urine drug screen for benzodiazepines or other drugs of abuse and/or a positive alcohol test and/or a history of substance abuse
- Subjects were diagnosed with sleep apnea and was not currently on stable continuous positive airway pressure (CPAP) therapy, or the investigator judged that the subject's risk of sleep apnea had increased during the double-blind Study 06-008 or 06-009

Outcomes/Endpoints

A single primary efficacy endpoint was specified in the analysis plan (the Pain Severity Response from the pain VAS) defined as the proportion of subjects had at least a 30% reduction in overall pain VAS from the prior study baseline to study endpoint.

Secondary efficacy endpoints included: pain severity (pain VAS as a continuous variable); Functionality Response, defined as the proportion of subjects had at least a 30% reduction in Fibromyalgia Impact Questionnaire (FIQ) total score from the prior study baseline to study endpoint; FIQ total score as a continuous variable; fatigue (fatigue VAS as a continuous variable); Patient Global Impression of Change (PGI-c, analyzed as an ordinal categorical and binary outcome variable); Short Form-36 (SF-36) Physical Component Summary (PCS), Mental Component Summary (MCS), and domain scores; Clinical Global Impression of Severity (CGI-s), Clinical Global Impression of Change (CGI-c, analyzed as an ordinal categorical and binary outcome variable); Tender Point Count and Index; Manual Tender Point Survey (MTPS) Site Scores; Functional Outcomes of Sleep Questionnaire (FOSQ) total score and subscale scores; pain by rescue medication use; Fibromyalgia Pain Composite Response; and Fibromyalgia Syndrome Composite Response.

Safety was assessed by the incidence of adverse events, study drug exposure, and concomitant medication usage; and by changes in clinical laboratory tests, vital sign measurements, electrocardiograms, and physical examination findings. The Beck Depression Inventory-II (BDI-II) and Mini International Neuropsychiatric Interview (MINI) were used to assess depression and suicidality.

Sample size

All subjects who completed Studies 06-008 or 06-009 were eligible for enrollment in this study. Enrolment was planned to achieve the following minimum targets for combined-study exposure to

active treatment (i.e., Studies 06-008 or 06-009, and Study 06-010): exposure of 6 months in at least 100 subjects and exposure of 1 year in at least 50 subjects. Because the rollover rate from the prior studies was higher than planned.

Per protocol, the interim report available for this assessment was prepared when 100 subjects with at least 6 months' and 50 subjects with at least 1 year's combined exposure to Xyrem (i.e., in Studies 06-008 or 06-009 and the current study) had been accrued. A total of 246 subjects (245 treated) were analyzed for the report available for this assessment.

Randomisation, Blinding (masking)

There was no randomization in this study. This was an open-label study.

Statistical methods

Each efficacy endpoint was analyzed using observed data in the all-treated population. Descriptive analyses were performed by time points assessed, summarized by final dose and, for some endpoints, by prior study treatment. Changes were analyzed relative to baseline at the beginning of the previous double-blind, placebo-controlled studies. Study endpoint in 06-010 was defined as the last available data, whether obtained at study completion or early discontinuation. In addition, statistical analyses of pain VAS and FIQ total score responders by gender were conducted. Safety data were summarized using descriptive statistics in the all-treated population. Changes were analyzed relative to baseline at the beginning of the previous double-blind, placebo-controlled studies. Treatment-emergent adverse events (TEAEs) were summarized by the last dose taken at the time of event onset. TEAEs were also summarized by time of onset and analyzed by gender. For vital signs and laboratory test data, the Study 06-010 endpoint was defined as the last value collected during the study, before the safety follow-up visit.

Results

With the initial submission, the MAH only submitted an interim analysis. The cut-off for the interim analysis was 10 July 2009, including subjects had completed or discontinued the study up to 02 December 2008. All patients in the interim analysis data set except one were US. Patients treated with placebo in the lead-in study have a higher withdrawal rate, particularly due to adverse events, compared to patients who were treated with Xyrem in the lead-in study.

During the evaluation, the MAH provided the final study report with the complete analysis. Results are summarised below.

Participant flows/Analysis populations

Disposition of Subjects in the long term study is presented in Table 13.

Table 13. Disposition of Subjects by Previous Randomized Treatment and Overall in Study 06-010

	Placebo n (%)	Xyrem 4.5 g n (%)	Xyrem 6 g n (%)	Total n (%)
Subjects Treated	186	199	175	560
Subjects Completed	95 (51.1)	122 (61.3)	102 (58.3)	319 (57.0)
Subjects Discontinued	91 (48.9)	77 (38.7)	73 (41.7)	241 (43.0)
Adverse event(s)	51 (27.4)	40 (20.1)	38 (21.7)	129 (23.0)
Death	0	0	0	0
Withdrawal of consent	11 (5.9)	12 (6.0)	13 (7.4)	36 (6.4)
Lost to follow-up	4 (2.2)	6 (3.0)	5 (2.9)	15 (2.7)
Lack of study drug efficacy	16 (8.6)	14 (7.0)	8 (4.6)	38 (6.8)
Sponsor decision	3 (1.6)	0	0	3 (0.5)
Investigator decision	2 (1.1)	1 (0.5)	5 (2.9)	8 (1.4)
Protocol deviation/violation	2 (1.1)	4 (2.0)	1 (0.6)	7 (1.3)
Other	2 (1.1)	0	3 (1.7)	5 (0.9)

Note: Primary reasons for discontinuation are listed. Percentages are based on the number of subjects treated.
Source: RSI Table 1.5 and CSR 06-010, Table 15.1.1.3

Baseline data

These were similar to the short term phase III studies.

Outcomes/Endpoints

Primary efficacy results are presented in Tables 14 and 15.

Table 14 Pain Severity Response from the pain VAS defined as the proportion of subjects had at least a 30% reduction in overall pain VAS from the prior study baseline to study endpoint.

≥30% Reduction in Pain VAS at Study Endpoint	Xyrem Final Dose				Total n (%)
	4.5 g n (%)	6 g n (%)	7.5 g n (%)	9 g n (%)	
Number of subjects	165	187	114	81	**551**
Yes	112 (67.9)	140 (74.9)	67 (58.8)	59 (72.8)	**379 (68.8)**
No	53 (32.1)	47 (25.1)	47 (41.2)	22 (27.2)	**172 (31.2)**

VAS=visual analog scale

Main secondary efficacy results are presented in Figures 3 and 4.

Figure 3 Proportion of pain VAS responders (≥30% reduction in pain VAS from baseline) by prior study treatment over time

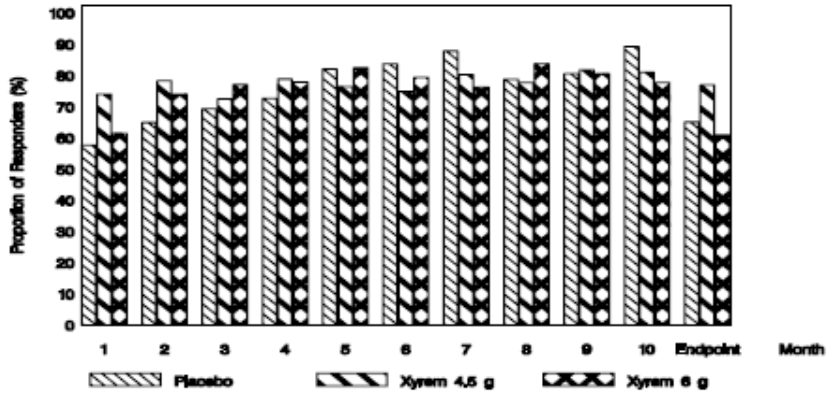
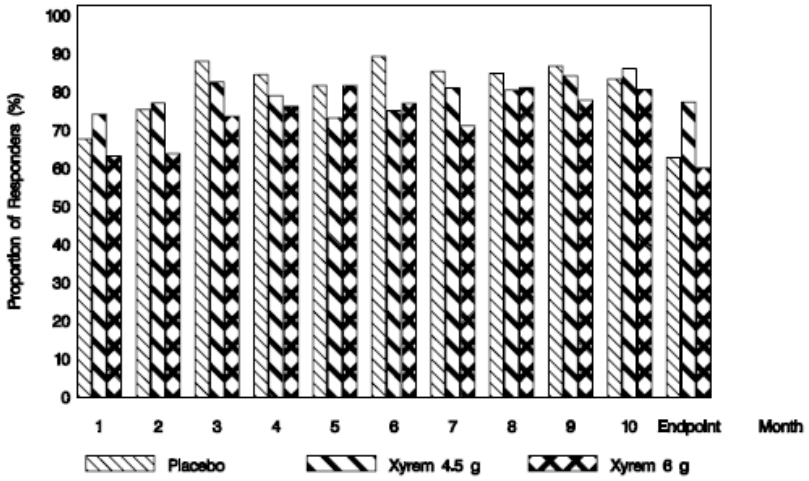


Table 15 Functionality Response, defined as the proportion of subjects had at least a 30% reduction in Fibromyalgia Impact Questionnaire (FIQ) total score from the prior study baseline to study endpoint.

≥30% Reduction in FIQ Total Score at Study Endpoint	Xyrem Final Dose 4.5 g n (%)	6 g n (%)	7.5 g n (%)	9 g n (%)	Total n (%)
Number of subjects	168	187	114	81	**554**
Yes	113 (67.3)	142 (75.9)	67 (58.8)	61 (75.3)	**386 (69.7)**
No	55 (32.7)	45 (24.1)	47 (41.2)	20 (24.7)	**168 (30.3)**

FIQ=Fibromyalgia Impact Questionnaire

Figure 4 Proportion of FIQ responders (≥30% reduction in FIQ from Baseline) by prior study treatment over time



3.4.2.2. Ancillary analyses

Effect on sleep pattern over time

At the CHMP request, the MAH provided data effect on sleep over time. In study OMC-SXB-26, results indicated that there was an improved sleep with Xyrem treatment (Xyrem 4.5 and 6 g/night) in

patients with fibromyalgia. Subjective sleep assessments revealed significant improvement in daytime sleepiness, sleep quality, and daytime functioning. Improvement was reported as early as 2 weeks after initiation of treatment, with effects maintained after 8 weeks of treatment compared to baseline. The earliest effects on objective sleep assessment were observed within two weeks of starting treatment, and effects on SWS and WASO were maintained throughout treatment. Both Xyrem doses decreased REM sleep compared to placebo. Xyrem 6 g/night had a profound impact on increasing Stage 3 & 4 sleep and non REM sleep and decreasing WASO. Moreover, these measures correlated well with improvement of subjective sleep quality. Unlike conventional hypnotics, Xyrem had no significant impact on total sleep time and sleep latency, as compared to placebo. In study 06-010, data from the FIQ Tired Upon Awakening Subscale revealed an early onset of effect with a consistent and sustained improvement of sleep quality, and support maintenance of the effect of Xyrem on sleep patterns for up to 52 weeks. However, these results should be interpreted cautiously due to uncontrolled setting and limitation of the subjective measures used to evaluate quality of sleep.

Extrapolation of US data to the EU population

Further information was submitted by the MAH to support extrapolation of the results observed in the US to the EU population including efficacy subgroup analyses. These are presented in Tables 16 and 17. Research findings from some authors (*de Souza et al, 2009*) suggested that the level of depression may indeed influence the treatment outcome and the perception of pain and other symptoms in fibromyalgia patients and that concomitant depressive symptoms did require treatment.

Efficacy subgroup analyses

Table 16

	US			EU		
	Placebo	Xyrem 4.5 g	Xyrem 6 g	Placebo	Xyrem 4.5 g	Xyrem 6 g
ALL SUBJECTS						
Pain VAS, n (%)	**N=307**	**N=305**	**N=316**	**N=64**	**N=72**	**N=57**
Responder (≥30% reduction)	73 (23.8)	131 (43.0)	121 (38.3)	15 (23.4)	22 (30.6)	18 (31.6)
Treatment difference to placebo (%)		19.2	14.5		7.2	8.2
p-value vs. placebo	N/A	<0.001	<0.001	N/A	0.352	0.316
FIQ Total Score, n (%)	**N=307**	**N=305**	**N=316**	**N=64**	**N=72**	**N=57**
Responder (≥30% reduction)	79 (25.7)	138 (45.2)	126 (39.9)	17 (26.6)	23 (31.9)	22 (38.6)
Treatment difference to placebo (%)		19.5	14.2		5.3	12
p-value vs. placebo	N/A	<0.001	<0.001	N/A	0.492	0.157
WITHOUT SUBJECTS WITH MODERATE OR SEVERE DEPRESSION (BDI ≥20)						
Pain VAS, n (%)	**N=261**	**N=268**	**N=272**	**N=42**	**N=47**	**N=42**
Responder (≥30% reduction)	67 (25.7)	111 (41.4)	106 (39.0)	9 (21.4)	19 (40.4)	12 (28.6)
Treatment difference to placebo (%)		15.7	13.3		19	7.2
p-value vs. placebo	N/A	<0.001	0.001	N/A	0.054	0.450
FIQ Total Score, n (%)	**N=261**	**N=268**	**N=272**	**N=42**	**N=47**	**N=42**
Responder (≥30% reduction)	71 (27.2)	121 (45.1)	110 (40.4)	13 (31.0)	20 (42.6)	15 (35.7)
Treatment difference to placebo (%)		17.9	13.2		11.6	4.7
p-value vs. placebo	N/A	<0.001	0.001	N/A	0.258	0.643
ALL SUBJECTS						
Pain VAS, n (%)	**N=307**	**N=305**	**N=316**	**N=64**	**N=72**	**N=57**
Responder (≥50% reduction)	49 (16.0)	105 (34.4)	93 (29.4)	7 (10.9)	14 (19.4)	13 (22.8)
Treatment difference to placebo (%)		18.4	13.4		8.5	11.9

Table 17

	US			EU		
	Placebo	Xyrem 4.5 g	Xyrem 6 g	Placebo	Xyrem 4.5 g	Xyrem 6 g
p-value vs. placebo	N/A	<0.001	<0.001	N/A	0.171	0.079
FIQ Total Score, n (%)	**N=307**	**N=305**	**N=316**	**N=64**	**N=72**	**N=57**
Responder (≥50% reduction)	48 (15.6)	90 (29.5)	91(28.8)	5 (7.8)	16 (22.2)	13 (22.8)
Treatment difference to placebo (%)		13.9	13.2		14.4	15
p-value vs. placebo	N/A	<0.001	<0.001	N/A	0.020	0.021
WITHOUT SUBJECTS WITH MODERATE OR SEVERE DEPRESSION (BDI ≥20)						
Pain VAS, n (%)	**N=261**	**N=268**	**N=272**	**N=42**	**N=47**	**N=42**
Responder (≥50% reduction)	46 (17.6)	87 (32.5)	83 (30.5)	4 (9.5)	13 (27.7)	10 (23.8)
Treatment difference to placebo (%)		14.9	12.9		18.2	14.3
p-value vs. placebo	N/A	<0.001	<0.001	N/A	0.030	0.079
FIQ Total Score, n (%)	**N=261**	**N=268**	**N=272**	**N=42**	**N=47**	**N=42**
Responder (≥50% reduction)	44 (16.9)	78 (29.1)	79 (29.0)	5 (11.9)	14 (29.8)	10 (23.8)
Treatment difference to placebo (%)		12.2	12.1		17.9	11.9
p-value vs. placebo	N/A	<0.001	<0.001	N/A	0.040	0.154

BDI=Beck's Depression Inventory, EU=European Union, FIQ=Fibromyalgia Impact Questionnaire, BOCF=baseline observation carried forward, ITT=intent to treat, US=United States, VAS=visual analog scale

Source: ISE Table 18 and Table 19; RSI Table 3.141, Table 3.142, Table 4.141, and Table 4.142

Rebound effect/Withdrawal Symptoms

Rebound was not specifically evaluated in the studies of fibromyalgia as efficacy endpoints were not assessed after cessation of treatment.

Both epidemiological and laboratory studies have reported that frequent, around-the-clock patterns of gamma-hydroxybutyrate (GHB) administration can produce physical dependence, as evidenced by a withdrawal syndrome (*Abanades et al. 2007*). Physical dependence (characterized by the emergence of withdrawal signs and/or symptoms upon cessation of use) was reported with daily use of illicit GHB at supra-therapeutic doses of 18 to 250 g/day (*Dyer et al. 2001*, *Glasper et al. 2005*). In patients who ingested these high doses of illicit GHB around-the-clock, withdrawal signs and symptoms included psychosis, agitation, tachycardia, hypertension, delirium with auditory and visual hallucinations, diaphoresis, nausea, and vomiting. The onset of these reactions occurred within 1 to 6 hours after the last dose of GHB and lasted 5 to 15 days. One death of a hospitalized patient occurred as the withdrawal symptoms were resolving (*Glasper et al. 2005*). However, there were no adverse events of severe withdrawal symptoms that occurred during any of the Phase 2/3 studies or during the 2-week period after the last dose of study drug in the Phase 3 studies (reflecting data after the final dose in Studies 06-008 or 06-009 for subjects who did not participate in Study 06-010, and after the final dose in Study 06-010), suggesting that withdrawal signs and symptoms were not observed in the population with fibromyalgia.

3.4.3. Discussion on clinical efficacy

Dose response

The Phase 2 study (OMC-SXB-26) provided preliminary evidence for the efficacy of Xyrem 4.5 and 6 g/night. The study was based solely in the US and conducted before the CHMP scientific advice was obtained. Hence, there were significant differences to the subsequent Phase 3 trials: shorter treatment duration, different study population and different primary endpoints. The study statistically failed to show efficacy of Xyrem on the primary endpoint which was a binary composite parameter for the treatment of fibromyalgia syndrome (overall p value=0.052). However, quite consistently, both doses

were superior to placebo with respect to both continuous and categorical (responder) pain and functional endpoints, including the ones used as co-primary endpoints (pain VAS, FIQ total score) in the later Phase 3 trials.

No clear dose-response pattern was observed in this study for the chosen primary analysis instrument in the LOCF analysis. However, in the secondary analyses, the 6 g/night dose seemed slightly better than the 4.5 g/night dose (responders: 41.4 % versus 47.6 % for severity of pain parameter; 48.1% versus 50.8% for FIQ total score) except for the patient global impression of change (PGIc). No clear dose-response pattern was observed from the BOCF results. The CHMP scientific advice to explore lower dose of 3g/night in the fibromyalgia population as possible minimum effective dose was not followed.

To support the dosing regimens used (4.5 g/night or 6 g/night), the MAH argumentation can be summarised as follows:

- Based on the pharmacology of Xyrem and binding affinity studies, it has been estimated that single doses of at least 2 to 3 g (roughly equivalent to the individual divided doses of the 4.5 g and 6 g/night) were required for sodium oxybate to act as an agonist at $GABA_B$ receptors;

- Previous submitted data suggested that 3 g dose was minimally effective in narcolepsy subjects. At 3g/night, change from baseline in the number of cataplexy attacks was not statistically significant in study OMC-GHB-2. Furthermore, a dose-dependent increase in non-REM sleep was observed in study OMC-SXB-15 where 4.5 g dose was found to be minimally effective.

- Polysomnographic (PSG) data in fibromyalgia subjects showed lesser effect on sleep parameters at the 4.5 g/night dose;

- The selection of 4.5 g and 6 g/night doses for the Phase 2 and 3 controlled studies was based on prior results from two clinical studies demonstrating efficacy of 4.5 and 6 g doses of sodium oxybate in fibromyalgia patients (Scharf et al. 1998a, Scharf et al. 2003) and on clinical data and over 7 years of postmarketing experience in narcolepsy subjects;

- A dose relationship for gastro-intestinal related adverse events was observed in study OMC-GHB-2. However, this was not the case for CNS related adverse events suggesting no additional benefit in exploring the lower dose. These AE were considered similar between Xyrem treatment groups (Xyrem 3 g was 47.1%, Xyrem 6 g was 51.5%, and Xyrem 9 g was 54.3%) and were considerably higher compared to placebo (29.4%).

The CHMP did not consider that the proposed dosing regimen (4.5 g or 6 g/night) was adequately justified as it is based on an extrapolation from the population presenting narcolepsy to fibromyalgia patients. Although some evidence has been presented by the MAH suggesting that tolerability in terms of CNS adverse events is not likely to be significantly worse with the 4.5 g/night dose compared to a 3 g/night dose (had this dose been tested in a fibromyalgia population), the CHMP still considered that the minimal effective dose has not been established and that doses lower than 4.5 g/night (e.g. 3 g/night or lower) should have been investigated. During evaluation, the MAH proposed to modify the remove the recommended 6 g/night from the posology for safety reasons (see section 3.5.10)

Short term efficacy

In two randomised controlled Phase 3 pivotal studies (06-008 and 06-009), of which only one (study 06-009) was double-blind (as the intended masking was insufficient in study 06-008), a statistically and clinically significant difference between 2 doses, i.e. 4.5 g and 6 g/night, of Xyrem and placebo was reported except for the 6g dosing regimen in study 06-008 for FIQ total score (p=0.062). The effect was consistent over the primary and co-primary endpoints: the proportions of patients who achieved at least 30 % reduction in pain (VAS) were 27.3% (placebo); 46.2% (4.5g dose); 39.3% (6g

dose) for study 06-008 and 20.2 % (placebo); 35.4% (4.5 g dose); 35.3 % (6g dose) for study 06-009. The proportions of patients who achieved at least 30 % reduction in FIQ total score (functionality response) were 30.1% (placebo); 46.2% (4.5g dose); 39.3% (6g dose) for study 06-008 and 21.8 % (placebo); 39.5% (4.5 g dose); 40.0% (6g dose) for study 06-009. Most of the secondary efficacy results were also consistent. In general, consistent results were also observed for the different statistical analyses (ITT, BOCF and PP) supporting of the robustness of the data. Further LOCF and MMRM analyses confirmed the results and showed a clearer dose response between 4.5 g/night and 6 g/night.

The primary and co-primary endpoints were selected in line with the CHMP scientific advice. The CHMP noted that the endpoints chosen fulfil the OMERACT 9 Fibromyalgia Workshop recommendations to study multiple core domains, including pain, tenderness, fatigue, patient global, multidimensional function, and sleep disturbance in all fibromyalgia treatment clinical studies. Overall, the outcome measures were considered relevant to the indication initially applied for (fibromyalgia).

In these studies, the distribution of the number of patients who discontinued the study was clearly dose dependent for the reason "adverse events". Conversely, the reason "lack of efficacy" was not evident as most patients, not surprisingly, were derived from the placebo groups, but numerically more patients in the high dose (6 g/night) than in the lower dose (4.5 g/night) dosing groups withdrew for this reason. Further information was provided by the MAH showing that some patients who were randomised to 6 g/night dose did discontinue at a dose of 4.5 g/night (down titration of dose was allowed) and that no dose relationship was observed in this regard. Most discontinuations occurred within the first 4 weeks of treatment.

Long term efficacy

The uncontrolled, open-label design used in the study was not considered as ideal for the assessment of maintenance of efficacy (and long-term safety). However, the CHMP scientific advice endorsed the use of this design, and given the difficulties of a long-term placebo-controlled study, both from a perspective of feasibility and interpretation, the uncontrolled design is considered to be acceptable.

Although the interim results of the long-term extension study (06-010) indicated that the efficacy of Xyrem seen in the two controlled pivotal studies was maintained over time, the CHMP requested the final analysis during the evaluation.

Overall, response rates at study endpoint by final dose varied for both Pain VAS (from 67.9 to 74.9%) and FIQ Total Score (from 67.3 to 75.9) with no evident dose relationship pattern, which makes the interpretation of these results difficult. The mean dose of Xyrem appeared to increase over time suggesting potential cause of tolerance development.

Interestingly, responder rates for those patients originally randomised to the 4.5 g dose was larger than for patients randomised to the 6 g/night dose for both the Pain VAS (77% versus 60.9%) and FIQ total score (77.3%versus 60%).

Considering that patients had been treated for the preceding 14 weeks and the open-label design of the study, completion rates in the extension study were not impressive: 51%, 61.3%, 58.3% for placebo, 4.5 g and 6 g Xyrem groups, respectively.

Extrapolation of US data to EU population

In the short term studies (06-008 and 06-009), the patient distribution between the EU and the US was very skew with a clear preponderance of centres in the US. This was not in line with the CHMP scientific advice, which recommended one of the pivotal trials to be conducted in the EU. In fact, the EU representation was only about a third of the population of one of the trial. In this sub-population

efficacy was not demonstrated. Furthermore, subjects based in the EU displayed markedly less efficacy than subjects from the US.

The proportions of patients who achieved at least 30 % reduction in pain (VAS) in the US were 23.8% (placebo); 43.0% (4.5g dose); 38.3% (6g dose) and the proportions of patients who achieved at least 30 % reduction in FIQ total score (functionality response) were 25.7% (placebo); 45.2% (4.5g dose); 39.9% (6g dose). The proportions of EU patients who achieved at least 30 % reduction in pain (VAS) were 23.4% (placebo); 30.6% (4.5g dose); 31.6% (6g dose) and the proportions of patients who achieved at least 30 % reduction in FIQ total score (functionality response) were 26.6% (placebo); 31.8% (4.5g dose); 38.6% (6g dose).

Inferior efficacy was also reported for the EU population as compared to the US population in responder rates analyses for pain VAS and FIQ total score in the long term study (06-010).

The CHMP also noted baseline differences between the US and EU. The severity of the disease judged from the pain VAS, FIQ total score and fatigue VAS was clearly more severe in the EU than in the US population, although the mean and median time since onset of fibromyalgia symptoms were similar. The EU population had higher BDI-II scores suggesting more severe degree of depression than in the US. The CHMP concluded that the results from the US population could not be extrapolated to the EU population and that EU patients may have different disease characteristics than the US population.

However, the MAH argued that there was a high degree of consistency in results for the EU and the US populations. Differences observed in the populations did not seem to be driven by regional differences in diagnosis or treatment practices, but patients with more severe symptoms in terms of fibromyalgia and depression appeared to be over-represented in the EU study population i.e consistent results across regions were found when patients with moderate to severe depression were excluded from the analysis. This may have influenced the treatment outcome in certain subgroups, but there is no indication that Xyrem would generally be less effective in patients from the EU, i.e., these results allowed for an extrapolation to the population that would be eligible for Xyrem treatment in Europe. Therefore, the MAH proposed to restrict the use in patients without moderate to severe depression.

However, the CHMP considered that the following issues remain to be addressed:

- Inconsistencies between the US and EU population were argued on the basis of post-hoc analysis that identified co-morbid depression as possible confounding factor. The robustness of these data is questioned due to limitation in the design and sample size, not supporting of the target population applied for.

- Results were not consistent for the higher 6 g dose of Xyrem in patients without moderate to severe depression (pain VAS: 28.6% versus 39.0%; FIQ total score: 35.7%versus 40.4%) suggesting that the proposed extrapolation was not valid;

- The limitation of the target population to patients without moderate to severe depression is considered a rather impractical and artificial proposal in the context of a disease where a greater or lower degree of depression is almost constant and variable across time. In fact, despite the exclusion criteria for major depression, some patients with BDI-II ≥20 were included in the trial suggesting that the proposed restricted use may not well match the population intended to be treated. The fact that EU patients presented higher severity of the disease and higher depression scores might not be necessarily a confounding factor but could indicate a different perception of fibromyalgia in the EU compared to the US and thus support the need for a separate EU study prior approval.

3.4.4. Conclusions on the clinical efficacy

The CHMP concluded the following:

- The proposed dosing regimen (4.5 g/night) was not adequately justified and the minimal effective dose has not been established.

- The short- and long-term efficacy has not been demonstrated in the EU population.

3.5. Clinical safety

3.5.1. Clinical safety

The safety database comprises short term and long term studies (OMC-SXB-26, 06-008, 06-009 and 06-010) conducted in patients with fibromyalgia.

3.5.2. Patient exposure

In Phase 2 and 3 studies (OMC-SXB-26, 06-008, 06-009, and 06-010), 958 subjects with fibromyalgia received Xyrem, including 139 subjects treated for at least 6 months and 76 subjects treated for at least 1 year. The present safety analysis used the interim data for study 06-010, a total of 161 subjects were ongoing in the study, these subjects were therefore not included in this analysis.

Treatment duration in the placebo-controlled studies was 8 weeks in OMC-SXB-26 and 14 weeks in 06-008 and 06-009, with a combined total 61,402 subject-nights of exposure (168 subject-years). The duration of treatment in the open-label extension study 06-010 was up to 38 weeks. The total subject-nights of exposure for subjects who received any dose of Xyrem in the Phase 2 and 3 studies were 101,853 nights (279 subject-years).

3.5.3. Adverse events

The summary of most frequent (≥2% Subjects in Any Treatment Group) Treatment-Emergent Adverse Events by Preferred Term, Phase 3 Placebo-Controlled Studies is presented in Table 18.

Table 18

Number (%) of Subjects with Adverse Events by Preferred Term	Placebo (N=371)	Xyrem 4.5 g (N=376)	Xyrem 6 g (N=371)	All Xyrem (N=747)
With any Adverse Event	231 (62.3)	295 (78.5)	301 (81.1)	596 (79.8)
Headache	56 (15.1)	69 (18.4)	85 (22.9)	154 (20.6)
Nausea	26 (7.0)	63 (16.8)	79 (21.3)	142 (19.0)
Dizziness	8 (2.2)	47 (12.5)	56 (15.1)	103 (13.8)
Diarrhoea	20 (5.4)	24 (6.4)	36 (9.7)	60 (8.0)
Vomiting	13 (3.5)	18 (4.8)	35 (9.4)	53 (7.1)
Anxiety	5 (1.3)	22 (5.9)	25 (6.7)	47 (6.3)
Nasopharyngitis	14 (3.8)	21 (5.6)	21 (5.7)	42 (5.6)
Insomnia	10 (2.7)	18 (4.8)	17 (4.6)	35 (4.7)
Somnolence	12 (3.2)	12 (3.2)	19 (5.1)	31 (4.1)
Fatigue	9 (2.4)	10 (2.7)	19 (5.1)	29 (3.9)
Muscle spasms	6 (1.6)	15 (4.0)	14 (3.8)	29 (3.9)
Sinusitis	6 (1.6)	17 (4.5)	9 (2.4)	26 (3.5)
Back pain	7 (1.9)	10 (2.7)	15 (4.0)	25 (3.3)
Paresthesia	5 (1.3)	11 (2.9)	14 (3.8)	25 (3.3)
Upper respiratory tract infection	16 (4.3)	13 (3.5)	12 (3.2)	25 (3.3)
Pain in extremity	9 (2.4)	12 (3.2)	12 (3.2)	24 (3.2)
Edema peripheral	7 (1.9)	5 (1.3)	15 (4.0)	20 (2.7)
Vertigo	4 (1.1)	9 (2.4)	11 (3.0)	20 (2.7)
Influenza	15 (4.0)	7 (1.9)	11 (3.0)	18 (2.4)
Pharyngolaryngeal pain	6 (1.6)	5 (1.3)	12 (3.2)	17 (2.3)
Nasal congestion	3 (0.8)	7 (1.9)	10 (2.7)	17 (2.3)
Fibromyalgia	7 (1.9)	8 (2.1)	9 (2.4)	17 (2.3)
Constipation	6 (1.6)	9 (2.4)	8 (2.2)	17 (2.3)
Depression	4 (1.1)	6 (1.6)	10 (2.7)	16 (2.1)
Rash	8 (2.2)	6 (1.6)	10 (2.7)	16 (2.1)
Weight decreased	1 (0.3)	8 (2.1)	8 (2.2)	16 (2.1)
Anorexia	1 (0.3)	9 (2.4)	7 (1.9)	16 (2.1)
Arthralgia	4 (1.1)	10 (2.7)	6 (1.6)	16 (2.1)
Vision blurred	2 (0.5)	6 (1.6)	8 (2.2)	14 (1.9)
Urinary tract infection	5 (1.3)	9 (2.4)	5 (1.3)	14 (1.9)
Dry mouth	3 (0.8)	3 (0.8)	9 (2.4)	12 (1.6)
Blood pressure increased	1 (0.3)	4 (1.1)	8 (2.2)	12 (1.6)
Hyperhidrosis	2 (0.5)	2 (0.5)	9 (2.4)	11 (1.5)
Hypertension	4 (1.1)	3 (0.8)	8 (2.2)	11 (1.5)
Pruritus	5 (1.3)	8 (2.1)	3 (0.8)	11 (1.5)
Disturbance in attention	1 (0.3)	8 (2.1)	2 (0.5)	10 (1.3)
Migraine	10 (2.7)	5 (1.3)	4 (1.1)	9 (1.2)

Note: This table includes data from Studies 06-008 and 06-009. Adverse events are summarized by randomized treatment.

The Summary of All Treatment-Emergent Adverse Events, Phase 3 Placebo-Controlled Studies is presented in Table 19.

Table 19

Table 19

Number (%) of Subjects	Placebo (N=371)	Xyrem 4.5 g (N=376)	Xyrem 6 g (N=371)	All Xyrem (N=747)
With any AE	231 (62.3)	295 (78.5)	301 (81.1)	596 (79.8)
With any treatment-related AE[a]	110 (29.6)	173 (46.0)	190 (51.2)	363 (48.6)
With any AE by maximum severity				
Mild	97 (26.1)	119 (31.6)	108 (29.1)	227 (30.4)
Moderate	117 (31.5)	143 (38.0)	147 (39.6)	290 (38.8)
Severe	17 (4.6)	32 (8.5)	46 (12.4)	78 (10.4)
Missing[b]	0	1	0	1
Who died due to AE	0	0	0	0
With any SAE	4 (1.1)	2 (0.5)	5 (1.3)	7 (0.9)
With any treatment-related SAE	0	1 (0.3)	2 (0.5)	3 (0.4)
Who discontinued study due to AE	30 (8.1)	64 (17.0)	81 (21.8)	145 (19.4)
Who discontinued study due to treatment-related AE	21 (5.7)	50 (13.3)	55 (14.8)	105 (14.1)
Who discontinued study due to SAE	2 (0.5)	1 (0.3)	3 (0.8)	4 (0.5)
Who discontinued study due to treatment-related SAE	0	1 (0.3)	2 (0.5)	3 (0.4)

AE=adverse event, SAE=serious adverse event

Note: This table includes data from Studies 06-008 and 06-009. AEs are summarized by randomized treatment.

[a] Includes AEs considered related to study medication/procedure and AEs with missing relationship to study medication/procedure

[b] Includes subjects with severity missing for all adverse events

3.5.4. Serious adverse event/deaths/other significant events

No deaths were reported. Among the 19 sodium oxybate-treated subjects who had treatment-emergent serious adverse events, 4 subjects had one or more serious adverse events considered related to treatment, (vomiting in one subject, sleep paralysis and unresponsive to stimuli in one subject, headache in one subject, and paresthesia and depression in one subject) and 14 subjects had study drug dosing interrupted or discontinued, or discontinued study participation due to the serious adverse events.

At the time of the interim analysis for the long term study, 3 single serious events (not covered in this database due to time of database lock), namely occurrences of transient toxic encephalopathy due to an accidental overdose of Xyrem, an unspecified psychiatric event (mental disorder), and a pseudo-obstruction of the small bowel were also reported.

3.5.5. Laboratory findings

A few changes in laboratory values were reported as adverse events; however, in no case the incidence exceeded 0.5 %. The incidences of alanine aminotransferase increased, liver function test abnormal, and hypercholesterolemia were similar in the All Xyrem and placebo treatment groups. Anaemia (0.3%) and hypokalemia (0.2%) were the only events that occurred in Xyrem-treated subjects and not in placebo-treated subjects. Adverse events from laboratory findings led to study discontinuation in two subjects: ketoacidosis in one subject while receiving Xyrem 7.5 g in 06-010,

and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased in subject while receiving Xyrem 9 g in 06-010 (associated with an unrelated hepatitis A infection).

3.5.6. Other safety findings

Psychiatric adverse events

The frequency of anxiety was up to three times higher in Xyrem-treated patient compared to patients in the placebo group: 5.9 and 6.7% in the Xyrem groups, respectively; 1.3% in the placebo group. Also depression was more commonly seen in the Xyrem groups than in the placebo group : 1.6 and 1.7% in the Xyrem groups, respectively; 1.1%. For both events, a clear dose-response relationship was observed. Additional analyses were provided by the MAH including full data on study 06-010 and are presented below.

Anxiety

In the Phase 3 placebo-controlled studies, respectively 5 (1.3%), 22 (5.9%) and 25 (6.7%) subjects reported an adverse event anxiety in the placebo, Xyrem 4.5 g and Xyrem 6 g groups. In about 70% of anxiety events, the onset occurred within six weeks after starting the study treatment in the Xyrem-treated subjects. Half of the anxiety events were reported as mild in the Xyrem-treated subjects and 90% as mild or moderate. Severe events were only observed with the 6 g dose. More than half of the anxiety events were intermittent in the Xyrem-treated subjects and about one third were reported as continuous. Thirty-four percent of the reported anxiety adverse events led to a discontinuation of Xyrem treatment, as compared to a slightly higher percentage (40%) in the placebo group. However, the limitation of the small sample sizes in the placebo group should be noted.

Anxiety was reported in a larger proportion by subjects between 50 and 64 years as compared to subjects between 40 and 49 years. No relevant difference in baseline fibromyalgia severity in subjects reporting anxiety as compared to the overall study population was observed.

Anxiety was reported in a larger proportion by subjects with baseline BDI-II scores indicating mild to moderate depression as compared to the overall study population, this effect is more pronounced in the placebo group. This trend was not observed for baseline BDI-II scores indicating severe depression and there was no consistent relationship with the Xyrem doses. There was no evidence that lack of efficacy is more frequent in subjects reporting anxiety as compared to the overall study population.

Depression

In the Phase 3 placebo-controlled studies, respectively 4 (1.1%), 6 (1.6%) and 10 (2.7%) subjects reported an adverse event depression in the placebo, Xyrem 4.5 g, and Xyrem 6 g groups. An adverse event 'major depression' was reported by respectively 2 (0.5%), 2 (0.5%), and 1 (0.3%) subjects in the placebo, Xyrem 4.5 g, and Xyrem 6 g groups. Although reported by few subjects, no dose-response relationship can be observed for this event. In 60% of depression events, the onset occurred within six weeks after starting the study treatment in the Xyrem-treated subjects. In Xyrem-treated subjects, 45% of the depression events were reported as mild and 95% as mild or moderate. In Xyrem-treated subjects, 60% of the depression events was reported as continuous. Forty percent of the reported depression events led to a discontinuation of Xyrem treatment, as compared to a higher proportion (67%) in the placebo group. However, the limitation of the small sample sizes in the placebo group should be noted.

No relevant differences can be observed regarding the age distribution of subjects who reported depression and in baseline fibromyalgia severity in subjects reporting depression as compared to the overall study population. Xyrem-treated subjects who reported depression tend to have higher BDI-II scores at baseline. Xyrem-treated subjects who reported depression tend to have lower efficacy as

compared to the overall population. This is also observed in the placebo group (except for pain response), however, the limitation of the small sample sizes in the depression subgroup should be noted.

Respiratory depression

Dyspnoea was the only one of these events that occurred in more than one subject across all treatment groups. Sleep apnoea syndrome occurred in one subject in the placebo group. The percentage occurrence of dyspnoea was highest in the Xyrem 6 g group (1.6%). Of the 12 subjects with dyspnoea events in the Xyrem treatment groups, dyspnoea in one subject in the Xyrem 6 g group was considered severe. Dyspnoea was considered related to treatment in the placebo (N=1), 4.5 g dose (N=1) and Xyrem 6 g dose (N=4) groups, respectively. In one subject who was randomized to Xyrem 6 g, dyspnoea, cyanosis (mild and related to treatment), and serious adverse events of sleep paralysis and unresponsive to stimuli occurred after the first dose of 2.25 g during the titration period in 06-008 (i.e., before the dose increase to 6 g/night); these adverse events led to study discontinuation. One serious adverse event of chronic obstructive pulmonary disease (COPD) was reported in one subject receiving Xyrem 9 g (06-010). This subject had no reported history of COPD. The COPD event (Days 258–265 during treatment with Xyrem 9 g) was considered to be severe and unrelated to treatment. This event led to hospitalization and study drug dosing was interrupted during this event.

CNS depression

The incidence of dizziness was higher in the Xyrem 6 g (15.5%) and 4.5 g (11.9%) groups compared to the placebo group (2.3%). The incidence of somnolence was highest in the Xyrem 6 g group (5.0%), but similar in the Xyrem 4.5 g (3.2%) and placebo (2.8%) groups; the rates of other events (sedation, lethargy, depressed level of consciousness, hangover) were similar across the groups and did not exceed 1%.

Of these events potentially related to CNS depression, adverse events of somnolence were considered severe in two subjects in the Xyrem 4.5 g group and one subject in the Xyrem 6 g group. Somnolence was considered related to treatment in the placebo (N=12), Xyrem 4.5 g dose (N=13), and Xyrem 6 g dose (N=20) groups, respectively. Sedation was considered related to treatment in the placebo (N=2), Xyrem 4.5 g dose (N=2), and Xyrem 6 g groups (N=3), respectively.

Weight changes

In the Phase 3 studies, mean values for body weight at screening were similar among the treatment groups. Mean changes from baseline in the placebo group were all increased, with a maximum mean increase of 0.51 kg noted at Week 12. Mean changes from baseline in the Xyrem groups were all decreased, with maximum mean decreases of -0.75 kg noted at Week 14 in the Xyrem 4.5 g group and -1.54 kg noted at Week 12 in the Xyrem 6 g group. The trend of mean decrease over time continued in the cohort of subjects who participated in 06-010, with a maximum mean decrease of -4.42 kg observed at Week 46. The rate of decrease from baseline appeared to plateau after Week 38. Adverse events related to body weight and appetite occurred at the following rates: weight decreased 3.7%, decreased appetite 3.3%, anorexia 2.9%, increased appetite 2.0%, and weight increased 1.2%.

Abuse

The abuse potential has not been elucidated in patients with fibromyalgia, likely to be more fragile than the narcolepsy population. Limited published data investigated the abuse liability of Xyrem. A risk between that of benzodiazepines and barbiturates is stated. However, these brief reviews were considered insufficient to address this matter.

3.5.7. Safety in special populations

Gender, Race

By age category, subjects ≥65 years of age (N=41) had a higher incidence of adverse events overall (92.7%) and discontinuations due to adverse events (31.7%) than subjects <65 years of age. No subject ≥65 years of age experienced a serious adverse event, compared to 2.1% in the younger age group. The incidence of the most frequent treatment-related adverse events was similar in both subgroups, except that no subject ≥65 years of age reported vomiting.

By gender, the incidence of adverse events overall was comparable between males (N=85; 76.5%) and females (N=873; 83.7%). Discontinuations due to adverse events were higher in female subjects (55.9% and 26.2%, respectively) than in male subjects (42.4% and 14.1%, respectively), while the incidence of serious adverse events was similar in males (2.4%) and females (1.9%).

By race, the incidence of adverse events and treatment-related adverse events overall was comparable between the two subgroups. The percentage of discontinuations due to adverse events was higher in Caucasians (N=877) than non-Caucasians (N=81; 26.2% and 13.6%, respectively).

Pregnancy

Three out of the six reported pregnancies during fibromyalgia trials resulted in spontaneous abortions reported in the fibromyalgia Trials. None of the spontaneous abortions were judged to be related to medication.

3.5.8. Discontinuation due to adverse events

In studies 06-008 and 06-009, 19.4% of subjects in the All Xyrem group discontinued due to adverse events compared to 8.1% of subjects in the placebo group. When the Phase 3 placebo-controlled studies were summarized by randomized dose, the incidence of adverse events leading to study discontinuation was 17.0% in the Xyrem 4.5 g group and 21.8% in the Xyrem 6 g group. Adverse events leading to discontinuation in ≥2% of the All Xyrem group in the Phase 3 placebo-controlled studies were nausea (3.3%), headache (2.8%), vomiting (2.4%), and dizziness (2.1%). The most common events leading to discontinuation in the placebo group were depression (1.1%) and somnolence (0.8%).

3.5.9. Post marketing experience

As part of post-marketing evaluation program (PMEP) designed to prospectively capture safety data on the first 1,000 patients receiving Xyrem post approval in the US, a total of 928 reports were received, representing 692 patients. Of those reports, 64% reported no adverse event. The ten most commonly reported adverse events from solicited and spontaneous reports were nausea, vomiting, feeling abnormal, headache, dizziness, somnolence, tremor, anxiety, confusional state, initial insomnia, and insomnia. After data from nearly 700 patients were collected, the PMEP requirement was terminated because of the lack of any new or significant findings and the difficulty in collecting physician responses.

3.5.10. Discussion on clinical safety

The safety database for patients with fibromyalgia is below the 1500 exposures recommended by the CHMP scientific advice. This is of concern since this patient population is often prone to adverse events resulting from various drugs.

Overall, 62.3 % of patients in the placebo group, 78.5% in the 4.5 g/night dosing group, and 81.1 % in the 6 g/night group had adverse events. Headache, nausea, dizziness, diarrhoea, vomiting, anxiety, nasopharyngitis, somnolence, and fatigue were the most common adverse events. Importantly, the incidence was greater for active than placebo treatment and the incidence for the 6 g group was greater than for the 4.5 g group. Therefore the CHMP considered that the posology recommendation to use dose up to 6g/day for patients with severe symptoms was not acceptable and the MAH modified the initial proposed posology accordingly.

Of most concern are the reported psychiatric and respiratory depression related adverse events. For both events, a clear dose-response relationship was observed. This is a significant concern considering that fibromyalgia patients are a vulnerable patient population that often exhibits depressive symptoms. Further analyses were provided by the MAH and led to SmPC changes. These included updating the warning on neuropsychiatric events, adding "sleep apnea" as adverse drug reaction with a warning as well as contraindicating Xyrem in patients with major depression. A recommendation that Xyrem treatment should be assessed six weeks after its initiation was also proposed in line with the onset of most of the reported anxiety and depression events (about 70% and 60%, respectively).

Regarding pregnancies, three out of the six reported pregnancies during fibromyalgia trials resulted in spontaneous abortions. None of the spontaneous abortions were judged to be related to medication. The CHMP recommended updating the information in the SmPC to include that data from a limited number of pregnant women exposed in the first trimester indicated a possible risk of spontaneous abortions. However, no other relevant epidemiological data are available to date.

Overall the CHMP considered that the safety profile for Xyrem in the fibromyalgia population remains unfavourable due to the high frequency of CNS related adverse events.

In addition, the abuse potential has not been elucidated in patients with fibromyalgia. The CHMP considered that this risk remains a concern in this population.

The MAH disagreed with the CHMP's view for the reasons outlined below:

- Abuse liability of sodium oxybate in drug abusers is comparable to other sedative drugs (*European School Survey Project on Alcohol and other drugs, ESPAD data*)

- Non drug abusers do not report positive subjective effects after administration of sodium oxybate (*Carter et al, 2009*)

- Abuse of GHB is low and has been trending downward in the US; introduction of Xyrem to the market did not increase any indicators of abuse.

Having considered the MAH argumentation, the CHMP still considered that the safety profile remain unfavourable in the population with fibromyalgia due to the high frequency of CNS related adverse events and abuse potential. As the safety information resulting from this assessment is relevant to the currently authorised indication, the SmPC have been amended accordingly (see section 3.8 for full details).

3.5.11. Conclusions on the clinical safety

The CHMP concluded the following:

- The safety profile for Xyrem in the fibromyalgia population is unfavourable due to the high frequency of CNS related adverse events;

- The abuse potential for Xyrem remains a concern in the fibromyalgia population.

Despite the negative outcome for the extension of indication, as a result of the assessment of the new data, the CHMP recommended the update of the SmPC, as described in section 3.8.

3.6. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3.7. Benefit-Risk Balance

Benefits

- Beneficial effects

Overall, the development program of Xyrem (sodium oxybate) provided evidence of short term efficacy in patients with fibromyalgia. This evidence was primarily based on two phase 3 trials (studies 06-008 and 06-009), which together randomized 1121 subjects of whom 371 received placebo, 377 received Xyrem 4.5 g/night and 373 received 6 g/night, respectively. As no pharmacotherapy for the treatment of fibromyalgia currently exists in the EU, approval of a drug would be advantageous for the patients.

In these pivotal studies, of which only one (study 06-009) was double-blind (as the intended masking was insufficient in study 06-008), a statistically and clinically significant difference between 2 doses, i.e. 4.5 g and 6 g/night, of Xyrem and placebo was reported except for the 6g dosing regimen in study 06-008 (p=0.062 for FIQ total score). The effect was consistent over the primary and co-primary endpoints which were selected in line with the CHMP scientific advice: the proportions of patients who achieved at least 30 % reduction in pain (VAS score) were 27.3% (placebo); 46.2% (4.5g dose); 39.3% (6g dose) for study 06-008 and 20.2 %(placebo); 35.4 %(4.5 g dose); 35.3% (6g dose) for study 06-009. The proportion of patients who achieved at least 30 % reduction in FIQ total score (functionality response) were 30.1% (placebo); 46.2 %(4.5g dose); 39.3% (6g dose) for study 06-008 and 21.8% (placebo); 39.5% (4.5 g dose); 40.0% (6g dose) for study 06-009.

There is considerable concordance between the results of the primary and secondary endpoints. These findings provided confidence in a robust and reliable outcome. The 30 % threshold has earlier been identified as a clinically relevant change in pain VAS and FIQ total score. The observed outcome is, thus, considered valuable from a clinical perspective for the fibromyalgia study population. Further LOCF and MMRM analyses confirmed the results and showed a clearer dose response between 4.5 g/night and 6 g/night.

- Uncertainty in the knowledge about the beneficial effects.

The results of the long-term extension study (06-010) suggested that the efficacy of Xyrem seen in the two controlled pivotal studies was maintained over time, but the data is limited to one year. In a very small number of cases there is a tendency for an increase of dose to 9 g/night which cannot exclude completely the development of tolerance.

The CHMP did not consider that the proposed initial dosing regimen (4.5 g or 6 g/night) was adequately justified as it is based on an extrapolation from the population presenting narcolepsy to fibromyalgia patients. Although some evidence has been presented by the MAH suggesting that tolerability in terms of CNS adverse events is not likely to be significantly worse with the 4.5 g/night dose compared to a 3 g/night dose (had this dose been tested in a fibromyalgia population), the CHMP still considered that the minimal effective dose has not been established and that doses lower than 4.5 g/night (e.g. 3 g/night or lower) should have been investigated.

Results from sub-analyses in the EU study population suggested markedly lower responder rates and effect sizes compared to the US population, both in the short term and in the long term studies. The EU representation was only about a third of the population of one of the pivotal trial.

Baseline differences were also observed between the US and EU. The severity of the disease judged from the pain VAS, FIQ total score and fatigue VAS was clearly more severe in the EU than in the US population, although the mean and median time since onset of fibromyalgia symptoms were similar. The EU population had higher BDI-II scores suggesting more severe degree of depression than in the US. The CHMP concluded that the results from the US population could not be extrapolated to the EU population and that EU patients may have different disease characteristics than the US population.

Risks

- Unfavourable effects

Considering that fibromyalgia patients often exhibit psychiatric symptoms, the observed higher frequency of anxiety in Xyrem-treated patients compared to patients in the placebo group (5.9 and 6.7% versus. 1.3%) were of concern. Also depression was more commonly seen in the Xyrem groups than in the placebo group (1.6 and 1.7% versus. 1.1%).

Xyrem treatment discontinuation related to AEs was 19.4% versus 8.1% in the active and placebo groups, respectively.

- Uncertainty in the knowledge about the unfavourable effects.

Possible withdrawal/rebound phenomena have not been investigated comprehensively.

The abuse potential of Xyrem is considered an important concern. Only limited long-term safety data have been provided. This is a particular concern with respect to the potential abuse liability and risk of dependence associated with Xyrem when used chronically in the fibromyalgia population. Thus, this risk remains a concern in this population.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects

Short and long term effects versus placebo were considered clinically relevant in the overall population that included mostly US patients. However, no minimal effective dose has been established and a beneficial outcome has not been demonstrated in EU patient population.

Subjects based in the EU displayed markedly less efficacy than subjects from the US in several analyses. Despite consistent results observed for the recommended 4.5g dose in a non prospectively defined subgroup of patients without moderate to severe depression, the extrapolation of the US data to the EU population was not considered valid in this population. The clinical data suggested that EU patients may have different disease characteristics than the US population.

Limited safety data are available in the population with fibromyalgia. The clear dose-response relationship that was observed for anxiety and depression related adverse events further emphasized the need for an adequate dose finding study. Therefore, the CHMP considered that the high incidence of CNS related adverse events remains a concern with a significant impact on the benefit-risk balance.

In addition, the abuse potential for Xyrem remains a concern in the fibromyalgia population.

- Benefit-risk balance

The benefit-risk balance for Xyrem is negative in the EU population with fibromyalgia.

3.8. Product Information

Having considered the CHMP assessment on the benefit-risk balance of Xyrem in the EU population with fibromyalgia, the MAH proposed to revise the Product Information, removing their proposal to include the indication initially applied for and maintaining the changes relevant to the authorised indication. The CHMP recommended the update of the SmPC. The revised SmPC proposal is described below (new text underlined, deleted text= strikethrough):

Section 4.2

Due to the well known potential of abuse of sodium oxybate, physicians should evaluate patients for a history of or susceptibility to drug abuse prior to commencing treatment. During treatment, patients should be monitored for the risk of diversion, misuse and abuse of sodium oxybate (see section 4.4).

If the patient stops taking the medicinal product ~~medication~~ for more than 14 consecutive days, titration should be restarted from the lowest dose.

Section 4.3

Patients with major depression

Section 4.4

Respiratory depression

Sodium oxybate also has the potential to induce respiratory depression. Apnoea and respiratory depression have been observed in a fasting healthy subject after a single intake of 4.5 g (twice the recommended starting dose). Patients should be questioned regarding signs of Central Nervous System (CNS) or respiratory depression. Special caution should be observed in patients with an underlying respiratory disorder. Because of the higher risk of sleep apnoea, patients with a BMI ≥40 kg/m2 should be monitored closely when taking sodium oxybate.

Abuse potential and dependence

Sodium oxybate, which is as the sodium salt of GHB, is a CNS depressant active substance with well known abuse potential. Prior to treatment ~~P~~physicians should evaluate patients for a history of or susceptibility to drug abuse. Patients should be routinely monitored~~closely~~ and in the case of suspected abuse, treatment with sodium oxybate should be discontinued.

Neuropsychiatric events

Patients may become confused while being treated with sodium oxybate. If this occurs, they should be evaluated fully, and appropriate intervention considered on an individual basis. Other neuropsychiatric events include anxiety, psychosis, paranoia, hallucinations, and agitation. The emergence of thought disorders and/or behavioural abnormalities when patients are treated with sodium oxybate requires careful and immediate evaluation.

The emergence of depression when patients are treated with sodium oxybate requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored especially carefully for the emergence of depressive symptoms while taking sodium oxybate. Major depression is contraindicated for use with Xyrem (section 4.3).

Section 4.5

~~Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate and protriptyline hydrochloride (an antidepressant), zolpidem tartrate (a hypnotic), and modafinil (a stimulant). However, pharmacodynamic interactions with these medicinal products have not been assessed.~~

Sedative hypnotics
Drug interaction studies in healthy adults with sodium oxybate (single dose of 2.25 g) and lorazepam (an anxiolytic [benzodiazepine]; single dose of 2 mg) and zolpidem tartrate (a hypnotic [non-benzodiazepine]; single dose of 5 mg) demonstrated no pharmacokinetic interactions. Increased sleepiness was observed after concomitant administration of sodium oxybate (2.25 g) and lorazepam (2 mg). The pharmacodynamic interaction with zolpidem has not been assessed. When higher doses up to 9 g/d of sodium oxybate are combined with higher doses of hypnotics (within the recommended dose range) pharmacodynamic interactions associated with symptoms of CNS depression and/or respiratory depression cannot be excluded (see section 4.3).

Tramadol
A drug interaction study in healthy adults with sodium oxybate (single dose of 2.25 g) and tramadol (a central acting opioid; single dose of 100 mg) demonstrated no pharmacokinetic/pharmacodynamic interaction. When higher doses up to 9 g/d of sodium oxybate are combined with higher doses of opioids (within the recommended dose range) pharmacodynamic interactions associated with symptoms of CNS depression and/or respiratory depression cannot be excluded (see sections 4.3).

Antidepressants
Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate (single dose of 2.25 g) and the antidepressants protriptyline hydrochloride (single dose of 10 mg) and duloxetine (60 mg at steady state). No additional effect on sleepiness was observed when comparing single doses of sodium oxybate alone (2.25 g) and sodium oxybate (2.25 g) in combination with duloxetine (60 mg at steady state). Antidepressants have been used in the treatment of cataplexy. A possible additive effect of antidepressants and sodium oxybate cannot be excluded. The rate of adverse events has increased when sodium oxybate is co-administered with tricyclic antidepressants.

Modafinil
A drug interaction study in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate (single dose of 4.5 g) and modafinil (a stimulant; single dose of 200 mg). Sodium oxybate has been administered concomitantly with CNS stimulant agents in approximately 80% of patients in clinical studies in narcolepsy. Whether this affected respiration during the night is unknown.

Section 4.6

Pregnancy
Animal studies have shown no evidence of teratogenicity but embryolethality was seen in both rat and rabbit studies (see section 5.3).

~~There are no adequate data on the use of sodium oxybate during the first trimester of pregnancy.~~Data from a limited number of pregnant women exposed in the first trimester indicate a possible increased risk of spontaneous abortions. To date no other relevant epidemiological data are available. Limited data from pregnant patients during second and third trimester indicate no malformative nor foeto/neonatal toxicity of sodium oxybate.

Breastfeeding
It is not known whether sodium oxybate and/or its metabolites ~~is~~ are excreted into breast milk. Breastfeeding is not recommended ~~when treating~~during treatment with sodium oxybate.

Section 4.8 Undesirable effects

Immune system disorders:
Uncommon ~~Not known (cannot be estimated from the available data~~): hypersensitivity

Metabolism and nutrition disorders:
Common: anorexia, decreased appetite

Psychiatric disorders:
Common: depression, cataplexy, anxiety, abnormal dreams, confusional state, disorientation, nightmares, sleepwalking, sleep disorder, insomnia, middle insomnia, nervousness
Uncommon: suicide attempt, psychosis, paranoia, hallucination, abnormal thinking, agitation, initial insomnia
Not known (cannot be estimated from the available data): suicidal ideation

Nervous system disorders:
Very common: dizziness, headache
Common: sleep paralysis, somnolence, tremor, balance disorder, disturbance in attention, hypoaesthesia, paraesthesia, sedation, dysgeusia
Uncommon: myoclonus, amnesia, restless legs syndrome
Not known (cannot be estimated from the available data): convulsion

Ear and labyrinth disorders:
Common: vertigo

Cardiac disorders:
Common: palpitations

Vascular disorders:
Common: hypertension

Respiratory, thoracic and mediastinal disorders:
Common: dyspnoea, snoring, nasal congestion
Not known (cannot be estimated from the available data): respiratory depression, sleep apnoea

Gastrointestinal disorders:
Very common: nausea (the frequency of nausea is higher in women than men)
Common: vomiting, diarrhoea, ~~upper~~ abdominal pain upper,
Uncommon: faecal incontinence

Skin and subcutaneous tissue disorders:
~~Common: sweating~~
~~Uncommon~~Common: hyperhidrosis, rash
Not known (cannot be estimated from the available data): urticaria

Musculoskeletal, connective tissue and bone disorders:
Common: arthralgia, muscle ~~cramps~~, spasms, back pain

Infections and infestations:
Common: nasopharyngitis, sinusitis

Investigations:
~~*Uncommon*~~ *Common*: blood pressure increased, weight decreased

Section 5.2

Sodium oxybate is rapidly and almost ~~but in~~completely absorbed after oral administration; absorption is delayed and decreased by a high fat meal. It is eliminated mainly by metabolism with a half-life of 0.5 to 1 hour. Pharmacokinetics are nonlinear with the area under the plasma concentration curve (AUC) versus time curve increasing 3.8-fold as dose is doubled from 4.5 g to 9 g. The pharmacokinetics are not altered with repeat dosing.

Absorption: Sodium oxybate is absorbed rapidly following oral administration with an absolute bioavailability of about 88 %~~25 %~~.

Special populations:

Elderly patients: ~~The pharmacokinetics of sodium oxybate in patients greater than the age of 65 years have not been studied.~~ In a limited number of patients greater than the age of 65 years the pharmacokinetics of sodium oxybate was not different compared to patients younger than 65 years of age.

Section 5.3

Drug discrimination studies show that GHB produces a unique discriminative stimulus that in some respects is similar to that of alcohol, morphine and certain GABA-mimetic medicinal products. Self-administration studies in rats, mice and monkeys have produced conflicting results, whereas tolerance to GHB as well as cross-tolerance to alcohol and baclofen ~~have~~ has been clearly demonstrated in rodents.

The Package Leaflet has been amended accordingly.

The CHMP considered the above-mentioned changes to be acceptable.

4. Conclusion

The MAH submitted a Type II variation to extend the indication as follows: *"Xyrem is indicated in adults: Treatment of moderate to severe symptoms of fibromyalgia."*

Variations requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

On the basis of the data provided, the CHMP did not support the extension of the indication. However, as a result of the evaluation of the new data, the CHMP recommends to update the SmPC and the Package Leaflet accordingly.

On 17 March 2011 the CHMP considered the variation:

"Update of relevant sections of the SmPC to include the following information relevant to the authorised indication: contraindication in patients with major depression (4.3), information on drug-

drug interactions with duloxetine, lorazepam and tramadol (4.5), pharmacokinetic results in elderly population (5.2) and safety information in relation to the clinical trials conducted in fibromyalgia patients (4.2, 4.4, 4.6 and 4.8). Information on absolute bioavailability and preclinical data were also updated in section 5.2, and 5.3, respectively. Package leaflet updated accordingly.

Annex II has been updated in order to delete the reference to the versions of the RMP and Pharmacovigilance system and to reflect the previously agreed yearly PSUR cycle."

to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics , Package Leaflet and Annex II.