EXTENDED REPORT

Sodium oxybate therapy provides multidimensional improvement in fibromyalgia: results of an international phase 3 trial

Michael Spaeth,[1] Robert M Bennett,[2] Beverly A Benson,[3]
Y Grace Wang,[3] Chinglin Lai,[3] Ernest H Choy[4]

ABSTRACT

Background Fibromyalgia is characterised by chronic musculoskeletal pain and multiple symptoms including fatigue, multidimensional function impairment, sleep disturbance and tenderness. Along with pain and fatigue, non-restorative sleep is a core symptom of fibromyalgia. Sodium oxybate (SXB) is thought to reduce non-restorative sleep abnormalities. This study evaluated effects of SXB on fibromyalgia-related pain and other symptoms.

Methods 573 patients with fibromyalgia according to 1990 American College of Rheumatology criteria were enrolled at 108 centres in eight countries. Subjects were randomly assigned to placebo, SXB 4.5 g/night or SXB 6 g/night. The primary efficacy endpoint was the proportion of subjects with ≥30% reduction in pain visual analogue scale from baseline to treatment end. Other efficacy assessments included function, sleep quality, effect of sleep on function, fatigue, tenderness, health-related quality of life and subject's impression of change in overall wellbeing.

Results Significant improvements in pain, sleep and other symptoms associated with fibromyalgia were seen in SXB treated subjects compared with placebo. The proportion of subjects with ≥30% pain reduction was 42.0% for SXB4.5 g/night (p=0.002) and 51.4% for SXB6 g/night (p<0.001) versus 26.8% for placebo. Quality of sleep (Jenkins sleep scale) improved by 20% for SXB4.5 g/night (p≤0.001) and 25% for SXB6 g/night (p≤0.001) versus 0.5% for placebo. Adverse events with an incidence ≥5% and twice placebo were nausea, dizziness, vomiting, insomnia, anxiety, somnolence, fatigue, muscle spasms and peripheral oedema.

Conclusion These results, combined with findings from previous phase 2 and 3 studies, provide supportive evidence that SXB therapy affordsimportant benefits across multiple symptoms in subjects with fibromyalgia.

Chronic musculoskeletal pain is common, and causes distress and reduced quality of life.[1] Patients with chronic musculoskeletal pain frequently experience unrefreshing sleep,[2] and while it seems logical to assume that pain leads to disturbed sleep, there is increasing evidence that dysfunctional sleep leads to hyperalgesia and allodynia.[3–6] These symptoms are the prototypical features of fibromyalgia and formed the basis for the 1990 diagnostic criteria promulgated by the American College of Rheumatology (ACR).[7] Based on these ACR criteria, fibromyalgia has a population prevalence of 2–5%

and incurs substantial medical costs.[8 9] While fibromyalgia is defined in terms of pain,[7] most patients are multisymptomatic, with core outcome domains that include pain, fatigue, multidimensional function, sleep disturbance, patient global impression of change (PGIC) in condition and tenderness.[10]

Polysomnographic studies in fibromyalgia patients typically report non-refreshing sleep associated with abnormal polysomnographic findings—in particular, alpha intrusion and reduced slow-wave sleep (SWS).[11] Furthermore, Moldofsky *et al*[12] showed that fibromyalgia-like symptoms could be induced in healthy normal volunteers by the deprivation of stage 4 (N3) sleep. There is also increasing evidence that 'non-restorative' sleep and its influence on peripheral functions promotes hyperalgesia, fatigue and bodily hypersensitivity.[5 10] Although the detailed mechanisms underlying sleep problems in fibromyalgia are not known, given that epidemiological evidence suggests that the attainment of restorative sleep resolves chronic widespread pain,[13] it is reasonable to hypothesise that sleep disturbance is a fundamental component of fibromyalgia pathophysiology, and the amelioration of sleep disturbance may be clinically beneficial to fibromyalgia patients.

Sodium oxybate (SXB) is the sodium salt of γ-hydroxybutyrate, an endogenous compound found in the central nervous system and a metabolite of γ-aminobutyric acid. The drug is approved in the USA, Canada and Europe for the treatment of symptoms in narcolepsy.

SXB is thought to improve the quantity and quality of SWS.[14] Previously, Scharf *et al*[15] observed that some narcoleptic subjects with co-existing fibromyalgia experienced a reduction of pain and fatigue while being treated with SXB. They conducted a small placebo-controlled study using polysomnography and reported that SXB reduced pain and fatigue in subjects with fibromyalgia and dramatically reduced non-restorative sleep abnormalities (α intrusion and decreased SWS) associated with fibromyalgia.[16] More recently, a larger, phase 2, placebo-controlled trial reported beneficial effects of two dosages of SXB (4.5 or 6 g) on multiple symptoms in patients with fibromyalgia, and the SXB 6 g dose improved sleep physiology as measured by polysomnography.[17 18] In addition, the first large, multicentre, phase 3, placebo-controlled trial conducted in the USA demonstrated clinically important benefits of SXB on multiple symptoms in subjects with fibromyalgia.[19]

This paper reports the results of a second phase 3, randomised, double-blind, placebo-controlled trial that evaluated the efficacy and safety of SXB in fibromyalgia patients from the USA and seven European countries.

METHODS
Study design and subjects
This double-blind, placebo-controlled, parallel-group study examined the efficacy and safety of SXB 4.5 g/night, SXB 6 g/night and placebo in fibromyalgia subjects. The study consisted of a screening and washout/withdrawal period, a baseline week, a 14-week randomised treatment and a post-treatment follow-up. Subjects were enrolled from February 2007 to April 2009 at 108 study centres in eight countries (France, Germany, Italy, The Netherlands, Poland, Spain, UK and USA). Women or men aged 18 years or over had to meet the ACR criteria for fibromyalgia,[7] have a body mass index less than 40 kg/m^2, and have an average score of 50 or greater on a 100-mm pain visual analogue scale (VAS) at baseline. Subjects had to discontinue medications, herbal remedies and/or devices that might influence outcome; non-pharmacological treatments for fibromyalgia needed to remain unchanged, and only paracetamol (acetaminophen) was allowed as rescue medication. Subjects with a body mass index of 35 kg/m^2 or greater and less than 40 kg/m^2 had to have polysomnography at screening to rule out obstructive sleep apnoea (OSA). Subjects with OSA had to be on stable continuous positive airway pressure (CPAP) for 30 days prior to baseline and continue CPAP for the study duration.

Potential subjects were excluded if they had any painful disorder other than fibromyalgia and/or any medical or psychiatric condition that might compromise study participation (including current major depressive disorder and generalised anxiety disorder). They were also excluded if they had a current or previous substance-use disorder, including alcohol abuse; had previously taken γ-hydroxybutyrate or SXB; or had previously participated in clinical trials with SXB.

This study was conducted in compliance with the Declaration of Helsinki, International Conference on Harmonisation Guidelines for Good Clinical Practice, the US Code of Federal Regulations and Directives of the European Parliament and was approved by the ethics committee or institutional review board at every study site. All participants provided written informed consent.

Procedures
During screening, eligibility evaluations included assessment for sleep apnoea by clinical judgement, assisted by the Berlin questionnaire, or polysomnography to rule out OSA.[20] All screened subjects on any prohibited medications underwent a washout for up to 30 days. At baseline, eligible subjects were issued electronic diaries (PHT Corporation, Charlestown, Massachusetts, USA) to rate their current pain and fatigue three times a day (morning, afternoon and evening) on a VAS ranging from 0 (none) to 100 mm (worst imaginable) throughout the following week and to record rescue medication use.

Subjects who met all eligibility criteria and demonstrated competency using the diary were randomly assigned to receive an oral solution of SXB 4.5 g/night, SXB 6 g/night, or placebo matched to active-treatment volume. The randomisation code was generated using permuted blocks (block size of six) and implemented centrally by an interactive voice-response system. Treatment assignment remained blinded until the study database was locked and ready for analysis. Subjects randomly assigned to SXB 6 g/night received SXB 4.5 g/night during the first 2 weeks and then SXB 6 g/night for the remaining 12 weeks. All study medication was taken nightly in two equal doses, one at bedtime and the second 2.5–4 h later.[21] Subjects discontinuing early were followed for an additional 2 weeks.

Study outcomes
Efficacy
Assessments were based on recommendations of the 9th Working Group of Outcome Measures in Rheumatology Clinical Trials (OMERACT), which includes measurement of tenderness and questionnaires on the domains of pain, fatigue, multidimensional function, sleep disturbance and global impression of change.[10]

Primary endpoint
The primary efficacy endpoint was the proportion of subjects recording 30% or greater reduction in pain VAS scores from the average baseline week value to the average final treatment week (week 14) value.

Secondary endpoints
Secondary efficacy parameters included mean change from baseline in fatigue VAS scores; the proportion of subjects with a 30% or greater reduction on the fibromyalgia impact questionnaire (FIQ) total score;[22] sleep assessment using the Jenkins sleep scale (JSS), a validated measure of sleep quality;[23 24] health-related quality of life based on the Medical Outcomes Study 36-item short-form health survey (SF-36);[25] and the EuroQol-5 dimensions (EQ-5D) self-report questionnaire, comprising five aspects of quality of life and overall health state.[26] Overall impression of wellbeing was evaluated by subjects using the PGIC, and the impact of daytime sleepiness and tiredness on activities of daily living was evaluated by subjects using the functional outcomes of sleep questionnaire (FOSQ).[27] The proportion of subjects meeting composite response measures was also determined. Fibromyalgia composite responders were predefined as subjects who had 30% or greater reduction in pain, a PGIC response of 'much better' or 'very much better' and a 30% or greater reduction in FIQ total score. The FIQ has 10 domains: pain, fatigue, sleep, physical function, work, general health, participation, stiffness, anxiety and depression. Functional composite responders were defined as subjects who had 30% or greater reduction in pain, a PGIC response of 'much better' or 'very much better', plus improved SF-36 scores using two cutoffs—scores of 5 or greater and scores 6 or greater. Clinician assessments included tenderness using the manual tender point survey (MTPS),[28] with a tender point count and tender point index and the clinician global impression of change.[29]

The number needed to treat (NNT) and its 95% CI were estimated as a post-hoc analysis for pain reduction (30%, 50% and 80%) and improvement in FIQ (14% and 30%).

Tolerability and safety
All observed or spontaneously reported treatment-emergent adverse events (AE) were determined by prespecified criteria and recorded. Physical findings, including vital signs, were also recorded, and 12-lead electrocardiograms were performed (at screening and at the end of the treatment period). Clinical laboratory tests (haematology, chemistry and urinalysis) were performed at screening, week 4 and the end of the treatment period.

Statistical analyses
Efficacy was assessed in the intent-to-treat population. For continuously distributed outcomes, the mean change in an active-treatment group (SXB 4.5 g/night or SXB 6 g/night) was
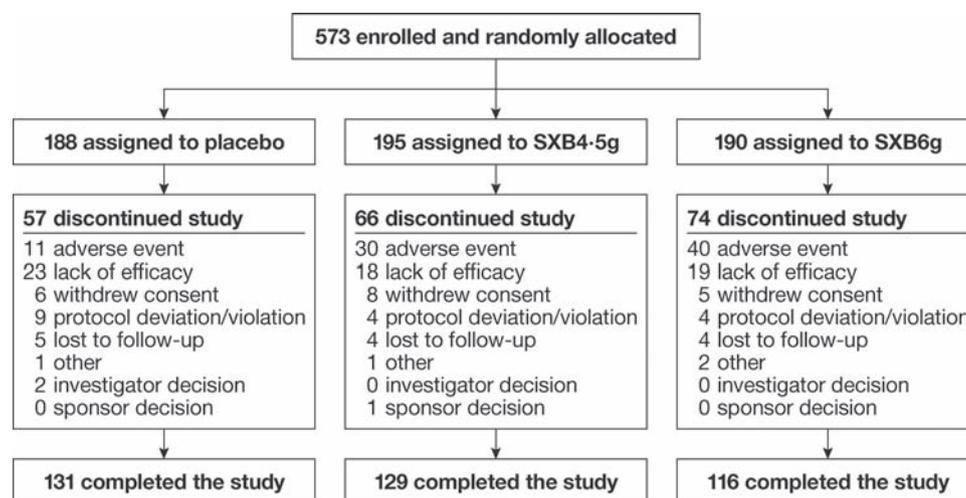
Figure 1 Subject disposition. SXB4.5g, sodium oxybate 4.5 g/night. SXB6g, sodium oxybate 6 g/night.

Table 1 Baseline demographic and clinical characteristics of the study population*

Characteristic	Placebo (n=188)	SXB4.5g (n=195)	SXB6g (n=190)	Total (N=573)
Age, years	46.8 (9.7)	46.6 (10.8)	46.4 (11.6)	46.6 (10.7)
Female, n (%)	168 (89.4)	175 (89.7)	170 (89.5)	513 (89.5)
Race, n (%)				
White	173 (92.0)	182 (93.3)	169 (88.9)	524 (91.4)
Black	10 (5.3)	11 (5.6)	18 (9.5)	39 (6.8)
Other	5 (2.7)	2 (1.0)	3 (1.6)	10 (1.7)
Body mass index, kg/m^2	27.4 (4.7)	27.4 (4.3)	28.0 (4.8)	27.6 (4.6)
Time since first fibromyalgia symptoms, years, mean (SD)	9.3 (7.9)	9.9 (8.8)	9.9 (9.5)	9.7 (8.8)
Time since first fibromyalgia diagnosis, years, mean (SD)	5.1 (6.3)	5.1 (5.5)	4.4 (5.0)	4.9 (5.6)
Previous pharmacological treatment for fibromyalgia, n (%)	182 (96.8)	185 (94.9)	182 (95.8)	549 (95.8)
Previous non-pharmacological treatment for fibromyalgia, n (%)	132 (70.2)	128 (65.6)	138 (72.6)	398 (69.5)
Baseline scores				
Pain VAS (scale 0–100)	72.6 (12.9)	70.5 (13.0)	72.2 (14.0)	71.8 (13.3)
Fatigue VAS (scale 0–100)	73.5 (15.0)	71.1 (15.4)	71.5 (17.2)	72.0 (15.9)
TPC (scale 0–18), median (range)†	18.0 (8, 18)	18.0 (11, 18)	18.0 (12, 18)	18.0 (8, 18)
TPI (scale 0–72)	39.5 (12.2)	37.9 (11.7)	38.2 (11.4)	38.6 (11.7)
MTPS (scale 0–180)	111.3 (33.3)	112.3 (32.4)	109.2 (30.9)	111.0 (32.2)
FIQ total score (scale 0–100)	63.7 (14.1)	62.3 (15.2)	62.1 (15.1)	62.7 (14.8)
SF-36 PCS (scale 0–100)	29.1 (7.9)	29.6 (8.7)	30.8 (7.5)	29.8 (8.1)
EQ-5D overall health state	46.6 (22.95)	48.8 (22.25)	47.4 (24.00)	47.6 (23.06)
JSS total score (scale 0–20), median (range)†	16.0 (3, 20)	16.0 (0, 20)	16.0 (2, 20)	16.0 (0, 20)
FOSQ (scale 5–20)	13.4 (3.8)	13.4 (3.8)	13.7 (3.8)	13.5 (3.8)
CGIS (scale 1–7)	4.3 (1.1)	4.5 (1.0)	4.4 (1.0)	4.4 (1.0)

*Except when indicated otherwise, values are mean (±SD).
†Median values are presented due to skewed distribution of data.
CGIS, clinical global impression of severity; EQ-5D, EuroQol-5 dimensions self-report questionnaire; FIQ, fibromyalgia impact questionnaire; FOSQ, functional outcomes of sleep questionnaire; JSS, Jenkins sleep scale; MTPS, manual tender point survey; PCS, physical component summary; SD, standard deviation; SF-36, Medical Outcomes Study 36-item short-form health survey; SXB4.5g, sodium oxybate 4.5 g/night; SXB6g, sodium oxybate 6 g/night; TPC, tender-point count; TPI, tender-point index; VAS, visual analogue scale.

compared with that for placebo using analysis of variance models adjusted for site and treatment-group-by-site interaction. If the p value for an interaction exceeded 0.1, the term was dropped from the model. For binary outcomes, a χ^2 test was used to compare the proportion of responders (percentage of subjects achieving a prespecified change) in an active-treatment group with placebo. All outcomes were assessed by last observation carried forward. In addition, all outcomes were assessed using the prespecified baseline observation carried forward method. Statistical analysis was performed using SAS version 9.1 for Windows, and all testing was two-sided with a significance level of 5%. Post-hoc correlation analyses using Pearson's correlation coefficient were performed between the FIQ subscale 7 (measure of restorative sleep) and pain VAS, fatigue VAS, global

assessments and JSS total score. In addition, a post-hoc analysis using Pearson's correlation coefficient was conducted between the changes in the JSS and FOSQ total scores with the changes in pain VAS, FIQ total score, PGIC and fatigue VAS. Finally, a post-hoc analysis was conducted of the proportion of subjects with a 14% or greater reduction in the FIQ total score, which is the minimal clinically important difference (MCID) in the FIQ.

All subjects who received at least one dose of study medication (SXB or placebo) were included in the safety analysis. AE, including serious AE, were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 9.1). Treatment-emergent AE were defined as events with onset, worsened severity or increased intensity on or after the date of randomisation and through the day after the last dose of study drug.

Subjects were counted once for maximum severity of an event, preferred term and system organ class.

The sample size of 525 subjects was planned based on data from an earlier study to provide at least 90% power to detect a target treatment difference in the primary endpoint for one dose of SXB based on χ^2 tests with a significance level of 5%.

RESULTS

Study subjects and baseline characteristics

A total of 573 subjects was randomly assigned and 376 subjects (65.6%) completed the study (figure 1). Although early discontinuations due to lack of efficacy occurred more frequently with placebo compared with SXB 4.5 g/night or SXB 6 g/night, the differences were less marked than for early discontinuations due to AE, which occurred in more subjects on SXB 4.5 g/night or SXB 6 g/night than on placebo (figure 1).

Baseline characteristics were well balanced across treatment groups; the majority of subjects were white and female (table 1). The mean baseline clinical global impression of severity score of 4.4 indicated moderately severe illness, and other baseline averages indicated clinically significant pain, fatigue, sleep impairment and impaired functionality.

Efficacy

Pain

During 14 weeks of treatment, pain was reduced with both SXB doses relative to placebo when assessed by multiple pain parameters. At week 14, the proportion of subjects with 30% or greater reduction in pain VAS, the primary efficacy endpoint, was significantly greater with SXB 4.5 g/night (42%, p=0.002) and SXB 6 g/night (51.4%, p<0.001) versus placebo (26.8%; table 2). Similarly, the proportion of subjects with 50% or greater reduction in pain VAS was significantly greater with both doses of SXB versus placebo (p≤0.003), and 80% or greater reduction in pain VAS was significantly greater with SXB 6 g/night versus placebo (p=0.003; table 2). Significant reductions in pain VAS were observed as early as week 1 and persisted through week 14 (figure 2A), indicating that pain reduction was rapid and sustained.

Categorical outcomes were analysed using the χ^2 test. Continuous outcomes were analysed using analysis of variance with treatment and centre as the factors. Interaction of centre by treatment was included if it was significant (p<0.1).

Tenderness

Significant differences were observed in MTPS for SXB 4.5 g/night and SXB 6 g/night and in tender-point count and tender-point index for the SXB 4.5 g/night group only versus placebo (table 2).

Fatigue

For both SXB doses, there were significant reductions in fatigue versus placebo (table 2). These decreases were observed as early as week 1 and persisted through week 14, suggesting rapid and sustained improvement (figure 2B).

Multidimensional function

Post-hoc analysis of the FIQ using the MCID of 14% or greater reduction in the total score[30] showed that significantly greater proportions of subjects reported clinically important differences with both SXB doses versus placebo (p<0.001; table 2). In a preplanned analysis, when a more stringent criterion of 30% or greater reduction in the FIQ total score was used to define moderate/good responders, significantly greater proportions of subjects in the SXB groups met the criterion versus placebo (p<0.001; table 2). Mean changes in total FIQ scores from
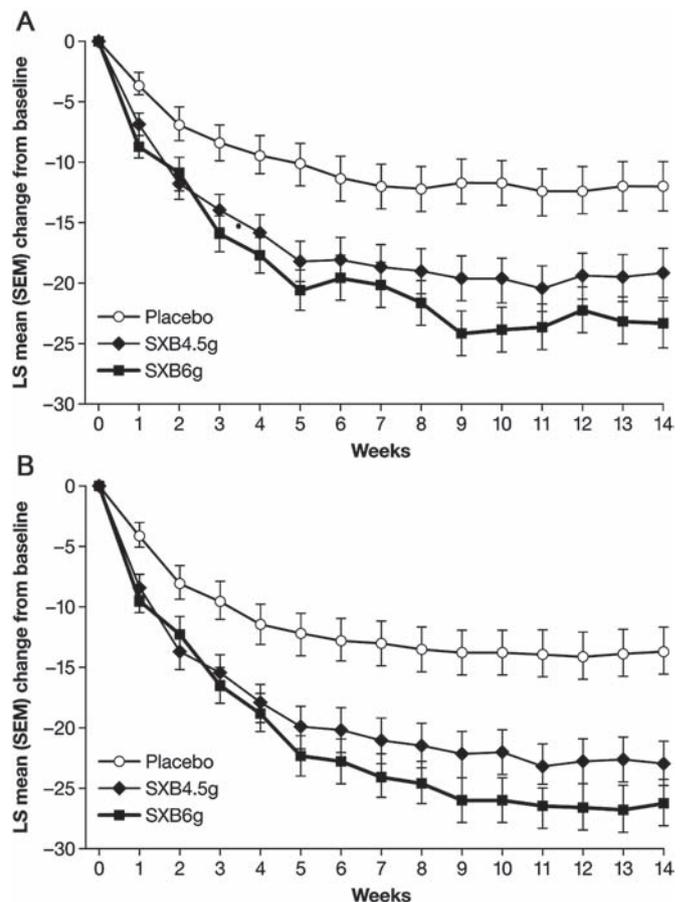

Figure 2 (A) Change from baseline in mean pain VAS score over time (ITT population, LOCF analysis). (B) Change from baseline in mean fatigue VAS score over time (ITT population, LOCF analysis). Note: error bars=SEM. ITT, intent to treat; LOCF, last observation carried forward; LS, least squares; SEM, standard error of LS mean; SXB4.5g, sodium oxybate 4.5 g/night; SXB6g, sodium oxybate 6 g/night; VAS, visual analogue scale.

baseline were significantly greater for both SXB doses versus placebo as early as week 1 and continued to week 14 (p<0.001 at all time points). The proportion of responders on the fibromyalgia syndrome composite score was significantly greater for SXB 4.5 g/night (p=0.005) and SXB 6 g/night (p<0.001) versus placebo. Analysis of the functional composite score based on the lower cut-off for SF-36 scores (≥5) demonstrated that significantly greater proportions of subjects treated with SXB 4.5 g/night (p=0.004) and SXB 6 g/night (p<0.001) showed significant clinical improvement versus placebo. Using an SF-36 cut-off of 6, the functional composite score showed that significantly greater proportions of subjects were responders with SXB 4.5 g/night (p=0.004) and SXB 6 g/night (p<0.001) versus placebo.

Significantly greater increases in the SF-36 physical component summary score were observed for SXB 4.5 g/night (p=0.002) and SXB 6 g/night (p=0.003) versus placebo, indicating a beneficial effect of SXB on physical functioning. Numerically greater increases in the EQ-5D overall health state scores were also observed for both SXB doses versus placebo.

Sleep

A significant improvement in sleep quality was observed by changes from baseline in JSS scores for SXB 4.5 g/night and SXB 6 g/night versus placebo (p<0.001). Improvements in functionality

Table 2 Changes in outcome variables from baseline to endpoint in subjects with fibromyalgia after blinded treatment with 4.5 g or 6 g sodium oxybate, compared with placebo*

Outcome	Placebo (n=188)	Sodium oxybate			
		4.5 g (n=195)	p Value vs placebo	6 g (n=190)	p Value vs placebo
Pain and tenderness					
Pain VAS					
n (%) of responders					
≥30% criteria	49 (26.8)	81 (42.0)	0.002	94 (51.4)	<0.001
≥50% criteria	28 (15.3)	54 (28.0)	0.003	69 (37.7)	<0.001
≥80% criteria	11 (6.0)	22 (11.4)	NS	29 (15.8)	0.003
Pain VAS (change in score from baseline)	−11.9±2.0	−19.2±2.0	0.010	−23.4±1.9	<0.001
Tender point					
TPC (change in score from baseline), median (range)†	0 (−16, 5)	0 (−16, 4)	0.003	0 (−17, 4)	NS
TPI (change in score from baseline)	−5.5±1.0	−9.1±1.0	0.007	−7.8±1.0	NS
MTPS (change in score from baseline)	−14.1±2.6	−27.9±2.6	<0.001	−21.7±2.6	0.036
Sleep and fatigue					
Fatigue VAS (change in score from baseline)	−13.7±1.9	−23.0±1.9	<0.001	−26.2±1.9	<0.001
JSS (change in score from baseline), median (range)†	−1.0 (−20, 7)	−4.0 (−18, 8)	<0.001	−5.0 (−20, 5)	<0.001
FOSQ (change in score from baseline)	1.0±0.3	2.1±0.3	0.003	2.1±0.3	0.004
Functionality and HRQOL					
FIQ (total score)					
n (%) of total FIQ responders					
≥14% criteria	79 (43.6)	119 (62.6)	<0.001	131 (70.8)	<0.001
≥30% criteria	54 (29.8)	95 (50.0)	<0.001	102 (55.1)	<0.001
Total FIQ (change in score from baseline)	−9.9±1.5	−19.2±1.5	<0.001	−20.6±1.5	<0.001
SF-36					
PCS (change in score from baseline)	3.6±0.7	6.4±0.7	0.002	6.3±0.7	0.003
EQ-5D overall health state					
EQ-5D (change in score from baseline)	5.1±2.2	9.2±2.2	NS	10.6±2.2	NS
Global impression of change					
PGIC responders‡ n (%)	29 (16.0)	61 (32.1)	<0.001	71 (39.7)	<0.001
CGIC responders§ n (%)	34 (18.7)	68 (35.4)	<0.001	69 (37.5)	<0.001
Composites					
Fibromyalgia composite responders¶ n (%)	21 (13.7)	42 (26.6)	0.005	53 (34.0)	<0.001
Functional composite responders** n (%)	15 (9.8)	34 (21.7)	0.004	40 (26.0)	<0.001

*Except when indicated otherwise, values are the least squares mean±SEM.
†Median values are presented due to skewed distribution of data.
‡Proportion of subjects who responded 'very much better' or 'much better'.
§Proportion of subjects whose disease was rated 'very much improved' or 'much improved' by the investigator.
¶Includes pain VAS (≥30% reduction), FIQ total score (≥30% reduction) and PGIC responders ('very much better' or 'much better').
**Includes pain VAS (≥30% reduction), PGIC ('very much better' or 'much better') and SF-36 PCS (≥6 increase) responders.
CGIC, clinical global impression of change; EQ-5D, EuroQol-5 dimensions self-report questionnaire; FIQ, fibromyalgia impact questionnaire; FOSQ, functional outcomes of sleep questionnaire; HRQOL, health-related quality of life; JSS, Jenkins sleep scale; MTPS, manual tender point survey; NS, not statistically significant; PCS, physical component summary; PGIC, patient global impression of change; SEM, standard error of least squares mean; SF-36, Medical Outcomes Study 36-item short-form health survey; TPC, tender-point count; TPI, tender-point index; VAS, visual analogue scale.

related to sleep, as measured by mean changes from baseline in FOSQ scores, were also significantly greater for SXB 4.5 g/night (p=0.003) and SXB 6 g/night (p=0.004) versus placebo.

In post-hoc analyses, there were strong correlations between the FIQ subscale 7, which is a subjective measure of restorative sleep ('tired upon awakening'; responses ranging from 0 indicating 'awoke well rested' to 10 indicating 'awoke very tired'), and pain VAS (r=0.68; p<0.001), fatigue VAS (r=0.78; p<0.001), global assessments (PGIC, r=0.59; p<0.001) and JSS total score (r=0.56; p<0.001). Strong correlations were also demonstrated between changes from baseline in pain VAS and fatigue VAS (r=0.84; p<0.001) and between the change in pain VAS and function (FIQ total score; r=0.78; p<0.001).

In addition, post-hoc analyses demonstrated a statistically significant association between the changes in sleep measures (JSS and FOSQ) and the changes in other clinical outcomes (pain VAS, FIQ total score, PGIC fatigue VAS). These associations were of moderate strength, with the highest correlation coefficient between the sleep measures and multidimensional function (FIQ). These data are presented in a supplementary table, available online only.

Global impression of change

Significantly greater proportions of subjects reported feeling 'much better' or 'very much better' at week 14 by PGIC with SXB 4.5 g/night and SXB 6 g/night versus placebo (both p<0.001; table 2). Similarly, significantly greater proportions of subjects in both SXB groups versus placebo (both p<0.001) had their condition rated as 'very much improved' or 'much improved' by investigators using the clinical global impression of change (table 2).

Number needed to treat

Table 3 shows the NNT for pain reduction and improvement in FIQ. The NNT represents the number of patients who would need to be treated with SXB for one additional patient to improve over the number of patients who would improve if placebo had been used. For all levels of pain reduction and multidimensional function, numerically fewer patients would need to be treated with SXB 6 g/night to obtain an improvement.

For all efficacy endpoints, results consistent with the last observation carried forward analysis were observed with the baseline observation carried forward analysis (data not shown).

Table 3 NNT for improvement in pain and multidimensional function estimated in a post-hoc analysis

	NNT (95% CI)	
	SXB4.5g	SXB6g
Pain VAS		
≥30%	7 (5 to 18)	5 (3 to 7)
≥50%	8 (5 to 23)	5 (4 to 8)
≥80%	19 (10 to ∞)	11 (7 to 29)
FIQ improvement		
≥14%	6 (4 to 12)	4 (3 to 6)
≥30%	5 (4 to 10)	4 (3 to 7)

FIQ, fibromyalgia impact questionnaire; NNT, number needed to treat; SXB4.5g, sodium oxybate 4.5 g/night; SXB6g, sodium oxybate 6 g/night; VAS, visual analogue scale.

Table 4 Most frequent treatment-emergent AE and AE leading to discontinuation

Number (%) of subjects with AE	Placebo (n=188)	SXB4.5g (n=194)	SXB6g (n=189)	Total (N=571)
Most frequent AE (≥5% and twice the placebo rate)				
Any AE	126 (67.0)	146 (75.3)	156 (82.5)	428 (75.0)
Nausea	16 (8.5)	37 (19.1)	40 (21.2)	93 (16.3)
Dizziness	3 (1.6)	23 (11.9)	25 (13.2)	51 (8.9)
Vomiting	6 (3.2)	10 (5.2)	16 (8.5)	32 (5.6)
Insomnia	6 (3.2)	15 (7.7)	8 (4.2)	29 (5.1)
Anxiety	3 (1.6)	10 (5.2)	15 (7.9)	28 (4.9)
Somnolence	3 (1.6)	7 (3.6)	11 (5.8)	21 (3.7)
Fatigue	4 (2.1)	6 (3.1)	11 (5.8)	21(3.7)
Muscle spasms	2 (1.1)	8 (4.1)	10 (5.3)	20 (3.5)
Oedema peripheral	4 (2.1)	3 (1.5)	12 (6.3)	19 (3.3)
Most frequent AE leading to discontinuation (≥3% and twice the placebo rate)				
Any AE leading to discontinuation	10 (5.3)	29 (14.9)	39 (20.6)	78 (13.7)
Nausea	1 (0.5)	6 (3.1)	10 (5.3)	17 (3.0)
Headache	0	4 (2.1)	8 (4.2)	12 (2.1)
Vomiting	1 (0.5)	3 (1.5)	6 (3.2)	10 (1.8)
Anxiety	1 (0.5)	1 (0.5)	6 (3.2)	8 (1.4)

AE, adverse event; SXB4.5g, sodium oxybate 4.5 g/night; SXB6g, sodium oxybate 6 g/night.

Tolerability and safety

The overall incidence of AE was comparable for SXB 4.5 g/night and SXB 6 g/night and higher than for placebo (table 4). Most AE were mild or moderate in severity. Treatment-emergent AE resulted in study discontinuation in 14.9% of SXB 4.5 g/night subjects and 20.6% of SXB 6 g/night subjects versus 5.3% for placebo.

The most frequently reported AE (≥5% and twice the rate for placebo) were nausea, dizziness, vomiting, insomnia, anxiety, somnolence, fatigue, muscle spasms and peripheral oedema. Eight subjects experienced treatment-emergent serious AE (three in the placebo, two in the SXB 4.5 g/night and three in the SXB 6 g/night groups); of these, two were considered to be related to study treatment (vomiting in one SXB 4.5 g/night subject and headache in one SXB 6 g/night subject). Weight loss was observed in the SXB-treated groups, with a mean (standard error) weight change from baseline of −1.19 (0.22) kg in the SXB 6 g/night group and −0.43 (0.20) kg in the SXB 4.5 g/night group compared with a mean weight gain of 0.43 (0.16) kg in the placebo group. There were no deaths. More subjects in the SXB groups discontinued the study due to an AE compared with placebo (14.9% for SXB 4.5 g/night, 20.6% for SXB 6 g/night and 5.3% for placebo); the most frequent AE leading to discontinuation (≥3% and twice that for placebo) were nausea, headache, vomiting and anxiety (table 4).

DISCUSSION

This is the first international study that evaluated the efficacy and safety of SXB in a large number of fibromyalgia patients. The rationale for using SXB was based on its ability to improve restorative sleep and the observation that disturbed sleep can cause hyperalgesia in chronic pain conditions by dysregulation of the descending pain inhibitory pathways.[31] It was hypothesised that the attainment of restorative sleep in SXB-treated patients should lead to a reduction in fibromyalgia-related pain and other symptoms by restoring a more normal balance in these pathways, which are known to be dysfunctional in fibromyalgia.[32] The improvement in sleep quality as reflected by changes in JSS (a validated measure for sleep quality in the fibromyalgia population)[24] and the improvement in 'tired upon awakening', one of the items in the FIQ that assesses sleep disturbance, suggest that SXB may improve restorative sleep in fibromyalgia patients. In addition, SXB treatment resulted in a statistically significant reduction in pain and fatigue with both SXB dose groups compared with placebo. Reductions in pain were demonstrated at 30% or greater and at 50% or greater and, in the SXB 6 g/night group, at 80% or greater pain reduction. Particularly for those patients experiencing higher levels of pain reduction, these findings represent clinically important changes that extend

beyond pain reduction and encompass a broad range of symptoms. The onset of pain reduction occurred relatively rapidly and was maintained during the 14-week trial in most patients. Tenderness, reflecting hyperalgesia and allodynia, a core domain to be assessed in all fibromyalgia clinical trials,[10] was decreased, as seen by a statistically significant reduction in MTPS.

Improvement was not limited to pain, as multiple symptoms and general health, measured by the FIQ total score and SF-36, were also improved. A reduction of 14% or greater in FIQ, achieved by 62.6–70.8% of the SXB groups, is consistent with the MCID definition,[33] whereas the reduction of 30% or greater in FIQ achieved by 50.0–55.1% of the SXB groups can be considered a moderate/good response. Moreover, the fibromyalgia syndrome composite score, which is a more stringent measure that includes pain, FIQ and PGIC, was significantly improved for both SXB 4.5 g/night and SXB 6 g/night versus placebo. In addition, a significant improvement in the functional composite score following both SXB doses versus placebo was observed, even when it was based on a more stringent cut-off value for the SF-36 (≥6; as established for fibromyalgia patients)[30] than the MCID (3–5).[34]

The estimated NNT for 50% or greater pain reduction for SXB 4.5 g/night and SXB 6 g/night, 8 and 5, respectively, compare favourably with an NNT of 6.4 for duloxetine (combined 60 and 120 mg doses) for a similar treatment period (12–13 weeks)[35] and are superior to the NNT of 16 for pregabalin 450 mg (the maximum recommended dose) for a 12-week treatment period.[36] This study is also the first to evaluate NNT for the improvement of multidimensional function (FIQ) and shows that four to six patients need to be treated to achieve clinically relevant improvements.

Several study limitations should be noted. There was a high rate of discontinuation; however, discontinuations in the current study were consistent with the 33–42% discontinuation rate in other fibromyalgia phase 3 clinical trials.[19 30 37–42] Another limitation, common to all clinical trials, is that the evaluated

population may not necessarily be representative of clinical practice. Demographically, the characteristics of patients in the current study were what may be expected clinically[43 44] and were comparable to study populations in clinical trials for the approved fibromyalgia agents (predominantly female, middle aged, Caucasian, overweight and with fibromyalgia symptoms for approximately 10 years).[30 35–40]

The results from this study, demonstrating the association of sleep quality restoration with the multidimensional improvements in fibromyalgia symptoms, are consistent with the long-held notion that non-restorative sleep may play a role in the pathophysiology of fibromyalgia[12] and reinforce the recommendation that the restoration of sleep quality should be a therapeutic aim in fibromyalgia.[10] However, this is a challenging goal as many current treatments, such as hypnotics and antidepressants, improve insomnia but may have limited effect on sleep quality and, in particular, non-refreshed sleep.[45] It is possible that SXB may improve fibromyalgia symptoms by other as yet unidentified mechanisms, aside from an improvement in sleep quality. Further analysis and mechanistic studies will be required to explore these possibilities.

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