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Sodium oxybate improves pain, fatigue, PGIc in fibromyalgia

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Introduction

The chronic condition known as fibromyalgia (FM) is primarily characterized by widespread and persistent musculoskeletal pain. While current guidelines have mainly focused on the treatment of pain,[1,2] patients with FM also frequently report the presence of myriad other symptoms including fatigue, impaired function, sleep disturbance, and depression.[3,4] The inclusion of these symptoms in a ranking of important patient concerns[5] suggests the need for broader treatment strategies.

Sodium oxybate (SXB) is the sodium salt of gamma-hydroxybutyrate (a metabolite of gamma-aminobutyric acid [GABA]). Its efficacy for the treatment of FM was demonstrated in proof of concept studies that showed reduced pain and fatigue as well as polysomnographic (PSG) improvements in sleep architecture relative to placebo.[6-8]

Objective

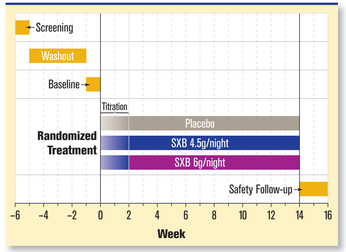
The objective of this phase III, multicenter, randomized, placebo-controlled clinical study was to evaluate the efficacy and safety of SXB oral solution at 4.5 and 6 g/night compared with placebo for the treatment of FM.

Methods

Study Design

- A Phase III, double-blind, randomized, multicenter, placebo-controlled trial (Figure 1)

Figure 1. Study Design



- Conducted in accordance with the Declaration of Helsinki; Institutional Review Board approval received for each study site; signed informed consent obtained from each subject enrolled
- Study periods:
  - Up to 30 days of washout following subject screening (up to 6 weeks in subjects who were referred for sleep apnea evaluation by polysomnography)
  - A 1-week baseline period during which pain scores (0–100 mm Visual Analogue Scale [VAS]) were recorded 3 times daily using an electronic patient diary
  - During the first 2 weeks of the treatment period, all randomized subjects began treatment with placebo or SXB 4.5 g/night; after the 2-week titration period, subjects randomized to SXB 6 g/night had their dose increased
- Dosing was equally divided between a dose at bedtime and another one 2.5 to 4 hours later

Eligibility Criteria

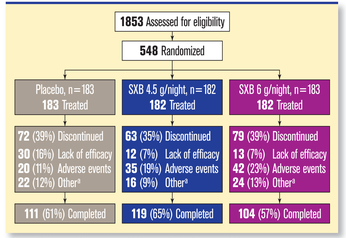
- Primary eligibility criteria
  - Inclusion criteria
    - Age ≥18 years
    - American College of Rheumatology classification criteria for FM[3]
    - Body mass index (BMI) <40 (PSG required for subjects with BMI ≥35 and <40 kg/m^2)
    - Average pain score of ≥50 mm on the VAS during the baseline period
    - Avoidance, for the duration of the study, of alcohol, opiates, benzodiazepines, muscle relaxants, anticonvulsants, antidepressants, dopamine agonists, tramadol, and/or other medications that might influence the efficacy outcome
    - Acceptable birth control during trial duration for women of childbearing potential
  - Exclusion criteria included the presence of an inflammatory rheumatic disease or a non-FM painful disorder; a medical, neurologic, or psychiatric disorder (including major depressive disorder and generalized anxiety disorder); sleep apnea not receiving stable continuous-positive-airway-pressure therapy; history of substance abuse disorder; succinic semialdehyde dehydrogenase deficiency; any prior exposure to SXB; investigational therapies within the prior 2 months; clinically significant laboratory or electrocardiogram abnormalities

Outcomes Assessments

- Pain (0–100 VAS) using a thrice daily electronic patient diary
  - Primary efficacy outcome was the proportion of subjects with ≥30% reduction in pain
  - Proportion of subjects with ≥50% reduction in pain was also assessed
- Fatigue (0–100 VAS) using a thrice daily electronic patient diary
- Fibromyalgia Impact Questionnaire (FIQ)[9]: a patient self-report questionnaire with a 1-week recall period that evaluates the impact of fibromyalgia on daily life
- Patient Global Impression of Change (PGIc; 7-point scale)
- Responder analysis: Pain Composite Responders were defined as the proportion of subjects with ≥30% reduction in pain and who also reported a PGIc response as "Much better" or "Very much better"
- Efficacy outcomes were based on last observation carried forward (LOCF)
- Outcomes were evaluated in the intent-to-treat population as change from baseline to end of double-blind phase at week 14
- Safety: adverse events (AEs), withdrawals due to AEs, laboratory analyses, and vital signs

Results

Figure 2. Disposition of Subjects



[a]Includes lost to follow-up, withdrawal of consent, protocol deviation/violation, and investigator or sponsor decision.

- A total of 548 subjects were randomized (Figure 2)
  - The safety population included all treated subjects (N=547)
  - 334 subjects (61%) completed the study

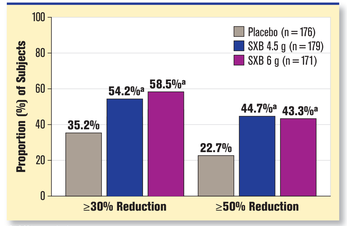
Table 1. Baseline Demographic and Clinical Characteristics

Characteristic		Placebo (n = 183)	SXB 4.5 g (n = 182)	SXB 6 g (n = 183)
Age:	Mean (SD), y	46.5 (11.4)	47.0 (11.8)	47.5 (10.6)
	≥65 years, n (%)	9 (4.9)	9 (4.9)	8 (4.4)
Sex, n (%):	Male	16 (8.7)	16 (8.8)	16 (8.7)
	Female	167 (91.3)	166 (91.2)	167 (91.3)
Race, n (%):	White	167 (91.3)	164 (90.1)	167 (91.3)
	Black	8 (4.4)	13 (7.1)	12 (6.6)
	Other	8 (4.3)	5 (2.8)	4 (2.1)
BMI, mean (SD), kg/m^2		28.9 (5.1)	28.1 (4.6)	28.4 (4.6)
Time since first FM symptoms, mean (SD), y		9.1 (7.3)	10.2 (9.6)	9.8 (8.4)
FIQ score [0–100], mean (SD)		63.3 (13.0)	63.0 (13.1)	62.4 (14.1)
Pain VAS [0–100mm], mean (SD)		71.6 (12.9)	71.9 (12.7)	72.3 (13.4)
Fatigue VAS [0–100mm], mean (SD)		73.6 (13.3)	72.9 (13.9)	74.6 (13.8)
Clinical Global Impression of Severity score [1–7], mean (SD)		4.3 (1.1)	4.3 (1.0)	4.3 (1.0)

BMI, body mass index; FIQ, Fibromyalgia Impact Questionnaire; FM, fibromyalgia; VAS, Visual Analogue Scale.

- Demographic characteristics were similar among the 3 treatment groups and were generally what could be expected for an FM population (Table 1)[10]
- Clinical characteristics related to fibromyalgia were also comparable among all groups (Table 1)
- Study entry requirement of pain VAS ≥50 mm resulted in a moderate/severe pain population

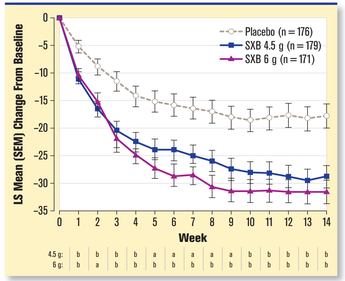
Figure 3. Proportion of Subjects Achieving Pain Reductions ≥30% and ≥50% at Week 14



[a]P<0.001 versus placebo.

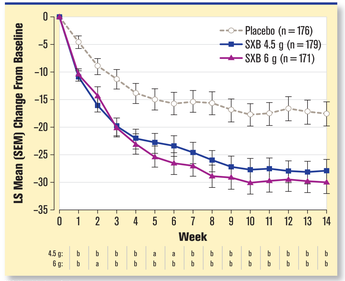
- The primary efficacy measure was the proportion of subjects who had ≥30% reduction in pain VAS from baseline to the end of the treatment period
- Both doses of SXB resulted in a significantly greater response for the primary efficacy endpoint relative to placebo
  - More than half the subjects on SXB had a reduction in pain ≥30%
- Additionally, the proportion of subjects with a reduction in pain ≥50% was significantly higher in both SXB groups relative to placebo
- Both of these levels of pain reduction are recommended for evaluation in chronic pain trials and are considered clinically relevant[11]
  - The 30% level represents moderate improvement and the 50% level represents substantial improvement[11]
- Significant divergence from placebo for reduction in pain was observed as early as 1 week after initiating treatment, with both dose groups of SXB resulting in significantly greater pain reduction relative to placebo (Figure 4)
- These differences were maintained, with SXB resulting in significantly greater improvement in pain relative to placebo over the duration of treatment (Figure 4)
- The decrease in pain VAS became greater for the SXB 6g group soon after titration from 4.5 g to 6 g (Week 2)
- Significant difference from placebo was observed for reduction of fatigue with SXB compared with placebo early as 1 week after initiating treatment (Figure 5)
- Both doses of SXB resulted in significantly greater improvement in fatigue relative to placebo over the duration of treatment

Figure 4. Change From Baseline in Pain VAS Scores During the 14-Week Duration of Treatment



VAS, Visual Analogue Scale.
[a]P<0.01 versus placebo; [b]P<0.001 versus placebo.

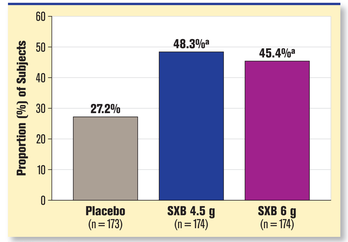
Figure 5. Change From Baseline in Fatigue VAS Scores During the 14-Week Duration of Treatment



VAS, Visual Analogue Scale.
[a]P<0.01 versus placebo; [b]P<0.001 versus placebo.

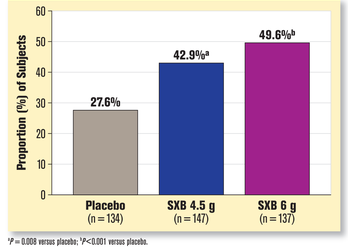
- The magnitude of change in fatigue VAS became greater for the SXB 6 g group soon after titration from 4.5 g to 6 g (Week 2) (Figure 5)
- At the end of the double-blind treatment phase, almost half of the subjects treated with SXB reported feeling "much better" or "very much better" (Figure 6)
  - These proportions were significantly greater for both SXB treatment groups compared with the placebo group
- Pain Composite Responders were defined as those subjects who at week 14 had a
  - ≥30% reduction from baseline in pain VAS and
  - PGIc response of "much better" or "very much better"
- The proportion of Pain Composite Responders was significantly higher for both SXB treatment groups relative to placebo (Figure 7)

Figure 6. Proportion of Subjects Who Reported Feeling "Much Better" or "Very Much Better" on the Patient Global Impression of Change (PGIc) at Week 14



[a]P<0.001 versus placebo.

Figure 7. Proportion of Subjects Meeting the Criteria for Pain Composite Responders



[a]P = 0.008 versus placebo; [b]P<0.001 versus placebo.

Table 2. Most Common Treatment-Emergent Adverse Events Having an Incidence ≥5% and at Least Twice the Rate of Placebo

Adverse Event, N (%)	Placebo (n = 183)	SXB 4.5 g (n = 182)	SXB 6 g (n = 182)
Headache	20 (11)	27 (15)	42 (23)
Nausea	10 (6)	26 (14)	39 (21)
Dizziness	5 (3)	24 (13)	31 (17)
Vomiting	7 (4)	8 (4)	19 (10)
Diarrhea	5 (3)	10 (6)	14 (8)
Anxiety	2 (1)	12 (7)	10 (6)
Sinusitis	1 (1)	12 (7)	8 (4)

- SXB was generally well tolerated
- The incidence of AEs was similar in the two SXB groups (82% and 80% for the 4.5 g and 6 g doses, respectively) and was higher than that observed with placebo (57%)
- Overall, 18% of subjects discontinued due to AEs; 11% of placebo, 19% of SXB 4.5 g, and 23% of SXB 6 g
- Adverse events were generally mild or moderate in severity
- Headache, nausea, and dizziness were the most common AEs reported (Table 2)

Conclusions

- Clinically meaningful improvements in pain were obtained with SXB
  - Pain was significantly improved relative to placebo as early as 1 week after initiating treatment and was maintained over the duration of the study
  - Among subjects treated with SXB, substantial improvements in pain (≥50% pain reduction) were achieved in more than 40%, and moderate improvements in pain (≥30% pain reduction) were achieved by greater than half the subjects
- Fatigue, a common complaint among patients with FM, was significantly reduced by SXB relative to placebo as early as 1 week after initiating treatment and was maintained over the study duration
- Reductions in pain and fatigue were paralleled by significantly greater proportions of subjects in the SXB treatment groups reporting global improvements relative to placebo
- Improvements on the Pain Composite, which required both a ≥30% pain reduction and a rating of "much better" or "very much better" on subject's global assessment of change, were significantly greater for both SXB treatment groups compared with the placebo treatment group
- SXB was well tolerated by subjects with FM in this trial; adverse events were generally mild or moderate in severity

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SXB is not approved by the FDA for the treatment of FM.

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