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Efficacy and Safety of AXS-12 in the Treatment of Narcolepsy: Results from a Phase 2, Double-Blind, Placebo-Controlled, Crossover Trial

CONCERT STUDY

Cedric O'Gorman[2], Amanda Jones[2], Angad Chhabra[2], Michael J. Thorpy[1], Herriot Tabuteau[2]

[1]Sleep-Wake Disorders Center, Montefiore Medical Center, Bronx, NY; [2]Axsome Therapeutics, New York, NY

AXSOME THERAPEUTICS

22 Cortlandt St, 16th Floor, New York, NY 10007 USA

For more information, please contact Cedric O'Gorman at **cogorman@axsome.com**

Introduction

Narcolepsy is a chronic and debilitating neurological condition

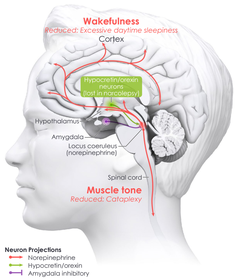
- Narcolepsy causes dysregulation of the sleep-wake cycle and is characterized clinically by excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations, sleep paralysis, and disrupted nocturnal sleep[1,2]
- Narcolepsy afflicts an estimated 185,000 individuals in the U.S. but is considerably both under-recognized and under-diagnosed, with approximately 50% of patients in the U.S undiagnosed[3,4]
- Cataplexy, occurring in an estimated 70% of narcolepsy patients, is a sudden reduction or loss of muscle tone while a patient is awake, typically triggered by strong emotions such as laughter, fear, anger, stress, or excitement
- Narcolepsy interferes with cognitive, psychological, and social functioning, increases the risk of work- and driving-related accidents, and is associated with a 1.5 fold higher mortality rate

There is an urgent need for new treatment options

- Existing treatment options are limited, do not address all symptoms, provide variable efficacy, have significant side effects, and are mostly controlled substances

AXS-12, a Highly Potent and Selective Norepinephrine Reuptake Inhibitor - Scientific Rationale for its Development in Narcolepsy

- AXS-12 (reboxetine) is a highly selective and potent norepinephrine reuptake inhibitor
- The scientific rationale for developing AXS-12 for the treatment of narcolepsy is based on mechanistic evidence and positive in vivo nonclinical results
- Results of physiological and pharmacological studies in canine narcolepsy models suggest a strong role for adrenergic neurotransmission in cataplexy[5]
- In orexin-deficient mice, a well-validated animal model of human narcolepsy, reboxetine treatment markedly and dose-dependently reduced episodes of cataplexy and sleep attacks[6]



- Narcolepsy Type 1 is caused by a loss of hypocretin neurons in the brain[7]
- Hypocretin neurons normally excite norepinephrine neurons which promote wakefulness and help maintain muscle tone[8]
- Hypocretin loss leads to dysregulation of norepinephrine neurons resulting in[8]:
  - Decreased wakefulness during the day (EDS)
  - Loss of muscle tone while awake (cataplexy)
- AXS-12 improves regulation of norepinephrine signaling in narcolepsy
- AXS-12 modulates noradrenergic activity to promote wakefulness, maintain muscle tone and enhance cognition

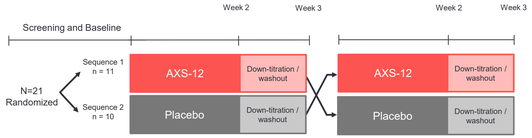
References

1. American Academy of Sleep Medicine. ICSD-2. Chicago, IL: 2005. 2. España RA, Scammell TE. Sleep. 2011;34(7):845-858. 3. Ahmed I, Thorpy M. Clin Chest Med. 2010;31(2):371-381. 4. Punjabi N et al. Sleep. 2000;23(4):471-480. 5. Nishino S, Mignot E. Prog Neurobiol. 1997 May;52(1):27-78. 6. Schmidt et al. Behav Brain Res. 2016 Jul 15;308:205-10. 7. Thorpy MJ, Krieger A. Sleep Med. 2014 May;15(5):502-7. 8. Szabo ST, et al. *Sleep Medicine Reviews* 43 (2019) 23-36.

Objective and Design of the CONCERT Trial

- The objective of the CONCERT trial was to evaluate the efficacy and safety of AXS-12 in the treatment of cataplexy and EDS as compared to placebo in patients with narcolepsy
- The CONCERT trial was a Phase 2, randomized, double-blind, placebo-controlled, 3-week crossover, multicenter, U.S. trial
- Patients with a confirmed diagnosis of narcolepsy with cataplexy were randomized in a 1:1 ratio either to treatment with AXS-12 followed by placebo (sequence 1), or to treatment with placebo followed by AXS-12 (sequence 2)

CONCERT Phase 2 Trial Design



Primary Endpoint:
- Change in the mean weekly number of cataplexy attacks, averaged over the 2-week treatment period (overall treatment effect)

Key Secondary Endpoints:
- Daytime sleepiness, measured by the Epworth Sleepiness Scale (ESS) and number of inadvertent naps
- Cognitive function assessed using the Ability to Concentrate item of the Narcolepsy Symptom Assessment Questionnaire (NSAQ)
- Sleep quality and sleep-related symptoms (incl. nighttime awakenings, sleep paralysis, and hypnagogic hallucinations items of the NSAQ)

Dose:
- Week 1: orally twice daily, total daily dose of 8 mg
- Week 2: orally twice daily, total daily dose of 10 mg

Key Inclusion Criteria:
- Adults with diagnosis of narcolepsy exhibiting cataplexy
- Male or female 18 – 70 years old
- ESS Score > 10
- A weekly average of at least 7 cataplexy attacks

Key Exclusion Criteria:
- Concurrent sleep disorder

Demographics and Baseline Characteristics

	All Subjects (n=21)
Mean Age (years)	32.6 (9.90)
Female gender, n (%)	81.0%
Race, n (%)	
White	66.7%
Black or African American	28.6%
Mean time since diagnosis (years)	3.8 (3.27)
Mean (ESS) Score at Baseline	18.1 (2.62)
Weekly average cataplexy attacks at Baseline	30.0 (30.23)
"Good" or "Very Good" Ability to Concentrate at Baseline	0%

Data are mean (SD) unless otherwise stated.

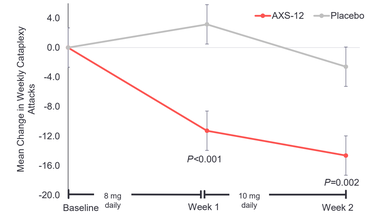
- Baseline disease severity represents patients with a confirmed diagnosis of narcolepsy with cataplexy

Safety and Tolerability

- AXS-12 was safe and well tolerated
- 42.9% of patients reported adverse events (AEs) when receiving AXS-12 compared to 40.0% with placebo
- There were no serious AEs or discontinuations due to AEs
- Most commonly reported AEs with AXS-12 were anxiety, constipation, and insomnia

Results

Rapid and Significant Reduction in Cataplexy Attacks



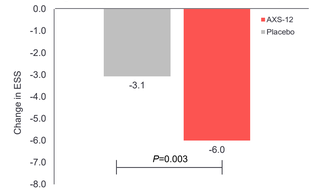
Primary Endpoint	AXS-12	Placebo	*P*-Value
Overall Change in Average Weekly Cataplexy Attacks	-13.0	-0.3	<0.001

Notes: *P*-value calculated from LSMean.

- AXS-12 achieved the primary endpoint by demonstrating a statistically significant reduction from baseline in the mean weekly number of cataplexy attacks, averaged for the 2-week treatment period, as compared to placebo (p<0.001)
- At Week 2, AXS-12 was associated with a statistically significant mean reduction from baseline in the weekly number of cataplexy attacks as compared to placebo (p=0.002), representing mean reductions from baseline of 48.8% and 8.6%, respectively
- The proportion of patients achieving a 50% or greater reduction in the weekly number of cataplexy attacks was 76.2% for AXS-12, compared to 30.0% for placebo at Week 2 (p=0.003)
- The effect of AXS-12 on cataplexy was rapid with AXS-12 demonstrating a statistically significant improvement in the frequency of cataplexy as compared to placebo as early as Week 1 (p<0.001)

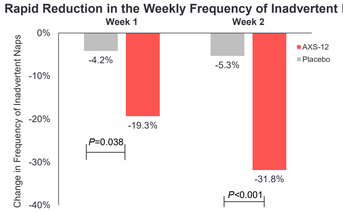
Rapid and Substantial Improvement in Excessive Daytime Sleepiness

Change in Epworth Sleepiness Scale (ESS) Score



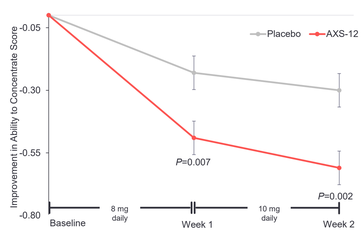
- AXS-12 demonstrated a statistically significant reduction in ESS score from baseline as compared to placebo, with mean reductions of 6.0 vs. 3.1 points, respectively (p=0.003)

Rapid Reduction in the Weekly Frequency of Inadvertent Naps



- AXS-12 demonstrated a statistically significant reduction from baseline in the mean weekly number of inadvertent naps as compared to placebo at Week 1 (19.3% vs. 4.2%; p=0.038) and Week 2 (31.8% vs. 5.3%; p<0.001)

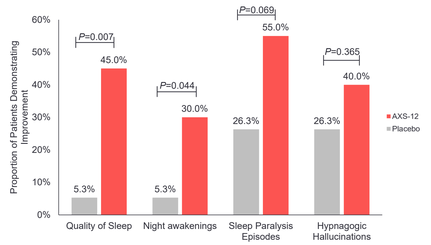
Rapid and Significant Improvement in Cognitive Function



- AXS-12 significantly improved cognitive function compared to placebo as measured by daily assessment of the Ability to Concentrate item of the Narcolepsy Symptom Assessment Questionnaire (NSAQ) (p<0.001)
- AXS-12 rapidly improved the ability to concentrate compared to placebo at Week 1 (p=0.007)
- Ability to concentrate was collected daily on a 5-point scale (1= very good, 2 = good, 3 = average, 4 = poor, 5 = very poor)

- None of the patients at study entry rated their ability to concentrate as good or better
- After 1 week of treatment with AXS-12, 38.1% of patients described their ability to concentrate as "very good" or "good" compared to 15.0% of patients treated with placebo
- After 2 weeks of treatment with AXS-12, 42.9% of patients described their ability to concentrate as "very good" or "good" compared to 25.0% of patients treated with placebo

Improved Sleep Quality Demonstrated Across Multiple Measures



- AXS-12 treatment resulted in greater proportion of patients demonstrating improvement in quality of sleep (45.0% vs. 5.3%; p=0.007), number of night awakenings (30.0% vs. 5.3%; p=0.044), sleep paralysis episodes (55.0% vs. 26.3%; p=0.069), and in hypnagogic hallucinations (40.0% vs. 26.3%; p=0.365), as compared to placebo

Conclusions

- **AXS-12 met the primary endpoint resulting in a highly statistically significant reduction in the number of cataplexy attacks as compared to placebo**
- **AXS-12 rapidly and significantly reduced excessive daytime sleepiness, assessed by the Epworth Sleepiness Scale and by the frequency of inadvertent naps or sleep attacks, as compared to placebo**
- **AXS-12 resulted in statistically significant improvements in cognitive function, sleep quality and other sleep-related symptoms**
- **The beneficial effects of AXS-12 were rapid being observed as early as Week 1**
- **AXS-12 was safe and well-tolerated with no reported serious adverse events (SAEs) and no discontinuations due to adverse events**

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Disclosures: COG, AJ, AC and HT are employees of Axsome Therapeutics. MJT is a consultant to Axsome Therapeutics.