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

Cedric O’Gorman, Amanda Jones, Angad Chhabra, Michael J. Thorpy,1 Herriot Tabuteau2
1Sleep-Wake Disorders Center, Montefiore Medical Center, Bronx, NY; 2Axsome Therapeutics, New York, NY

Introduction

Narcolepsy is a chronic and debilitating neurological condition

- Narcolepsy is characterized by excessive daytime sleepiness (EDS), cataplexy, hypnic hallucinations, sleep paralysis, and disrupted nocturnal sleep.
- Narcolepsy affects an estimated 150,000 individuals in the U.S., but is incompletely understood and underdiagnosed, with approximately 50% of patients in the U.S.
- Cataplexy, occurring in an estimated 70% of narcolepsy patients, is a sudden reduction of muscle tone, while otherwise fully 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 Noradrenergic Reuptake Inhibitor

- AXS-12 is a potent and selective noradrenergic 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 animal models suggest a strong noradrenergic effect in narcolepsy.
- In an opossum model, a well-validated animal model of human narcolepsy, reboxetine treatment markedly and dose-dependently reduced episodes of cataplexy.

Objective and Design of the CONCERT Trial

- AXS-12 was evaluated for the safety and efficacy of AXS-12 in the treatment of cataplexy and EDS as compared to placebo in patients with narcolepsy.
- 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).
- The CONCERT trial was a Phase 2, randomized, double-blind, placebo-controlled, 3-week crossover trial, multi-site, U.S. trial.
- The CONCERT Phase 2 Trial Design was completed in May 2018.

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)
- Change in the mean weekly number of inadvertent naps
- Change in self-reported ability to concentrate
- Change in frequency of sleep paralysis episodes
- Change in hypnic hallucinations
- Change in the frequency of body jolt episodes
- Change in quality of life
- Change in the frequency of morning headaches
- Change in the frequency of early morning sleep
- Change in the frequency of sleepwalking
- Change in the frequency of nightmare episodes
- Change in the frequency of narcolepsy-related EDSS

Results

Rapid and Significant Reduction in Cataplexy Attacks

- AXS-12 demonstrated a statistically significant reduction from baseline in the mean weekly number of cataplexy attacks, averaged for the 3-week treatment period, as compared to placebo (p=0.002).
- At Week 2, AXS-12 was associated with a statistically significant mean reduction from baseline in the mean weekly number of cataplexy attacks, as compared to placebo (p<0.001).
- In clinical trials with reboxetine, a comparable noradrenergic reuptake inhibitor, patients with narcolepsy showed a significant reduction in the frequency of cataplexy attacks as early as Week 1 (p<0.001).

- AXS-12 met the primary endpoint resulting in a highly statistically significant reduction in the frequency of cataplexy as compared to placebo.
- AXS-12- treated patients reported fewer cataplexy episodes than placebo-treated patients, as evidenced by a 31.8% reduction in the mean number of cataplexy episodes from baseline to Week 2, as compared to placebo.
- AXS-12 met the primary endpoint resulting in a highly statistically significant reduction in the frequency of cataplexy as compared to placebo.
- AXS-12 was safe and well-tolerated with no reported serious adverse events (SAEs) and no discontinuations due to adverse events.

References

- España RA, Scammell TE. Sleep. 2011;34(7):845-858.
- 11th World Congress on Narcolepsy, 2018.
- 10th World Congress on Narcolepsy, 2016.
- 9th World Congress on Narcolepsy, 2014.
- 8th World Congress on Narcolepsy, 2012.
- 7th World Congress on Narcolepsy, 2010.
- 6th World Congress on Narcolepsy, 2008.
- 5th World Congress on Narcolepsy, 2006.
- 4th World Congress on Narcolepsy, 2004.
- 3rd World Congress on Narcolepsy, 2002.
- 1st World Congress on Narcolepsy, 1998.