NASDAQ: AXSM

AXSOME THERAPEUTICS

Axsome Announces AXS-12 for Narcolepsy

Conference Call

October 16, 2018

AXS-12 and Unmet Needs in Narcolepsy

Introduction	**Mark Jacobson**, Senior Vice President, Operations
Summary	**Herriot Tabuteau, MD**, Chief Executive Officer
AXS-12 Overview and Clinical Development	**Cedric O'Gorman, MD**, Senior Vice President, Clinical Development & Medical Affairs
Narcolepsy: Clinical Features, Treatment Options, and Potential for AXS-12	**Michael J. Thorpy, MB, ChB**, Professor of Neurology, Albert Einstein College of Medicine
Q&A	**Presenters & Nick Pizzie**, Chief Financial Officer
Closing Remarks	**Herriot Tabuteau, MD**, Chief Executive Officer

Forward-Looking Statements & Safe Harbor

Certain information contained in this presentation may include “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. We may, in some cases, use terms such as “predicts,” “believes,” “potential,” “continue,” “estimates,” “anticipates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “will,” “should” or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. In particular, the Company’s statements regarding trends and potential future results are examples of such forward-looking statements. The forward-looking statements include risks and uncertainties, including, but not limited to, the success, timing and cost of our ongoing clinical trials and anticipated clinical trials for our current product candidates, including statements regarding the timing of initiation and completion of the trials, interim analyses and receipt of interim results; the timing of and our ability to obtain and maintain U.S. Food and Drug Administration or other regulatory authority approval of, or other action with respect to, our product candidates; the Company’s ability to obtain additional capital necessary to fund its operations; the Company’s ability to generate revenues in the future; the Company’s ability to successfully defend its intellectual property or obtain the necessary licenses at a cost acceptable to the Company, if at all; the successful implementation of the Company’s research and development programs; the enforceability of the Company’s license agreements; the acceptance by the market of the Company’s product candidates, if approved; and other factors, including general economic conditions and regulatory developments, not within the Company’s control. These factors could cause actual results and developments to be materially different from those expressed in or implied by such statements. Forward-looking statements are not guarantees of future performance, and actual results may differ materially from those projected. The forward-looking statements are made only as of the date of this presentation and the Company undertakes no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstance.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. Neither we nor any other person makes any representation as to the accuracy or completeness of such data or undertakes any obligation to update such data after the date of this presentation. In addition, these projections, assumptions and estimates are necessarily subject to a high degree of uncertainty and risk.

Summary

Herriot Tabuteau, MD

AXSOME THERAPEUTICS

Chief Executive Officer
Axsome Therapeutics, Inc.

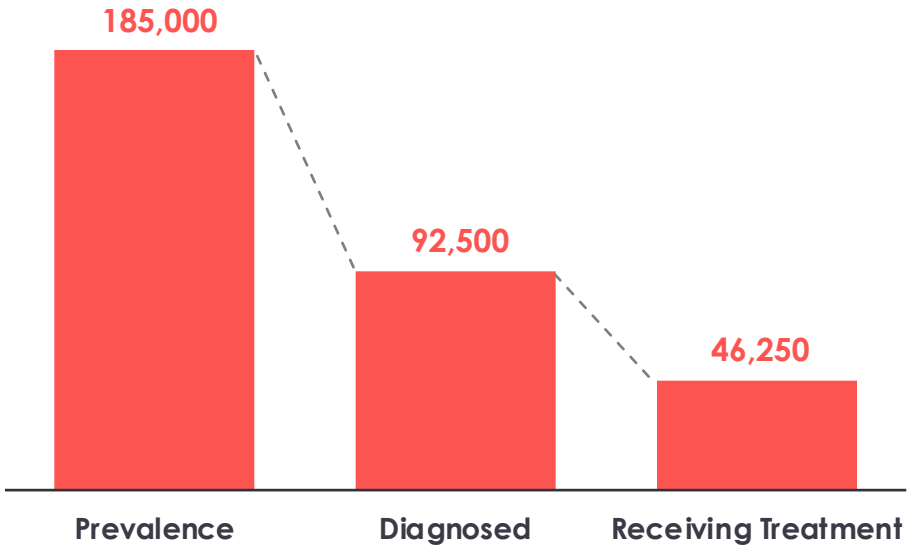
Narcolepsy:
AXS-12 (reboxetine) Summary

- Narcolepsy: chronic, debilitating, orphan neurologic condition characterized by excessive daytime sleepiness (EDS) and cataplexy.
- Existing treatment options are limited, do not address all symptoms, provide variable efficacy, have significant side effects, and are all controlled substances.
- AXS-12 has the potential to address both cataplexy and EDS symptoms of narcolepsy and would not be scheduled.
- Phase 2 start anticipated in 4Q 2018 with data readout estimated in 1H 2019.
  - Trial already included in current financial guidance: cash runway in to 1Q 2020.
- Expands Axsome's CNS pipeline and adds another potentially value-driving near-term catalyst.

Narcolepsy: U.S. Patient Population in Need

FDA Narcolepsy Report Conclusion:

"Thus, there is a continued need for additional effective and tolerable treatment options for patients to improve their daily functioning."



- Only one drug (sodium oxybate) currently approved for cataplexy
  - $1.19 Billion in 2017 revenues with only 13K patients treated

AXS-12 Overview and Clinical Development

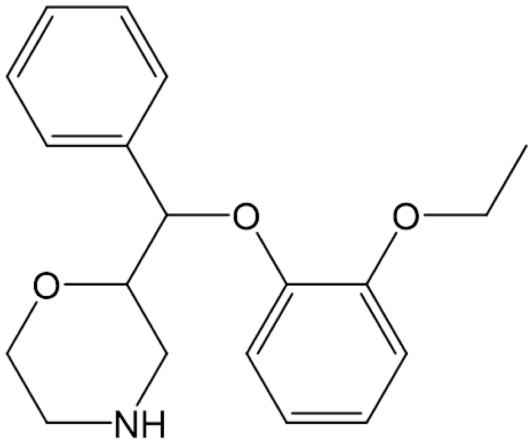
Cedric O'Gorman, MD, MBA

AXSOME THERAPEUTICS

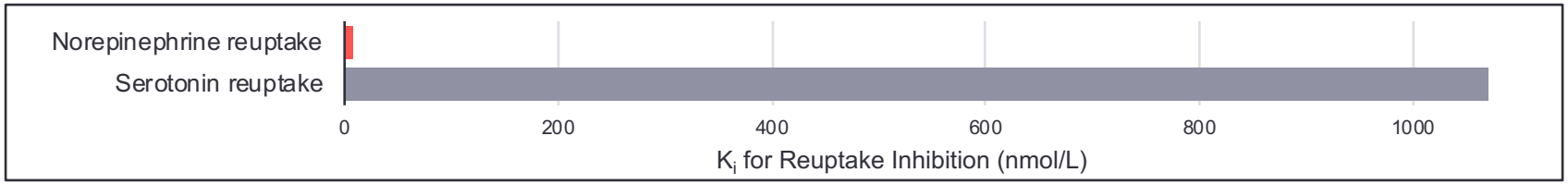
Senior Vice President, Clinical Development and Medical Affairs
Axsome Therapeutics, Inc.

Narcolepsy:
AXS-12 (reboxetine) Overview

- AXS-12 (reboxetine) is a potent, selective norepinephrine reuptake inhibitor.
- New chemical entity
  - Approved for depression in over 40 countries outside of the U.S.
  - Large safety database, well tolerated
- Scientific rationale
  - Positive effects in genetic mouse narcolepsy model
  - Positive pilot trial in patients with narcolepsy
  - Depression reported in 57% of narcoleptics[1]



Reboxetine Selectivity for Norepinephrine Reuptake in Rat Hypothalamic Synaptosomes



Adapted from Wong et al. Biol Psychiatry. 2000 May 1;47(9):818-29.

1. Daniels E et al. *J Sleep Res*. 2001;10:75-81.

Narcolepsy:
AXS-12 (reboxetine) Clinical Development

- FDA Pre-IND Meeting written guidance received: agreement on proposed clinical development plan.
- Preparations underway for IND filing
- Intend to initiate Phase 2 trial in 4Q 2018
  - Randomized, placebo-controlled trial
- Phase 2 top-line results expected in 1H 2019
- Phase 3 planned 2H 2019 assuming successful Phase 2 outcome

AXSOME THERAPEUTICS

Narcolepsy: Clinical Features, Treatment Options, and Potential for AXS-12

Michael Thorpy, MB, ChB

EINSTEIN
Albert Einstein College of Medicine

Professor of Neurology
Albert Einstein College of Medicine

Director of the Sleep-Wake Disorders Center
Montefiore Medical Center, Bronx, New York

Narcolepsy: Clinical Overview

- Debilitating and incurable neurologic disorder that disrupts the boundaries between sleep and wake states[1-3]
- Characterized by:
  - Excessive Daytime Sleepiness (EDS)
  - Cataplexy
  - Hypnagogic hallucinations
  - Sleep paralysis
  - Disturbed nocturnal sleep
- Patients usually present initially with EDS
- Two distinct groups of patients with narcolepsy:
  - Those with cataplexy (Type 1 narcolepsy as per the ICSD-3 classification)
  - Those without cataplexy (Type 2 narcolepsy as per the ICSD-3 classification)

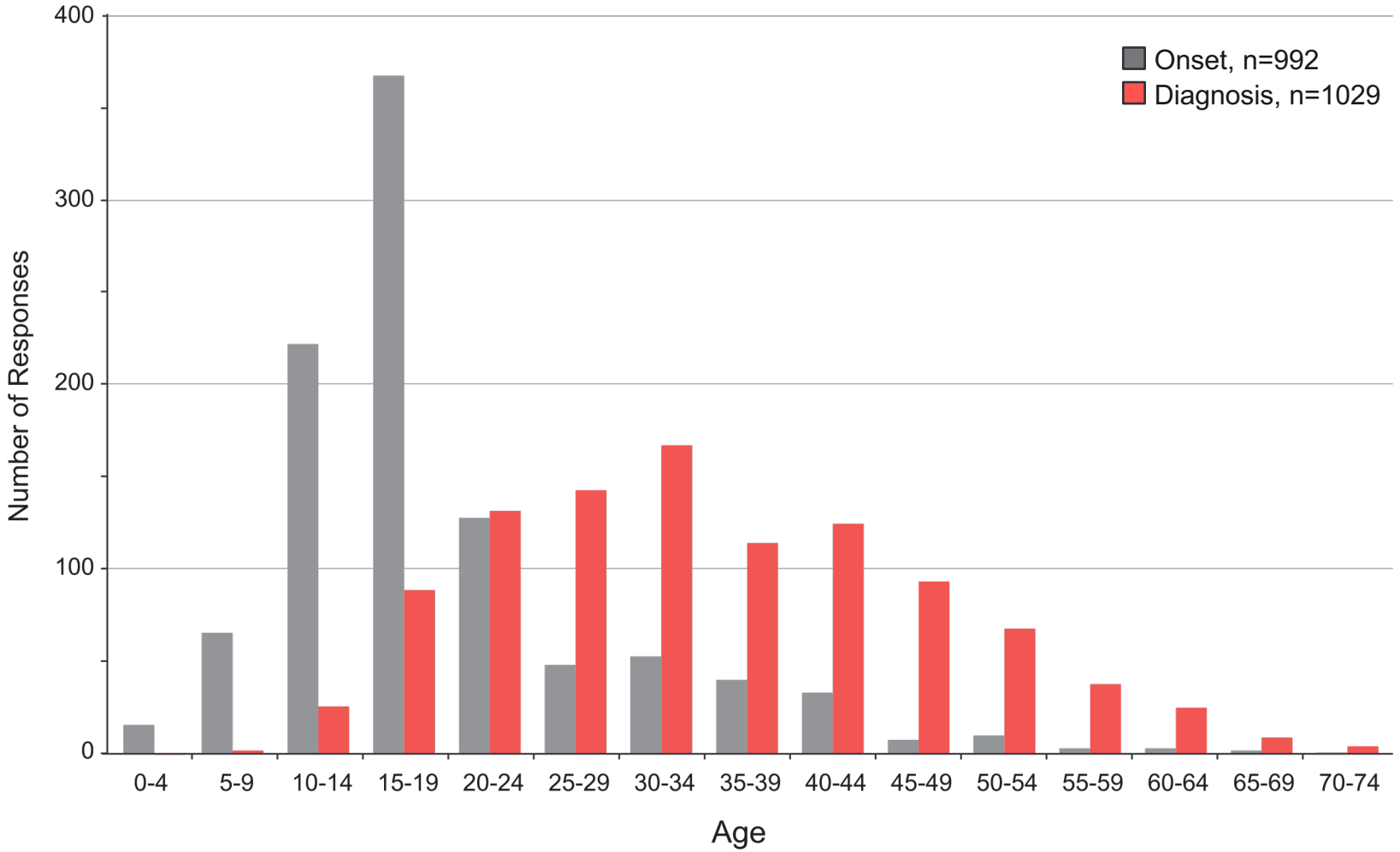
1. American Academy of Sleep Medicine. ICSD-2. Chicago, IL: 2005.
2. National Institute of Neurological Disorders and Stroke. 2011. http://www.ninds.nih.gov/disorders/narcolepsy/narcolepsy.htm. Accessed July 15, 2013.
3. España RA, Scammell TE. *Sleep*. 2011;34(7):845-858.

Narcolepsy: Under-diagnosis

- Under-recognized and under-diagnosed[1,2]
  - Approximately 50% of the nearly 200,0000 patients in the U.S. are undiagnosed
- It may take patients many years to receive a definitive narcolepsy diagnosis[3,4]
- Time to diagnosis is between 8-15 years[1,2]
- Many patients see at least two physicians before getting a diagnosis[5]

1. Ahmed I, Thorpy M. *Clin Chest Med*. 2010;31(2):371-381.
2. Punjabi N et al. *Sleep*. 2000;23(4):471-480.
3. Morrish E, et al. *Sleep Med*. 2004;5(1):37-41.
4. US MOD Study Group. *Neurology*. 2000;54(5):1166-1175.
5. Kryger MH, Walid R and Manfreda J. Diagnoses received by narcolepsy patients in the year prior to diagnosis by a sleep specialist. *Sleep*. 2002;25:36-41.

Narcolepsy:
Age of Symptom Onset versus Age of Diagnosis



1. Thorpy MJ, Krieger A. Delay in Diagnosis of Narcolepsy. *Sleep Med*. 2014 May;15(5):502-7.

Narcolepsy:
Type 1 Narcolepsy Diagnostic Criteria[1]

Criteria A and B must be met:

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months

B. The presence of one or both of the following:

1. Cataplexy (as defined under *Essential Features*) and a mean sleep latency of ≤8 minutes and ≥2 Sleep-Onset REM Periods (SOREMPs) on an Mean Sleep Latency Test (MSLT) performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal PSG may replace one of the SOREMPs on the MSLT
2. CSF hypocretin-1 concentrations measured by immunoreactivity either <110 pg/mL or <⅓ of mean values obtained in normal subjects with the same assay

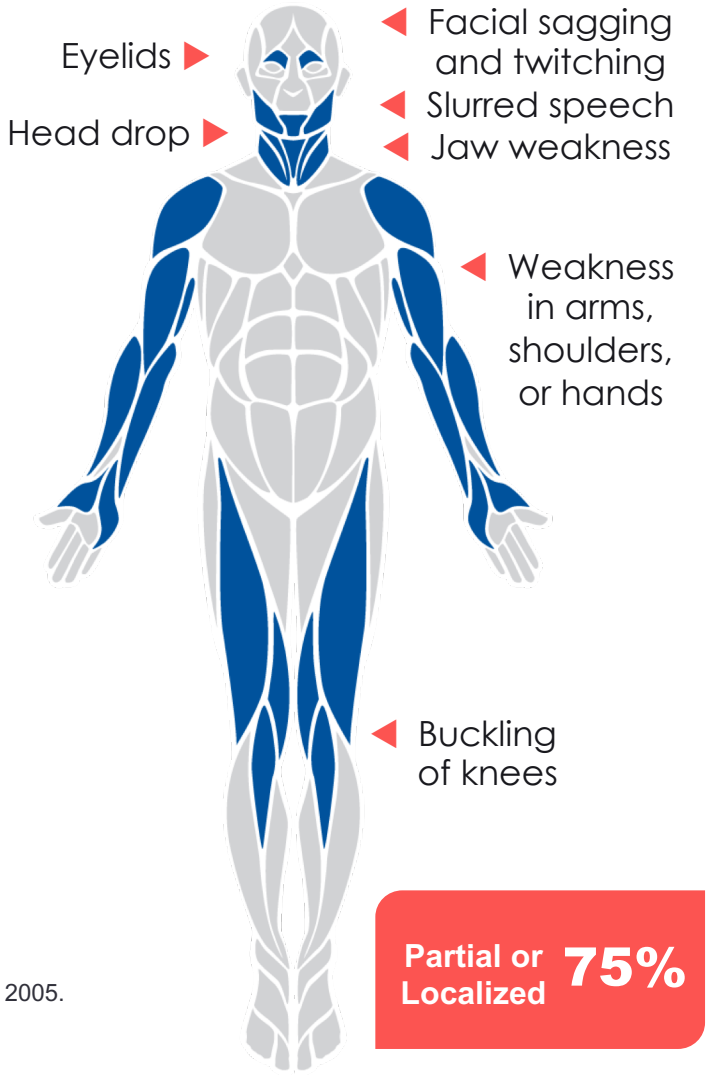
Note:

1. In young children, narcolepsy may sometimes present as excessively long night sleep or by resumption of previously discontinued daytime napping
2. If narcolepsy Type 1 is strongly suspected clinically but criteria B2 are not met, a possible strategy is to repeat the MSLT

1. American Academy of Sleep Medicine. The International Classification of Sleep Disorders. 3rd ed.; 2014.

Narcolepsy:
Cataplexy in Narcolepsy

- Pathognomonic for narcolepsy
- Sudden and transient loss or reduction of muscle tone
- Triggered by strong emotions:
  - Laughter, elation, surprise, anger
- Typically partial or localized (~75%)
- Usually of short duration
- Frequency varies widely
- Narcolepsy with cataplexy can be socially disabling and isolating



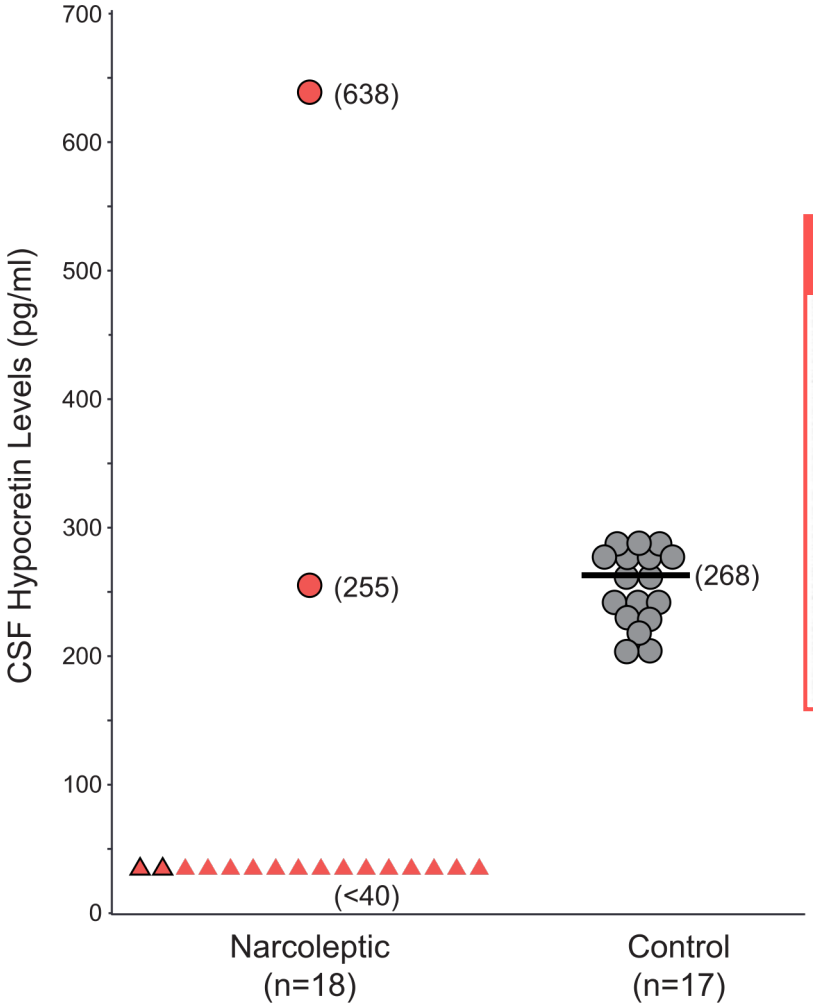
1. American Academy of Sleep Medicine. The International Classification of Sleep Disorders. 2nd ed.; 2005.
2. Overeem S et al. *Sleep Med*. 2011;12(1):12-18.
3. Ahmed I, Thorpy M. *Clin Chest Med*. 2010;31(2)371-381.

Narcolepsy: Pathophysiology Overview

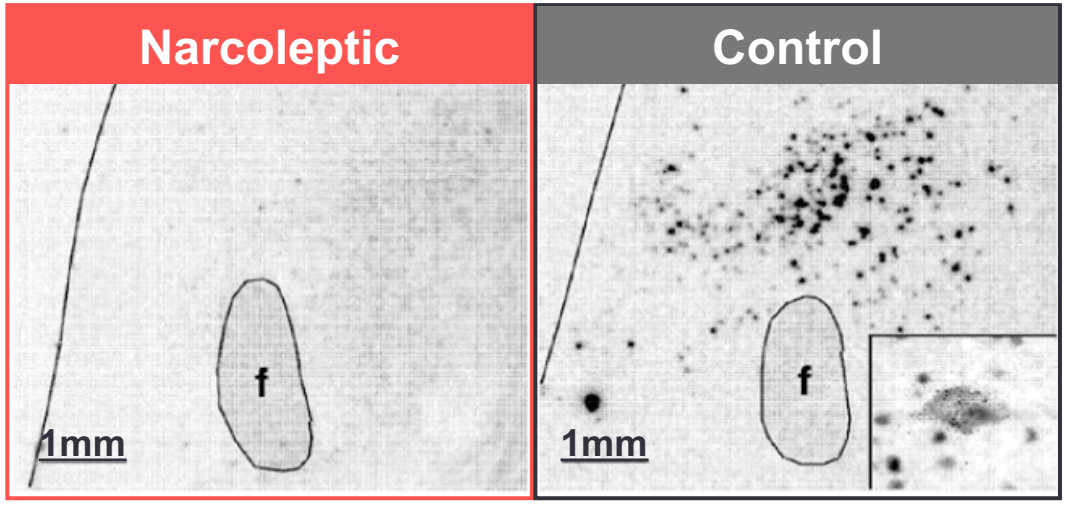
- Hypocretins (orexins) are hypothalamic-specific peptides with neuroexcitatory activity[1]
- Narcolepsy with cataplexy (Type 1) is an autoimmune disorder resulting in a loss of hypocretin (orexin)-producing neurons in the CNS[2]:
  - Occurs in predisposed individuals with specific genetic markers including human leukocyte antigen (HLA DQB1⁄06:02) and T-cell receptor alpha variants
- Not all cases of narcolepsy are associated with loss of hypocretin neurons
- Narcolepsy can also be precipitated by seasonal Streptococcus infections, H1N1 influenza, and H1N1 vaccination in genetically predisposed individuals

1. de Lecea L et al. *Proc Natl Acad Sci U S A*. 1998 Jan 6;95(1):322-7.
2. Thorpy MJ, Krieger A. *Sleep Med*. 2014 May;15(5):502-7.

Narcolepsy:
Hypocretin Deficiency in Human Narcolepsy



Preprohypocretin mRNA in the Lateral Hypothalamic Area



f; fornix

Adapted from Nishino S et al. *Lancet*. 2000 Jan 1;355(9197):39-40, and Peyron C et al. *Nat Med*. 2000 Sep;6(9):991-7.

Narcolepsy: Goals of Treatment

- Reduce daytime sleepiness
- Reduce cataplexy
- Control ancillary symptoms:
  - Nightmares and unpleasant frequent dreams
  - Hallucinations
  - Sleep paralysis
  - Disturbed nocturnal sleep
- Improve psychosocial and work functioning
- Improve safety of patient and public

Narcolepsy: Current Narcolepsy Management

- Excessive daytime sleepiness (EDS) – Approved agents:
  - Stimulants (methylphenidate, amphetamines)
  - Modafanil (Provigil®) / armodafanil (Nuvigil®)
- Cataplexy:
  - Only 1 approved treatment: sodium oxybate (Xyrem®)
  - Off-label treatments: tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs)

Narcolepsy: Need for Additional Treatment Options

- Relatively few treatment options:
  - Only 5 approved agents
  - Only 1 agent approved to treat both cataplexy and EDS
- Limitations of current agents:
  - Variability of effect
  - Tolerability issues
  - Failure to address all key symptoms of narcolepsy
  - All current agents are DEA-scheduled

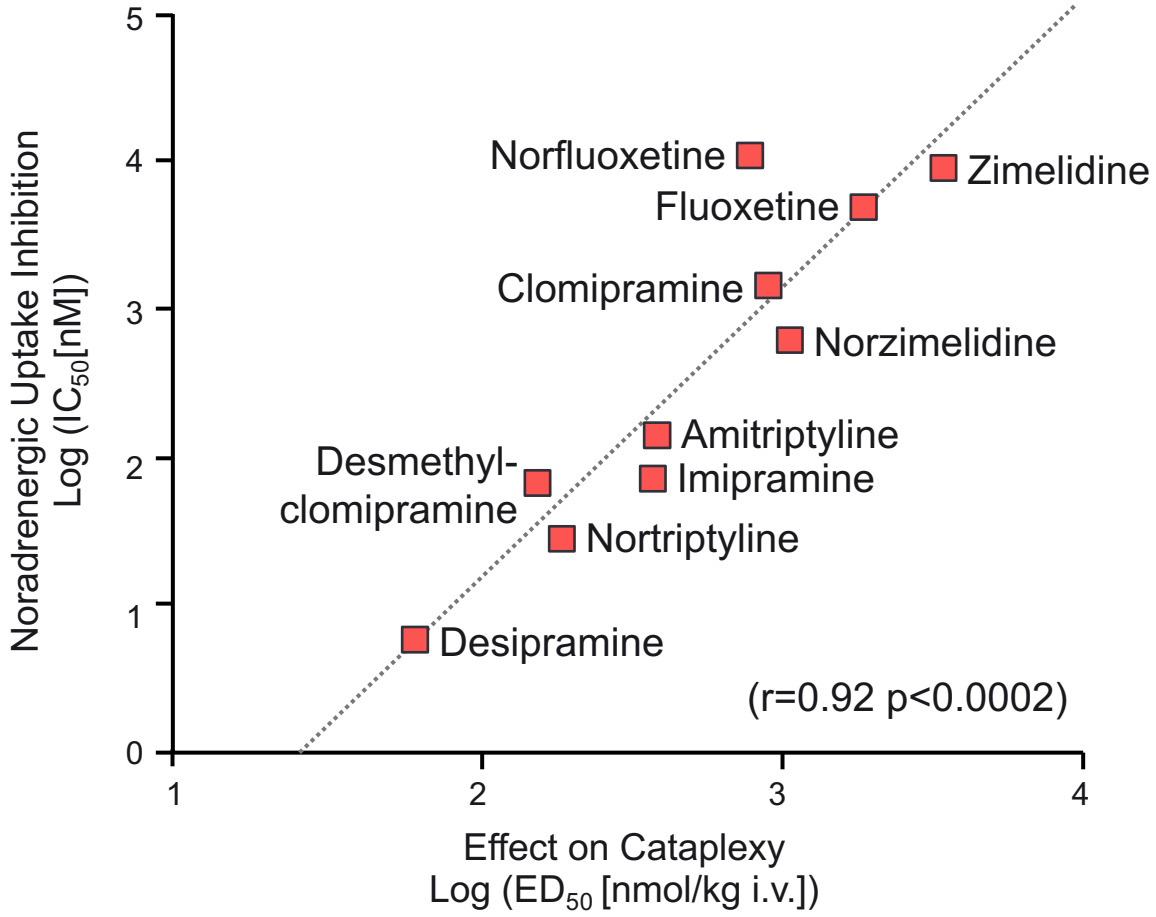
Narcolepsy:
AXS-12 (reboxetine) Potential in Narcolepsy

- AXS-12 (reboxetine) is a highly selective and potent norepinephrine reuptake inhibitor[1]
- Potential in narcolepsy is supported by:
  - Mechanistic evidence for importance of norepinephrine transmission in narcolepsy
  - Studies in hypocretin (orexin)-deficient mouse model of narcolepsy
  - Preliminary clinical data from published human pilot trial
- American Academy of Sleep Medicine (AASM) Narcolepsy Guidelines:
  - Reboxetine recommended for treatment of cataplexy, and as an option for sleep paralysis and hypnagogic hallucinations, even though it is not available in the U.S.[2]

1. Wong EH et al. *Biol Psychiatry*. 2000 May 1;47(9):818-29.
2. Morgenthaler TI. *Sleep*. 2007 Dec;30(12):1705-11.

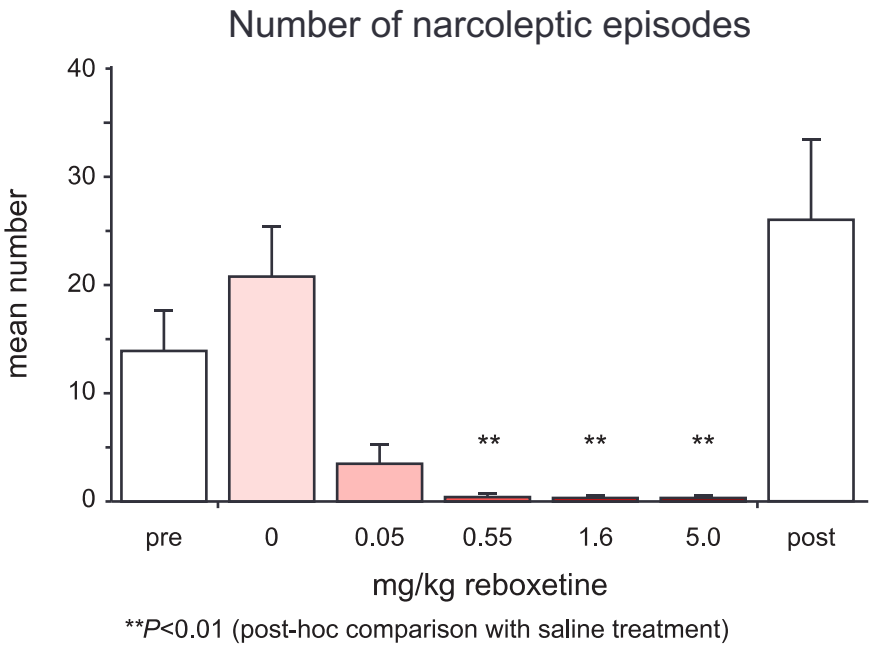
Narcolepsy:
Norepinephrine reuptake inhibition and cataplexy

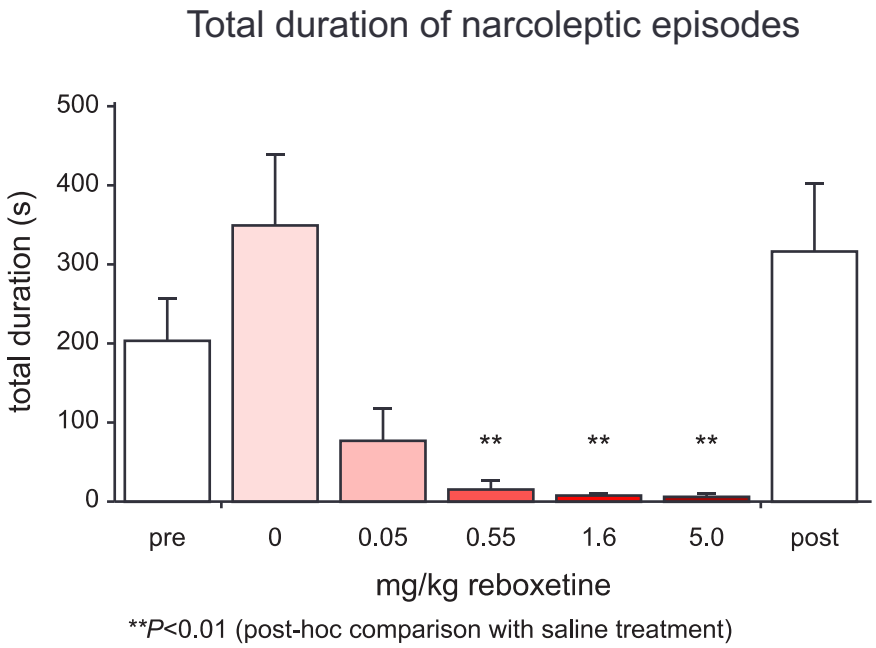
- Norepinephrine reuptake inhibition correlates with inhibition of cataplexy in canine narcolepsy



Nishino S, Mignot E. *Prog Neurobiol.* 1997 May;52(1):27-78.

Narcolepsy:
Reboxetine Effective in Mouse Narcolepsy Model

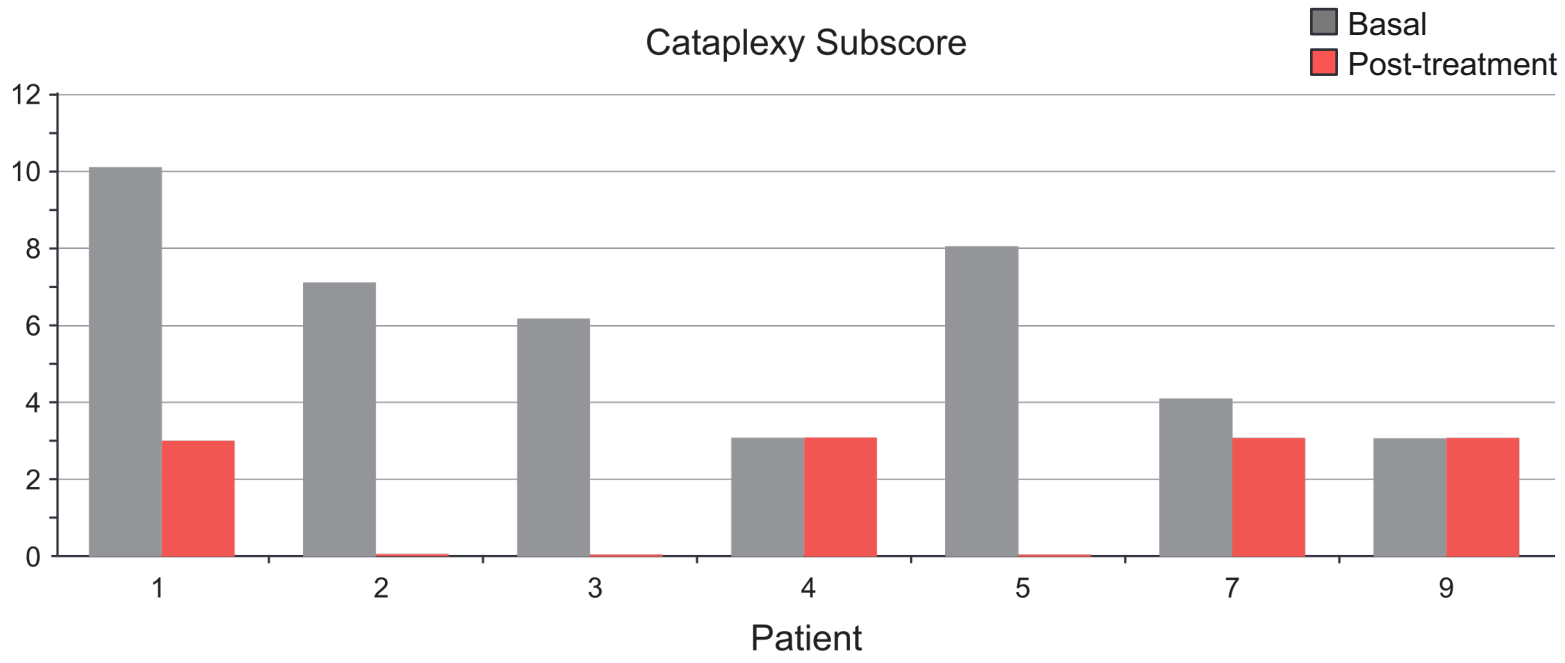




- Reboxetine dose-dependently reduced the number of narcoleptic episodes in hypocretin (orexin)-deficient mice (P<0.0001)
- Reboxetine significantly more potent than the SSRI escitalopram: median effective dose (ED_{50}) for reboxetine of 0.012 mg/kg), and for escitalopram of 0.44 mg/kg

Adapted from Schmidt et al. *Behav Brain Res.* 2016 Jul 15;308:205-10.

Narcolepsy: Reboxetine Effects in Patients with Narcolepsy



- 12 narcolepsy patients treated for 2 weeks with reboxetine (up to 10 mg) under open conditions
- 71% decrease in the cataplexy subscore on the UNS. Of 7 patients with cataplexy at baseline, 5 improved with scores going to zero for 3 patients
- Mean increase of 54.7% in sleep latency on the MSLT with 8 out of 12 patients experiencing an improvement of at least 65%

Adapted from Larossa et al. *Sleep*. 2001 May 1;24(3):282-5.

Narcolepsy: Conclusions

- Narcolepsy is a debilitating neurological disorder with limited treatment options
- Limitations of current treatments include variable effects, tolerability, inability to address all symptoms, and DEA scheduling
- AXS-12 is a potential new treatment for cataplexy and EDS
- Potential of AXS-12 is supported by mechanistic evidence, effects in mouse model, and preliminary clinical data from pilot human trial with reboxetine
- Potential efficacy and safety of AXS-12 in cataplexy in patients with narcolepsy will be evaluated in upcoming Phase 2 clinical trial

Q&A

Closing Remarks

Herriot Tabuteau, MD

AXSOME THERAPEUTICS

Chief Executive Officer
Axsome Therapeutics, Inc.

Clinical Milestones

Product Candidate	Indication	2018	2019
AXS-05 (DM + BUP)	**TRD**	✓ **STRIDE-1** interim analysis ● **STRIDE-1** interim efficacy analysis (4Q 2018)	● **STRIDE-1** top-line results (1H 2019)
	AD Agitation	● **ADVANCE-1** interim analysis (4Q 2018)	● **ADVANCE-1** interim efficacy analysis ● **ADVANCE-1** top-line results (2H 2019/1H 2020)
	MDD	✓ **Ph 2** trial start ● **Ph 2** top-line results (4Q 2018)	
	Smoking Cessation	✓ **Ph 2** trial start	● **Ph 2** top-line results (1Q 2019)
AXS-07 (MoSEIC™ Mx + Riz)	**Migraine**	● **Ph 3** trial start (4Q 2018)	● **Ph 3** top-line results
AXS-12 (Reboxetine)	**Narcolepsy**	● **Ph 2** trial start (4Q 2018)	● **Ph 2** top-line results (1H 2019)

Abbreviations: AD = Alzheimer's Disease; BUP = Bupropion; DM = Dextromethorphan; MDD = Major Depressive Disorder; Mx = Meloxicam; OA = Osteoarthritis; Riz = Rizatriptan; *S*-BUP = Esbupropion; TRD = Treatment Resistant Depression.

✓ Accomplished milestone.

● Upcoming milestone.

AXSOME

THERAPEUTICS

Thank you.

axsome.com