

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): December 07, 2023

Axsome Therapeutics, Inc.

(Exact name of Registrant as Specified in Its Charter)

Delaware
(State or Other Jurisdiction
of Incorporation)

001-37635
(Commission File Number)

45-4241907
(IRS Employer
Identification No.)

One World Trade Center, 22nd Floor
New York, New York
(Address of Principal Executive Offices)

10007
(Zip Code)

Registrant's Telephone Number, Including Area Code: (212) 332-3241

(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, Par Value \$0.0001 Per Share	AXSM	Nasdaq Global Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Item 8.01 Other Events.

On December 7, 2023, Axsome Therapeutics, Inc. (the “Company”) held its “Solriamfetol Investor Day Event.” A copy of the press release dated December 7, 2023 announcing this event is filed as Exhibit 99.1 hereto and a copy of the materials used in connection with this event are filed as Exhibit 99.2 hereto, and both are incorporated by reference herein.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press Release dated December 7, 2023.
99.2	Corporate Presentation.
104	Cover Page Interactive Data File (embedded within the Inline XBRL document).

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Axsome Therapeutics, Inc.

Date: December 7, 2023

By: /s/ Herriot Tabuteau, M.D.
Name: Herriot Tabuteau, M.D.
Title: President and Chief Executive Officer



Axsome Therapeutics Hosts Solriamfetol Virtual Investor Event with Expert Thought Leaders Today

NEW YORK, Dec. 7, 2023 (Globe Newswire) – Axsome Therapeutics, Inc. (NASDAQ: AXSM), a biopharmaceutical company developing and delivering novel therapies for the management of central nervous system (CNS) disorders, is hosting a virtual investor event and conference call today from 8 a.m. – 10 a.m. Eastern Time to provide an update on solriamfetol, a dual-acting dopamine and norepinephrine reuptake inhibitor (DNRI) and trace amine-associated receptor 1 (TAAR1) agonist.

At the event, invited physician thought leaders will discuss current and potential future indications. The Axsome senior leadership team will provide an overview of clinical development plans. The presenters will be available to answer questions at the end of the presentations. To access the event, please click here.

Expert thought leaders presenting at the event include:

- **Craig Chepke, MD**, Medical Director of Excel Psychiatric Associates in Huntersville, N.C. and Adjunct Associate Professor of Psychiatry for Atrium Health. Dr. Chepke will provide an overview of TAAR1 signaling and major depressive disorder (MDD).
- **Andrew Cutler, MD**, Clinical Associate Professor of Psychiatry SUNY Upstate Medical University. Dr. Cutler will provide an overview of attention deficit hyperactivity disorder (ADHD).
- **Susan McElroy, MD**, Chief Research Officer and Director of Psychopharmacology Research at the Lindner Center of HOPE at the University of Cincinnati. Dr. McElroy will provide an overview of binge eating disorder (BED).
- **Richard Bogan, MD**, Associate Clinical Professor at the University of South Carolina School of Medicine and at the Medical University of South Carolina in Charleston, S.C., and is Principal of Bogan Sleep Consultants. Dr. Bogan will provide an overview of the SHARP study of solriamfetol in patients with excessive daytime sleepiness (EDS) associated with obstructive sleep apnea (OSA), and impaired cognitive function.
- **Charles Czeisler, MD, PhD**, Baldino Professor of Sleep Medicine, Director of the Division of Sleep Medicine at Harvard Medical School and Chief of the Division of Sleep Medicine in the Department of Medicine at Brigham and Women's Hospital in Boston. Dr. Czeisler will provide an overview of shift work disorder (SWD).

Webcast and Conference Call Information

A live webcast of the event can be accessed on the "Webcasts & Presentations" page of the "Investors" section of the Company's website at www.axsome.com. To participate in the live conference call, please dial (877) 405-1239 (toll-free domestic). A replay of the webcast will be available for approximately 30 days following the live event.

About Solriamfetol

Solriamfetol is a dual-acting dopamine and norepinephrine reuptake inhibitor and trace amine-associated receptor 1 (TAAR1) agonist. Solriamfetol is protected by a robust patent estate with expiries out to 2042.

About Axsome Therapeutics, Inc.

Axsome Therapeutics, Inc. is a biopharmaceutical company developing and delivering novel therapies for central nervous system (CNS) conditions that have limited treatment options. Through development of therapeutic options with novel mechanisms of action, we are transforming the approach to treating CNS conditions. At Axsome, we are committed to developing products that meaningfully improve the lives of patients and provide new therapeutic options for physicians. For more information, please visit the Company's website at axsome.com. The Company may occasionally disseminate material, nonpublic information on the company website.

Forward Looking Statements

Certain matters discussed in this press release are “forward-looking statements”. 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 continued commercial success of our Sunosi® and Auvelity® products and the success of our efforts to obtain any additional indication(s) with respect to solriamfetol and/or AXS-05; 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, pace of enrollment and completion of the trials (including our ability to fully fund our disclosed clinical trials, which assumes no material changes to our currently projected revenues or expenses), futility analyses and receipt of interim results, which are not necessarily indicative of the final results of our ongoing clinical trials, and the number or type of studies or nature of results necessary to support the filing of a new drug application (“NDA”) for any of our current product candidates; our ability to fund additional clinical trials to continue the advancement of our product candidates; the timing of and our ability to obtain and maintain U.S. Food and Drug Administration (“FDA”) or other regulatory authority approval of, or other action with respect to, our product candidates; whether issues identified by FDA in the complete response letter may impact the potential approvability of the Company’s NDA for AXS-07 for the acute treatment of migraine in adults with or without aura, pursuant to our special protocol assessment for the MOMENTUM clinical trial; 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 and collaborations; the success of the Company’s license agreements; the acceptance by the market of the Company’s products and product candidates, if approved; the Company’s anticipated capital requirements, including the amount of capital required for the continued commercialization of Sunosi and Auvelity and for the Company’s commercial launch of its other product candidates, if approved, and the potential impact on the Company’s anticipated cash runway; unforeseen circumstances or other disruptions to normal business operations arising from or related to COVID-19; and other factors, including general economic conditions and regulatory developments, not within the Company’s control. The factors discussed herein could cause actual results and developments to be materially different from those expressed in or implied by such statements. The forward-looking statements are made only as of the date of this press release and the Company undertakes no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstance.

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nasdaq: axsm



Solriamfetol Investor Day

December 7, 2023

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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 continued commercial success of our Sunosi® and Auvelity® products and the success of our efforts to obtain any additional indication(s) with respect to solriamfetol and/or AXS-05; 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, pace of enrollment and completion of the trials (including our ability to fully fund our disclosed clinical trials, which assumes no material changes to our currently projected revenues or expenses), futility analyses and receipt of interim results, which are not necessarily indicative of the final results of our ongoing clinical trials, and the number or type of studies or nature of results necessary to support the filing of a new drug application (“NDA”) for any of our current product candidates; our ability to fund additional clinical trials to continue the advancement of our product candidates; the timing of and our ability to obtain and maintain U.S. Food and Drug Administration (“FDA”) or other regulatory authority approval of, or other action with respect to, our product candidates; whether issues identified by FDA in the complete response letter may impact the potential approvability of the Company’s NDA for AXS-07 for the acute treatment of migraine in adults with or without aura, pursuant to our special protocol assessment for the MOMENTUM clinical trial; 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 and collaborations; the success of the Company’s license agreements; the acceptance by the market of the Company’s products and product candidates, if approved; the Company’s anticipated capital requirements, including the amount of capital required for the continued commercialization of Sunosi and Auvelity and for the Company’s commercial launch of its other product candidates, and the potential impact on the Company’s anticipated cash runway; unforeseen circumstances or other disruptions to normal business operations arising from or related to COVID-19; and other factors, including general economic conditions and regulatory developments, not within the Company’s control. The factors discussed herein could cause actual results and developments to be materially different from those expressed in or implied by such statements. The forward-looking statements are made only as of the date of this press release and the Company undertakes no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstance..

This presentation contains statements regarding the Company’s observations based upon the reported clinical data. This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about the Company’s 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.

Axsome, Auvelity, Sunosi, and MoSEIC, are trademarks or registered trademarks of Axsome Therapeutics, Inc. or its affiliates. Except as with respect to Auvelity and Sunosi for their approved indications, the development products referenced herein have not been approved by the FDA.



Today's KOL Speakers



Craig Chepke, MD, DFAPA
Medical Director of Excel Psychiatric Associates
Adjunct Associate Professor of Psychiatry for
Atrium Health



Susan McElroy, MD
Chief Research Officer and Director of
Psychopharmacology Research at the Lindner
Center of HOPE at the University of Cincinnati



Charles Czeisler, MD, PhD
Baldino Professor of Sleep Medicine, Director
of the Division of Sleep Medicine at Harvard
Medical School and Chief of the Division of
Sleep Medicine in the Department of Medicine
at Brigham and Women's Hospital



Andrew J. Cutler, MD
Clinical Associate Professor of Psychiatry
SUNY Upstate Medical University



Richard Bogan, MD
Associate Clinical Professor at the University of
South Carolina School of Medicine and Medical
University of South Carolina in Charleston, South
Carolina and Principal of Bogan Sleep
Consultants

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Welcome	Mark Jacobson, COO
Solriamfetol Overview	Dr. Herriot Tabuteau, CEO
TAAR1 MOA And Major Depressive Disorder (MDD)	Dr. Craig Chepke
Attention Deficit Hyperactivity Disorder (ADHD)	Dr. Andrew Cutler
Q+A on TAAR1, MDD and ADHD	Drs. Chepke and Cutler
Binge Eating Disorder (BED)	Dr. Susan McElroy
Cognition	Dr. Richard Bogan
Shift Work Disorder (SWD)	Dr. Charles Czeisler
Q+A on Cognition, BED, SWD	Drs. McElroy, Bogan, and Czeisler
Closing Remarks	Dr. Herriot Tabuteau, CEO



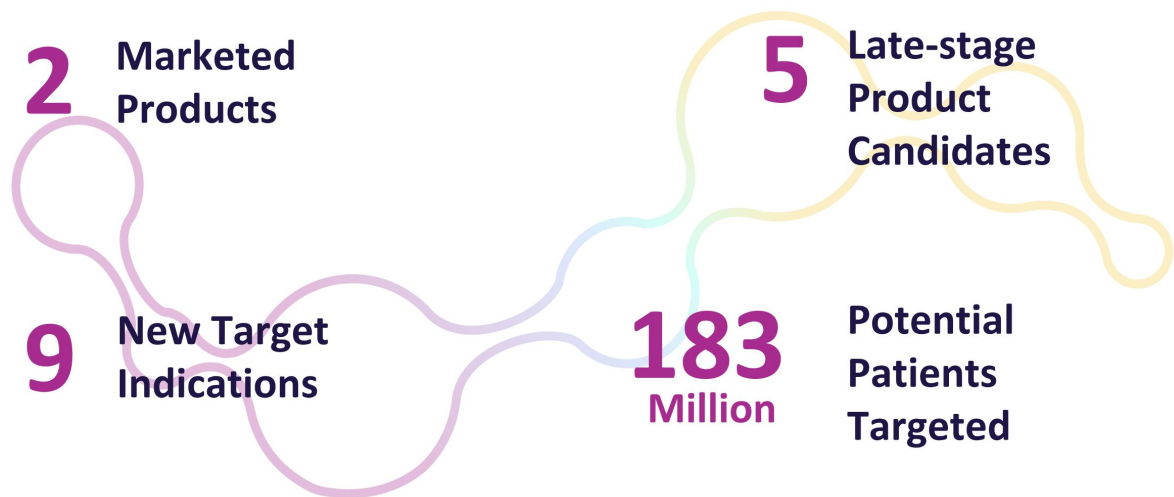


Solriamfetol Overview

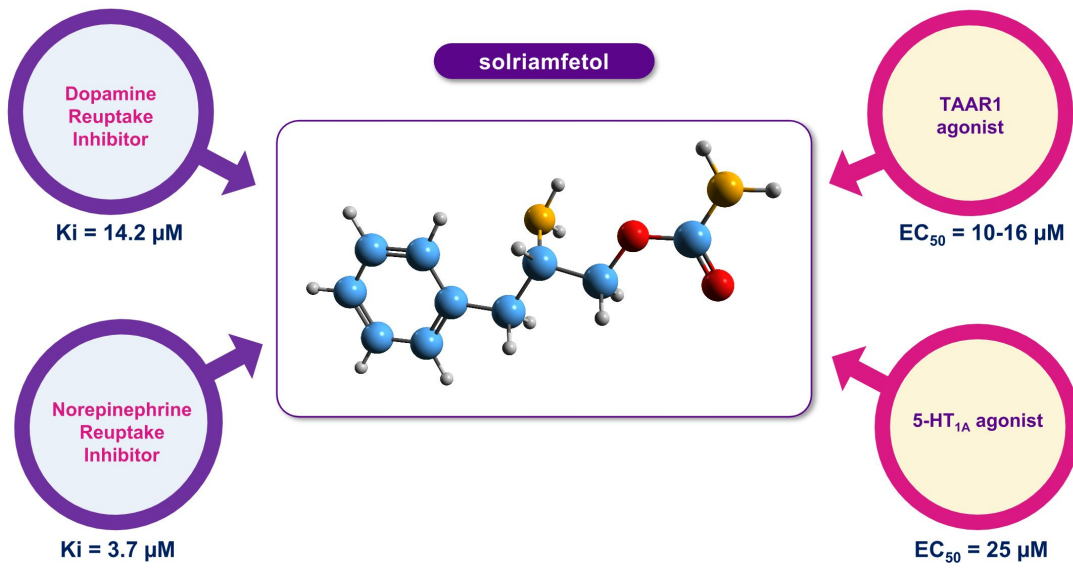
Herriot Tabuteau, MD

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Rapidly Growing, CNS-Focused Biopharma



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Preclinical / Clinical Effects

- ◉ Wake Promoting
- ◉ Pro-Cognitive
- ◉ Antidepressant-like
- ◉ Weight and Appetite

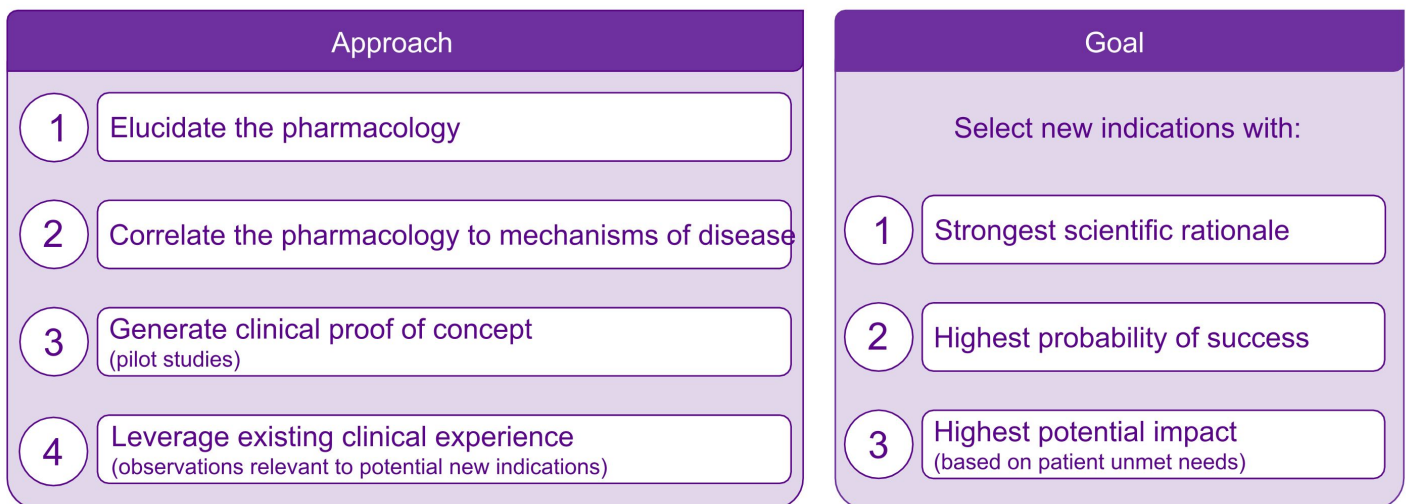
Relevant Target Indication

- ◉ EDS in narcolepsy; OSA; ES in SWD
- ◉ ADHD, cognitive impairment in OSA, narcolepsy, MDD
- ◉ MDD, Anxiety
- ◉ Binge eating disorder

ADHD: attention deficit hyperactivity disorder ; MDD: major depressive disorder ; EDS: excessive daytime sleepiness ; OSA: obstructive sleep apnea ; SWD: shift work disorder
ES: excessive sleepiness


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Unlocking the Clinical and Commercial Potential of Solriamfetol



Solriamfetol Target Indications

Product	Phase 1	Phase 2	Phase 3	NDA
solriamfetol	Attention Deficit Hyperactivity Disorder (ADHD)			
	Major Depressive Disorder (MDD)			
	Binge Eating Disorder (BED)			
	Shift Work Sleep Disorder (SWD)			

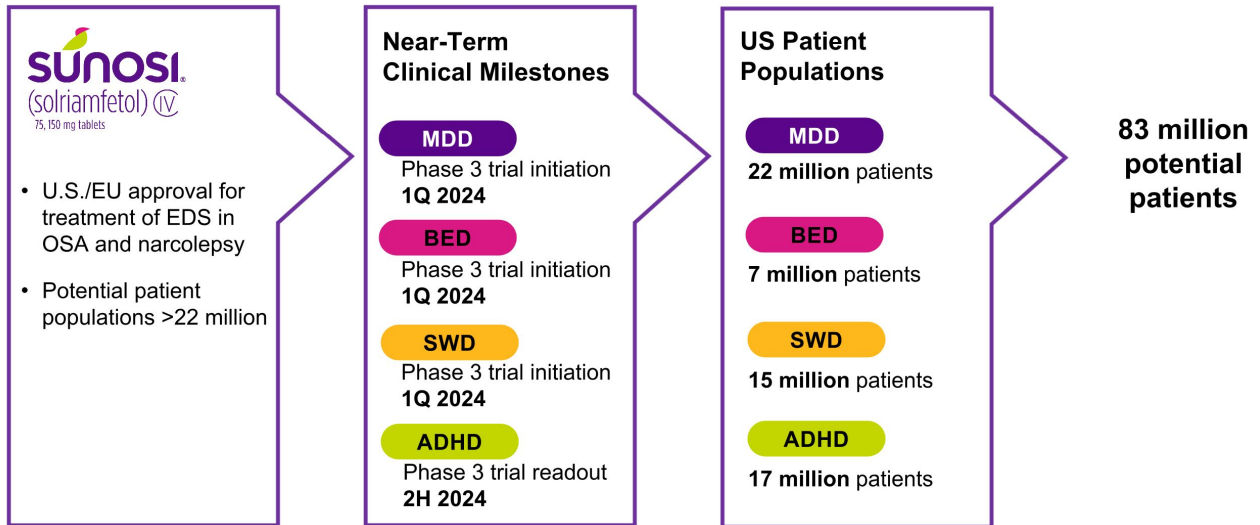
Product	Phase 1	Phase 2	Phase 3	NDA	Marketed
	Excessive Daytime Sleepiness (EDS) Associated with Narcolepsy or Obstructive Sleep Apnea (OSA)				

Solriamfetol for ADHD, BED, SWD, and MDD is not approved by the FDA, and their safety and effectiveness have not been established
 Abbreviations: TAAR1 = Trace amine-associated receptor 1
 Please see full Prescribing Information for Sunosi at www.Sunosi.com.

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Unlocking Solriamfetol Franchise Value



Trace Amine Associated Receptor Signaling and Psychiatric Disorders

Craig Chepke, MD, DFAPA

Adjunct Associate Professor of Psychiatry, Atrium Health

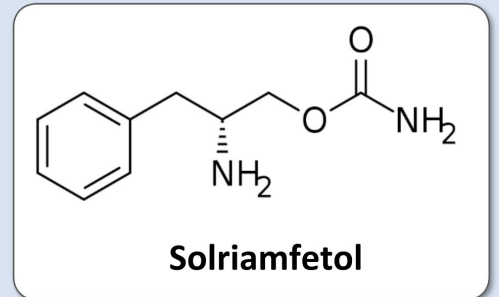
Medical Director, Excel Psychiatric Associates



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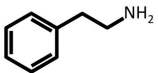
Solriamfetol

- Solriamfetol initially developed as a **dual-acting dopamine and norepinephrine reuptake inhibitor (DNRI)** with wake-promoting effects
- **2019 U.S. FDA and 2020 EMEA approval** to improve wakefulness in adult patients with excessive sleepiness (EDS) due to narcolepsy and obstructive sleep apnea (OSA)
- **Recently uncovered TAAR1 and 5HT_{1A} agonist activity** and preclinical evidence support exploration of solriamfetol in new neuropsychiatric conditions
- Clinical and preclinical evidence suggest potential utility of **TAAR1 agonists in several psychiatric and neurological disorders**

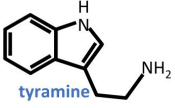


What is TAAR1?

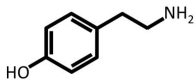
Trace Amines



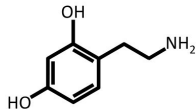
b-phenylethylamine



tyramine

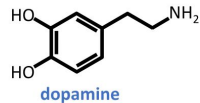


p-tyramine

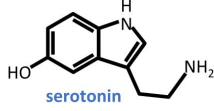


p-octopamine

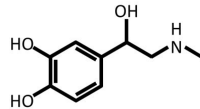
Monoamines



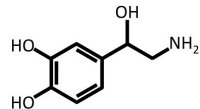
dopamine



serotonin



epinephrine

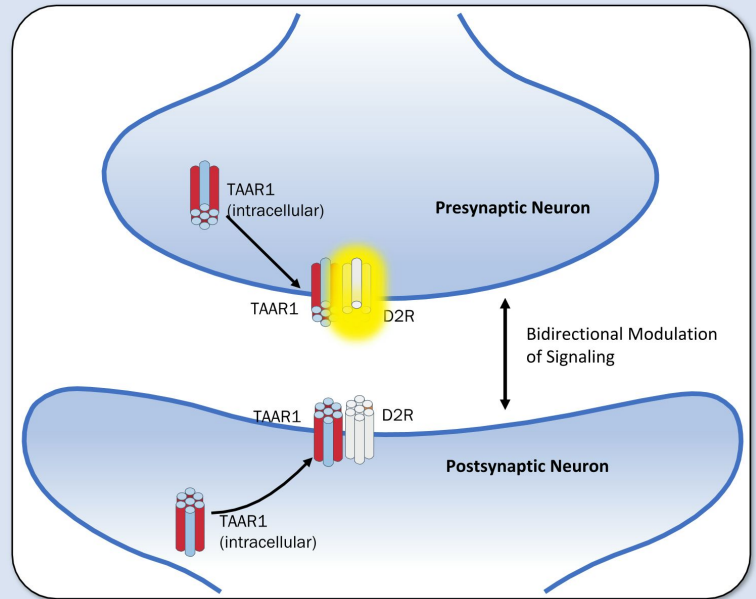


norepinephrine

- **Trace amines (TAs)** are structurally related to monoamine neurotransmitters, but found at much lower concentrations in the brain
 - The existence of trace amines has been known for a century, but they were thought to be incidental metabolites of monoamines
- **TAARs (Trace Amine-Associated Receptors)** were discovered in 2001
 - TAARs are activated by trace amines
 - Humans express 6 of 26 known TAAR receptors
 - TAAR1 is best studied and believed to be relevant to neuropsychiatric conditions

TAAR1: Adaptive Modulation of Neurotransmitters

- TAAR1 is expressed both pre- and post-synaptically.
 - Expression primarily intracellular but can be on cell membrane
- Adaptively modulates activity of several major neurotransmitter systems:
 - TAAR1 modulates **dopamine** tone in the brain
 - Dimerizes with D2 receptors
 - Pre- and post synaptic regulation of dopamine signaling
 - Regulates **glutamate** circuits
 - Modulates **serotonin** (5-HT) activity



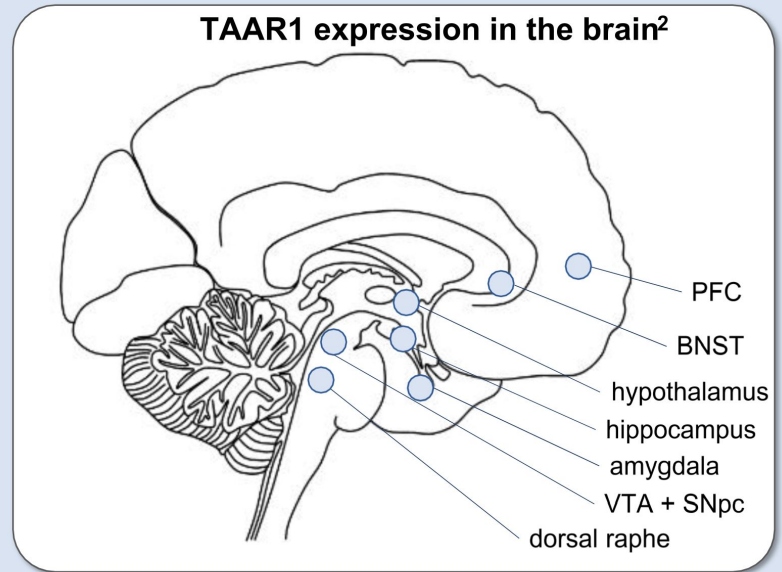
Dedic N, et al. *Int J Mol Sci.* 2021;22(24):13185. Nair PC, et al. *Mol Psychiatry.* August 10, 2021. Kantrowitz JT, et al. *CNS Drugs.* 2021;35(11):1153-1161. Dodd S, et al. *Neurosci Biobehav Rev.* 2021;120:537-541; Moore et al. *Front Pharmacol.* 2018 Feb 27;9:129.

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TAAR1 is Expressed in Brain Regions Important to Neuropsychiatric Disorders

TAAR1 is expressed in areas of the brain relevant to neuropsychiatric disorders:

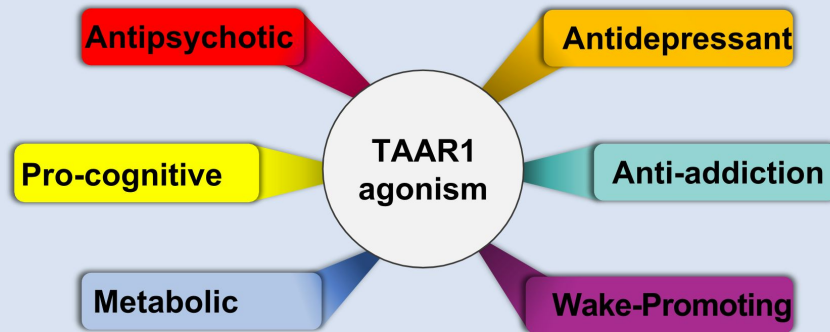
- Ventral tegmental area (VTA)
- Substantia nigra pars compacta (SNpc)
- Dorsal raphe
- Prefrontal cortex (PFC)
- Limbic areas:
 - Amygdala
 - Hippocampus
 - Hypothalamus
 - Bed nucleus of the stria terminalis (BNST)



Gainetinov et al. Pharmacological Reviews 2018, 70 (3) 549-620; Lindemann et al. 2008. J Pharmacol Exp Ther 324:948-956 2. Adapted from Rutigliano G et al. Front Pharmacol. (2018) 8:987

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TAAR1 Agonists Have Wide-Ranging Effects in Preclinical Models

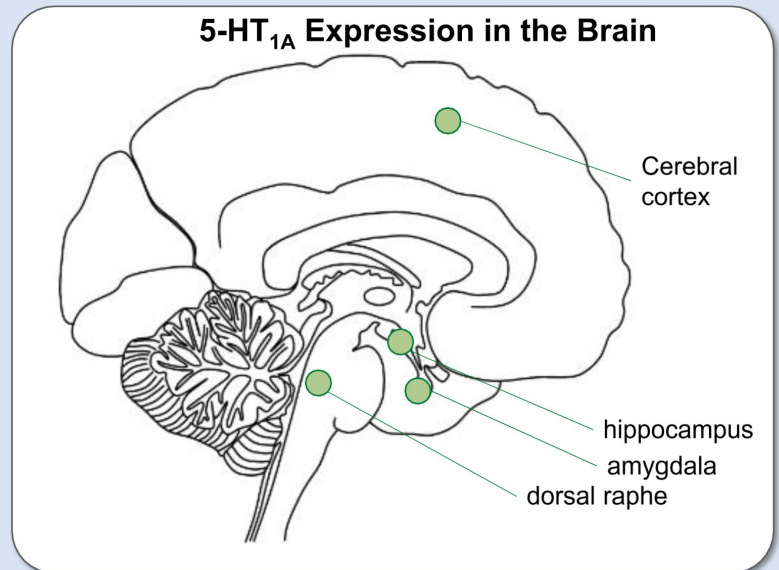


Revel FG, et al. *Mol Psychiatry*. 2013;18(5):543-556. Rutigliano G, et al. *Cell Mol Neurobiol*. 2020;40(2):239-255. Dedic N, et al. *J Pharm Exp Ther*. 2019;371:1-14. Dedic N, et al. *J Pharm Exp Ther*. 2019;371(Suppl):1-38.

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5-HT_{1A} in the Brain

- Serotonin receptor 5-HT_{1A} is widely distributed in the CNS in areas including the cerebral cortex, hippocampus, amygdala, and raphe nucleus¹
- 5-HT_{1A} modulates several major neurotransmitter systems including norepinephrine, serotonin (5HT), dopamine²
- 5-HT_{1A} activation may modulate mood, reward and addictive behaviors, food intake, and cognitive function³⁻⁵
- TAAR1 agonism is believed to enhance the potency of the effects of 5-HT_{1A} agonists⁶⁻⁸



1. Ito et al. 1999. *Journal of Nuclear Medicine*. 40 (1): 102-9; 2. Celada et al. 2013. *CNS Drugs* 27:703-716; 3. Meltzer et al. 2008. *Behavioral Brain Research*. 195 (1): 98-102 4. Muller et al. 2007. *Progress in Neurobiology*. 81 (3): 133-78. 5. Ebenezzer et al. 2007. *Methods and Findings in Experimental and Clinical Pharmacology*. 29 (4): 269-72 6. Berry MD, et al. *Pharmacol Ther*. 2017;180:161-180. 7. Revel FG, et al. *PNAS*. 2011;108(20):8485-84905. 8. Dedic N, et al. *JPET*. 2019;371(1):1-14.

TAAR1 agonists in clinical development

- 1. Solriamfetol (Axsome):** DNRI with TAAR1 and 5-HT_{1A} agonist activity
 - Only commercially-available TAAR1 agonist (for treatment of excessive daytime sleepiness in obstructive sleep apnea or narcolepsy)
- 2. Ralmitaront (Roche):** TAAR1 partial agonist
 - Evaluated in two Phase 2 studies (schizophrenia and schizoaffective disorder) that were terminated due to inadequate efficacy
- 3. Ulotaront (Sumitomo/Otsuka):** TAAR1 agonist with 5-HT_{1A} agonist activity
 - Currently under clinical development for treatment of schizophrenia, generalized anxiety disorder and adjunctive major depressive disorder

Other TAAR1 agonists have been studied preclinically but none have reached clinical trials

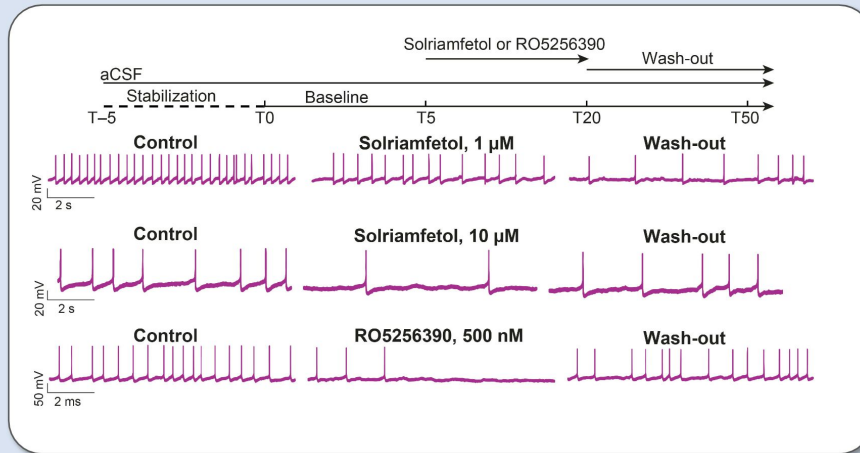
Solriamfetol activates TAAR1 and 5-HT_{1A}

Drug	hTAAR1 EC ₅₀ μ M (Emax)	5-HT _{1A} IC ₅₀ μ M	hDAT IC ₅₀ μ M	hNET IC ₅₀ μ M
Solriamfetol	10-16 (100%)	25	3.21	14.4
Modafinil	No dose response*	Unknown	2.8	>100
Bupropion	No dose response*	No functional activity	0.26	2.79

- Solriamfetol and stimulants had TAAR1 activity while modafinil did not
- Solriamfetol had 5-HT_{1A} activity at lower potency

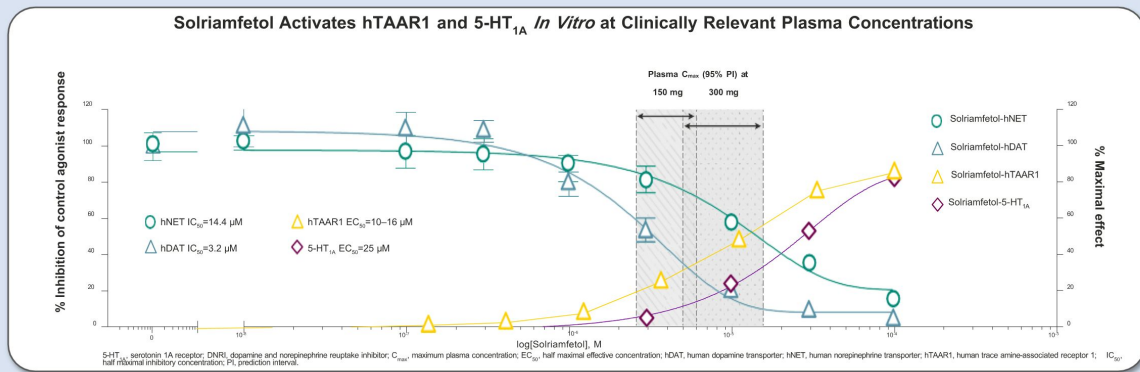
5HT_{1A}: serotonin 1A receptor; EC50: half maximal effective concentration; Emax: maximal effect; hDAT: human dopamine transporter; hNET: human norepinephrine transporter; hTAAR1: human trace amine-associated receptor 1; IC50: half maximal inhibitory concentration; WPA: wake-promoting agent.
* Data based on current studies and confirmed by Eshleman AJ, et al. J Pharmacol Exp Ther. 1999;289(2):877-85.

Solriamfetol inhibits VTA neuron firing similar to known TAAR1 agonist



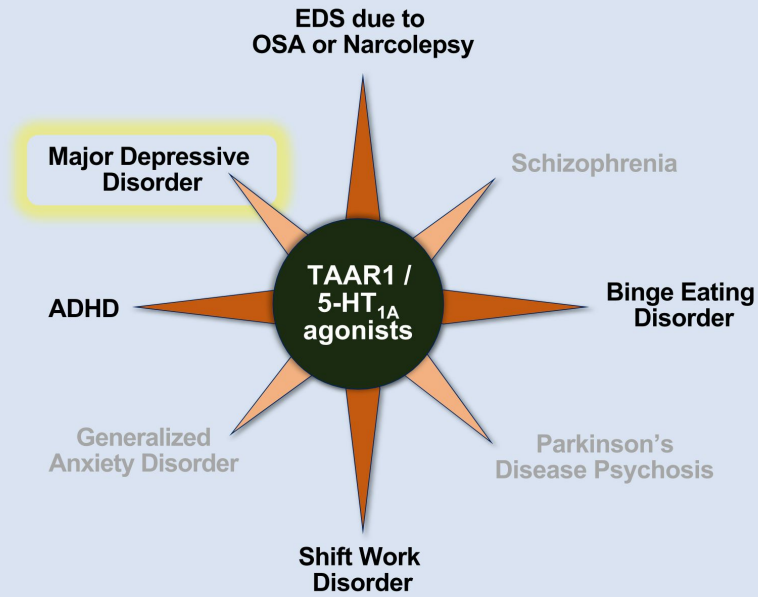
Solriamfetol inhibited firing by VTA neurons in a dose-dependent manner, similar to TAAR1 agonist RO5256390

Solriamfetol activates TAAR1 and 5-HT_{1A} at clinically relevant concentrations



- Solriamfetol activated Trace Amine-Associated Receptor 1 (TAAR1) and Serotonin Receptor 1a (5-HT_{1A}) at the same plasma levels as its inhibition of DAT and NET
- Inhibition of DAT and NET and activation of TAAR1 and 5-HT_{1A} occurred at clinically relevant concentrations
- TAAR1 and 5-HT_{1A} activity may contribute to the effects of solriamfetol

TAAR1 / 5-HT_{1A} agonists may have applications in psychiatric and neurological disorders



Major Depressive Disorder (MDD)

Craig Chepke, MD, DFAPA

Adjunct Associate Professor of Psychiatry, Atrium Health

Medical Director, Excel Psychiatric Associates

Major Depressive Disorder (MDD) Is a Highly Prevalent and Heterogenous Disorder¹⁻³



Approximately **1 in 5 individuals** in the US will experience MDD at some point in their life^{1,*}

According to DSM-5-TR criteria, MDD is associated with key symptoms that present nearly every day for ≥ 2 weeks and represent a change from previous functioning, including^{2,†}:

- ✓ Depressed mood
- ✓ Diminished interest or pleasure in activities
- ✓ Insomnia or hypersomnia
- ✓ Psychomotor agitation or retardation
- ✓ Fatigue or loss of energy
- ✓ Significant weight changes
- ✓ Feelings of worthlessness or excessive or inappropriate guilt
- ✓ Diminished ability to think or concentrate or indecisiveness
- ✓ Suicidal ideation or a suicide attempt



227 unique symptom profiles exist that may qualify for a diagnosis of MDD^{3,‡}

DSM-5-TR, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision*.

*According to a study of 36,309 adult participants surveyed in the 2012-2013 National Epidemiologic Survey on Alcohol and Related Conditions III.

†At least 1 of the symptoms must be either depressed mood or loss of interest or pleasure.

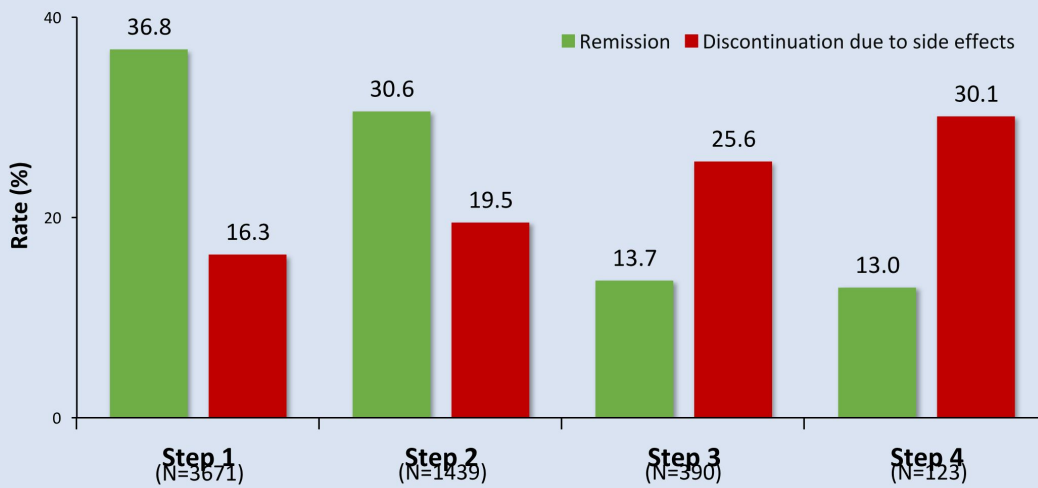
‡Based on the combination of 9 DSM-5 symptoms that qualify for a diagnosis of MDD.

1. Hasin DS et al. *JAMA Psychiatry*. 2018;75(4):336-346. 2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed, Text Revision. American Psychiatric Publishing, Inc; 2022. 3. Fried EI, Nesse RM. *J Affect Disord*. 2015;172:96-102.

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Remission Rates Decreased and Discontinuations Due to Side Effects Increased with Each Change in STAR*D

Rates of remission and discontinuation due to intolerable side effects



Each step of therapy included options to **switch or augment**, including various SSRIs, SNRIs, lithium, T₃, TCAs, MAOIs, combinations, and cognitive therapy.

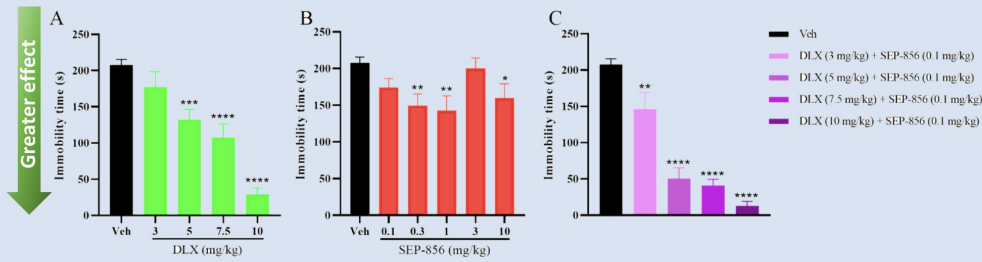
1 in 3

After 4 lines of treatment, approximately **1/3** of patients still do not achieve remission

SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; T₃ = triiodothyronine.
References: 1. Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917. 2. Trivedi MH, et al. *Am J Psychiatry*. 2006;163:28-40.

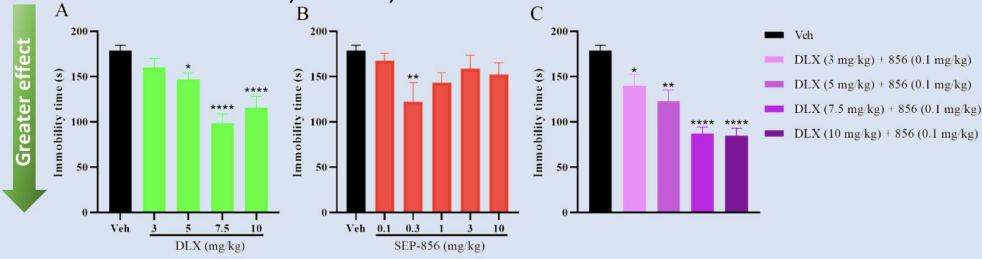
TAAR1 Agonists Show Preclinical Evidence of Potential Benefits in MDD

Effects of duloxetine, SEP-856, and their co-administration on the FST in ICR mice



The combination of a monoamine reuptake inhibitor and TAAR1/5-HT1A agonist showed synergistic results in two mouse models of MDD which often reliably predict antidepressant efficacy

Effects of duloxetine, SEP-856, and their co-administration on the TST in ICR mice

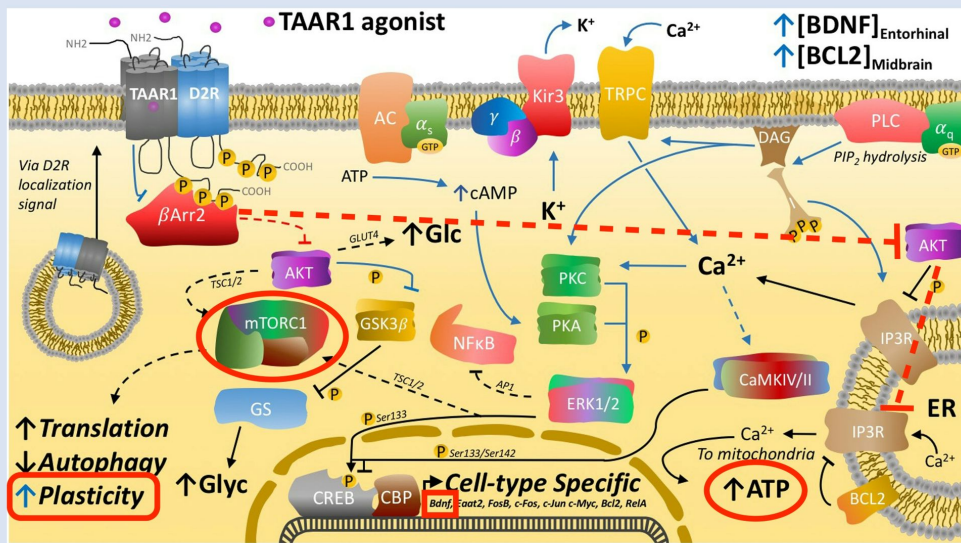


FST=forced swimming test; TST= tail suspension test

References: Ren, Xia, et al. "The Potential Antidepressant Action of Duloxetine Co-Administered with the TAAR1 Receptor Agonist SEP-363856 in Mice." *Molecules* 27.9 (2022): 2755.

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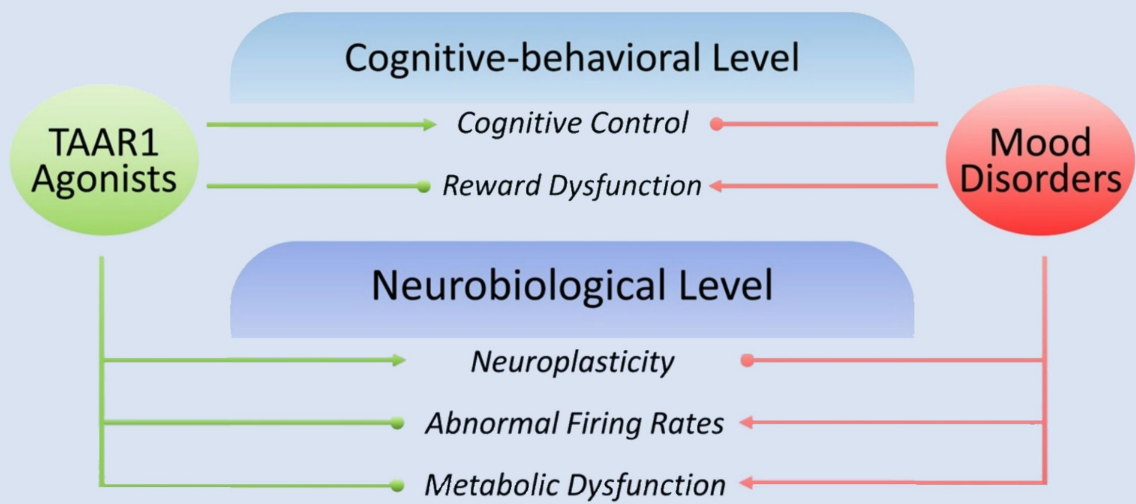
Hypothesized MOA of TAAR1 Agonists in MDD Involves Multiple Intracellular Signal Transduction Cascades



TAAR1 agonism may have downstream effects leading to increased neuroplasticity, which other treatments for MDD are believed to potentiate

References: adapted from Alnefeesi, Yazen, et al. "Trace amine-associated receptor 1 (TAAR1): Potential application in mood disorders: A systematic review." *Neuroscience & Biobehavioral Reviews* 131 (2021): 192-210.

High Level Summary of TAAR1 MOA in MDD

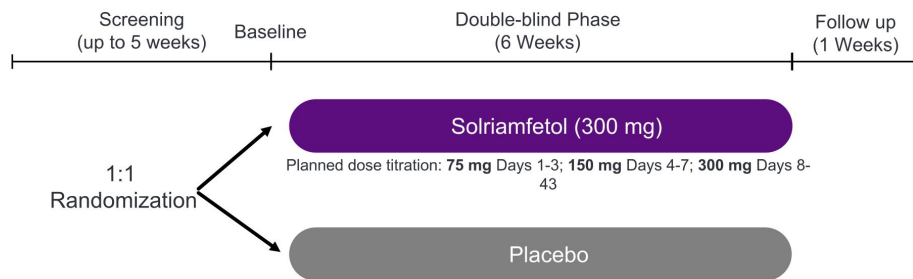


References: Anefeesi, Yazen, et al. "Trace amine-associated receptor 1 (TAAR1): Potential application in mood disorders: A systematic review." *Neuroscience & Biobehavioral Reviews* 131 (2021): 192-210.

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Major Depressive Disorder (MDD): Axsome Planned Phase 3 Trial

A Phase 3 trial to assess the safety of **solriamfetol** as compared to placebo in the treatment of MDD.



• Key Inclusion Criteria:

- Meets DSM-5 criteria for MDD
- MADRS score of ≥ 25 and a CGI-S ≥ 4 at screening and baseline

- **Primary Endpoint:** Safety measures including AEs, TEAEs, ECG readings and C-SSRS

MADRS: Montgomery-Åsberg Depression Rating Scale ; CGI-S: Clinical Global Impressions-Severity ; C-SSRS: Columbia – Suicide Severity Rating Scale ; AE: adverse event ; TEAE: treatment emergent adverse event

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Key Takeaways for TAAR1 MOA in MDD

TAAR1 and 5-HT_{1A} agonists as compelling drug development target in neuropsychiatry

- Agents with TAAR1 and 5-HT_{1A} agonist activity have shown potential in neuropsychiatry
- Solriamfetol, the only commercially available TAAR1 agonist, has potential in multiple new target indications because of its recently uncovered TAAR1/ 5-HT_{1A} agonist activity

Major Depressive Disorder (MDD)

- Cognitive deficits are a major driver of disability in MDD, and based on its MOA solriamfetol could have cognitive benefits in MDD.
- The multiple MOAs (NRI, DRI, 5-HT_{1A} agonism, TAAR1 agonism) may be beneficial for a broad range of patients, including potentially patients not well served by traditional antidepressants
- Solriamfetol tolerability profile is well-characterized and is devoid of the adverse reactions often considered the most bothersome for people with MDD: weight gain, sexual dysfunction, and sedation

Overview of Attention Deficit Hyperactivity Disorder (ADHD)

Andrew Cutler, MD

SUNY Upstate Medical University and Neuroscience Education
Institute, Syracuse, NY

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What is ADHD?

Main Features of ADHD Diagnosis

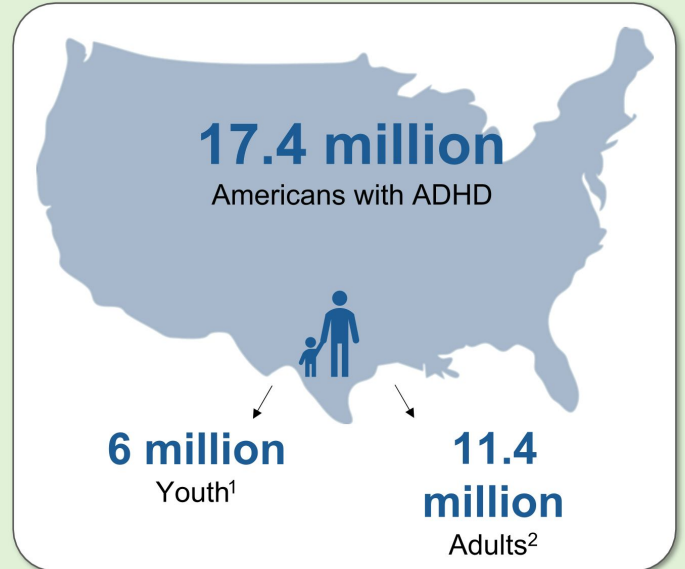
(American Psychiatric Association, 2013¹ & 2 other sources^{2,3})

- The presence of **developmentally inappropriate levels** of hyperactive-impulsive and/or inattentive symptoms for at least 6 months.
 - Six or more symptoms in one or both domains required for youth
 - Five or more for adults
- Symptoms occur in **different settings** (e.g., home and school).
- Some symptoms present **prior to age 12**.
- Symptoms cause **impairments** in living.
- No other disorder **better explains the symptoms**.
- Expression of ADHD symptoms changes with time/age of patient

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders 5th ed.*. Arlington, VA: American Psychiatric Publishing; 2013. 2. World Health Organization, 2018. *International statistical classification of diseases and related health problems (11th Revision)* 3. Yi Z, Jing L. *Guidelines for prevention and treatment of attention deficit hyperactivity disorder in China [M]*. 2015.

ADHD is a Common Disorder in Childhood and Adulthood

- An estimated 17.4 million people in the U.S. are affected by ADHD^{1,2}
- The prevalence of ADHD has not changed over the past three decades that have data available³
- No significant differences in prevalence between North America and Europe, Asia, Africa, South America, and Oceania³

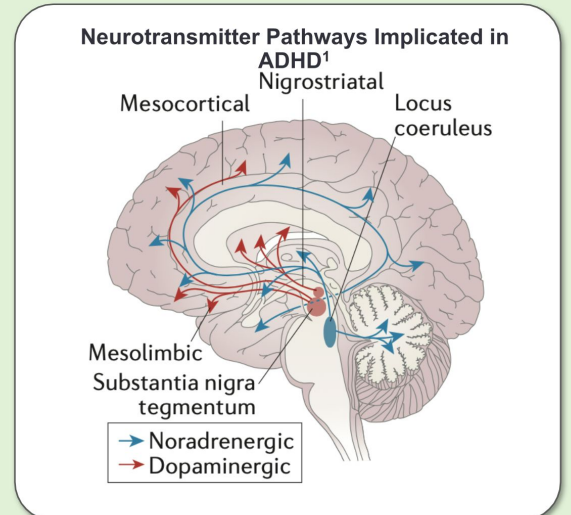


1. Bitsko RH, et al. 2013–2019. MMWR Suppl. 2022;71(2):1-48. 2. Kessler RC, et al. Am J Psychiatry. 2006 Apr;163(4):716-23. 3. Polanczyk GV, et al. Int J Epidemiol. 2014;43(2):434-442.

Neural basis of ADHD

Fronto-striatal and fronto-parietal networks in ADHD

- Under-activation of fronto-striatal and fronto-parietal networks consistent with **impaired goal-directed executive processes**
- Under-activation of frontal control over the limbic system consistent with the **emotional dysregulation** seen in ADHD
- Lower activation of the ventral striatum in ADHD in anticipation of reward leads to **poor executive control over reward regulation**
- Under-activation of ventral attention networks leads to **poor executive control of attention to behaviorally relevant external stimuli**



Current Treatments and Unmet Need

FDA-Approved Stimulants

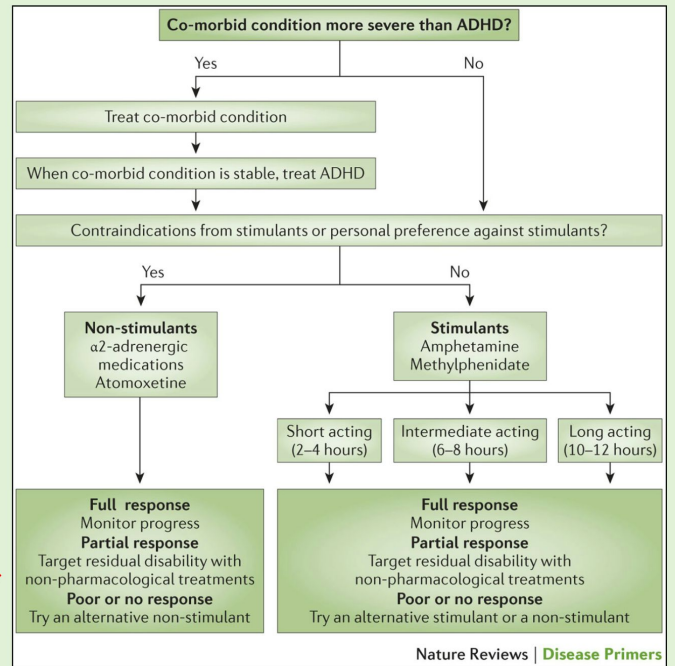
- Methylphenidate and Amphetamine
- IR and ER formulations
- Duration range 4 to 16 hours
- Liquid and chewable forms available

FDA-Approved Non-Stimulants

- Atomoxetine (NET reuptake inhibitor)
- Viloxazine ER (NET reuptake inhibitor; binds to 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C})
- Alpha-2 agonists
- Guanfacine ER
- Clonidine ER

50% discontinuation after six months leads to low response rates

NET, norepinephrine transporter; DAT, dopamine transporter; SERT, serotonin transporter. 5-HT: serotonin
Faraone, S. V. et al. *Attention-deficit/hyperactivity disorder. Nat. Rev. Dis. Primers.* 2015.



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Current Treatments and Unmet Need

Stimulants

- Schedule II controlled substances
- Misuse, abuse and diversion risk
- Irritability/rebound phenomena; Loss of 'sparkle'

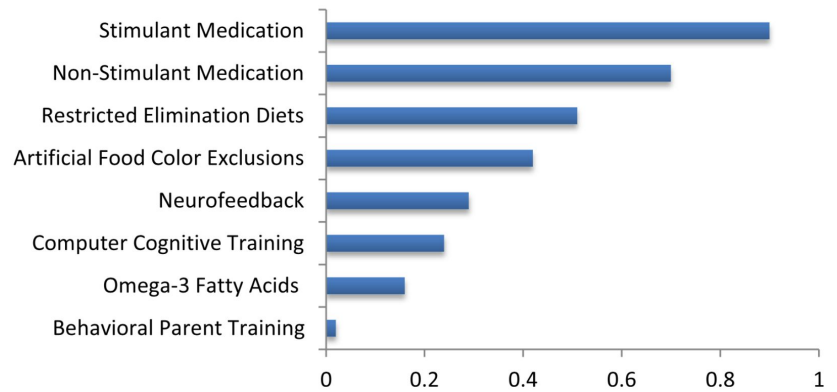
Non-Stimulants

- Low effect sizes for all
- Clonidine and guanfacine: sedation, lack of data in adults with ADHD
- Atomoxetine: black box for suicidality, nausea

All Medications for ADHD

- Non-adherence
- Emotional dysregulation
- Executive dysfunction

ADHD Treatment Effect Sizes (Larger is Better)



Solriamfetol for ADHD in Adults: A Double-Blind Placebo-Controlled Pilot Study

Trial Design:

- 6 week randomized double-blind placebo-controlled study of adults with ADHD
 - 60 participants enrolled
- Participants administered solriamfetol 75mg for 2 weeks; dose increased to 150mg for subsequent 4 weeks* if well tolerated

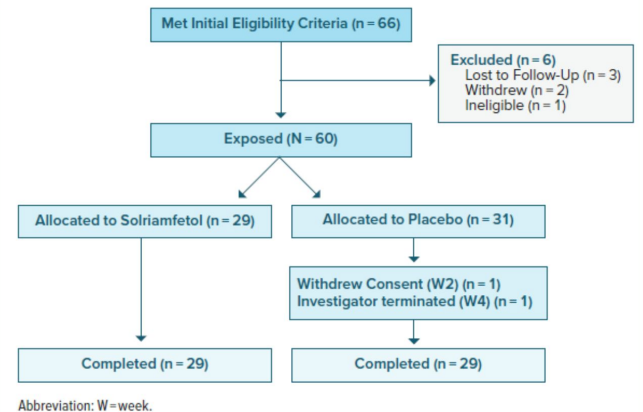
Key Efficacy Endpoints:

- Adult ADHD Investigator Symptom Rating Scale (AISRS) - primary endpoint
- Clinical Global Impression (CGI) improvement AISRs improvement

Secondary Measures:

- Global Assessment of Functioning Scale (GAF)
- Modified ADHD Self-Report Scale (MADHD-RS)
- Behavior Rating Inventory of Executive Function – Adult (BRIEF-A)
- Pittsburg Sleep Quality Index (PSQI)
- Epworth Sleepiness Scale (ESS)

Flow of Participants Through the Study



*4 patients did not follow the standard dosing regimen; 2 patients had a final dose of 75mg

Solriamfetol for ADHD in Adults: Demographic and Baseline Characteristics

Patient Characteristics at Baseline

Characteristic	Treatment Group	
	Solriamfetol	Placebo
Total enrolled, n	29	31
Age, y		
Mean	36.2	36.9
Minimum	19.0	22.0
Maximum	61.0	60.0
Gender, n (%)		
Male	10 (34.5)	17 (54.8)
Female	17 (58.6)	12 (38.7)
Other	2 (6.9)	2 (6.5)
Race, n (%)		
White/Caucasian	19 (65.5)	25 (80.6)
Black/African American	2 (6.9)	2 (6.5)
Asian	3 (10.3)	2 (6.5)
Native Hawaiian/Pacific Islander	5 (17.2)	2 (6.5)
Ethnicity, n (%)		
Hispanic or Latino	4 (13.8)	2 (6.5)
Not Hispanic or Latino	25 (86.2)	29 (93.5)
CGI Severity score (baseline), n (%)		
Moderately ill	22 (75.9)	25 (80.6)
Markedly ill	7 (24.1)	6 (19.4)
GAF score (baseline)		
Mean (SD)	63.8 (1.9)	63.8 (1.5)
Minimum	60.0	61.0
Maximum	68.0	66.0

- Nearly half of patients were stimulant-naïve
- ADHD CGI-Severity score moderate for most participants
- Baseline AISRS 25.5 (4.7) in solriamfetol group, 24.4 (4.2) in placebo group
- All but 1 participant met definition for executive function impairment

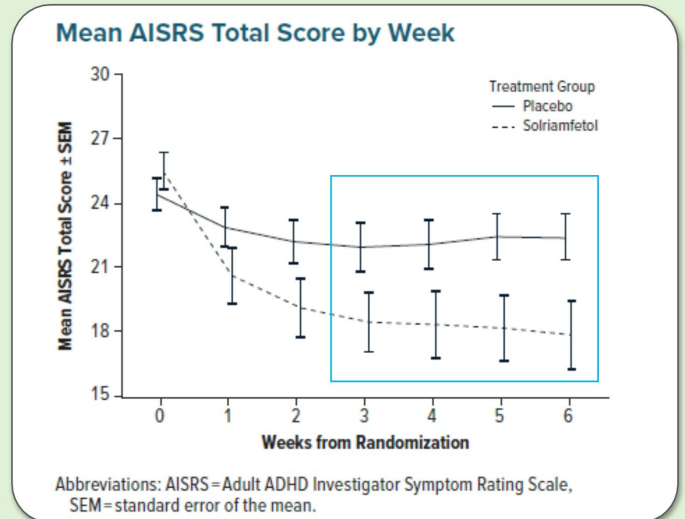
Abbreviations: CGI = Clinical Global Impressions scale; GAF = Global Assessment of Functioning

1. Adapted from: Surman, C. B. H. et al. Solriamfetol for Attention-Deficit/Hyperactivity Disorder in Adults: A Double-Blind Placebo-Controlled Pilot Study. *J. Clin Psychiatry* 2023;84(0):23m14934

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Solriamfetol for ADHD in Adults: A Double-Blind Placebo-Controlled Pilot Study

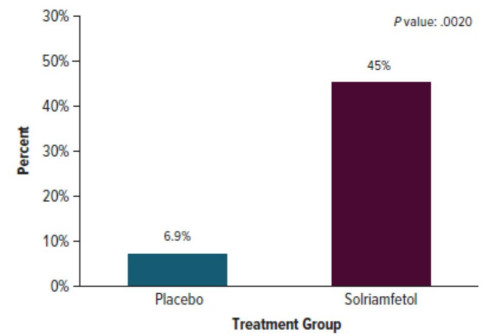
- For Weeks 3-6, mean improvement in total AISRS ratings was significantly greater for solriamfetol-treated individuals than for placebo-treated
- The mean total improvement in AISRS score by Week 6 was **-7.6** for active study drug participants, and **-2.1** for individuals on placebo ($P = .0012$; effect size = 1.09)
- By week 6, significantly more individuals on solriamfetol met remission AISRS total score definitions of 12 (24% vs 3% on placebo; $P = .0517$) or 18 (59% vs 21% on placebo; $P = .0067$)



Solriamfetol for ADHD in Adults: A Double-Blind Placebo-Controlled Pilot Study

- By week 6, CGI ratings of much or very much improved occurred for significantly more individuals on solriamfetol (45%, 13/29) than placebo (6%, 2/31) ($P = .0020$).
 - Solriamfetol treatment:
 - much improved: 24% (7 individuals)
 - very much improved: 20% (6 individuals)
 - Placebo treatment:
 - much improved: 3% (1 individual)
 - very much improved: 3% (1 individual)

CGI Score Indicating Much or Very Much Improved and 25% Improvement in AISRS Score With Solriamfetol vs Placebo



Abbreviations: AISRS=Adult ADHD Investigator Symptom Rating Scale, CGI=Clinical Global Impressions scale.

Solriamfetol for ADHD in Adults: Safety and Tolerability

Comparison of Rates of Adverse Events (Regardless of Severity) Between Groups

Adverse Effect	Solriamfetol (n = 29), n (%)	Placebo (n = 31), n (%)	P Value
Cold/infection/allergy	13 (45)	17 (55)	.6058
Increased appetite	0 (0)	1 (3)	1.0000
Decreased appetite	5 (17)	2 (6)	.2472
Headache	14 (48)	9 (29)	.1844
Nausea/vomiting/diarrhea (gastrointestinal)	7 (24)	2 (6)	.0756
Insomnia	9 (31)	5 (16)	.2271
Sedation	3 (10)	1 (3)	.3455
Increased energy	4 (14)	1 (3)	.1877
Cardiovascular	5 (17)	1 (3)	.0977
Tense/jittery	1 (3)	0 (0)	.4833
Agitated/irritable	3 (10)	2 (6)	.6658
Anxious/worried	0 (0)	1 (3)	1.0000
Mucosal dryness	3 (10)	4 (13)	1.0000
Dizzy/lightheaded	1 (3)	0 (0)	.4833
Neurologic	4 (14)	1 (3)	.1877
Musculoskeletal	7 (24)	7 (23)	1.0000
Genitourinary	3 (10)	2 (6)	.6658
Dermatologic	1 (3)	4 (13)	.3547
Other	1 (3)	3 (10)	.6128

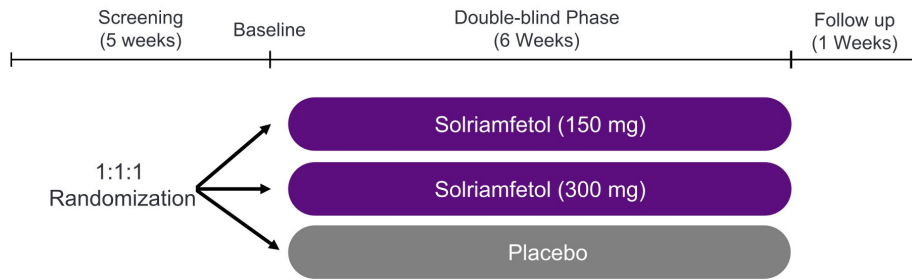
**Safety and tolerability of
solriamfetol was in line with
previous clinical studies**

Solriamfetol Pilot ADHD Trial Conclusions

- In this single-center pilot trial conducted at Massachusetts General Hospital in Boston, solriamfetol was associated with significantly greater improvement in ADHD symptoms compared to placebo on the AISRS (primary endpoint).
- Results on secondary endpoints including both clinician- and patient-reported measures were consistent with the findings on the primary endpoint.
- Solriamfetol was well tolerated in the study with a safety profile consistent with prior experience.

Attention Deficit Hyperactivity Disorder: Axsome FOCUS Phase 3 Trial

A Phase 3 trial to assess efficacy and safety of **solriamfetol** as compared to placebo in the treatment of ADHD.



- **Primary Endpoint:** Change in the Adult ADHD Investigator Symptom Report Scale (AISRS)
- **Key Inclusion Criteria:**
 - Adults, aged 18 to 55 inclusive.
 - Primary diagnosis of ADHD (inattentive, hyperactive, or combined subtype) using DSM-5 criteria and confirmed via the clinician administered ACDS
- **Target Enrollment:** 450



Key Takeaways for Solriamfetol in ADHD

- An estimated 17.4 million people in the U.S. are affected by ADHD and prevalence has not changed for the past three decades that have data available^{1,2}
- ADHD is associated with significant impairment in social, academic, and occupational functioning or development
- Significant need remains for safe and effective, non-stimulant, non-addictive treatments for ADHD in both adults and children
- Solriamfetol has multi-mechanistic action through DNRI and TAAR1 which is a compelling potential advancement in the treatment of ADHD including a favorable product profile:
 - Non-stimulant with low abuse potential (Schedule IV)¹
 - De-risked safety and tolerability profile compared with traditional ADHD medications¹

1. Bitsko RH, et al. 2013–2019. MMWR Suppl. 2022;71(2):1–48. 2. Kessler RC, et al. Am J Psychiatry. 2006 Apr;163(4):716–23. 3. Polanczyk GV, et al. Int J Epidemiol. 2014;43(2):434–442.

Q+A

on TAAR1, MDD, and ADHD



**Craig Chepke, MD,
DFAPA**



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Solriamfetol in Binge Eating Disorder

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Disclosures 2023

Principal/Co-Investigator

Allergan, Avanir, Brainsway, Marriott Foundation, Myriad, Neurocrine, Novo Nordisk, Shire, Sunovion

Consultant/Ad Board

Allergan, Avanir, Bracket, F. Hoffman-La Roche Ltd., Idorsia, Mitsubishi Tanabe, Myriad, Shire, Sunovian

Patents

Inventor on United States Patent No. 6,323,236 B2, Use of Sulfamate Derivatives for Treating Impulse Control Disorders, and, along with the patent's assignee, University of Cincinnati, Cincinnati, Ohio has received payments from Johnson & Johnson Pharmaceutical Research & Development, L.L.C., which has exclusive rights under the patent.

Outline

- Brief overview of Binge Eating Disorder (BED)
 - Brief overview of treatment of BED
 - Overview for rationale of solriamfetol in BED
-

Definition of a “Binge”

1. Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances
2. A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)



Binge Eating Disorder (BED)

Binge Eating:

- Eating in a discrete period of time an amount of food larger than most people would eat in a similar amount of time under similar circumstances
AND a sense of lack of control overeating

Binge Eating Disorder:

- BED broadly defined as recurrent binge eating without inappropriate compensatory behaviors
- BED is the most common eating disorder
 - **More common** than anorexia nervosa (AN) and bulimia nervosa (BN) combined

DSM-5 Criteria for BED

General Presentation

- Recurrent episodes of binge eating occurring at least once a week for 3 months*
- Eating a larger amount of food than normal during a short time frame (any two-hour period)
- A sense of lack of control overeating during the binge episode (feeling you can't stop eating or control what or how much you are eating)

Binge eating episodes associated with ≥ 3 of the following

- Eating until feeling uncomfortably full
- Eating large amounts of food when not physically hungry
- Eating much more rapidly than normal
- Eating alone out of embarrassment over quantity eaten
- Feeling disgusted, depressed, ashamed, or guilty after overeating

Additional Characteristics

- Marked distress regarding binge eating is also present
- Binge eating is **not** associated with regular inappropriate compensatory behavior, such as purging, excessive exercise, etc.
- Binge eating does not occur exclusively during the course of bulimia nervosa or anorexia nervosa

* Denotes a change from DSM-IV criteria

1. APA. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. 2013.

BED Epidemiology/Course

BED is the most common eating disorder

- 2.8% (US adults), 1.6% (adolescents), 1.9% worldwide
- Prevalence for other eating disorders:
 - Anorexia Nervosa 0.6%, Bulimia Nervosa 1%
- BED affects women(3.5%) more often than men (2.0%)
- BED is more common in men than other eating disorders:
 - AN, BN 3x more common in women than men
 - BED 1.75x more common in women than men
- Frequently presents in young to middle adulthood
- Course may be remitting, recurrent, or chronic

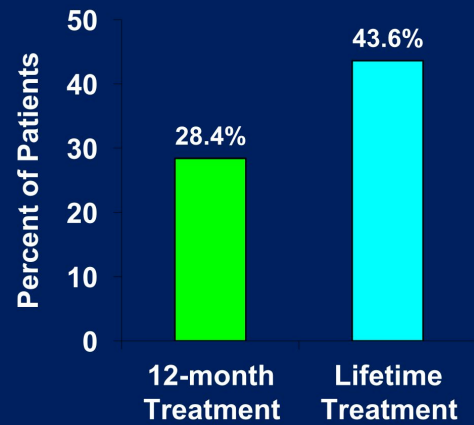
BED is Associated With...

- Overeating (night eating, grazing, LOC) and weight gain
- Obesity, including severe obesity (BMI ≥ 40), & obesity-related conditions
- Mood, anxiety, substance use, impulse control (e.g., ADHD) disorders
 - 80% have ≥ 1 comorbid disorder
- Reduced quality of life, impairment in functioning (comparable to BN), & increased health care use and costs
- Marked distress - shame, guilt, self disgust
- BED is NOT a trivial disorder

Hudson JI et al. *Biol Psych*. 2007;61:348.; Preti A et al. *J Psychiatric Res*. 2009;43:1125.; Swanson SA et al. *Arch Gen Psychiatry*. 2011;68:714.
Kessler RC et al. *Biol Psych*. 2013;73:904.

Most People With BED Remain Untreated

- **12-Month Treatment for BED:** 28.4% of those with disorder have received treatment
- **Lifetime Treatment for BED:** 43.6% of those with disorder have received treatment



Standard of Care for BED not yet clearly defined

- Psychoeducation, self-help strategies
- Behavioral weight loss treatment
- Empirically based psychotherapies (ex.CBT-E)
- Pharmacotherapy
- Obesity surgery
- Combination therapy

Pharmacotherapy of BED

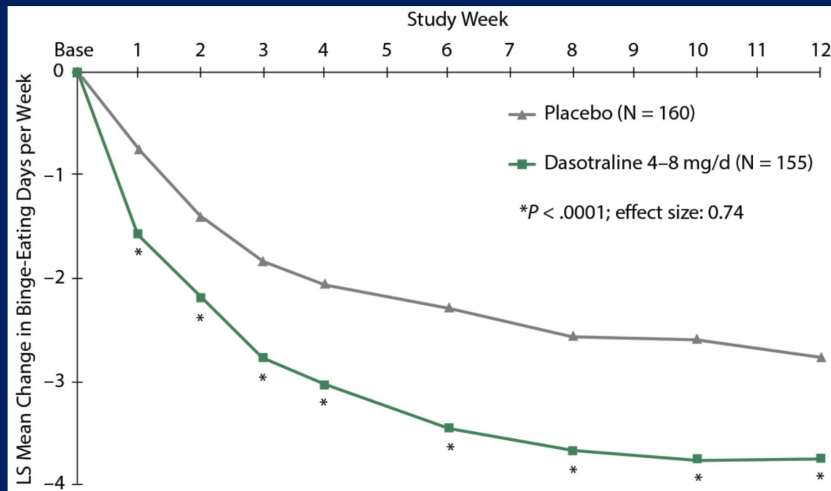
- Only 1 drug with FDA approval for BED:
 - Lisdexamfetamine for BED
 - Fluoxetine for BN
 - Dasotraline development for BED halted despite 2 positive RCTs
 - Problems with lisdexamfetamine:
 - Addiction (schedule 2)
 - Cardiovascular side effects
 - Can be mood destabilizing
 - Not everyone responds or tolerates
 - Need new medications with novel MOAs
-

Dasotraline

- Selective DA-NE reuptake inhibitor
- Was being developed for ADHD and BED
- 2 positive registration trials for BED

Dasotraline in BED

Change in binge-eating days per week in randomized, placebo-controlled, flexible-dose clinical trial:

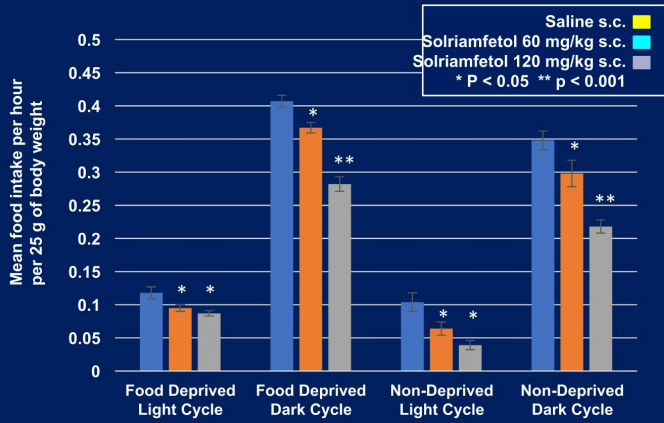


Rationale for Solriamfetol in BED

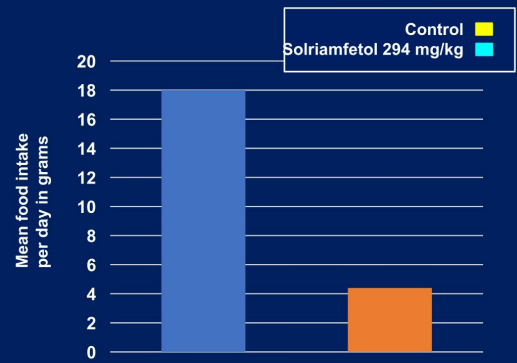
- DNRI like dasotraline
 - Decreased appetite and weight loss
 - Link between narcolepsy and BED
-

Solriamfetol: Preclinical Effects on Food Intake

Administration of solriamfetol to mice and rats under a variety of conditions consistently resulted in reductions of food consumption and weight¹



In male C57BL/6 mice, 60 and 120 mg/kg s.c. doses significantly decreased food intake relative to saline control, regardless of time of day or nutritional status (food-deprived or not)²



In Wistar rats, 7-day dietary treatment of 294 mg/kg solriamfetol induced significant decreases in food consumption compared to controls³

1. Axsome Therapeutics, Inc., "Solriamfetol (previously JZP-110) [Investigator's Brochure]." 2023. 2. Study No. JNJ-7006, non-GLP 3. Study No. 95-4a, non-GLP

Solriamfetol: Clinical Effects on Appetite and Weight

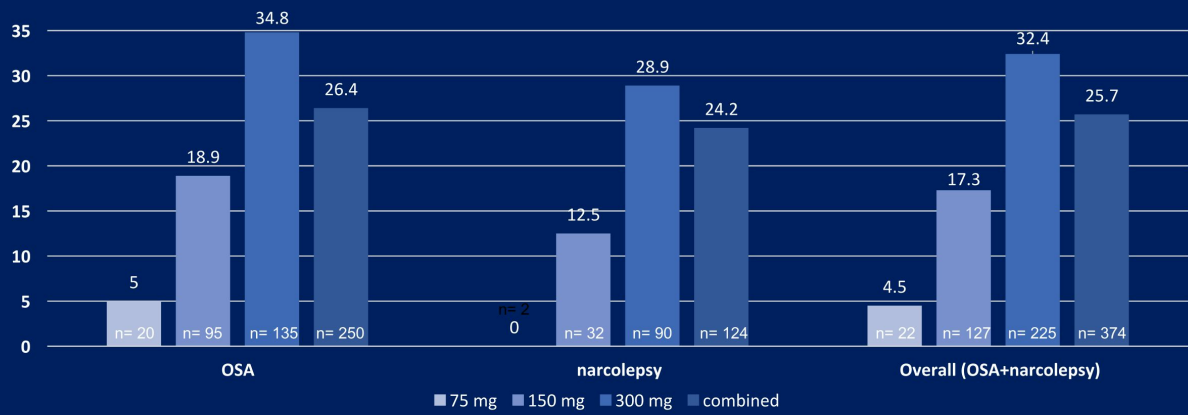
During 12-week randomized clinical trials for OSA and narcolepsy, decreased appetite was one of the most common adverse events with solriamfetol and occurred in a dose-dependent fashion

TEAE, n(%)	Obstructive Sleep Apnea					Narcolepsy			
	Placebo (n=119)	Solriamfetol (n)				Placebo (n=59)	Solriamfetol (n)		
		37.5mg (58)	75 mg (62)	150 mg (117)	300 mg (118)		75 mg (59)	150 mg (59)	300 mg (59)
↓ appetite	1 (0.8)	1 (1.7)	3 (4.8)	9 (7.7)	14 (11.9)	1 (1.7)	5 (8.5)	5 (8.5)	9 (15.3)
↓ weight	0	0	0	1 (0.9)	1 (0.8)	0	1 (1.7)	1 (1.7)	3 (5.1)
↑ appetite	0	0	0	0	0	0	1 (1.7)	1 (1.7)	0
↑ weight	0	0	0	0	0	3 (5.1)	2 (3.4)	0	1 (1.7)

Abbreviation: TEAE = treatment emergent adverse event; OSA = obstructive sleep apnea
 1. Malhotra A et al. Sleep Med. 100(2022) pp 165-173.

Solriamfetol: Clinical Effects on Weight

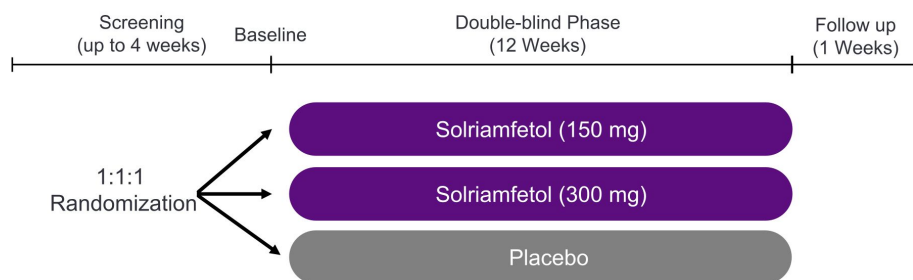
Percent of patients with $\geq 5\%$ weight decrease during 40-week open-label clinical trials for OSA and narcolepsy:



Abbreviation: TEAE = treatment emergent adverse event
1. Malhotra A et al. Sleep Med. 100(2022) pp 165-173.

Binge Eating Disorder: Axsome Planned Phase 3 Trial

A Phase 3 trial to assess efficacy and safety of **solriamfetol** as compared to placebo in the treatment of BED.



- **Key Inclusion Criteria:**

- Meets DSM-5 criteria for BED
- Diagnosis confirmed by EDE-Q

- **Primary Endpoint:** Change from baseline in the diary reported number of binge eating days per week

- **Registrational Trial**

EDE-Q: Eating Disorder Examination Questionnaire



© Axsome Therapeutics, Inc.

Key Takeaways for Solriamfetol in Binge Eating Disorder

- BED is the **most common eating disorder**, affecting almost 3% of the U.S. population¹
- BED is associated with a **2- to 3-fold increased risk** of psychiatric and medical comorbidities²
- Despite high prevalence and burden, there is **currently only one** FDA-approved medication for BED
- **Evaluation of solriamfetol in BED** is supported by solriamfetol pharmacology, preclinical effects, and clinical effects on appetite and weight observed in OSA and narcolepsy patients.

References:

1. Hudson JI, et al. *Biol. Psychiatry*, vol. 61, no. 3, pp. 348–358, Feb. 2007
 2. McElroy SL et al. *J. Clin. Psychiatry*, vol. 81, no. 5, Sep. 2020
-

SHARP Study:
**Effects of Solriamfetol on Cognitive Function in Participants
With Cognitive Impairment Associated With Excessive Daytime
Sleepiness in Obstructive Sleep Apnea**

Richard Bogan, M.D.

Associate Clinical Professor at the University of South Carolina School of Medicine and Medical University of
South Carolina

Principal of Bogan Sleep Consultants

Background

- Excessive daytime sleepiness (EDS) is a common symptom of obstructive sleep apnea (OSA). It can persist in 10%–28% of patients, despite use of primary airway therapy
- Patients with EDS associated with OSA may have performance deficits in several cognitive domains
- Solriamfetol (Sunosi®) is a dopamine and norepinephrine reuptake inhibitor with agonistic properties at trace amine-associated receptor 1 (TAAR1) and serotonin 1A receptors
- Solriamfetol (37.5–150 mg/day) is approved in United States, Canada, and select European countries to treat EDS associated with OSA

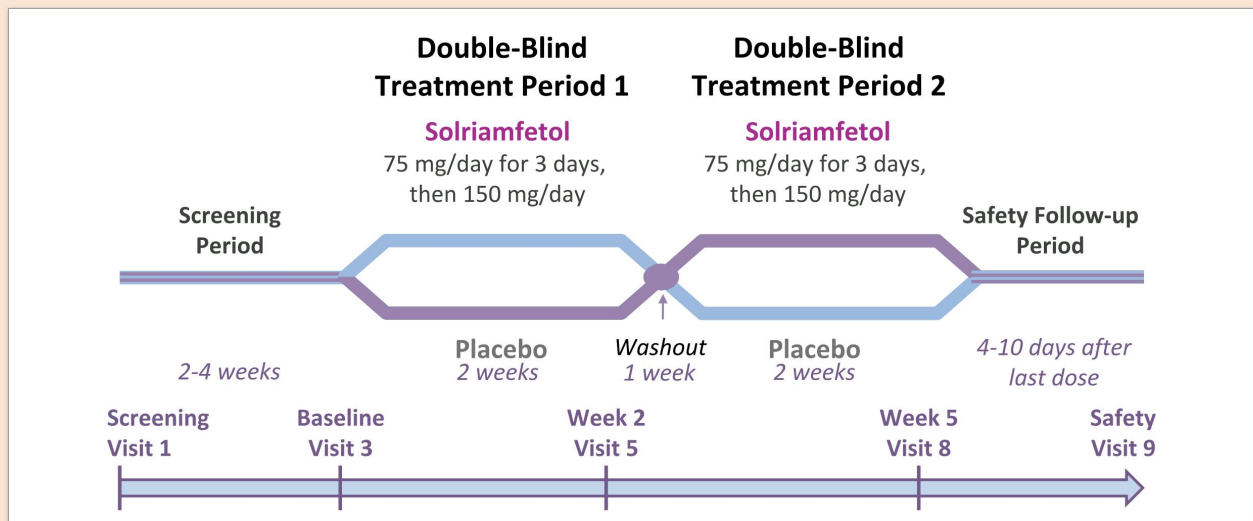
Bonsignore MR et al., 2021
Gasa M et al., 2013
Gursahani H et al., 2022
Pepin JL et al., 2009
Vasudev P et al., 2020
Zhou J et al., 2016

SHARP Trial (NCT04789174)

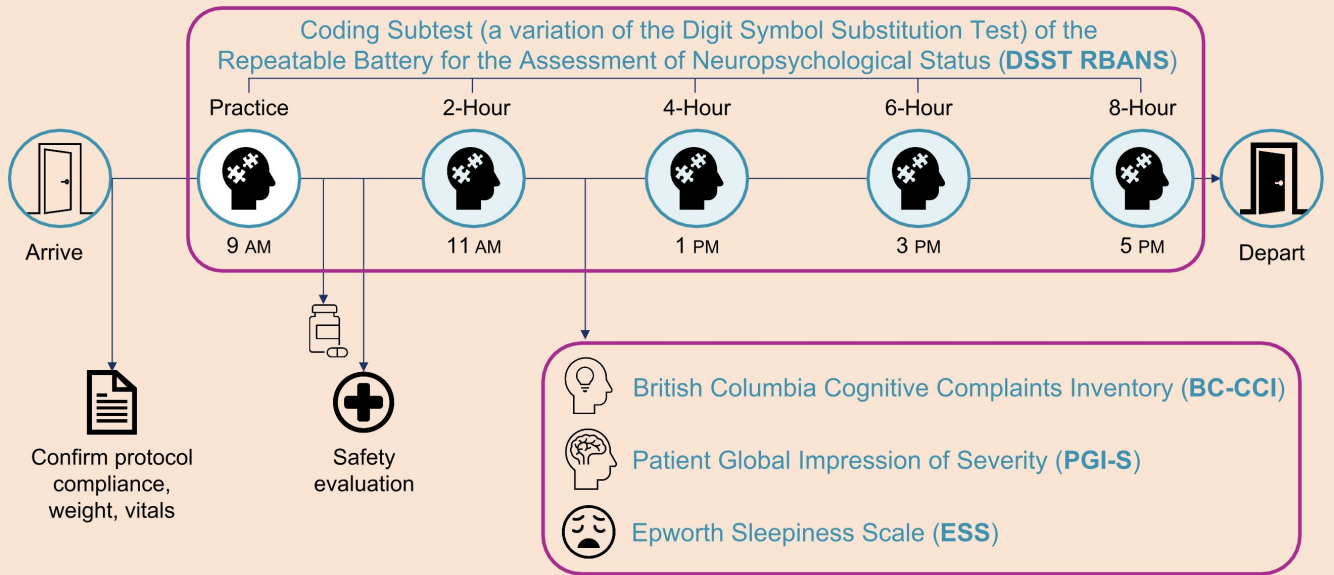
- Objective: to assess whether solriamfetol improves cognitive function in patients with EDS associated with OSA and extant impaired cognition

SHARP Trial Study Design

Phase IV, randomized, double-blind, placebo-controlled, crossover trial



Clinical Visit Structure



Baseline Demographics and Clinical Characteristics

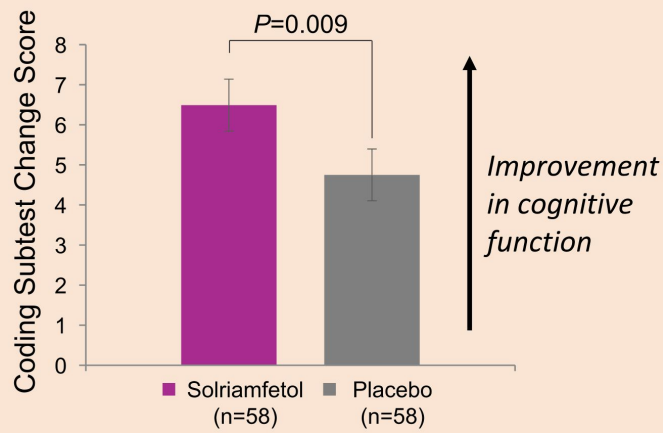
- Of 173 participants screened, 59 were enrolled, and 57 completed the study
- Among participants using positive airway pressure, average use was ≥ 6 hours per night

	Solriamfetol/ placebo (n=30)	Placebo/ solriamfetol (n=29)	Overall (N=59)
Age (years), mean (SD)	52.5 (10.5)	51.9 (11.1)	52.2 (10.7)
Sex (female), n (%)	10 (33.3)	11 (37.9)	21 (35.6)
Race, n (%)			
White	24 (80.0)	19 (65.5)	43 (72.9)
Black or African American	4 (13.3)	8 (27.6)	12 (20.3)
Asian	1 (3.3)	2 (6.9)	3 (5.1)
Unknown	1 (3.3)	0	1 (1.7)
Body mass index (kg/m ²), mean (SD)	32.8 (4.7)	31.6 (4.0)	32.2 (4.4)
Digit Symbol Substitution Test (age-corrected), mean (SD)	6.6 (1.3)	6.9 (0.8)	6.8 (1.1)
British Columbia Cognitive Complaints Inventory, mean (SD)	11.4 (2.5)	11.4 (2.5)	11.4 (2.5)
Patient Global Impression of Severity (cognitive function), mean (SD)	2.2 (0.8)	2.3 (0.7)	2.3 (0.7)
Positive airway pressure use, n (%)	22 (73)	20 (69)	42 (71)
Adherent use (≥ 4 h/night for 70% of nights), n (%)	18 (60)	16 (55)	34 (58)
Hours of use (among all users), mean (SD)	6.0 (2.4)	6.6 (2.7)	6.3 (2.5)



Study Findings: Objective Cognitive Function

Change from baseline to end of treatment in objective cognitive function was measured with the Coding Subtest (a variation of the Digit Symbol Substitution Test) of the Repeatable Battery for the Assessment of Neuropsychological Status (average across all post-dose timepoints)



Solriamfetol significantly improved objective cognitive function compared with placebo

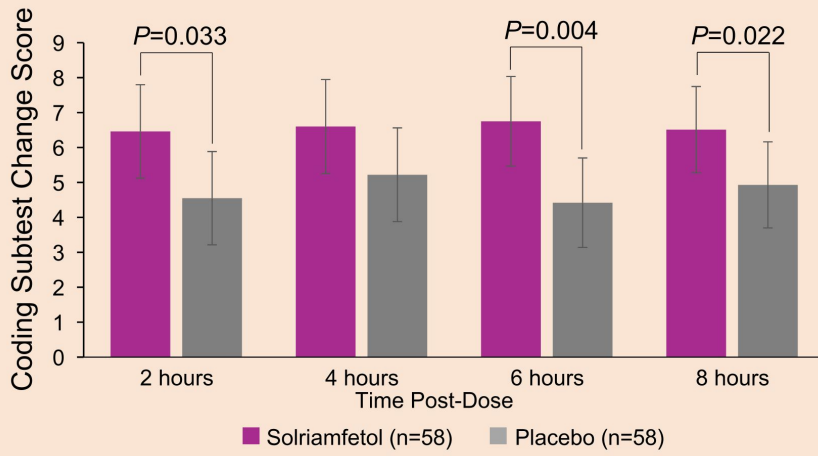
Mean difference: 1.75
(95% CI: 0.46, 3.04)

Cohen's *d*: 0.36



Study Findings: Objective Cognitive Function

Change from baseline to end of treatment in objective cognitive function was measured with the Coding Subtest (a variation of the Digit Symbol Substitution Test) of the Repeatable Battery for the Assessment of Neuropsychological Status (at each post-dose timepoint)



Solriamfetol significantly improved objective cognitive function compared with placebo at 2, 6, and 8 hours after dosing

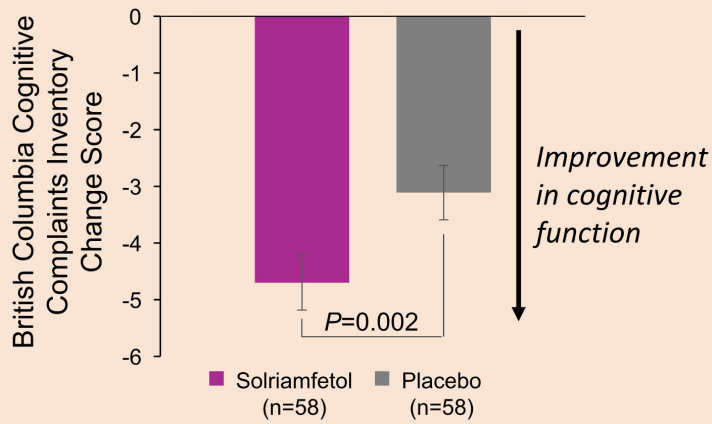
Mean difference (95% CI)

- **2-hour:** 1.91 (0.16, 3.65)
- **4-hour:** 1.38 (-0.22, 2.97)
- **6-hour:** 2.33 (0.78, 3.88)
- **8-hour:** 1.58 (0.23, 2.93)



Study Findings: Subjective Cognitive Function

Change from baseline to end of treatment in subjective cognitive function was measured with the British Columbia Cognitive Complaints Inventory



Solriamfetol significantly improved subjective cognitive function compared with placebo

Mean difference: -1.58
(95% CI: -2.53, -0.63)

Cohen's d : 0.43

Study Findings: Safety

- All treatment-emergent adverse events (TEAEs) were mild or moderate in severity
- There were no deaths, serious TEAEs, or TEAEs that led to discontinuation of the study

Common TEAEs (reported by ≥ 2 participants)

n (%)	Solriamfetol (n=58)	Placebo (n=58)
Any TEAE	11 (19)	6 (10)
Nausea	4 (7)	1 (2)
Anxiety	2 (3)	0
Insomnia	1 (2)	1 (2)
Nasopharyngitis	1 (2)	1 (2)

Conclusions

- Solriamfetol provided sustained improvement in objective cognition, reduced participants' perceived severity of cognitive impairment, and reduced subjective sleepiness
- The adverse event profile and high study completion rate suggest solriamfetol was well tolerated
- Solriamfetol has the potential to improve cognitive function in patients with cognitive impairment associated with OSA and EDS

Shift Work Disorder

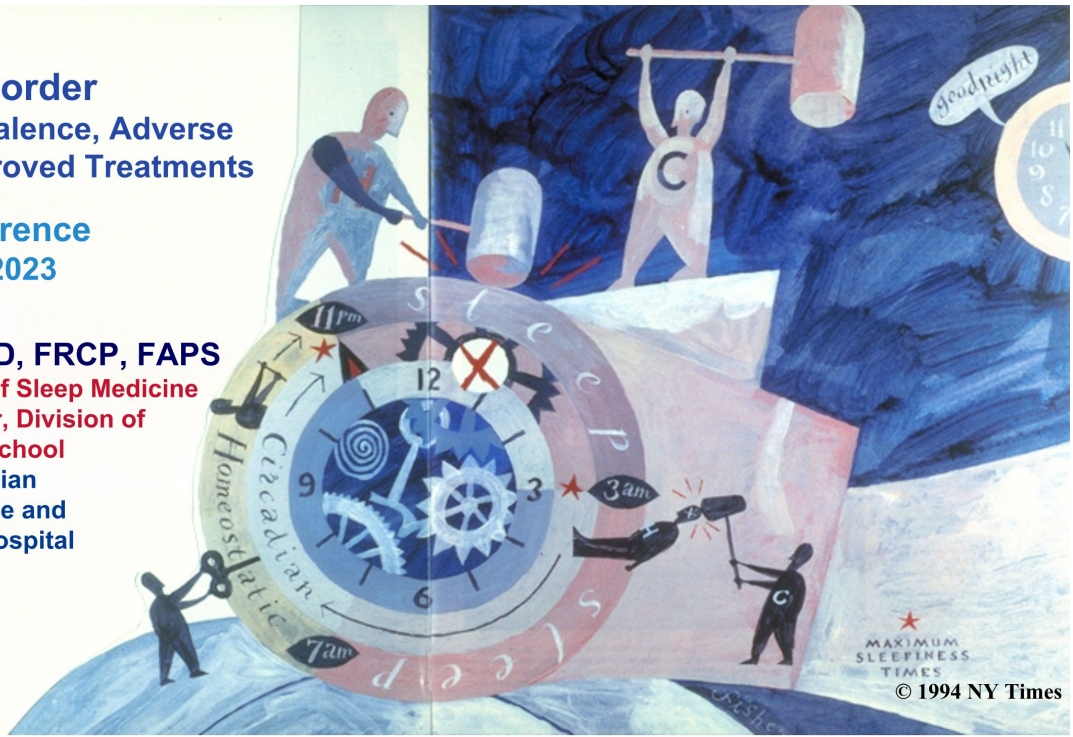
Diagnostic Features, Prevalence, Adverse Health Outcomes, and Approved Treatments

Investor Conference

December 7, 2023

Charles A. Czeisler, PhD, MD, FRCP, FAPS

Frank Baldino, Jr, PhD Professor of Sleep Medicine
Professor of Medicine and Director, Division of Sleep Medicine, Harvard Medical School
Chief, Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham & Women's Hospital



DIVISION OF SLEEP MEDICINE
HARVARD MEDICAL SCHOOL



Brigham and Women's Hospital
Founding Member, Mass General Brigham

3 FDA-approved treatments for circadian rhythm sleep-wake disorders I have contributed to:

1. **Modafinil** for Shift-Work Sleep-Wake Disorder^{1,3}
2. **Armodafinil** for Shift-Work Sleep-Wake Disorder²
3. **Tasimelteon** for Non-24-Hour Sleep-Wake Disorder^{4,5}

1. Czeisler CA *et al.* (2005). Modafinil for excessive sleepiness associated with **shift work sleep disorder**. *N Engl J Med* 353: 476-486.

2. Czeisler CA, Walsh JK, Wesnes KA, Arora S, Roth T. (2009). Armodafinil for treatment of excessive sleepiness associated with **shift work disorder**: a randomized controlled study. *Mayo Clin Proc* 84: 958-972.

3. Grady S, Aeschbach D, Wright KP, Jr., Czeisler CA. Effect of modafinil on impairments in neurobehavioral performance and learning associated with extended wakefulness and circadian misalignment. *Neuropsychopharmacology* 2010;35:1910-20.

4. Rajaratnam SM, Polymeropoulos MH, Fisher DM, Roth T, Scott C, Birnieks G, Klerman EB (2008). Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: two randomised controlled multicentre trials. *Lancet* 373(9662): 482-491.

5. Lockley SW, Dressman MA, Licamele L, Xiao C, Fisher DM, Flynn-Evans EE, Hull JT, Torres R, Lavedan C, Polymeropoulos MH. Tasimelteon for **non-24-hour sleep-wake disorder** in totally blind people (SET and RESET): two multicentre, randomised, double-masked, placebo-controlled phase 3 trials. *Lancet* 386(10005): 1754-1764.

*Dr. Czeisler reports grants and contracts to BWH from Dayzz Live Well, Delta Airlines, Jazz Pharmaceuticals PLC Inc, Puget Sound Pilots, Regeneron Pharmaceuticals/Sanofi; is/was a paid consultant to or speaker for Boston Celtics, Boston Red Sox, Cleveland Browns, Columbia River Bar Pilots, Ganésco, Inc., Institute of Digital Media and Child Development, Klarman Family Foundation, M. Davis and Co, Physician's Seal, Samsung, State of Washington Board of Pilotage Commissioners, Tencent Holdings Ltd, Teva Pharma Australia, Vanda Pharmaceuticals Inc (in which Dr. Czeisler holds an equity interest), and With Deep, Inc. (in which he holds an equity interest); receives/received research/education support through BWH from Cephalon, Mary Ann & Stanley Snider via Combined Jewish Philanthropies, Harmony Biosciences LLC, Johnson & Johnson, NeuroCare, Inc., Philips Respironics Inc/Philips Homecare Solutions, Regional Home Care, Teva Pharmaceuticals Industries Ltd, Optum, ResMed, San Francisco Bar Pilots, Sanofi, Schneider, Simmons, Sysco, Philips, Vanda Pharmaceuticals; is/was an expert witness in legal cases, including those involving Advanced Power Technologies, Aegis Chemical Solutions LLC, Amtrak; Casper Sleep Inc, C&J Energy Services, Complete General Construction Co, Dallas Police Association, Enterprise Rent-A-Car, Steel Warehouse, FedEx, Greyhound Lines, Palomar Health District, PAR Electrical Contractors, Product & Logistics Services LLC, Puckett Emergency Medical Services LLC, South Carolina Central Railroad Company LLC, Union Pacific Railroad, UPS, and Vanda Pharmaceuticals; serves as the incumbent of an **endowed professorship provided to Harvard University by Cephalon, Inc.**; and receives royalties from McGraw Hill, and Philips Respironics for the Actiwatch-2 and Actiwatch Spectrum devices. Dr. Czeisler's interests were reviewed and are managed by the Brigham and Women's Hospital and Mass General Brigham in accordance with their conflict-of-interest policies

Shift Work Disorder: Diagnostic Features

- **Insomnia during daytime sleep or excessive sleepiness during night work**, accompanied by reduced total sleep time
- Associated with **work schedule that overlaps usual sleep time**
- Symptoms **cause clinically significant distress or impairment** in important areas of functioning for **at least 3 months**
- Symptoms **not better explained by another disorder**
- **Overnight and early morning work shifts** (starting between 3:00 and 7:00 am) can also cause SWD

Ref: International Classification of Sleep Disorders, 3rd Revision, 2014, American Academy of Sleep Medicine

Prevalence of Shift Work Disorder (SWD): Between 15-30 percent of employed persons in US work non-standard hours

Study	Prevalence estimate
2004 Drake CL et al. Shift work sleep disorder: prevalence and consequences.... <i>Sleep</i>	Insomnia during day sleep OR excessive sleepiness during night work: 32% night workers; 26% rotating shift workers (vs 18% of day workers)
2009 Waage S et al. Shift work disorder among oil rig workers in the North Sea. <i>Sleep</i>	SWD Prevalence: 23.3% of rotating shift workers working 12-hour shifts on an oil rig
2011 Rajaratnam SM, Barger LK ... Czeisler CA. Sleep disorders, health, and safety in police officers . <i>JAMA</i>	SWD Prevalence: 14.5% (excessive sleepiness AND insomnia) 31.6% (excessive waketime sleepiness) 36.8% (insomnia during daytime sleep) 53.9% (excessive waketime sleepiness OR insomnia)
2012 Flo et al. Shift work disorder in nurses--assessment, prevalence and related health problems. <i>PLoS One</i>	SWD Prevalence: 6.2% day work only; 28.9% two-shift rotation; 44.3% night shift only; 44.3% three-shift rotation
2019 Vanttola Prevalence of shift work disorder among hospital personnel: A cross-sectional <i>Sleep Res</i>	33.5% (ICSD-2, 1 night shift/month); 9.5% (ICSD-3, 1 night shift/month, including criterion of reduced sleep duration)

Prevalence of Shift Work Disorder (SWD): Between 15-30 percent of employed persons in US work non-standard hours

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2004 Drake CL et al. Shift work sleep disorder: prevalence and consequences.... <i>Sleep</i>	Insomnia during day sleep OR excessive sleepiness during night work: 32% night workers; 26% rotating shift workers (vs 18% of day workers)
2009 W: workers	an
2011 Ra disorder	
<p>Bottom line</p> <p>Of 160 million employed persons in US:</p> <ul style="list-style-type: none"> • About 40 million employees work non-standard hours • About 12 million employees may suffer from excessive sleepiness when working at night or early morning shifts 	
	53.9% (excessive waketime sleepiness OR insomnia)
2012 Flo et al. Shift work disorder in nurses--assessment, prevalence and related health problems. PLoS One	SWD Prevalence: 6.2% day work only; 28.9% two-shift rotation; 44.3% night shift only; 44.3% three-shift rotation
2019 Vanttola Prevalence of shift work disorder among hospital personnel: A cross-sectional <i>Sleep Res</i>	33.5% (ICSD-2, 1 night shift/month); 9.5% (ICSD-3, 1 night shift/month, including criterion of reduced sleep duration)

Genetic background matters

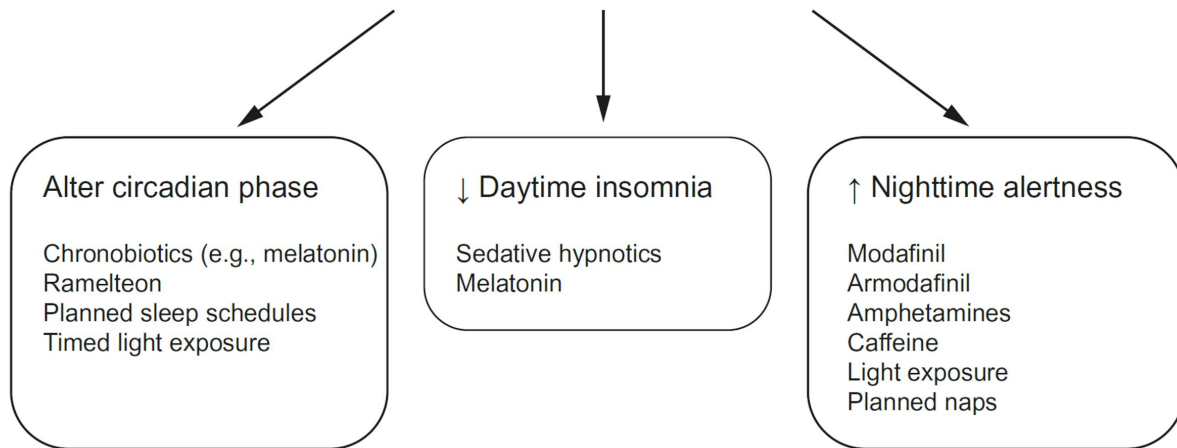
- Night-shift workers carrying the **five-repeat variant of the Period 3 gene (Period 3⁻⁵)**, which make up about 35–40% of the population, showed elevated levels of nocturnal sleepiness and earlier circadian phase compared with homozygotes for the four-repeat allele (Period 3^{4/4}).
 - **Long-allele carrier** shift workers had significantly lower multiple sleep latency test during overnight work hours compared with Period 3^{4/4} workers (3.5 ± 23.4 minutes versus 10.39 ± 6.41 minutes, $P = 0.003$).
 - **Period 3⁻⁵ night** workers showed a mean circadian phase 6 h earlier (i.e. less adapted) than Period 3^{4/4} workers.

Ref: Drake CL, Belcher R, Howard R, Roth T, Levin AM, Gumenyuk V. Length polymorphism in the Period 3 gene is associated with sleepiness and maladaptive circadian phase in night-shift workers. *J Sleep Res.* 2015 Jun;24(3):254-61.

Outcomes Associated with Shift Work Disorder

Study	Outcomes
1999 Bøggild H, Knutsson A. Shift work, risk factors and cardiovascular disease. <i>Scand J Work Environ Health</i>	Night shift work associated with 40% increased risk of cardiovascular disease (not specific to Shift Work Disorder)
2004 Drake CL et al. Shift work sleep disorder: prevalence and consequences.... <i>Sleep</i>	Ulcers , sleepiness-related accidents , absenteeism , depression , and missed family and social activities; morbidity greater than day workers with insomnia or excessive sleepiness
2009 Waage S et al. Shift work disorder among oil rig workers in the North Sea. <i>Sleep</i>	Employees with SWD reported poorer sleep quality and more subjective health complaints in the non-work period than shift workers without SWD.
2017 Jørgensen JT et al. Shift work and overall and cause specific mortality in the Danish nurse cohort. <i>Scand J Work Environ Health</i>	Women working night and evening shifts have increased all-cause mortality , cardiovascular , diabetes , and Alzheimer's and dementia mortality (not specific to Shift Work Disorder)

Management Strategy for Shift Work Disorder



Ref: Roth T. Appropriate therapeutic selection for patients with shift work disorder. *Sleep Med.* 2012 Apr;13(4):335-41. doi: 10.1016/j.sleep.2011.11.006. Epub 2012 Feb 20. PMID: 22353444.

Efficacy of non-pharmacological interventions for sleepiness during night work **not established**

“Given the methodological diversity of the included studies, in terms of interventions, settings, and assessment tools, their limited reporting and the **very low to low quality of the evidence** they present, it is not possible to determine whether shift workers' sleepiness can be reduced or if their sleep length or quality can be improved with these interventions.

We found 17 randomized controlled trials (with 556 participants) to include in this review. We rated the **quality of evidence provided by most of the included studies to be between low and very low**. The studies could be divided into three different types of interventions: (1) exposure to bright light; (2) a napping opportunity during the night shift; or (3) others, like physical activity or sleep education.

We **need better** and adequately powered Randomized Clinical **Trials** of the effect of bright light, and naps, either on their own or together and other nonpharmacological interventions that also consider shift workers' chronobiology on the investigated sleep parameters.”

Refs: Slanger TE, Gross JV, Pinger A, Morfeld P, Bellinger M, Duhme AL, Reichardt Ortega RA, Costa G, Driscoll TR, Foster RG, Fritschi L, Sallinen M, Liira J, Erren TC. Person-directed, non-pharmacological interventions for sleepiness at work and sleep disturbances caused by shift work. *Cochrane Database Syst Rev.* 2016 Aug 23;2016(8):CD010641. doi: 10.1002/14651858.CD010641.pub2. PMID: 27549931; PMCID: PMC8406755.

Only five (5) randomized trials have ever been conducted of wake-promoting therapeutics to treat the excessive sleepiness associated with Shift Work Disorder—all on modafinil or armodafinil

A scoping review of the evidence for the impact of pharmacological and non-pharmacological interventions on shift work related sleep disturbance in an occupation setting

Author	Year	Country	Design	Intervention	Population	Outcomes	Sample Size	Control	Intervention	Design	Outcomes	Duration	Comparator	Industry	Conflicts
Erman, M K**	2011 & 2012	USA	Varied	Mixture, 93% permanent	≥5 nights per month, each 6-12 hours, with ≥5 hours between 22:00-08:00 and ≥3 consecutive nights	Excessive sleepiness late in shift associated with ICD2 SWD. Functionally impaired (GAf-7b)	158 (184)	167 (187)	Armodafinil 150mg OD	RCT	Wake outcomes and AE	6 weeks	6 weeks	Cephalon Inc	Yes
Tembe, D V	2011	India	Unspecified	Unspecified		ICD criteria for SWSD	104 (105)	105 (106)	Armodafinil 150mg OD (Control: Modafinil 200mg OD)	RCT	Wake outcomes and AE	12 weeks	12 weeks	Emcure Pharmaceuticals Ltd.	Yes
Czeisler, C A	2009	USA & Canada	Varied	Mixture, 86.5% permanent		ICD2 criteria; <6 minutes on MSLT during a night shift; SE of 87.5% or less on daytime polysomnography	93 (127)	84 (127)	Armodafinil 150mg OD	Randomized, double-blind, placebo-controlled, parallel-group, multicenter study	Sleep outcomes, wake outcomes, other & AE	12 weeks	12 weeks	Cephalon Inc	Yes
Erman, M K	2007	USA	Varied	Unspecified		JCD	129 (185)	60 (93)	Modafinil 200mg or Modafinil 300mg OD	Randomised double blind placebo controlled parallel group trial	Other	12 weeks	12 weeks	Cephalon Inc	Yes
Czeisler, C	2005	USA	Varied	Mixture, 90% permanent		ICD2 criteria; <6 minutes on MSLT during a night shift; SE of 87.5% or less on daytime polysomnography	76 (96)	81 (108)	Modafinil 200mg OD	RCT	Sleep outcomes, wake outcomes, other & AE	12 weeks	12 weeks	Cephalon Inc	Yes

Ref: Conway-Jones R, Dunlop E, Kyle S, Ray D, Roberts N, Farmer A. A scoping review of the evidence for the impact of pharmacological and non-pharmacological interventions on shift work related sleep disturbance in an occupational setting. *Wellcome Open Res.* 2023 Jan 6;6:198. doi: 10.12688/wellcomeopenres.17002.2. PMID: 37346814.

ORIGINAL ARTICLE

Modafinil for Excessive Sleepiness Associated with Shift-Work Sleep Disorder

Charles A. Czeisler, Ph.D., M.D., James K. Walsh, Ph.D., Thomas Roth, Ph.D.,
Rod J Hughes, Ph.D., Kenneth P. Wright, Ph.D., Lillian Kingsbury, Ph.D.,
Sanjay Arora, Ph.D., Jonathan R.L. Schwartz, M.D.,
Gwendolyn E. Niebler, D.O., and David F. Dinges, Ph.D.,
for the U.S. Modafinil in Shift Work Sleep Disorder Study Group*

N ENGL J MED 353;5 WWW.NEJM.ORG AUGUST 4, 2005

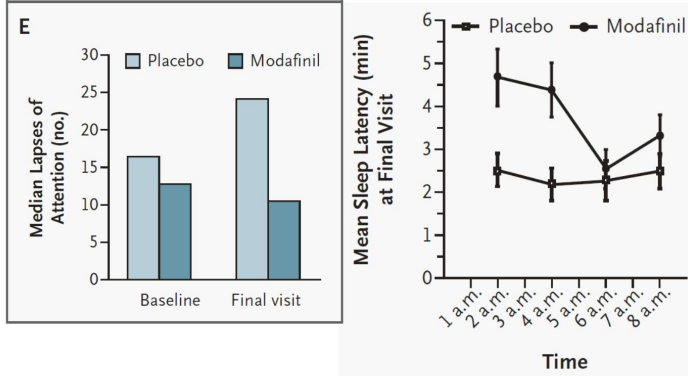


Only Two Treatments are FDA-approved for Excessive Sleepiness Associated with SWD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Modafinil for Excessive Sleepiness Associated with Shift-Work Sleep Disorder

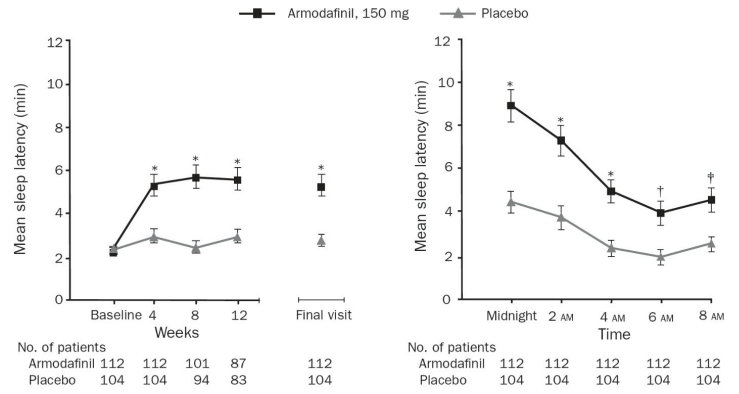


Ref: Czeisler CA, Walsh JK, Roth T, Hughes RJ, Wright KP, Kingsbury L, Arora S, Schwartz JR, Niebler GE, Dinges D. Modafinil for excessive sleepiness associated with shift-work sleep disorder. *N Engl J Med.* 2005 Aug 4;353(5):476-86.

ORIGINAL ARTICLE

MAYO CLINIC PROCEEDINGS

Armodafinil for Treatment of Excessive Sleepiness Associated With Shift Work Disorder: A Randomized Controlled Study



Ref: Czeisler CA, Walsh JK, Wesnes KA, Arora S, Roth T. Armodafinil for treatment of excessive sleepiness associated with shift work disorder: a randomized controlled study. *Mayo Clin Proc.* 2009 Nov;84:958-72.

Shift Work Disorder is simple to identify by a primary care physician:

“A final 4-item questionnaire has 89% positive predictive value and 62% negative predictive value (sensitivity = 0.74; specificity = 0.82).”



Ref: Barger LK, Ogeil RP, Drake CL, O'Brien CS, Ng KT, Rajaratnam SM. Validation of a questionnaire to screen for shift work disorder. *Sleep*. 2012;35:1693-1703.

1	In the past month, <u>while working non-standard shifts</u> , did you have a <i>problem with waking up too early and not being able to get back to sleep?</i>				
	1.No problem	2.Minor problem	3.Considerable problem	4.Serious problem	
2	In the past month, <u>while working non-standard shifts</u> , your <i>sense of well-being during the time you were awake</i> was				
	1. Normal	2.Slightly decreased	3.Somewhat decreased	4.Very decreased	
3	In the past month, how likely were you to <i>doze off at work during your non-standard shift?</i>				
	1.Not at all	2.Slight chance	3.Moderate change	4.Highly likely	
4	How likely were you to <i>doze off or fall asleep</i> while driving <u>after at least two days off from work?</u>				
	1.Not at all	2.Slight chance	3.Moderate change	4.Highly likely	5.Not applicable

Figure S2—The final shift work disorders screening questionnaire consists of 4 questions.

Improvement in Objective Measure of Sleepiness (measured using the Maintenance of Wakefulness Test) after 12 Weeks of Treatment with Solriamfetol in OSA patients

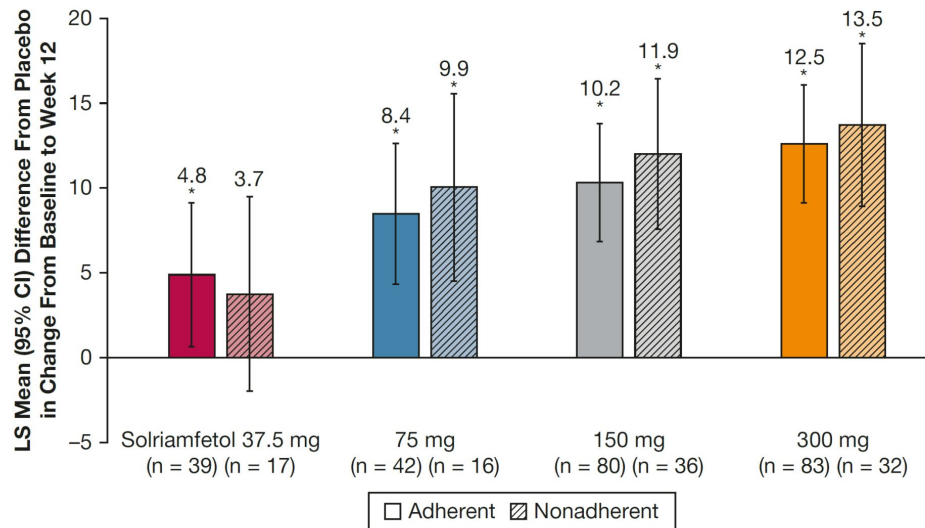


Figure 2 – Bar graph showing the difference from placebo in change in Maintenance of Wakefulness Test score from baseline to week 12 in adherent and nonadherent subgroups (modified intention-to-treat population). * $P < .05$ vs placebo. P values are nominal. LS = least squares.

Ref: Schweitzer PK, Mayer G, Rosenberg R, Malhotra A, Zammit GK, Gotfried M, Chandler P, Baladi M, Strohl KP. Randomized Controlled Trial of Solriamfetol for Excessive Daytime Sleepiness in OSA: An Analysis of Subgroups Adherent or Nonadherent to OSA Treatment. *Chest*. 2021;160:307-318.

Improvement in Subjective Measure of Sleepiness (measured using the Epworth Sleepiness Scale) after 12 Weeks of Treatment with Solriamfetol in OSA patients

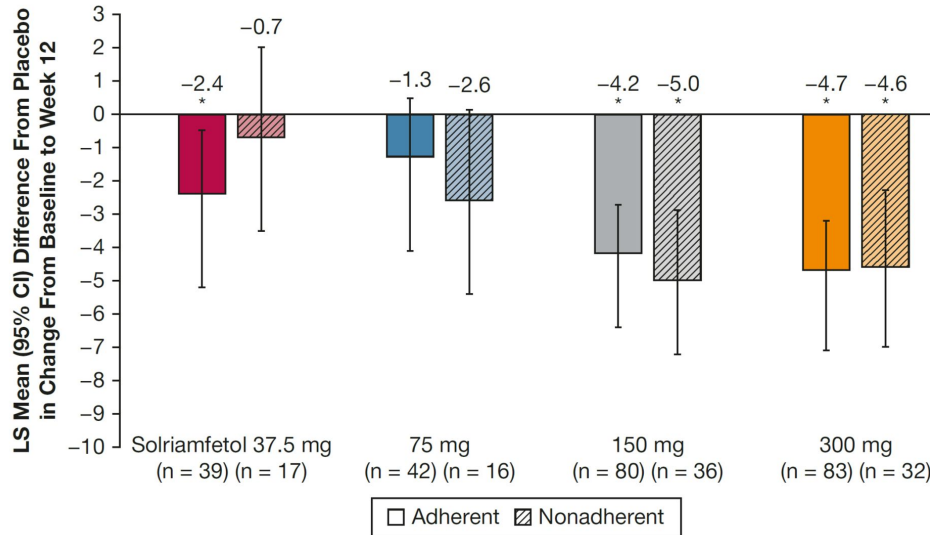
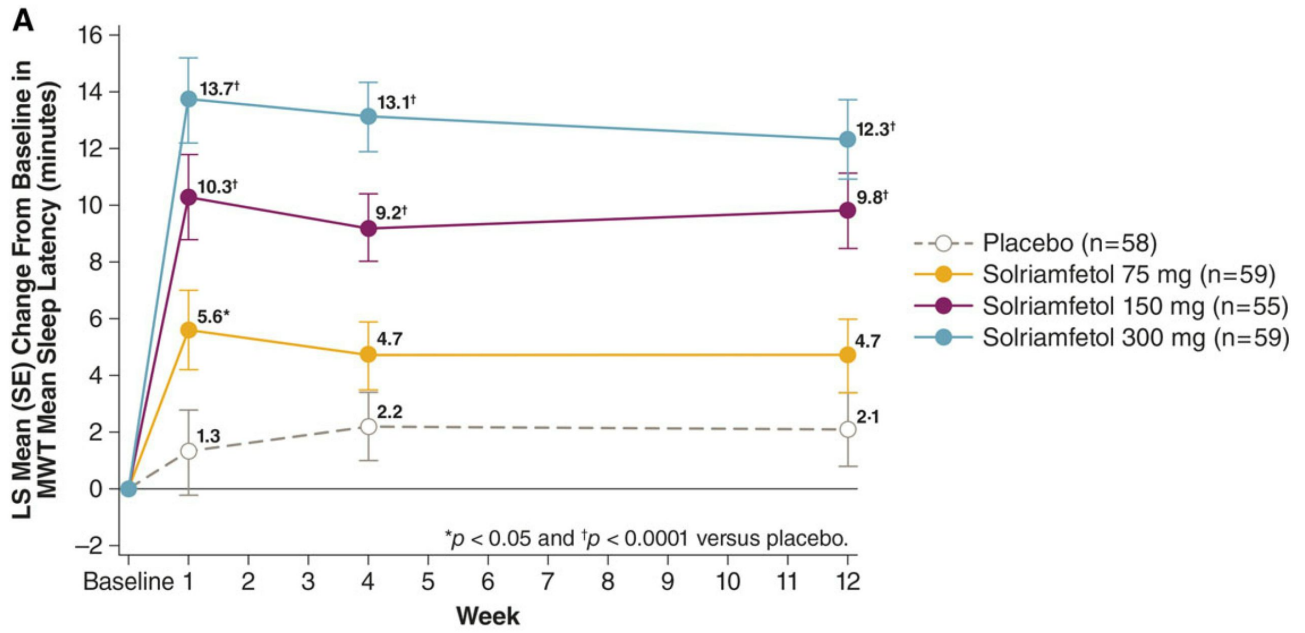


Figure 3 – Bar graph showing the difference from placebo in change in Epworth Sleepiness Scale score from baseline to week 12 in adherent and nonadherent subgroups (modified intention-to-treat population). *P < .05 vs placebo. Reported P values are nominal. LS = least squares.

Ref: Schweitzer PK, Mayer G, Rosenberg R, Malhotra A, Zammit GK, Gotfried M, Chandler P, Baladi M, Strohl KP. Randomized Controlled Trial of Solriamfetol for Excessive Daytime Sleepiness in OSA: An Analysis of Subgroups Adherent or Nonadherent to OSA Treatment. Chest. 2021;160:307-318.

Improvement in Subjective Measure of Sleepiness (measured using the Epworth Sleepiness Scale) after 12 Weeks of Treatment with Solriamfetol in OSA patients



Ref: Thorpy MJ, Shapiro C, Mayer G, Corser BC, Emsellem H, Plazzi G, Chen D, Carter LP, Wang H, Lu Y, Black J, Dauvilliers Y. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. Ann Neurol. 2019;85:359-370

Shift Work Disorder: Need for Treatment

- **Shift work disorder** affects about **12 million American workers**
 - Patients with **shift work disorder** are at increased risk of errors and accidents, including motor vehicle crashes, and adverse health outcomes
 - Evidence for efficacy of commonly used **non-pharmacological** interventions for **excessive sleepiness in SWD is weak**
 - Only two pharmacological treatments (modafinil and armodafinil) have been FDA-approved for shift work disorder, and **EMA withdrew approval for modafinil** after post-marketing severe skin reactions
 - **Solriamfetol effective** in treating **excessive sleepiness** in OSA and narcolepsy
-

Q+A

on Cognition and BED



**Susan McElroy,
MD**



**Richard Bogan,
MD**



Closing Remarks
Herriot Tabuteau, MD

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nasdaq: axsm



thank you

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