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Today’s KOL Speakers

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

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

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

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

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

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Today’s Agenda

Welcome
Solriamfetol Overview
TAAR1 MOA And Major Depressive Disorder (MDD)
Attention Deficit Hyperactivity Disorder (ADHD)
Q+A on TAAR1, MDD and ADHD
Binge Eating Disorder (BED)
Cognition
Shift Work Disorder (SWD)
Q+A on Cognition, BED, SWD
Closing Remarks

Mark Jacobson, COO
Dr. Herriot Tabuteau, CEO
Dr. Craig Chepke
Dr. Andrew Cutler
Drs. Chepke and Cutler
Dr. Susan McElroy
Dr. Richard Bogan
Dr. Charles Czeisler
Drs. McElroy, Bogan, and Czeisler
Dr. Herriot Tabuteau, CEO
Solriamfetol Overview
Herriot Tabuteau, MD
Rapidly Growing, CNS-Focused Biopharma

- 2 Marketed Products
- 5 Late-stage Product Candidates
- 9 New Target Indications
- 183 Million Potential Patients Targeted
Solriamfetol Pharmacology

**Dopamine Reuptake Inhibitor**
- Ki = 14.2 μM

**Norepinephrine Reuptake Inhibitor**
- Ki = 3.7 μM

**TAAR1 agonist**
- EC$_{50}$ = 10-16 μM

**5-HT$_{1A}$ agonist**
- EC$_{50}$ = 25 μM

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### Applications of Solriamfetol Pharmacology

#### 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
Unlocking the Clinical and Commercial Potential of Solriamfetol

<table>
<thead>
<tr>
<th>Approach</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Elucidate the pharmacology</td>
<td>Select new indications with:</td>
</tr>
<tr>
<td>2. Correlate the pharmacology to mechanisms of disease</td>
<td>1. Strongest scientific rationale</td>
</tr>
<tr>
<td>3. Generate clinical proof of concept (pilot studies)</td>
<td>2. Highest probability of success</td>
</tr>
<tr>
<td>4. Leverage existing clinical experience (observations relevant to potential new indications)</td>
<td>3. Highest potential impact (based on patient unmet needs)</td>
</tr>
</tbody>
</table>
Solriamfetol Target Indications

<table>
<thead>
<tr>
<th>Product</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>NDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>solriamfetol</td>
<td>Attention Deficit Hyperactivity Disorder (ADHD)</td>
<td>Major Depressive Disorder (MDD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Binge Eating Disorder (BED)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shift Work Sleep Disorder (SWD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunosi</td>
<td>Excessive Daytime Sleepiness (EDS) Associated with Narcolepsy or Obstructive Sleep Apnea (OSA)</td>
<td></td>
<td></td>
<td>Marketed</td>
</tr>
</tbody>
</table>

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
Unlocking Solriamfetol Franchise Value

- U.S./EU approval for treatment of EDS in OSA and narcolepsy
- Potential patient populations >22 million

**Near-Term Clinical Milestones**

- **MDD**
  - Phase 3 trial initiation
  - 1Q 2024
- **BED**
  - Phase 3 trial initiation
  - 1Q 2024
- **SWD**
  - Phase 3 trial initiation
  - 1Q 2024
- **ADHD**
  - Phase 3 trial readout
  - 2H 2024

**US Patient Populations**

- **MDD**
  - 22 million patients
- **BED**
  - 7 million patients
- **SWD**
  - 15 million patients
- **ADHD**
  - 17 million patients

83 million potential patients
Trace Amine Associated Receptor Signaling and Psychiatric Disorders

Craig Chepke, MD, DFAPA

Adjunct Associate Professor of Psychiatry, Atrium Health
Medical Director, Excel Psychiatric Associates
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 5HT₁A 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

1. H. Gursahani et al., CNS Spectr., vol. 28, no. 2, pp. 222–222, Apr. 2023 2. placeholder
What is TAAR1?

<table>
<thead>
<tr>
<th>Trace Amines</th>
<th>Monoamines</th>
</tr>
</thead>
<tbody>
<tr>
<td>b-phenylethylamine</td>
<td>dopamine</td>
</tr>
<tr>
<td>tyramine</td>
<td>serotonin</td>
</tr>
<tr>
<td>p-tyramine</td>
<td>epinephrine</td>
</tr>
<tr>
<td>p-octopamine</td>
<td>norepinephrine</td>
</tr>
</tbody>
</table>

- **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


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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

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 terminalus (BNST)
TAAR1 Agonists Have Wide-Ranging Effects in Preclinical Models

Serotonin receptor 5-HT\textsubscript{1A} is widely distributed in the CNS in areas including the cerebral cortex, hippocampus, amygdala, and raphe nucleus\textsuperscript{1}

5-HT\textsubscript{1A} modulates several major neurotransmitter systems including norepinephrine, serotonin (5HT), dopamine\textsuperscript{2}

5-HT\textsubscript{1A} activation may modulate mood, reward and addictive behaviors, food intake, and cognitive function\textsuperscript{3-5}

TAAR1 agonism is believed to enhance the potency of the effects of 5-HT\textsubscript{1A} agonists\textsuperscript{6-8}
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\textsubscript{1A}

<table>
<thead>
<tr>
<th>Drug</th>
<th>hTAAR1 EC\textsubscript{50} μM (Emax)</th>
<th>5-HT\textsubscript{1A} IC\textsubscript{50} μM</th>
<th>hDAT IC\textsubscript{50} μM</th>
<th>hNET IC\textsubscript{50} μM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solriamfetol</td>
<td>10-16 (100%)</td>
<td>25</td>
<td>3.21</td>
<td>14.4</td>
</tr>
<tr>
<td>Modafinil</td>
<td>No dose response*</td>
<td>Unknown</td>
<td>2.8</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Bupropion</td>
<td>No dose response*</td>
<td>No functional activity</td>
<td>0.26</td>
<td>2.79</td>
</tr>
</tbody>
</table>

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

\textsuperscript{5HT}_{1A}: serotonin 1A receptor; EC\textsubscript{50}: half maximal effective concentration; Emax: maximal effect; hDAT: human dopamine transporter; hNET: human norepinephrine transporter; hTAAR1: human trace amine-associated receptor; IC\textsubscript{50}: half maximal inhibitory concentration; WPA: wake-promoting agent.

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.

DAT: dopamine transporter; NET: norepinephrine transporter

DAT: dopamine transporter; NET: norepinephrine transporter
TAAR1 / 5-HT$_{1A}$ agonists may have applications in psychiatric and neurological disorders

- Schizophrenia
- Generalized Anxiety Disorder
- Parkinson's Disease
- Psychosis
- Shift Work Disorder
- EDS due to OSA or Narcolepsy
- Major Depressive Disorder
- ADHD
- Binge Eating Disorder
- TAAR1 / 5-HT$_{1A}$ agonists
- Parkinson's Disease Psychosis

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Major Depressive Disorder (MDD)
Craig Chepke, MD, DFAPA
Adjunct Associate Professor of Psychiatry, Atrium Health
Medical Director, Excel Psychiatric Associates
Approximately 1 in 5 individuals in the US will experience MDD at some point in their life.*

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, including2,†:

<table>
<thead>
<tr>
<th>✓ Depressed mood</th>
<th>✓ Significant weight changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Diminished interest or pleasure in activities</td>
<td>✓ Feelings of worthlessness or excessive or inappropriate guilt</td>
</tr>
<tr>
<td>✓ Insomnia or hypersomnia</td>
<td>✓ Diminished ability to think or concentrate or indecisiveness</td>
</tr>
<tr>
<td>✓ Psychomotor agitation or retardation</td>
<td>✓ Suicidal ideation or a suicide attempt</td>
</tr>
<tr>
<td>✓ Fatigue or loss of energy</td>
<td></td>
</tr>
</tbody>
</table>

227 unique symptom profiles exist that may qualify for a diagnosis of MDD.‡

---

*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.


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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

<table>
<thead>
<tr>
<th>Step</th>
<th>Remission</th>
<th>Discontinuation due to side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>36.8</td>
<td>16.3</td>
</tr>
<tr>
<td>(N=3671)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td>30.6</td>
<td>19.5</td>
</tr>
<tr>
<td>(N=1439)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 3</td>
<td>13.7</td>
<td>25.6</td>
</tr>
<tr>
<td>(N=390)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 4</td>
<td>13.0</td>
<td>30.1</td>
</tr>
<tr>
<td>(N=123)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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.

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.

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

High Level Summary of TAAR1 MOA in MDD


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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 $\geq 25$ and a CGI-S $\geq 4$ 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
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
Main Features of ADHD Diagnosis
(American Psychiatric Association, 2013 & 2 other sources)

• 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


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ADHD is a Common Disorder in Childhood and Adulthood

- An estimated 17.4 million people in the U.S. are affected by ADHD\textsuperscript{1,2}
- The prevalence of ADHD has not changed over the past three decades that have data available\textsuperscript{3}
- No significant differences in prevalence between North America and Europe, Asia, Africa, South America, and Oceania\textsuperscript{3}

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.

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)*

- Stimulant Medication
- Non-Stimulant Medication
- Restricted Elimination Diets
- Artificial Food Color Exclusions
- Neurofeedback
- Computer Cognitive Training
- Omega-3 Fatty Acids
- Behavioral Parent Training

---

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)

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


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Solriamfetol for ADHD in Adults: Demographic and Baseline Characteristics

- 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

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

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
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).


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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)

---

Solriamfetol for ADHD in Adults: Safety and Tolerability

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

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 medications\(^1\)


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Q&A on TAAR1, MDD, and ADHD

Craig Chepke, MD, DFAPA
Andrew J. Cutler, MD
Solriamfetol in Binge Eating Disorder

Susan L. McElroy, MD

Chief Research Officer, Lindner Center of HOPE
Linda & Harry Fath Professor of Psychiatry & Behavioral Neuroscience
University of Cincinnati College of Medicine
Cincinnati, Ohio
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

<table>
<thead>
<tr>
<th>General Presentation</th>
<th>Binge eating episodes associated with $\geq 3$ of the following</th>
<th>Additional Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recurrent episodes of binge eating occurring at least once a week for 3 months*</td>
<td>• Eating until feeling uncomfortably full</td>
<td>• Marked distress regarding binge eating is also present</td>
</tr>
<tr>
<td>• Eating a larger amount of food than normal during a short time frame (any two-hour period)</td>
<td>• Eating large amounts of food when not physically hungry</td>
<td>• Binge eating is not associated with regular inappropriate compensatory behavior, such as purging, excessive exercise, etc.</td>
</tr>
<tr>
<td>• 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)</td>
<td>• Eating much more rapidly than normal</td>
<td>• Binge eating does not occur exclusively during the course of bulimia nervosa or anorexia nervosa</td>
</tr>
<tr>
<td></td>
<td>• Eating alone out of embarrassment over quantity eaten</td>
<td></td>
</tr>
</tbody>
</table>
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 $\geq 40$), & obesity-related conditions
- Mood, anxiety, substance use, impulse control (e.g., ADHD) disorders
  - 80% have $\geq 1$ 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

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

Navia B et al, 2017. APA 170th Meeting
Change in binge-eating days per week in randomized, placebo-controlled, flexible-dose clinical trial:

![Graph showing change in binge-eating days per week](image)

- Placebo (N = 160)
- Dasotraline 4–8 mg/d (N = 155)

*P < .0001; effect size: 0.74

Navia B et al, 2017. APA 170th Meeting
Rationale for Solriamfetol in BED

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

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

Abbreviation: TEAE = treatment emergent adverse event; OSE = obstructive sleep apnea
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
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

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Key Takeaways for Solriamfetol in Binge Eating Disorder

- BED is the most common eating disorder, affecting almost 3% of the U.S. population\(^1\)
- BED is associated with a **2- to 3-fold increased risk** of psychiatric and medical comorbidities\(^2\)
- 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:
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
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.

**SHARP Trial (NCT04789174)**

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

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

**Double-Blind Treatment Period 1**
- **Solriamfetol**
  - 75 mg/day for 3 days, then 150 mg/day

**Double-Blind Treatment Period 2**
- **Solriamfetol**
  - 75 mg/day for 3 days, then 150 mg/day

**Screening Period**
- 2-4 weeks

**Baseline Visit 3**

**Week 2 Visit 5**

**Week 5 Visit 8**

**Safety Follow-up Period**
- 4-10 days after last dose

**Screening Visit 1**

© Axsome Therapeutics, Inc.
Clinical Visit Structure

Arrive

Confirm protocol compliance, weight, vitals

Depart

Practice

2-Hour

4-Hour

6-Hour

8-Hour

9 AM

11 AM

1 PM

3 PM

5 PM

Coding Subtest (a variation of the Digit Symbol Substitution Test) of the Repeatable Battery for the Assessment of Neuropsychological Status (DSST RBANS)

Safety evaluation

British Columbia Cognitive Complaints Inventory (BC-CCI)

Patient Global Impression of Severity (PGI-S)

Epworth Sleepiness Scale (ESS)
• 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

<table>
<thead>
<tr>
<th></th>
<th>Solriamfetol/placebo (n=30)</th>
<th>Placebo/solriamfetol (n=29)</th>
<th>Overall (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>52.5 (10.5)</td>
<td>51.9 (11.1)</td>
<td>52.2 (10.7)</td>
</tr>
<tr>
<td>Sex (female), n (%)</td>
<td>10 (33.3)</td>
<td>11 (37.9)</td>
<td>21 (35.6)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>24 (80.0)</td>
<td>19 (65.5)</td>
<td>43 (72.9)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>4 (13.3)</td>
<td>8 (27.6)</td>
<td>12 (20.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (3.3)</td>
<td>2 (6.9)</td>
<td>3 (5.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (3.3)</td>
<td>0</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>32.8 (4.7)</td>
<td>31.6 (4.0)</td>
<td>32.2 (4.4)</td>
</tr>
<tr>
<td>Digit Symbol Substitution Test (age-corrected), mean (SD)</td>
<td>6.6 (1.3)</td>
<td>6.9 (0.8)</td>
<td>6.8 (1.1)</td>
</tr>
<tr>
<td>British Columbia Cognitive Complaints Inventory, mean (SD)</td>
<td>11.4 (2.5)</td>
<td>11.4 (2.5)</td>
<td>11.4 (2.5)</td>
</tr>
<tr>
<td>Patient Global Impression of Severity (cognitive function), mean (SD)</td>
<td>2.2 (0.8)</td>
<td>2.3 (0.7)</td>
<td>2.3 (0.7)</td>
</tr>
<tr>
<td>Positive airway pressure use, n (%)</td>
<td>22 (73)</td>
<td>20 (69)</td>
<td>42 (71)</td>
</tr>
<tr>
<td>Adherent use (≥4 h/night for 70% of nights), n (%)</td>
<td>18 (60)</td>
<td>16 (55)</td>
<td>34 (58)</td>
</tr>
<tr>
<td>Hours of use (among all users), mean (SD)</td>
<td>6.0 (2.4)</td>
<td>6.6 (2.7)</td>
<td>6.3 (2.5)</td>
</tr>
</tbody>
</table>
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)
Solriamfetol significantly improved subjective cognitive function compared with placebo.

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

- 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

<table>
<thead>
<tr>
<th>Common TEAEs (reported by ≥2 participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>n (%)</td>
</tr>
<tr>
<td>Solriamfetol (n=58)</td>
</tr>
<tr>
<td>Placebo (n=58)</td>
</tr>
<tr>
<td>Any TEAE</td>
</tr>
<tr>
<td>11 (19)</td>
</tr>
<tr>
<td>6 (10)</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>4 (7)</td>
</tr>
<tr>
<td>1 (2)</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>2 (3)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td>1 (2)</td>
</tr>
<tr>
<td>1 (2)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>1 (2)</td>
</tr>
<tr>
<td>1 (2)</td>
</tr>
</tbody>
</table>
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

© 1994 NY Times
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 Disorder\(^2\)

3. **Tasimelteon** for Non-24-Hour Sleep-Wake Disorder\(^4,5\)

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*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, Ganesco, 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

<table>
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<td>SWD Prevalence: 6.2% day work only; 28.9% two-shift rotation; 44.3% night shift only; 44.3% three-shift rotation</td>
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**Bottom line**

Of 160 million employed persons in US:
- 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)
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.

## Outcomes Associated with Shift Work Disorder

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

- **Alter circadian phase**
  - Chronobiotics (e.g., melatonin)
  - Ramelteon
  - Planned sleep schedules
  - Timed light exposure

- **↑ Nighttime alertness**
  - Modafinil
  - Armodafinil
  - Amphetamines
  - Caffeine
  - Light exposure
  - Planned naps

- **↓ Daytime insomnia**
  - Sedative hypnotics
  - Melatonin

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.”

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.

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**Systematic Review**

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.

| Erman, M K | 2011 & 2012 | USA | Varied | Mixture: 93% permanent | Excessive sleepiness late in shift associated with ICD2 SWD. Functionally impaired (GAP=70) | 158 (184) | 167 (187) | Armodafinil 150mg OD | RCT | Wake outcomes and AE | 6 weeks | 6 weeks | Cephalon Inc | Yes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tombe, D V | 2011 | India | Unspecified | Unspecified | ICD criteria for SWD | 104 (109) | 105 (109) | Armodafinil 150mg OD (Control: Modafinil 200mg OD) | RCT | Wake outcomes and AE | 12 weeks | 12 weeks | Emencor Pharmaceuticals Ltd. | Yes |
| Czeisler, C A | 2009 | USA & Canada | Varied | Mixture: 86.5% permanent | ICD criteria: ≤5 minutes on MSLT during a night shift, ≤5 of 87.5% or less on daytime polysonnography | 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 | ICD | 129 (183) | 60 (93) | Modafinil 200mg or Modafinil 300mg OD | Randomized double blind placebo-controlled parallel-group trial | Other | 12 weeks | 12 weeks | Cephalon Inc | Yes |
| Czeisler, C | 2005 | USA | Varied | Mixture: 90% permanent | ICD criteria: ≤5 minutes on MSLT during a night shift, ≤5 of 87.5% or less on daytime polysonnography | 76 (96) | 81 (108) | Modafinil 200mg OD | RCT | Sleep outcomes, wake outcomes, other & AE | 12 weeks | 12 weeks | Cephalon Inc | Yes |

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., Lilliam 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


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).”

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.

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.

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

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

© Axsome Therapeutics, Inc.
Closing Remarks
Herriot Tabuteau, MD
thank you