Auvelity™ (dextromethorphan HBr-bupropion HCl) for the Treatment of Major Depressive Disorder in Adults
FDA Approval Investor Call

August 19, 2022
Forward Looking Statements & Safe Harbor

Certain matters discussed in this presentation 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® product and the success of our efforts to obtain any additional indication(s) with respect to Sunosi; the commercial success of our Auvelity™ product and the success of our efforts to obtain any additional indication(s) with respect to 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 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 (including, but not limited to, 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 product candidates, if approved; the Company’s anticipated capital requirements, including the amount of capital required for the successful 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 presentation and the Company undertakes no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstance.

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

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Herriot Tabuteau, MD
Chief Executive Officer
Axsome Therapeutics, Inc.
Overview
FDA has approved AUVELITY™ for the treatment of major depressive disorder (MDD) in adults
- Breakthrough Therapy Designation for MDD, and Priority Review for the NDA, from the FDA

AUVELITY is the first and only oral NMDA receptor antagonist, and the first and only rapid-acting oral antidepressant, labeled with efficacy starting at one week, approved for MDD

AUVELITY represents the first new oral mechanism of action approved for MDD in over 60 years

Approval is timely for patients in need given recent sharp increase in depression prevalence:
- More than 80 million U.S. adults estimated with elevated depressive symptoms as of 2021

Commercial launch of AUVELITY is planned for early fourth quarter

AUVELITY is protected by a robust patent estate extending out at least to 2037-2040
Axsome: Leading Neuroscience Portfolio

- Axsome is committed to developing novel therapies for the millions of patients living with serious central nervous system disorders

- Axsome’s industry-leading neuroscience portfolio → 5 commercial or late-stage product candidates, 8 different indications:
  - 2 FDA-approved, differentiated commercial products each with blockbuster potential (AUVELITY™ for MDD, and SUNOSI® for EDS in narcolepsy and OSA)
  - 1 NDA-stage product candidate (AXS-07 for migraine)
  - 2 Phase 3-stage product candidates with potential NDA filings in 2023 (AXS-12 for narcolepsy, and AXS-14 for fibromyalgia)
  - 3 follow-on indications in or ready to enter Phase 3 (Alzheimer’s disease agitation, smoking cessation for AXS-05; ADHD for solriamfetol)

- Overall, our portfolio has the potential to impact the lives of more than 100 million patients living with brain disorders in the U.S.
## Robust, Commercial and Late-stage Neuroscience Portfolio

<table>
<thead>
<tr>
<th>PRODUCTS</th>
<th>MOA</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>NDA</th>
<th>APPROVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auvelity™&lt;br&gt;(dopamine/NMDA antagonist)&lt;br&gt;extended-release tablets 45mg/10mg</td>
<td>NMDA receptor antagonist with multimodal activity</td>
<td>Major Depressive Disorder: Breakthrough Therapy Designation &amp; Priority Review</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUNOSI™&lt;br&gt;[solriamfetol]&lt;br&gt;(7.5-15 mg tablets)</td>
<td>Dual-acting dopamine and norepinephrine reuptake inhibitor (DNRI)</td>
<td>Excessive daytime sleepiness (EDS) associated with narcolepsy or obstructive sleep apnea (OSA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AXS-05</td>
<td>NMDA receptor antagonist with multimodal activity</td>
<td>Alzheimer’s Disease Agitation: Breakthrough Therapy Designation</td>
<td>Smoking Cessation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AXS-07</td>
<td>MoSEIC™ COX-2 pref. inhibitor + 5-HT1A/1D agonist</td>
<td>Migraine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AXS-12</td>
<td>Highly selective NE reuptake inhibitor</td>
<td>Narcolepsy: Orphan Drug Designation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AXS-14</td>
<td>Highly selective NE reuptake inhibitor</td>
<td>Fibromyalgia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>solriamfetol</td>
<td>Dual-acting dopamine and norepinephrine reuptake inhibitor (DNRI)</td>
<td>Attention deficit hyperactivity disorder (ADHD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CNS = Central Nervous System; MOA = Mechanism of Action; NMDA = N-Methyl-D-aspartate; COX-2 = Cyclooxygenase-2; 5-HT = 5-Hydroxytryptamine; NE = Norepinephrine.

Please see full Prescribing Information, including Boxed Warning, for Auvelity at [www.Auvelity.com](http://www.Auvelity.com), Please see full Prescribing Information for Sunosi at [www.Sunosi.com](http://www.Sunosi.com).

Except where otherwise indicated, the products and/or investigational product candidates listed on this page are not approved by the FDA or have not been approved for the above-referenced indications and the safety and effectiveness of such has not been established.
Auvelity™
Development and Label Highlights
ASCEND Phase 2 trial initiated
Primary endpoint in ASCEND achieved
Breakthrough Therapy designation granted by FDA for MDD

GEMINI Phase 3 trial initiated
Primary endpoint in GEMINI achieved
Enrollment complete in COMET Phase 3 long-term safety study

NDA acceptance and Priority Review granted by FDA

FDA Approval of AUVELITY™ for MDD
U.S. launch planned
Product Label
Key Features

INDICATIONS AND USAGE

AUVELITY is a combination of dextromethorphan, an uneoective N-methyl-
D-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist; and
bupropion, an aminoketone and CYP450 2D6 inhibitor, indicated for the
treatment of major depressive disorder (MDD) in adults. (1)

DOSE AND ADMINISTRATION

- Prior to initiating treatment with AUVELITY: assess blood pressure; screen
  patients for history of bipolar disorder, mania, or hypomania; and determine
  if patients are receiving any other medications that contain bupropion or
dextromethorphan. (2.1)
- Starting dosage is one tablet once daily in the morning. After 3 days, increase
to the maximum recommended dosage of one tablet twice daily, separated
by at least 8 hours. Do not exceed two doses within the same day. (2.2)
- Swallow tablets whole, do not crush, divide, or chew. (2.2)
- Moderate renal impairment: One tablet by mouth once daily in the morning.
  (2.3, 8.6)
- CYP2D6 poor metabolizers: One tablet by mouth once daily in the morning.
  (2.4, 8.8, 12.3)

DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 45 mg/105 mg dextromethorphan hydrobromide/
bupropion hydrochloride. (3)

The change from baseline in MADRS total score by week in Study 1 is displayed in Figure 3. The change in MADRS total score from baseline to Week 1 and from baseline to Week 2 were pre-specified secondary efficacy endpoints. The difference between AUVELITY and placebo in change from baseline in MADRS total score was statistically significant at Week 1 and at Week 2.

scores indicating more severe depression. AUVELITY was statistically significantly superior to placebo in improvement of depressive symptoms as measured by decrease in MADRS total score at Week 6 (see Table 4).
Product Label
Safety

Table 2: Adverse Reactions Occurring in ≥2% of Adult Patients with MDD Treated with AUVELITY and More Frequently than in Patients Treated with Placebo in a 6-Week Placebo-Controlled Study (Study 1)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>AUVELITY (N=162) %</th>
<th>Placebo (N=164) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Somnolence</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Sexual dysfunction*</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Paraesthesia*</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

*Sexual dysfunction includes orgasm abnormal, erectile dysfunction, libido decreased, anorgasmia

- Safe and well-tolerated
- Not associated with psychotomimetic effects
- Not associated with weight gain
Product Label
Warnings & Precautions

• Antidepressant class boxed warning of increased risk of suicidal thoughts and behaviors in pediatric and young adult patients
Dan V. Iosifescu, MD
Professor of Psychiatry
New York University School of Medicine
Director of the Clinical Research Division
Nathan Kline Institute for Psychiatric Research
Overview of Major Depressive Disorder
Major Depressive Disorder
Overview

• Major depressive disorder (MDD) is a serious, chronic, disabling, and life-threatening condition with high rates of morbidity\(^1\):
  o Causes profound distress, impaired social functioning, and inability to work
  o In severe cases can result in hospitalization, and attempted and successful suicide
  o Associated with increased mortality rates (median rate of 10 years of life lost)\(^2\)

• MDD is ranked by WHO as the single largest contributor to global disability (7.5% of all years lived with disability in 2015)\(^3\)

• Involvement of the glutamatergic system in the pathogenesis of MDD is suggested by data from neuroimaging, cellular, and clinical studies.\(^4\)

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Depression Prevalence is High and Rising

• The 3-fold increase in depression prevalence at the start of the COVID-19 pandemic persisted and increased

Major Depressive Disorder
Unmet Medical Need

• Majority of patients experience inadequate response to current treatments\textsuperscript{1-2}:
  - 63% fail to achieve remission to initial therapy, and of those 69% fail second line therapy

• Current antidepressants are associated with prolonged time to clinically meaningful response: up to 6-8 weeks for those who respond\textsuperscript{2}

• Delayed onset of action with current treatments leads to greater suffering, expense, and risk

• All currently approved oral MDD agents work primarily through monoaminergic mechanisms\textsuperscript{3}

\textsuperscript{3} Machado-Vieira R, Henter ID, Zarate CA Jr. New targets for rapid antidepressant action. Prog Neurobiol. 2017;152:21–37
Antidepressant MOAs over Time\textsuperscript{1-3}

First new oral MOA for MDD in over 60 years

- **AUVELITY™** (dextromethorphan-bupropion) extended-release tablets:
  - oral NMDA (ionotropic glutamate) receptor antagonist, and sigma-1 receptor agonist; plasma levels of dextromethorphan increased through metabolic inhibition

Abbreviations: MDD, major depressive disorder; MOA, mechanism of action; MAOI, monoamine oxidase inhibitor; NMDA, N-methyl-D-aspartate; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin receptor antagonist.

Auvelity™ Clinical Profile:
Phase 3 Trial Results
Auvelity™ Phase 3 Trial in MDD
Change from Baseline in MADRS Total Score by Week

Abbreviations: MADRS = Montgomery-Åsberg Depression Rating Scale

<table>
<thead>
<tr>
<th>Time (week)</th>
<th>LS Mean (SE) Change from Baseline</th>
<th>Placebo (n=162)</th>
<th>AUVELITY (n=156)</th>
<th>LS Mean Difference</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>-5.0</td>
<td>-7.2</td>
<td>-2.2</td>
<td>0.007</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>-9.7</td>
<td>-11.1</td>
<td>-1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>-13.4</td>
<td>-14.5</td>
<td>-1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>-17.1</td>
<td>-18.0</td>
<td>-0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>-20.8</td>
<td>-21.7</td>
<td>-0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>-24.5</td>
<td>-25.6</td>
<td>-1.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Primary Endpoint:** Change in MADRS Total Score at Week 6  
-15.9  -12.0  -3.9  0.002

**Key Secondary Endpoints**

- Change in MADRS Total Score at Week 1  
  -7.2  -5.0  -2.2  0.007

- Change in MADRS Total Score at Week 2  
  -11.1  -7.7  -3.4  <0.001
Auvelity™ Phase 3 Trial in MDD
Achievement of Remission (MADRS ≤ 10) by Week

Percentage of Subjects Achieving Remission (MADRS ≤ 10)

<table>
<thead>
<tr>
<th>Time (week)</th>
<th>AUVELITY</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3%</td>
<td>2%</td>
<td>0.013</td>
</tr>
<tr>
<td>2</td>
<td>17%</td>
<td>8%</td>
<td>0.002</td>
</tr>
<tr>
<td>3</td>
<td>24%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>32%</td>
<td>12%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6</td>
<td>40%</td>
<td>17%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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Auvelity™ Phase 3 Trial in MDD

Safety

• AUVELITY was safe and well-tolerated
• The most common adverse events in the AUVELITY group were dizziness, nausea, headache, somnolence, dry mouth, and sexual dysfunction
• Rates of individual adverse events were low
• AUVELITY was not associated with psychotomimetic effects, or weight gain.
Auvelity™ in MDD Conclusions

- AUVELITY demonstrated rapid, sustained, substantial, and statistically significant efficacy in MDD as compared to placebo.
- AUVELITY demonstrated statistically significant efficacy in MDD compared to placebo starting 1 week after treatment.
- Achievement of remission was greater with AUVELITY compared to placebo starting at week 2.
- The treatment difference for AUVELITY compared to placebo was substantial at all timepoints.
- AUVELITY was well tolerated, and was not associated with psychotomimetic effects or weight gain.
- Due to its novel MOA targeting glutamate and sigma-1, and its rapid and robust antidepressant efficacy, AUVELITY is a welcome, new and important treatment for patients with MDD.
Lori Englebert, MBA
Executive Vice President
Axsome Therapeutics, Inc.
Commercial Overview
Designed to bring innovation to the treatment of major depressive disorder (MDD)
MDD Prevalence and Contribution to Disability

21 million
U.S. adults in 2020 had at least one major depressive episode in the previous year\(^1\)

85 million
U.S. adults living with elevated depressive symptoms Mar-Apr 2021\(^2,3\)

#1 contributor to disability worldwide\(^4\)

1. Key Substance Use and Mental Health Indicators in the United States: Results from the 2020 National Survey on Drug Use and Health. Published October 2021.
SUPPORT Survey of Patients with MDD: High unmet need for better therapeutic options

2022 SUPPORT Survey* Key Highlights
N=385 U.S. adult patients with MDD

- **78%** were not satisfied with at least one of their current MDD treatments
- **68%** reported symptoms consistent with moderate, severe or very severe depression despite being on MDD therapy
- **52%** reported having difficulty with work or daily life productivity as a result of depression despite being on MDD therapy
- **48%** reported that at least one of their side effects from MDD therapy was at least somewhat bothersome
- **82%** think that people with depression deserve better medications than what is currently available

*Support Survey: Axsome Therapeutics partnered with the Depression and Bipolar Support Alliance (DBSA) to quantify and better understand treatment experiences and expectations, along with the treatment-related impacts on those taking antidepressants for major depressive disorder (MDD). The survey was designed to elicit detail on MDD disease burden and treatment experiences and was conducted in 2022 with 385 U.S. adults living with MDD.
Axsome Patient-focused Disease Education Campaign: High MDD patient engagement and dissatisfaction

**Could I Be DEPRESSETTLING?**

A person with depression who is taking an antidepressant & accepting symptoms or side effects without speaking up

<table>
<thead>
<tr>
<th>Platform</th>
<th><a href="http://www.talkdepressettling.com">www.talkdepressettling.com</a> / social media</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose</td>
<td>Provide a platform for patient empowerment, support and education for those impacted by major depressive disorder</td>
</tr>
<tr>
<td>Reach</td>
<td>11 Million unique individuals reached via social media</td>
</tr>
<tr>
<td></td>
<td>785 Thousand website visits</td>
</tr>
<tr>
<td>Treatment Satisfaction Metrics</td>
<td>78% of all registrants were neutral to very disappointed with their depression treatment experience</td>
</tr>
<tr>
<td>Patient / HCP discussion Metrics</td>
<td>69% of all registrants were planning to talk to their doctor about their depression treatment experience</td>
</tr>
</tbody>
</table>
Launch Strategy

Drive HCP Adoption
- Target highest potential prescribers
- Optimize engagements through Digital Centric Commercialization™

Empower Patients
- Deploy patient-focused digital campaign
- Provide patient education materials, tools and tactics

Enable Patient Access
- Provide comprehensive patient support services
- Educate payers on the clinical benefits of Auvelity
Meaningful innovation for patients living with Major Depressive Disorder

Novel Oral MOA

1st and only oral NMDA receptor antagonist approved to treat MDD, representing the 1st new oral MOA approved for MDD in over 60 years1-4

Rapid Efficacy

1st and only rapid-acting oral antidepressant labeled to show significant symptom improvement vs. placebo at week 1 approved to treat adults with MDD1-4,*

Rapid achievement of remission vs. control starting at Week 25

Durable Efficacy

Early significant symptom improvement sustained and increased vs. placebo through Week 64

Early achievement of remission sustained and increased vs. control through Week 65

Substantial Efficacy

Substantial symptom improvement vs. control demonstrated at all timepoints on MADRS total score, and across several other clinician- and patient-rated measures1,5,6

Long-term safety and efficacy: Open-label 1 year safety and efficacy were consistent with controlled clinical trials1,7,8


*As measured by MADRS total score

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Launch Focus: High Potential HCPs

**Strategic Targeting**
- Psychiatrists / mental health focused - MDD specialized PCPs

**Focused Targeting**
- 25,000 HCPs capture >70% of the addressable market for Auvelity

**Digital Centric Commercialization™**
- Digital Centric Commercialization™ enabled field force

**Prescriber Targeting and Engagement**

**Hybrid Engagement Model**
- Optimized engagements through mix of face-to-face and remote interactions
Digital Centric Commercialization (DCC)™
to enable optimized engagements

Real-time Data  Seamless Integration  Sophisticated Analytics  Targeted Deployment  Omni-Channel

Versatile targeting driven by omni-channel activity
Antidepressant Rx volume flows primarily through the commercial channel

Channel Contribution of MDD Rx’s

Distribution of Commercial MDD Rx’s by PBM/Payer

Permitted payer discussions for over 1 year

Source: MMIT
Comprehensive patient support

Sample Program
Savings Program
Prior Authorization Support

All programs plus additional support tools will be available at launch
Launch Readiness

- HCP and consumer now-approved websites are live
  - www.auvelity.com
  - www.auvelityhcp.com
- Field force hired per contingent approval offers; Start date in coming weeks
- Patient support services will be available immediately upon launch
- Product availability and commercial launch anticipated in early Q4
Closing Remarks

Herriot Tabuteau, MD
Chief Executive Officer