



**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



Presenter	Topic
Mark Jacobson Chief Operating Officer	Introduction
Herriot Tabuteau, MD Chief Executive Officer	Overview Auvelity™ Development and Label Highlights
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 Auvelity™ Clinical Profile: Phase 3 Trial Results
Lori Englebert, MBA Executive Vice President, Commercial and Business Development	Commercial Overview
Herriot Tabuteau, MD Chief Executive Officer	Closing Remarks
Axsome Presenters	Axsome Q&A



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



PRODUCTS	MOA	Phase 1	Phase 2	Phase 3	NDA	APPROVED
 Auvelity™ (dextromethorphan HBr and bupropion HCl) extended-release tablets 45mg/105mg	NMDA receptor antagonist with multimodal activity	Major Depressive Disorder: Breakthrough Therapy Designation & Priority Review				
 SUNOSI (solriamfetol) (V) 75, 150 mg tablets	Dual-acting dopamine and norepinephrine reuptake inhibitor (DNRI)	Excessive daytime sleepiness (EDS) associated with narcolepsy or obstructive sleep apnea (OSA)				
AXS-05	NMDA receptor antagonist with multimodal activity	Alzheimer's Disease Agitation: Breakthrough Therapy Designation				
		Smoking Cessation				
AXS-07	MoSEIC™ COX-2 pref. inhibitor + 5-HT _{1B/1D} agonist	Migraine				
AXS-12	Highly selective NE reuptake inhibitor	Narcolepsy: Orphan Drug Designation				
AXS-14	Highly selective NE reuptake inhibitor	Fibromyalgia				
solriamfetol	Dual-acting dopamine and norepinephrine reuptake inhibitor (DNRI)	Attention deficit hyperactivity disorder (ADHD)				

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

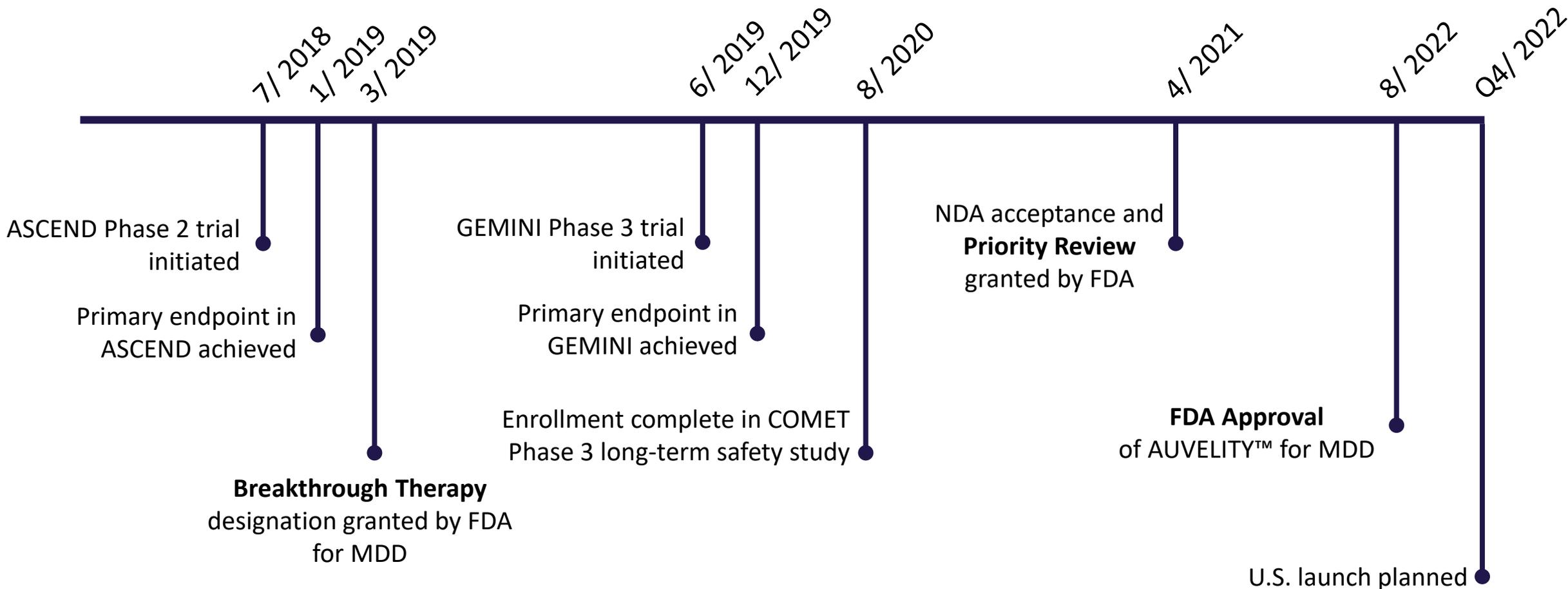
Please see full Prescribing Information, including Boxed Warning, for Auvelity at www.Auvelity.com. Please see full Prescribing Information for Sunosi at www.Sunosi.com.

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

: Milestones in Development



Product Label Key Features



-----INDICATIONS AND USAGE-----
 AUVELITY is a combination of dextromethorphan, an uncompetitive *N*-methyl *D*-aspartate (NDMA) 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)

-----DOSAGE 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)



Novel MOA

Oral NMDA receptor antagonist and sigma-1 receptor agonist



Broad label

Treatment of major depressive disorder (MDD) in adults



Rapid-acting

Efficacy starting at Week 1



Durable

Efficacy at Week 6

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).

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)

Adverse Reaction	AUVELITY (N=162) %	Placebo (N=164) %
Dizziness	16	6
Nausea	13	9
Headache	8	4
Diarrhea	7	3
Somnolence	7	3
Dry mouth	6	2
Sexual dysfunction ^a	6	0
Hyperhidrosis	5	0
Anxiety	4	1
Constipation	4	2
Decreased appetite	4	1
Insomnia	4	2
Arthralgia	3	0
Fatigue ^b	3	2
Paraesthesia ^c	3	0
Vision blurred	3	0

^aSexual dysfunction includes orgasm abnormal, erectile dysfunction, libido decreased, anorgasmia

^bFatigue includes fatigue, lethargy

^cParaesthesia includes paraesthesia, hypoaesthesia



- Safe and well-tolerated
- Not associated with psychotomimetic effects
- Not associated with weight gain

Product Label

Warnings & Precautions

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

Increased risk of suicidal thoughts and behavior in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. AUVELITY is not approved for use in pediatric patients. (5.1, 8.4)

-----**WARNINGS AND PRECAUTIONS**-----

- Seizure: Risk is dose-related. Discontinue if seizure occurs. (4, 5.2)
- Increased Blood Pressure and Hypertension: AUVELITY can increase blood pressure and cause hypertension. Assess blood pressure before initiating treatment and monitor periodically during treatment. (5.3)
- Activation of Mania or Hypomania: Screen patients for bipolar disorder. (5.4)
- Psychosis and Other Neuropsychiatric Reactions: Instruct patients to contact a healthcare provider if such reactions occur. (5.5)
- Angle-Closure Glaucoma: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants. (5.6)
- Dizziness: AUVELITY may cause dizziness. Take precautions to reduce falls and use caution when operating machinery. (5.7)
- Serotonin Syndrome: Use of AUVELITY with selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants increases the risk. Discontinue if occurs. (5.8, 7.1)
- Embryo-fetal Toxicity: May cause fetal harm. Advise pregnant females of the potential risk to a fetus. Discontinue treatment in pregnant females and use alternative treatment for females who are planning to become pregnant. (5.9, 8.1, 8.3)

- Antidepressant class boxed warning of increased risk of suicidal thoughts and behaviors in pediatric and young adult patients



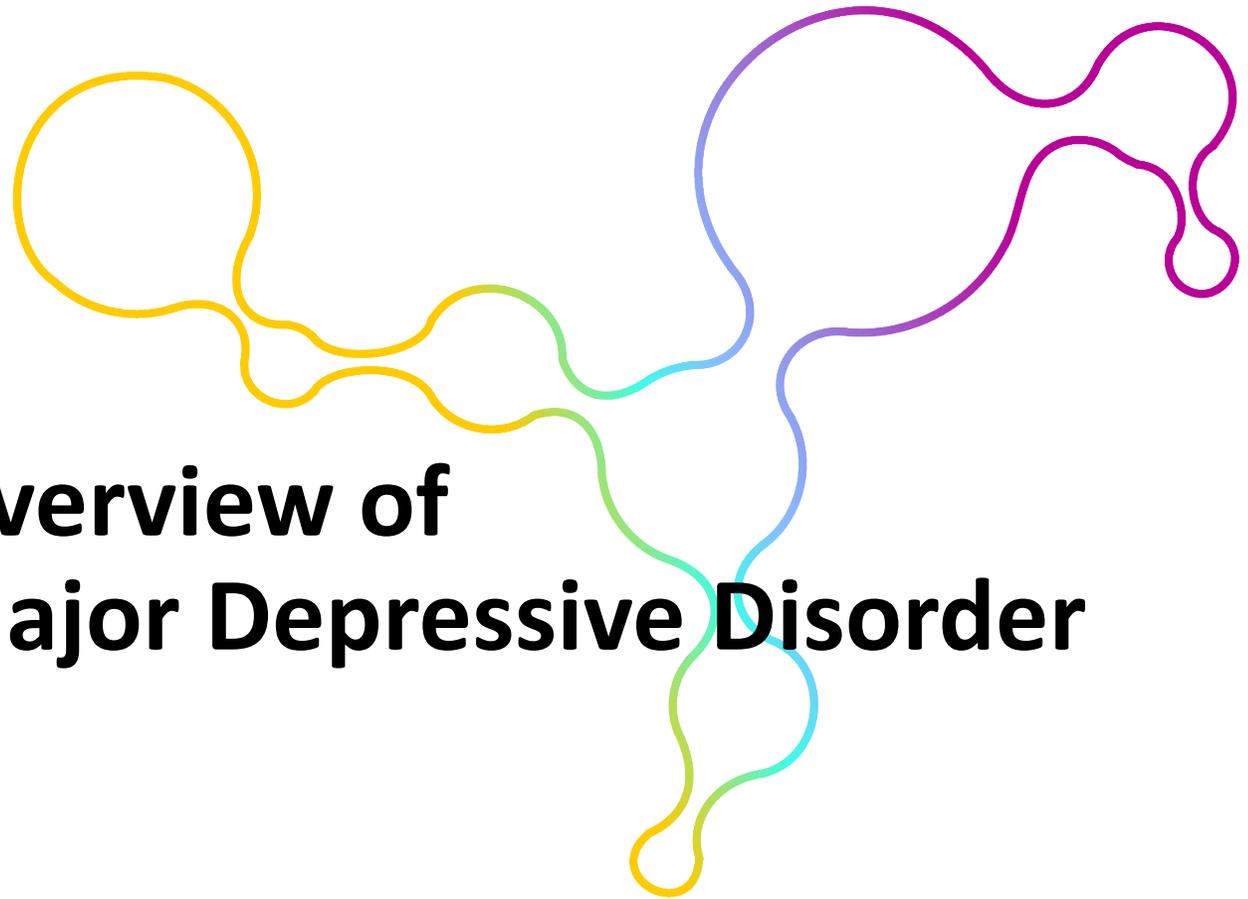
Dan V. Iosifescu, MD

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 morbidity¹:
 - Causes profound distress, impaired social functioning, and inability to work
 - In severe cases can result in hospitalization, and attempted and successful suicide
 - 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

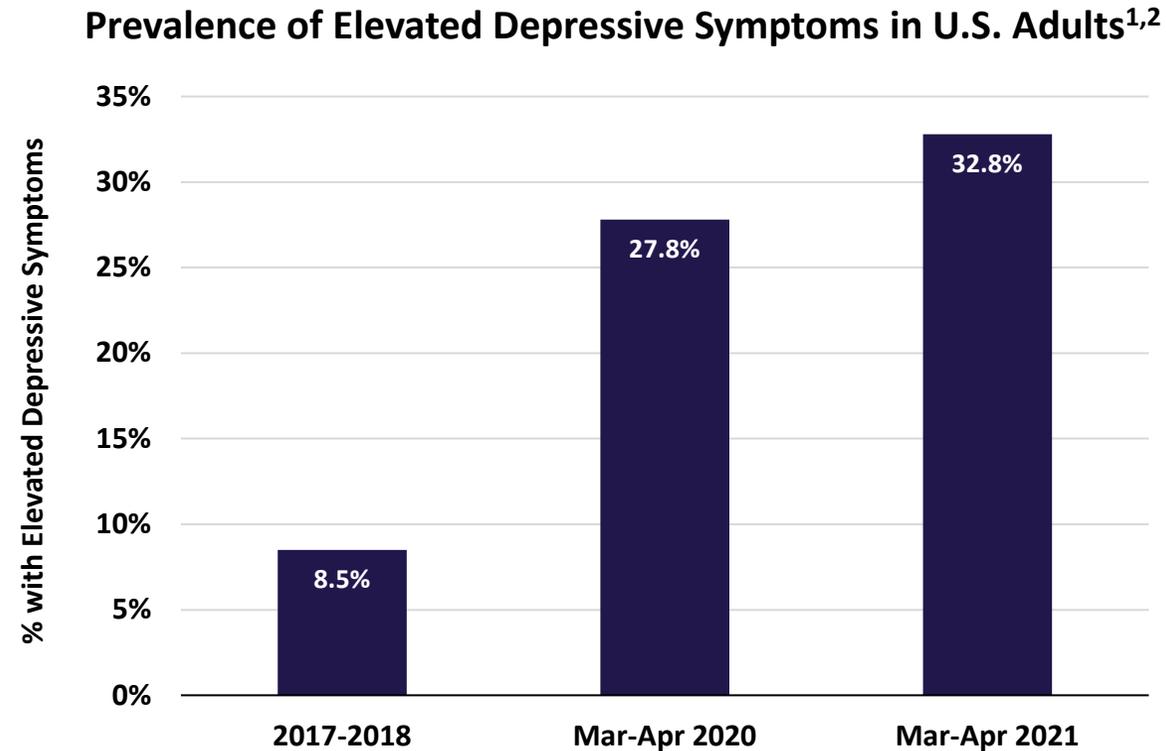
¹ Herrman H, et al. Time for united action on depression: a Lancet-World Psychiatric Association Commission. *Lancet*. 2022 Mar 5;399(10328):957-1022.

² Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry*. 2015;72:334-341.

³ World Health Organization. Depression and other common mental disorders. Global health estimates. (Geneva:World Health Organization; 2017.)

⁴ Iosifescu DV, et al. Efficacy and Safety of AXS-05 (Dextromethorphan-Bupropion) in Patients With Major Depressive Disorder: A Phase 3 Randomized Clinical Trial (GEMINI). *J Clin Psychiatry*. 2022 May 30;83(4):21m14345.

Depression Prevalence is High and Rising



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

1. Ettman CK, et al. Prevalence of Depression Symptoms in US Adults Before and During the COVID-19 Pandemic. JAMA Netw Open. 2020;3(9):e2019686. 2. Ettman CK, et al. Persistent depressive symptoms during COVID-19: a national, population-representative, longitudinal study of U.S. adults. Lancet Reg Health Am. 2022 Jan;5:100091. 3. US Census Bureau Household Pulse Survey 2020-2021.

Major Depressive Disorder

Unmet Medical Need



- Majority of patients experience inadequate response to current treatments¹⁻²:
 - 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 respond²
- Delayed onset of action with current treatments leads to greater suffering, expense, and risk
- All currently approved oral MDD agents work primarily through monoaminergic mechanisms³

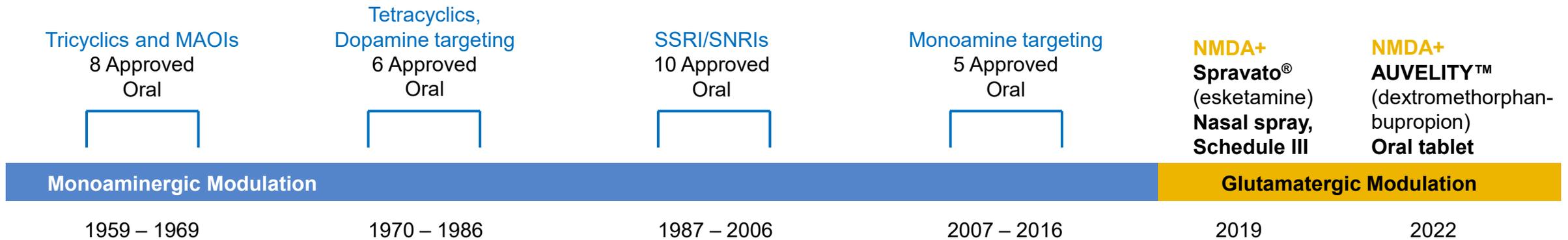
¹ Rush AJ, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163:1905-1917.

² Fava M, Kendler KS. Major depressive disorder. *Neuron*. 2000;28(2):335-341.

³ Machado-Vieira R, Henter ID, Zarate CA Jr. New targets for rapid antidepressant action. *Prog Neurobiol*. 2017;152:21-37

Antidepressant MOAs over Time¹⁻³

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

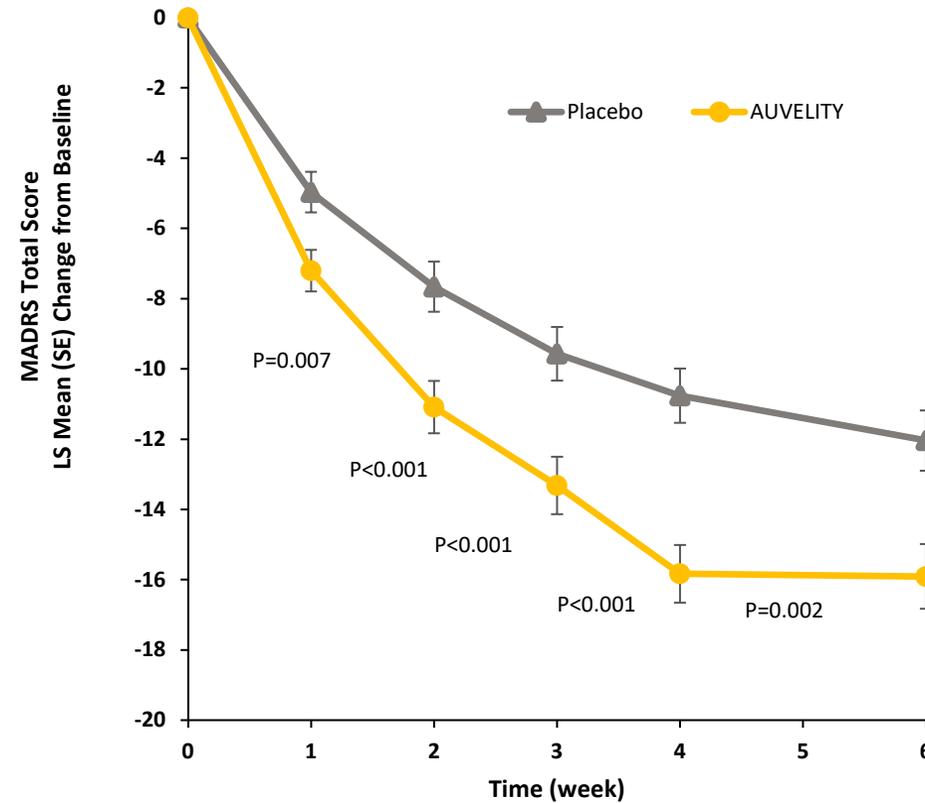
Abbreviations: MDD, major depressive disorder; MOA, mechanism of action; MAOI, monoamine oxidase inhibitor; NMDA, N-methyl-D-aspartate; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin receptor antagonist.
1. Bio. Published December 2017. Accessed April 8, 2021. https://www.bio.org/sites/default/files/BIO_HPCD_Series-Depression_2018-01-03.pdf. 2. Machado-Vieira R, et al. *Prog Neurobiol.* 2017;152:21–37. 3. FDA Depression Medicines. <https://www.fda.gov/media/132665/download>. Accessed March 21, 2022.



Auvelity™ Clinical Profile: Phase 3 Trial Results

Auvelity™ Phase 3 Trial in MDD

Change from Baseline in MADRS Total Score by Week

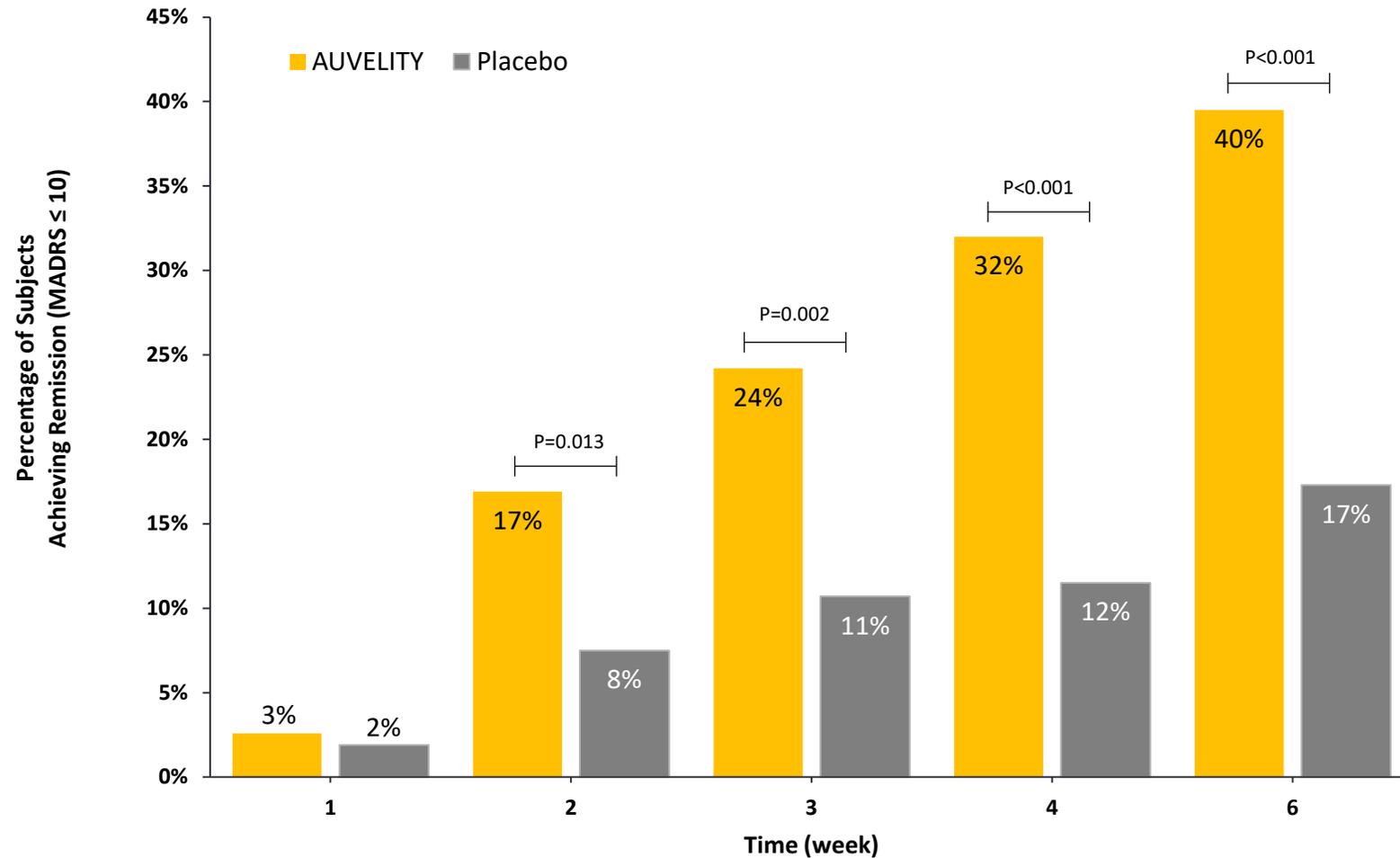


	AUVELITY (n=156)	Placebo (n=162)	LS Mean Difference	P-Value
Primary Endpoint: Change in MADRS Total Score at Week 6	-15.9	-12.0	-3.9	0.002
Key Secondary Endpoints				
Change in MADRS Total Score at Week 1	-7.2	-5.0	-2.2	0.007
Change in MADRS Total Score at Week 2	-11.1	-7.7	-3.4	<0.001

Abbreviations: MADRS = Montgomery-Åsberg Depression Rating Scale

Auvelity™ Phase 3 Trial in MDD

Achievement of Remission (MADRS ≤ 10) by Week



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 Englebort, MBA

Executive Vice President
Axsome Therapeutics, Inc.



Commercial Overview

Designed to bring innovation to the treatment of major depressive disorder (MDD)



 **Auvelity™**
(dextromethorphan HBr and bupropion HCl)
extended-release tablets 45mg/105mg

MDD Prevalence and Contribution to Disability



85 million

U.S. adults living with elevated depressive symptoms
Mar-Apr 2021^{2,3}

#1 contributor to disability worldwide⁴

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.
2. Ettman CK, et al. Persistent depressive symptoms during COVID-19: a national, population-representative, longitudinal study of U.S. adults. Lancet Reg Health Am. 2022 Jan;5:100091.
3. US Census Bureau Household Pulse Survey 2020-2021.
4. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization; 2017. License: CC BY-NC-SA 3.0 IGO.

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

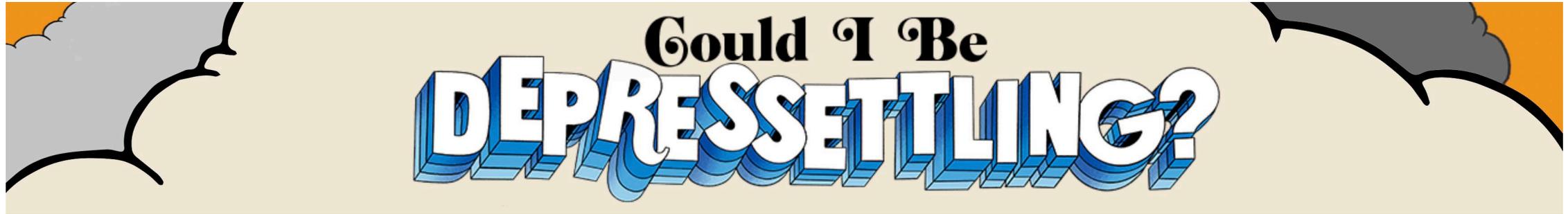


82%

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



A person with depression who is taking an antidepressant

&

accepting symptoms or side effects without speaking up

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

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 MDD^{1-4,}*

Rapid achievement of remission vs. control starting at Week 2⁵

Durable Efficacy

Early significant symptom improvement sustained and increased vs. placebo through Week 6¹

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

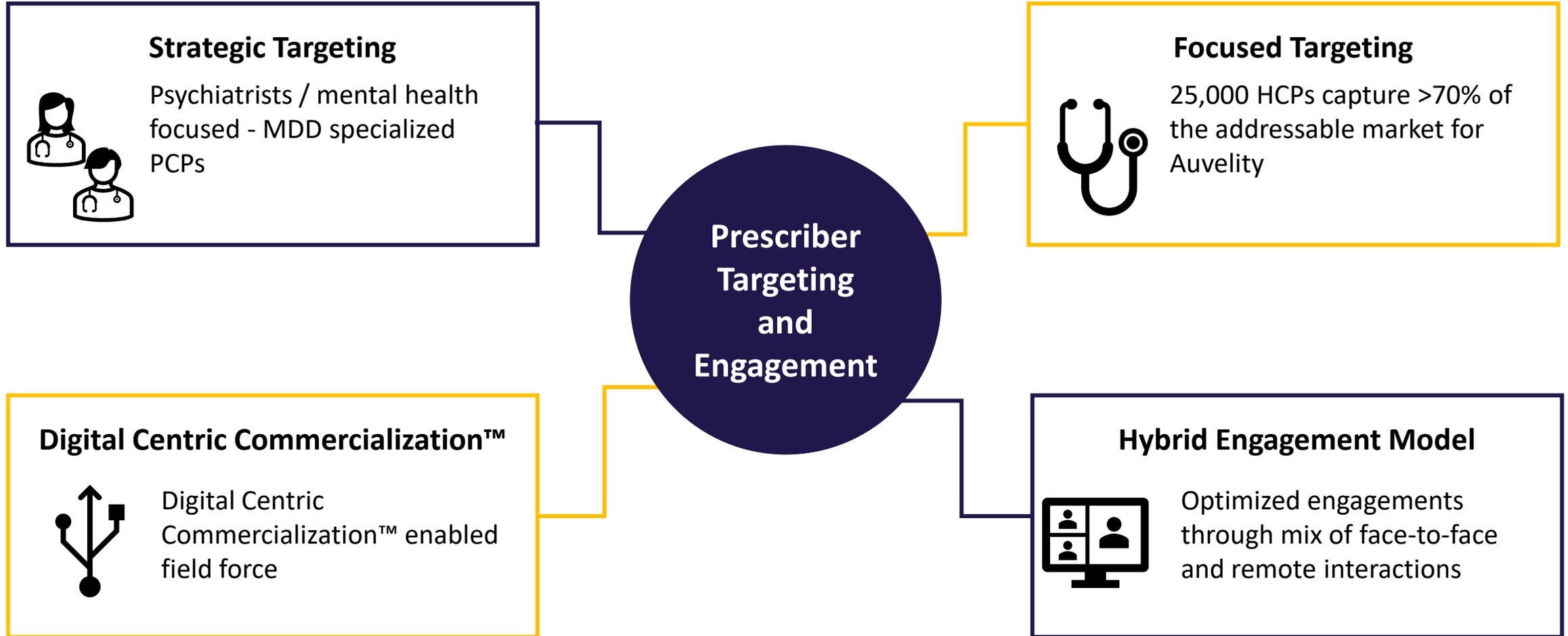
Substantial Efficacy

Substantial symptom improvement vs. control demonstrated at all timepoints on MADRS total score, and across several other clinician- and patient-rated measures^{1,5,6}

Long-term safety and efficacy: Open-label 1 year safety and efficacy were consistent with controlled clinical trials^{1,7,8}

1. AUVELITY [Prescribing Information]. New York, NY: Axsome Therapeutics, Inc.; 2. Thomas D, et al. The state of innovation in highly prevalent chronic diseases volume I: Depression therapeutics. December 2017. Accessed March 21, 2022; 3. FDA Depression Medicines. <https://www.fda.gov/media/132665/download>. Accessed March 21, 2022; 4. Machado-Vieira R, et al. Prog Neurobiol 2017;152:21–37; 5. Iosifescu D, et al. J Clin Psychiatry. 2022;83(4):21m14345; 6. Tabuteau H, et al. Am J Psychiatry 2022; 179(7):490-499; 7. Data on File. AXS0060921; 8. Data on File. AXS0070921.

*As measured by MADRS total score



Digital Centric Commercialization (DCC)™ to enable optimized engagements



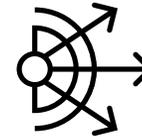
Real-time Data



Seamless Integration



Sophisticated Analytics



Targeted Deployment



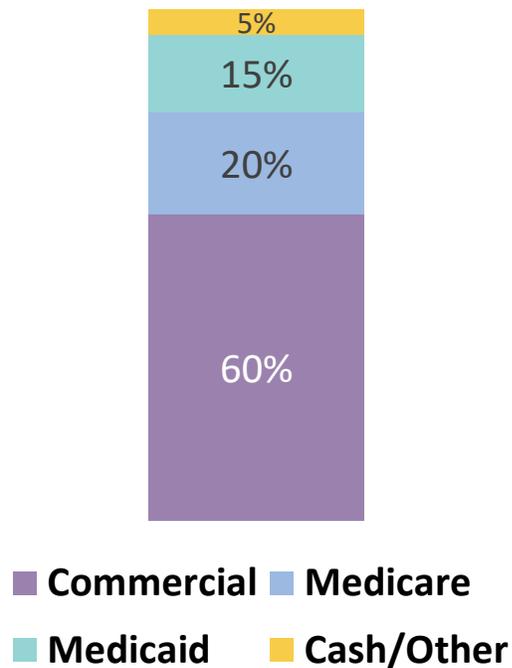
Omni-Channel

Versatile targeting driven by omni-channel activity

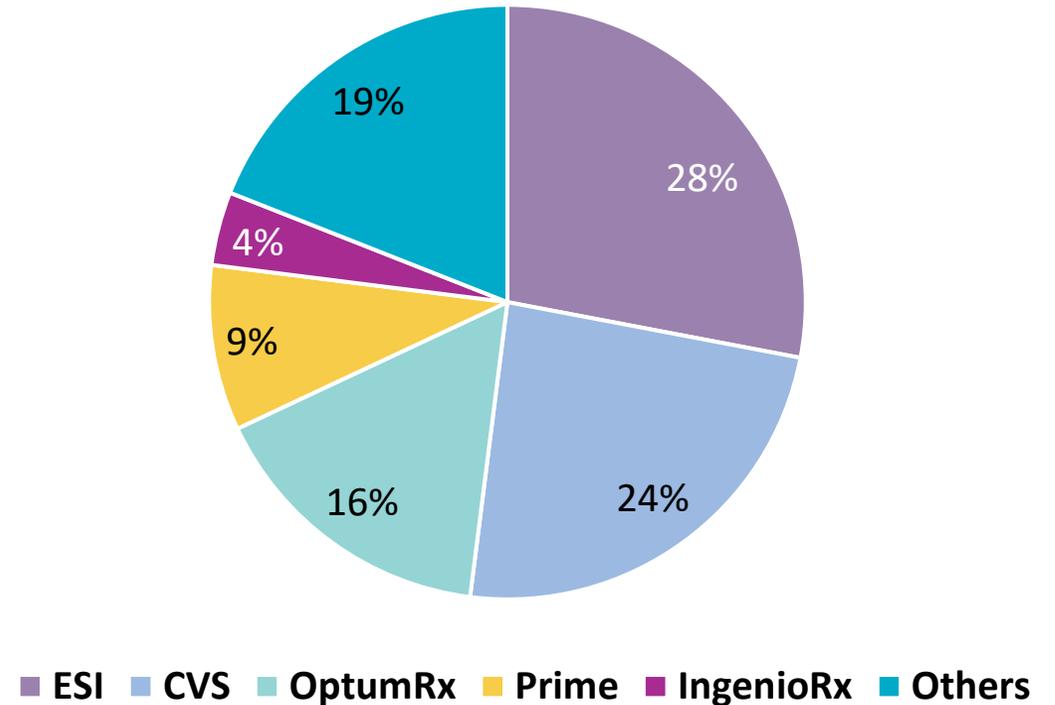
Antidepressant Rx volume flows primarily through the commercial channel



Channel Contribution of MDD Rx's



Distribution of Commercial MDD Rx's by PBM/Payer



Permitted payer discussions for over 1 year

Auvelity™ On my side



Sample Program



Savings Program



Prior Authorization
Support

All programs plus additional support tools will be available at launch

- ◎ 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



Q & A



Closing Remarks

Herriot Tabuteau, MD
Chief Executive Officer