AXSOME THERAPEUTICS

Unmet Needs in Smoking Cessation and the Potential for AXS-05

James Davis, MD

DukeHealth

Medical Director, Duke Center for Smoking Cessation
Director, Duke Smoking Cessation Program
Co-Director Duke-UNC Tobacco Treatment Specialist Training Program
Associate Professor of Medicine, Duke University School AP of Medicine

Forward-Looking Statements & Safe Harbor

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

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

Disclosures

- NIDA P50 Center Award – Adaptive Pharmacotherapies
- NIDA R01 Award – Electronic Cigarettes
- NCI P30 Award – Cancer Center Treatment
- American Lung Association Award – Lung Cancer Screening Study
- Pfizer – Varenicline Study
- Rose Research Center – Consultant on Participant Safety
- Axsome Therapeutics – Pharmacotherapy Development Study

Overview

- Smokers as a Population
- Smoking Cessation Medications (Efficacy, Side Effects, Adherence)
- AXS-05 (Bupropion, Dextromethorphan, Opportunities)
- Study Design
- Study Progress

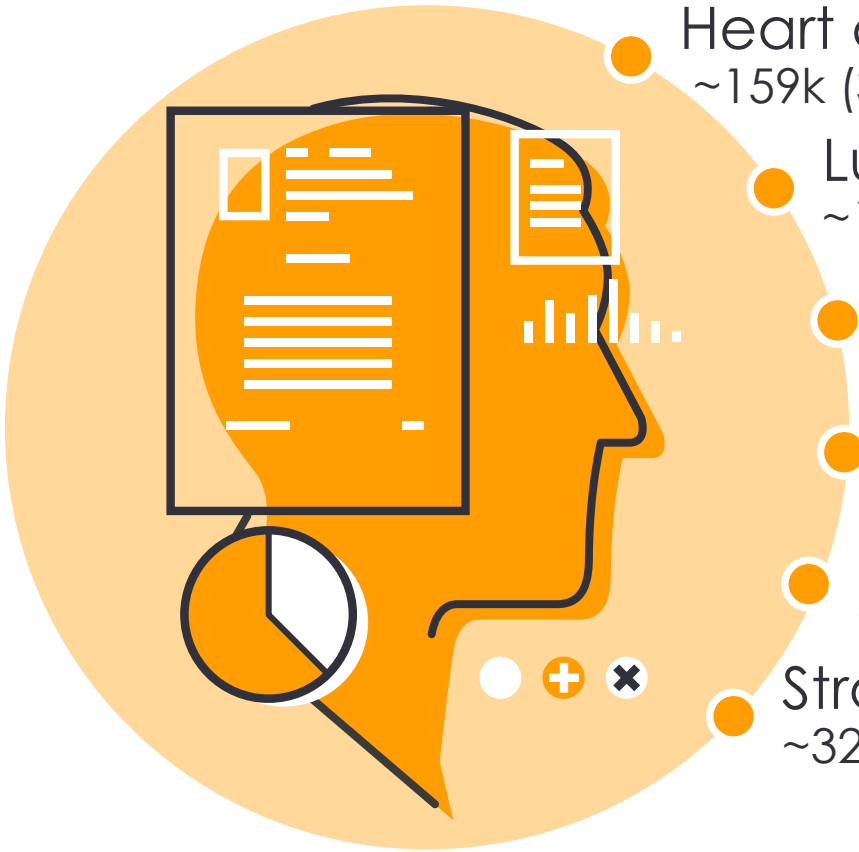
US Statistics

#1

cause of preventable morbidity & mortality in US

>540k

deaths every year are from smoking (67%)



Banks et al. 2015.

2014 Surgeon General Report

- **Pulm:** COPD, asthma exacerbation, pneumonia recurrence.
- **CV:** Cardiac events, stroke (dose response), DVT/PE (OR = 1.2 dose response), PVD (OR = 5.1).
- **Wound healing:** (OR = 3.6 all cause – necrosis, infection, dehiscence).
- **Ophtho:** Cataracts (OR = 1.6), macular degeneration.
- **OB:** Preterm delivery (OR = 1.7), stillbirth, ectopic pregnancy.
- **Endo:** Diabetes (30% higher incidence). Higher complication rate.

Take home message: *Each year we learn more about the illness caused by smoking. With this there is a growing recognition of need for effective treatment.*

Cancers Caused by Smoking

CANCER	SMOKERS vs. NON-SMOKERS
Bladder	RR = 2.77 (2.17-3.54)
Breast	RR = 1.32 (1.10-1.57)
Cervical	RR = 1.83 (1.51-2.21)
Lung	RR = 8.43 (7.63-9.31)
Colorectal	RR = 1.70 (1.40-2.10)
Esophageal	RR = 2.50 (2.00-3.13)
Renal	RR = 1.52 (1.33-1.74)
Leukemia	RR = 1.60 (0.84-2.98)
Gastric	RR = 1.64 (1.37-1.95)
Pancreatic	RR = 1.74 (1.61-1.87)
Liver	RR = 1.70 (1.50-1.90)
Oral	RR = 3.43 (2.37-4.94)

Gandini, S., E. Botteri, S. Iodice et al. 2008. Tobacco smoking and cancer: a meta-analysis. *International Journal of Cancer* 122: 155-64.

Lee, P.N., B.A. Forey, & K.J. Coombs. 2012. Systematic review with meta-analysis of the epidemiological evidence in the 1900s relating smoking to lung cancer. *BMC Cancer 12: 385.*

Musselman, J.R.B., C.K. Blair, J.R. Cerhan et al. 2013. Risk of adult acute and chronic myeloid leukemia with cigarette smoking and cessation. *Cancer Epidemiology* 37 (4): 410-6.

Theis, R.P., S.M. Dolwick Grieb, D. Burr, T. Siddiqui, and N. R. Asal. 2008. Smoking, environmental tobacco smoke, and risk of renal cell cancer: a population based case-control study. *BMC Cancer* 8: 387.

USDHHS. 2014. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*.

Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

US Statistics

25.3% use some form of tobacco

49m of the US population smoke (15.1%)

70% ***would like to quit*** at any one time

21m (42.7%) ***make an attempt*** on any given year

6m (29%) ***use medication*** on any given quit attempt

BMC Medicine, 2017.
Emily Banks et. al. (N=200,000, Australia).
Centers for Disease Control and Prevention, April 2015).
National Health Survey.

Abstinence Rates

3-5% self-directed quit attempt
(OTC nicotine patch, gum, lozenge, do not significantly increase abstinence rates).

10-12% provider-directed quit attempt

30-40% most effective treatments

Take home message: *The current population of smokers is normally not able to quit on their own. They do much better with medical treatment.*

Fiore, Clinical Practice Guideline, Treating Tobacco Use and Dependence 2008.
John Hughes 2011 Effectiveness of Over-the-Counter Nicotine Replacement Therapy: A Qualitative Review of Nonrandomized Trials 2011.
J. Davis Observational study, 2016

Mental Health Conditions

36.5% of people *with* a mental illness use tobacco.

25% of US adults *have a mental illness*.

These individuals smoke **40%** **of all cigarettes.**

Take home message: *When we treat smokers we are often treating people with psychiatric illness. The medications we use for smoking cessation need to work well in patients with psychiatric illness.*

Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. The NSDUH Report. March 20, 2013. Rockville, MD

FDA Approved Medications:
Abstinence Rates

SUSTAINED RELEASE	ABSTINENCE RATE (RELATIVE RISK vs. PLACEBO)	TRANSLATED ABSTINENCE RATE (BASELINE RATE = 10%)
Varenicline	RR = 2.43	24%
Bupropion	RR = 1.71	17%
Nicotine patch	RR = 1.75	18%
IMMEDIATE RELEASE	ABSTINENCE RATE	TRANSLATED ABSTINENCE RATE
Nicotine gum	RR = 1.59	16%
Nicotine lozenge	RR = 1.59	16%
Nicotine inhaler	RR = 1.82	18%
Nicotine nasal spray	RR = 1.83	18%

Cahill et al, Cochrane Review. Meta-analysis of Smoking Cessation Medications.

FDA Approved Medications:
Side Effects and Adherence

MEDICATION	MAIN SIDE EFFECTS	ADHERENCE RATE
Varenicline	Insomnia, Nausea, Emotional lability	33% (side effects)
Bupropion	Insomnia	63%
Nicotine patch	Insomnia, Nausea, Skin irritation	35% (skin application)
Nicotine gum	Minimal	26% (PRN dosing)
Nicotine lozenge	Minimal	20% (PRN dosing)
Nicotine inhaler	Minimal	< 10% (expensive)
Nicotine nasal spray	Nasal Irritation	< 10% (90% get nasal irritation)

Cahill et al, Cochrane Review. Meta-analysis of Smoking Cessation Medications.

Varenicline vs. Placebo Side Effects

INDICATION	VARENICLINE	PLACEBO
Nausea	28.1%	8.4%
Headache	15.5%	12.2%
Insomnia	14.0%	12.8%
Abnormal dreams	10.3%	5.5%

Gonzales D, Rennard SI, Nides M, et al. *JAMA.* 2006;296:47-55.

Varenicline Adherence over 12 weeks

67% stopped using Varenicline prematurely

- **45.4%** stopped due to side effects
- **23.8%** felt it was not working

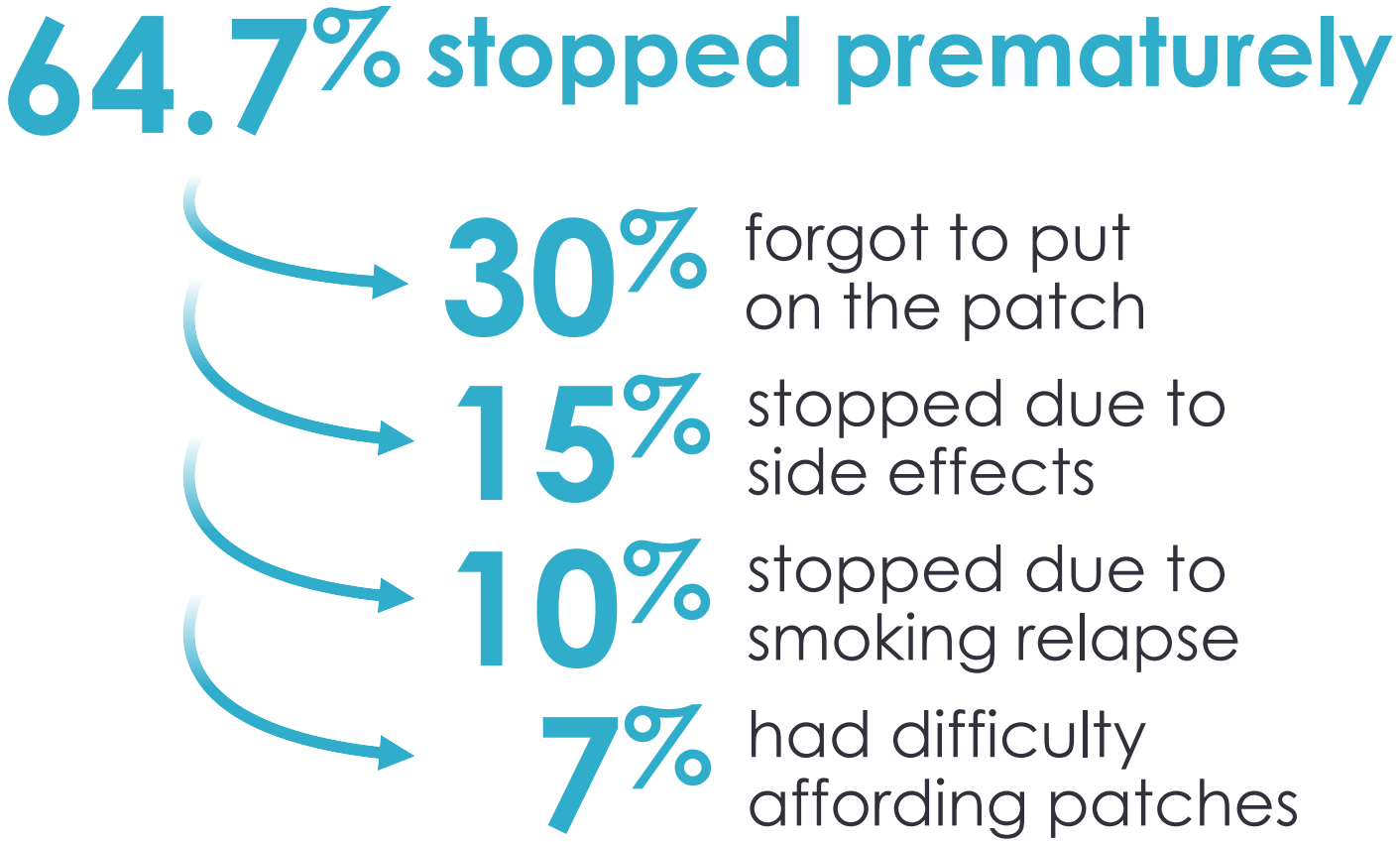
Catz SL, Jack LM, McClure JB, et al. Adherence to Varenicline in the COMPASS Smoking Cessation Intervention Trial. *Nicotine & Tobacco Research.* 2011;13:361-368.

Nicotine Patch vs. Placebo Side Effects

SIDE EFFECT	INCIDENCE
Skin irritation related to nicotine	90%
Adhesive allergy	0.3%
Chest pain	OR = 2.00
Nausea	OR = 1.67
Insomnia	OR = 1.42
Hiccoughs	OR = 7.68

Mills 2010 Meta-analysis N > 177,000.
OR = Odds Ratio

Nicotine Patch Adherence Over 12 weeks



(N=225) on nicotine patch adherence for 28 days.
Yingst 2015

Immediate Release Nicotine Adherence

Gum:

73.4% were non-adherent at 8 weeks. Most commonly people forget to use it.

Nasal spray:

57% stopped in the first week, more stop the next week. Almost all experience nasal irritation.

Okuyemi 2010, N=662.
Rubenstein: A Randomized Trial of Nicotine Nasal Spray in Adolescent Smokers, 2008.

Bupropion SR vs. Placebo Side Effects

SIDE EFFECT	NICOTINE PATCH	PLACEBO
Insomnia	11-20%	4-7%
Dry mouth	16%	7%
Constipation	5-10%	0-5%
Seizure with 150 mg SR Dose*	1 in 1000	-

*Same incidence as SSRIs, seizure most often occurs in patients with identifiable seizure risk.

Mills 2010 Meta-analysis N > 177,000.

Bupropion Adherence Over 8 weeks

37% of users were non-adherent

- **26%** most common reason reported for missing a dose of Wellbutrin SR was forgetting to take it
- **11%** stopped due to side effects

Take home message: *Best adherence rate of current smoking cessation medications.*

(N=225) on nicotine patch adherence for 28 days.
Yingst 2015

FDA Approved Medications:
Specific Uses and Contraindications

MEDICATIONS (FDA APPROVED)	SPECIFIC USES	CONTRAINDICATIONS
Varenicline	High dependence	Suicide attempt, Psychiatric Hx
Bupropion	Weight issues, depression	Seizure history
Nicotine patch	Most commonly used	Adhesive allergy, Post-op
Nicotine gum	Combo with patch	Dentures
Nicotine lozenge	Combo with patch	Gum disease
Nicotine inhaler	Combo with patch	None
Nicotine nasal spray	Combo with patch	Sinus problems

Cahill et al, Cochrane Review. Meta-analysis of Smoking Cessation Medications.

FDA Approved Medications:
Which Meds are Used the Most?

Among smokers making a quit attempt **29%** **use medications**

MEDICATION	INCIDENCE OF USING THIS MEDICATION
Varenicline	27.3%
Bupropion	9.4%
Nicotine patch	57.3%
Nicotine gum	28.0%
Nicotine lozenge	18.6%
Nicotine inhaler	6.2%
Nicotine nasal spray	2.1%

Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting smoking among adults- United States, 2000-2015. *Morbidity and Mortality Weekly Report.* Vol 65: Center for Disease Control and Prevention; 2017:1457-1464.

Smoking Cessation Medications: Bottom Line

- 3 long-acting meds: Varenicline, Bupropion, Nicotine Patch.
- 4 short-acting meds: Nicotine Gum, Lozenge, inhaler, nasal spray.
- All medications are about equally effective, except Varenicline (higher).
- Varenicline has high side effect rate and docs are hesitant to prescribe it.
- Nicotine patch has low side effect rate, but also poor adherence.
- Short-acting medications show very poor adherence.
- **Bupropion** has the highest adherence rates of all smoking cessation medications.
- **Bupropion** has special roll in smokers with depression or weight problems.

Smoking Cessation Medication: What do we Want?

1. Want to decrease withdrawal symptoms caused by low levels of dopamine (dysphoria, anhedonia), norepinephrine (cognitive dysfunction), serotonin (emotion dysregulation).
2. Want to decrease distress and agitation (component of the withdrawal syndrome that is highly associated with relapse).
3. Want to decrease the reward associated with smoking.
4. Want to help with “unlearning” cue-based smoking (major cause of relapse) after the relapse period (3 weeks).
5. Want a medication with low incidence of side effects and high adherence.
6. Want a medication that is more effective than bupropion or nicotine patch.
7. Want a medication that is is helpful to individuals with psychiatric challenges.

Bupropion: Neurologic Mechanism

- Bupropion is a selective norepinephrine and dopamine reuptake inhibitor (decreases withdrawal symptoms).

- Bupropion also as a non-competitive antagonist at α3β2 nicotinic acetylcholine receptor within ventral tegmental area (VTA) (makes smoking less rewarding).

Stephen M. Stahl, 2004.
Mansvelder 2007.

Bupropion: Targeted Uses

DEPRESSION

- 6.7% of all Americans have a diagnosis of Major Depression[1], but roughly 25% of primary care patients have symptoms of depression.[2]
- Bupropion shows a decrease in depression symptoms during smoking cessation[3]

WEIGHT GAIN

- 15% of smokers experience over 20 lb. of post-cessation weight gain.[4]
- Bupropion has been shown to attenuate weight gain in smokers more than Varenicline or nicotine-based medications.[5]

[1]CDC 2016.
[2]US Department of Health and Human Service.
[3]Lehrman et al. 2004.
[4]Aubin et al. 2012 Cochrane Review - meta-analysis of 62 studies.
[5]Farley et al. 2012 Cochrane Review Interventions for preventing weight gain after smoking cessation.

AXS-05: Bupropion and Dextromethorphan (DM)

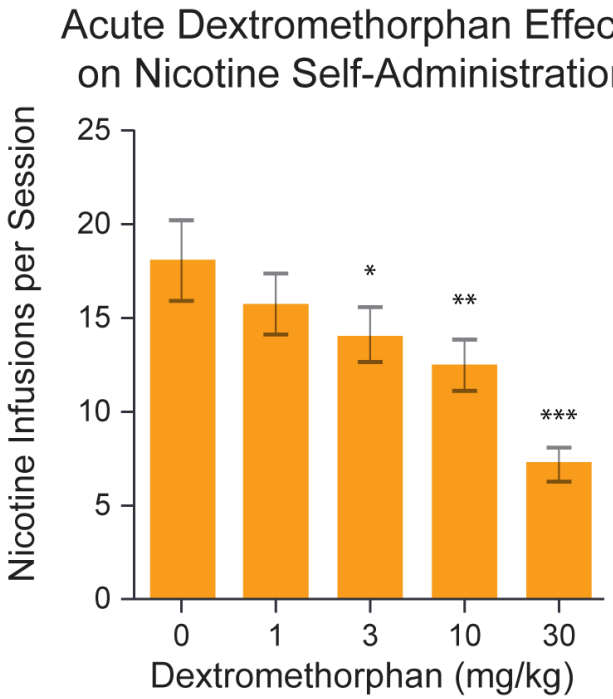
- Dextromethorphan is metabolized into Dextrophan by CYP2D6 - roughly 90% on first pass of the liver.
- Dextromethorphan easily crosses the blood brain barrier, Dextrophan does not.
- If Dextromethorphan is given alone at FDA approved doses, only a minimal amount of Dextromethorphan in the brain.
- Bupropion is a potent inhibitor of the CYP2D6 metabolic pathway.
- When Dextromethorphan is given with Bupropion (both at FDA approved doses) CNS concentrations of Dextromethorphan are about 90% of that in serum – and are high enough to exhibit receptor binding and central effects.

Dextromethorphan Central Mechanisms

- Non-competitive α3β4 nicotinic acetylcholine receptor (nAChR) antagonist (similar bupropion – this is expected to enhance the effect of bupropion in decreasing the reinforcing effects of smoking).[1]
- Sigma-1 receptor agonist (this may actually improve tolerance to withdrawal – which includes pain/distress) evidence in animals.[2]
- N-methyl-D-aspartate (NMDA) channel blocker (glutamatergic pathway is critical in learning – activates very rapidly. Part of quitting smoking is managing withdrawal the other is “unlearning smoking triggers.” Animal studies show that NMDA receptor activity increases time in cue-conditioned learning and unlearning.[3]
- Non-selective Serotonin (5-HT) reuptake inhibitor. This is the other neurotransmitter that is low during withdrawal (dopamine, norepinephrine, serotonin).[4]
- Norepinephrine Reuptake inhibitor (reinforce the cognitive enhancement seen in Bupropion).[5]

[1]Kulak et al., 2001
[2](Brown et al., 2004;Kim et al., 2003).
[3]Ferrer-Montiel et al., 1998
[4]Paquette et al., 2012
[5] Codd et al., 1995

Dextromethorphan Reduces Nicotine Administration in Nicotine Dependent Rats



Dextromethorphan main effect, p<0.0005 vs. Control

* p<0.025

** p<0.005

*** p<0.0005

- Finding: DM showed a significant and dose-dependent decrease in nicotine self-administration in nicotine dependent rats.
- Effects significant at 3 mg/kg and most effective at 30 mg/kg in the rat.
- Because humans are extensive DM metabolizers, translating these findings to humans necessitates metabolic inhibition.

Briggs, Levin et al. 2016.

Potentially Effective Dextromethorphan Concentrations for Smoking Cessation in Humans

- AXS-05 results in human DM plasma concentrations in the range shown to reduce several CNS symptoms: agitation, depression, inappropriate emotional expression.
  - Many of these symptoms are also seen in smokers attempting to quit: agitation, depression.
- Plasma concentrations of DM correlate to CNS concentrations.
- AXS-05 dosing results in DM concentrations that are high enough to exhibit receptor binding and central effects.
- These receptor interactions may result in efficacy in smoking cessation.

Briggs, Levin et al. 2016.

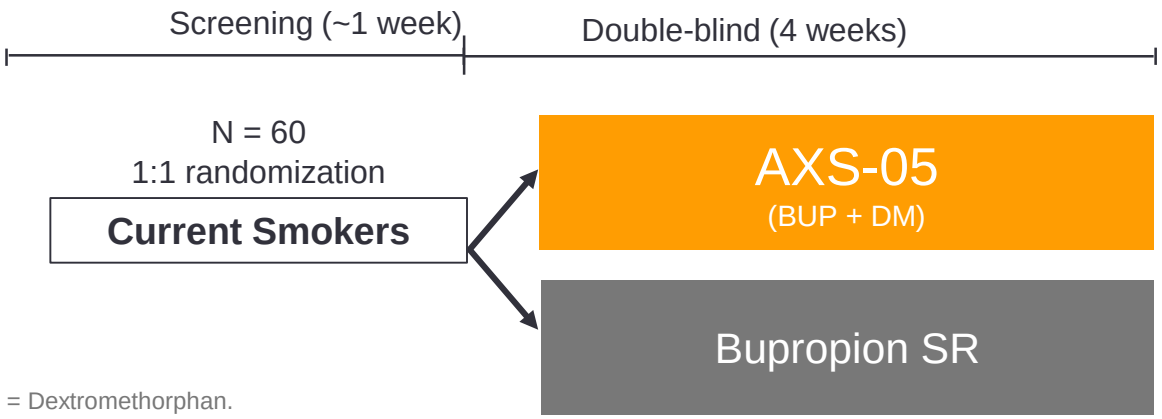
AXS-05: Opportunities

- **Opportunity 1:** AXS-05 is more effective than Bupropion and has a side effect profile that is similar to Bupropion (better than Varenicline).

- **Opportunity 2:** If AXS-05 shows similar efficacy as Bupropion, but greater efficacy for decreasing symptoms of depression, agitation, distress, withdrawal symptoms, cue-induced craving.

AXS-05 Smoking Cessation Phase 2 Study: Study Design

A Randomized, Double-Blind 4-Week Study to Evaluate the Impact of AXS-05 on Smoking Behavior



BUP = Bupropion; DM = Dextromethorphan.

- **Key Inclusion Criteria**:
  - Male or female 18 years hold or above
  - Daily smoker using 10 or more cigarettes per day
- **Dosage**: Twice daily for four weeks.
- **Outcomes:**
  - Biochemically confirmed smoking reduction and abstinence
  - Mood changes, withdrawal, depression, agitation, distress, craving
  - Tolerability

AXS-05 Smoking Cessation Phase 2 Study: Outcome Measures

Primary Objective

1. To evaluate the impact of AXS-05 compared to Bupropion (BUP) on change in smoking intensity from baseline to 3-week post-drug initiation by
   I. Salivary cotinine
   II. Expired carbon monoxide (CO) breath testing
   III. Number of cigarettes smoked per day (smoking diaries).
2. Smoking abstinence at 4-weeks post-drug initiation by the same.

Secondary Objectives

1. To assess adherence to treatment
2. To assess withdrawal symptoms, stress, anxiety, depression, and other measures.

AXS-05 Smoking Cessation Phase 2 Study: Activities

STUDY ACTIVITIES	STAGE 1	STAGE 2	STAGE 3	STAGE 4
Staff Hiring and Training	✓			
IRB/Data Base Build	✓			
Procedure Development	✓			
Recruitment + Enrollment		✓		
Assessment Visits		✓	✓	
Analysis and Publication				✓

✓ = This activity occurs at this time point

AXS-05 Smoking Cessation Phase 2 Study:
Study Progress

Stage 1 – Complete:

- FDA /IRB Approval,
- Staff Hiring + Training,
- Outcomes data-base/ recruitment data-based built,
- SOPs manual completed

Stage 2 – Initiated:

- First patients recently enrolled
- Screening and enrollment activities continuing as anticipated

SUMMARY: We are recruiting at the predicted pace and should complete the study in 1 year.

Summary

1. There is a large need for effective medications to treat tobacco dependence.
2. There is a large gap in desirable FDA approved smoking cessation medications. Available medications show high side effects + poor adherence. Only Varenicline is more effective than nicotine patch, and it is not well tolerated.
3. Dextromethorphan shows promising receptor binding characteristics and has been found to effective for treatment of nicotine dependent rats.
4. AXS-05 has potential to lead to a greater clinical effect than Bupropion alone.
5. AXS-05 may be well tolerated in smokers with a similar side effect profile as Bupropion alone.
6. AXS-05 may have beneficial effects in specific populations – those with symptoms of depression, distress, agitation, weight gain.
7. We are now running a study to capture evidence of AXS-05 efficacy, adherence and side effects compared to Bupropion, and also capture potential advantages of AXS-05 in specific populations.
8. The study is going well.

Q&A

AXSOME
THERAPEUTICS

Thank you.

For more information, please contact

Mark Jacobson
SVP, Operations

212-332-3243
mjacobson@Axsome.com

axsome.com