xywav™

(calcium, magnesium, potassium, and sodium oxybates) oral solution

C-III

XYWAV INVESTOR UPDATE

October 26, 2020

Jazz Pharmaceuticals®

Life-Changing Medicines.
Redefining Possibilities.

Forward-Looking Statements
"Safe Harbor" Statement Under The Private Securities Litigation Reform Act of 1995

This slide deck and the accompanying oral presentation contain forward-looking statements, including, but not limited to, statements related to Jazz Pharmaceuticals' growth strategy and opportunities and expectations for growth; the company's expectations regarding Xywav launch strategy, including regarding payer coverage, patient access and strong adoption of Xywav; future product sales, revenue and volume; the company's expectations regarding future competition for its products; capital deployment and other investment activities; statements about the sNDA submission, approval and launch of Xywav for idiopathic hypersomnia; the timing of the foregoing events and activities; and other statements that are not historical facts. These forward-looking statements are based on the company's current plans, objectives, estimates, expectations and intentions and inherently involve significant risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, without limitation, risks and uncertainties associated with: the ultimate duration and severity of the COVID-19 pandemic and resulting global economic, financial and healthcare system disruptions and the current and potential future negative impacts to the company's business operations and financial results; maintaining or increasing sales of and revenue from its oxybate products; effectively launching and commercializing Xywav and the company's other products and product candidates; the time-consuming and uncertain regulatory approval process, including the risk that the company's planned regulatory submissions may not be submitted, accepted or approved by applicable regulatory authorities in a timely manner or at all; the costly and time-consuming pharmaceutical product development and the uncertainty of clinical success, including risks related to failure or delays in initiating or completing clinical trials; protecting and enhancing the company's intellectual property rights; delays or problems in the supply or manufacture of the company's products and product candidates; complying with applicable U.S. and non-U.S. regulatory requirements; government investigations, legal proceedings and other actions; obtaining and maintaining adequate coverage and reimbursement for the company's products; and other risks and uncertainties affecting the company, including those described from time to time under the caption "Risk Factors" and elsewhere in Jazz Pharmaceuticals plc's Securities and Exchange Commission filings and reports (Commission File No. 001-33500), including the company's Quarterly Report on Form 10-Q for the quarter ended June 30, 2020 and future filings and reports by the company. In addition, while the company expects the COVID-19 pandemic to continue to adversely affect its business operations and financial results, the extent of the impact on the company's ability to generate sales of and revenues from its approved products, execute on new product launches, its clinical development and regulatory efforts, its corporate development objectives and the value of and market for its ordinary shares, will depend on future developments that are highly uncertain and cannot be predicted with confidence at this time, such as the ultimate duration and severity of the pandemic, governmental "stay-at-home" orders and travel restrictions, quarantines, social distancing and business closure requirements in the U.S., Ireland and other countries, and the effectiveness of actions taken globally to contain and treat the disease. Moreover, other risks and uncertainties of which the company is not currently aware may also affect the company's forward-looking statements and may cause actual results and the timing of events to differ materially from those anticipated. The forward-looking statements made in this slide deck and the accompanying oral presentation are made only as of the date hereof or as of the dates indicated in the forward-looking statements, even if they are subsequently made available by the company on its website or otherwise. The company undertakes no obligation to update or supplement any forward-looking statements to reflect actual results, new information, future events, changes in its expectations or other circumstances that exist after the date as of which the forward-looking statements were made.

Agenda

Kathee Littrell VP, Investor Relations, Jazz Pharmaceuticals	Welcome/Opening comments
Bruce Cozadd Chairman and Chief Executive Officer, Jazz Pharmaceuticals	Introduction
William B. White, M.D. Professor of Medicine University of Connecticut School of Medicine, Farmington Cardiovascular Safety Consultant	Sodium, Blood Pressure and Cardiovascular Health
Robert Iannone, M.D., M.S.C.E EVP, Research & Development, Jazz Pharmaceuticals	Xywav & Narcolepsy Overview
Kim Sablich EVP, General Manager of North America, Jazz Pharmaceuticals	Narcolepsy Launch & Commercial Landscape
Richard Bogan, M.D., FCCP, FAASM President of Bogan Sleep Consultants, LLC Associate Clinical Professor, University of South Carolina School of Medicine	Idiopathic Hypersomnia Disease Overview
Robert Iannone, M.D., M.S.C.E EVP, Research & Development, Jazz Pharmaceuticals	Xywav Phase 3 Top-Line Results in IH*
Dan Swisher President and Chief Operating Officer, Jazz Pharmaceuticals	IH Commercial Overview
All	Q&A

*This is an investigational use not approved by FDA

INTRODUCTION

Bruce Cozadd
Chairman and CEO

Jazz Pharmaceuticals®

Significant Momentum

Sleep Franchise: Poised for Continued Growth and Diversification

Strong Commercial Execution

#1
Sleep disorder medicine by sales since 2014 (Xyrem)

>50%
of oxybate patients on Xywav by 2023

$1.7-1.8B
2020 Neuroscience net sales guidance[1]

3
Approved products

2020 - A year of execution

Poised for sustainable growth

Xywav

Approval and upcoming launch in narcolepsy

Positive top-line IH[2] data; FDA Fast Track Designation; sNDA planned for 1Q21

[1] Guidance provided by Jazz Pharmaceuticals plc on and as of August 4, 2020. Jazz Pharmaceuticals plc is not confirming or updating that guidance and actual results may differ.
[2] Not currently approved for use in IH

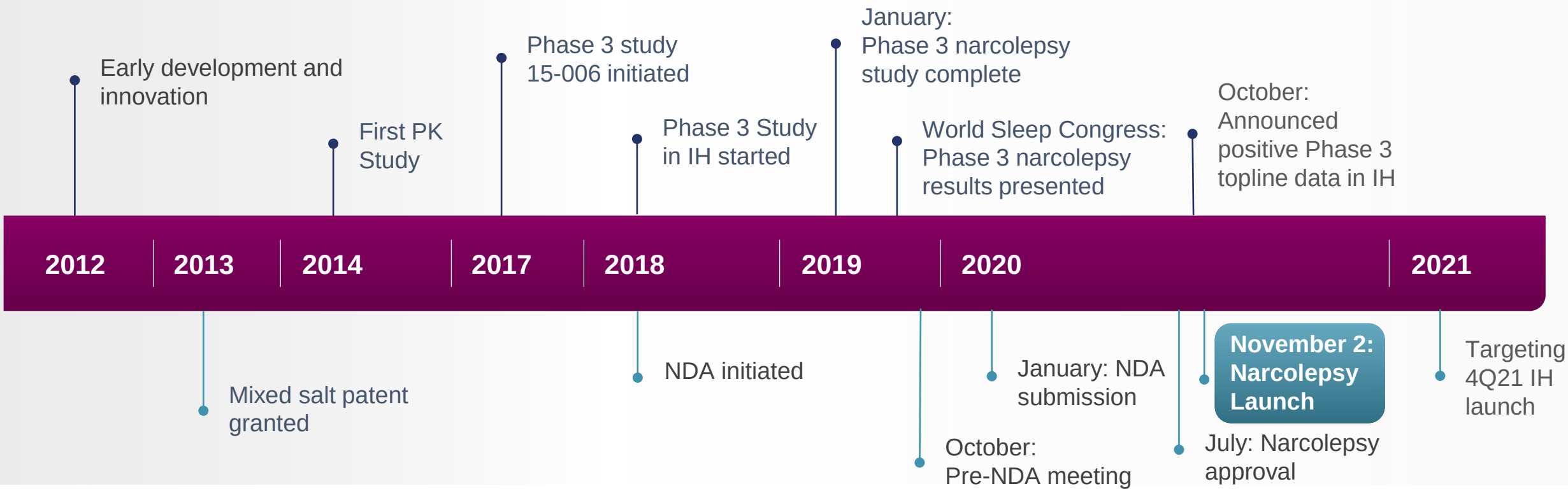
A Decade Focused on Improving The Health of Patients With Sleep Disorders

Xywav: From Concept to Launch

Tackling the lifelong burden of high sodium intake

New FDA approved treatment option for narcolepsy patients

Positive top-line data for the treatment of idiopathic hypersomnia*



*This is an investigational use not approved by FDA

Xywav: The First and Only Lower-Sodium Oxybate

Expect a Majority of Oxybate Patients on Xywav by 2023

LOWER-SODIUM OXYBATE FOR THE TREATMENT OF NARCOLEPSY

- 92% less sodium than Xyrem with the same active moiety for the treatment of cataplexy and EDS in patients >7 years of age with narcolepsy
- Narcolepsy is a chronic disease associated with increased prevalence of cardiovascular / cardiometabolic comorbidities[1]

A DIFFERENTIATED LABEL

- No warning to monitor patients sensitive to sodium intake
- Administration instructions in the label for patients transitioning from Xyrem to Xywav
- Twice-nightly with ability to take unequal first and second doses

EXPECT STRONG ADOPTION OF XYWAV

- Priced at parity to Xyrem with expected U.S. launch Nov. 2
- Existing Xyrem patients start Xywav at same dose
- Opportunity to add patients previously not prescribed Xyrem based on sodium concerns
- Focused on providing strong patient assistance programs and payer access

POTENTIAL FURTHER INDICATION FOR IH

- Positive Phase 3 top-line results announced in IH
- Planned sNDA submission 1Q21 and targeting U.S. launch of Xywav for IH 4Q21
- Significant unmet need with diagnosed prevalence of ~37,000 patients[2]

[1] Black, J, et al. SleepMed. 2017; 33: 13-18. [2] SHA Claims data

Please see the full prescribing information at www.xywav.com, including BOXED Warning and Medication Guide

SODIUM, BLOOD PRESSURE, AND CARDIOVASCULAR HEALTH

William B. White, MD, Professor of Medicine
University of Connecticut School of Medicine, Farmington
Cardiovascular Safety Consultant
williambwhitemd@gmail.com

Presentation Outline

- Salt consumption in the USA
- Projected impact of salt reduction on cardiovascular disease
- Sodium intake and reduction in heart disease
- Sodium intake guidelines
- Sodium in medications

Nearly Half of Sodium Intake in the US Comes from 10 Food Categories

Ten Food Categories Account for 44% of Consumed Sodium

Breads and rolls (7.4%)

Cold cuts and cured meats (5.1%)

Pizza (4.9%)

Fresh and processed poultry (4.5%)

Soups (4.3%)

Sandwiches (4.0%)

Cheese (3.8%)

Pasta mixed dishes (3.3%)

Meat dishes (eg, meat loaf with tomato sauce, 3.2%),

Snacks (eg, chips and pretzels, 3.1%)

Data derived from Centers for Disease Control and Prevention.[51]

Antman E et al. *Circulation* 2014; 129: e660-e679.

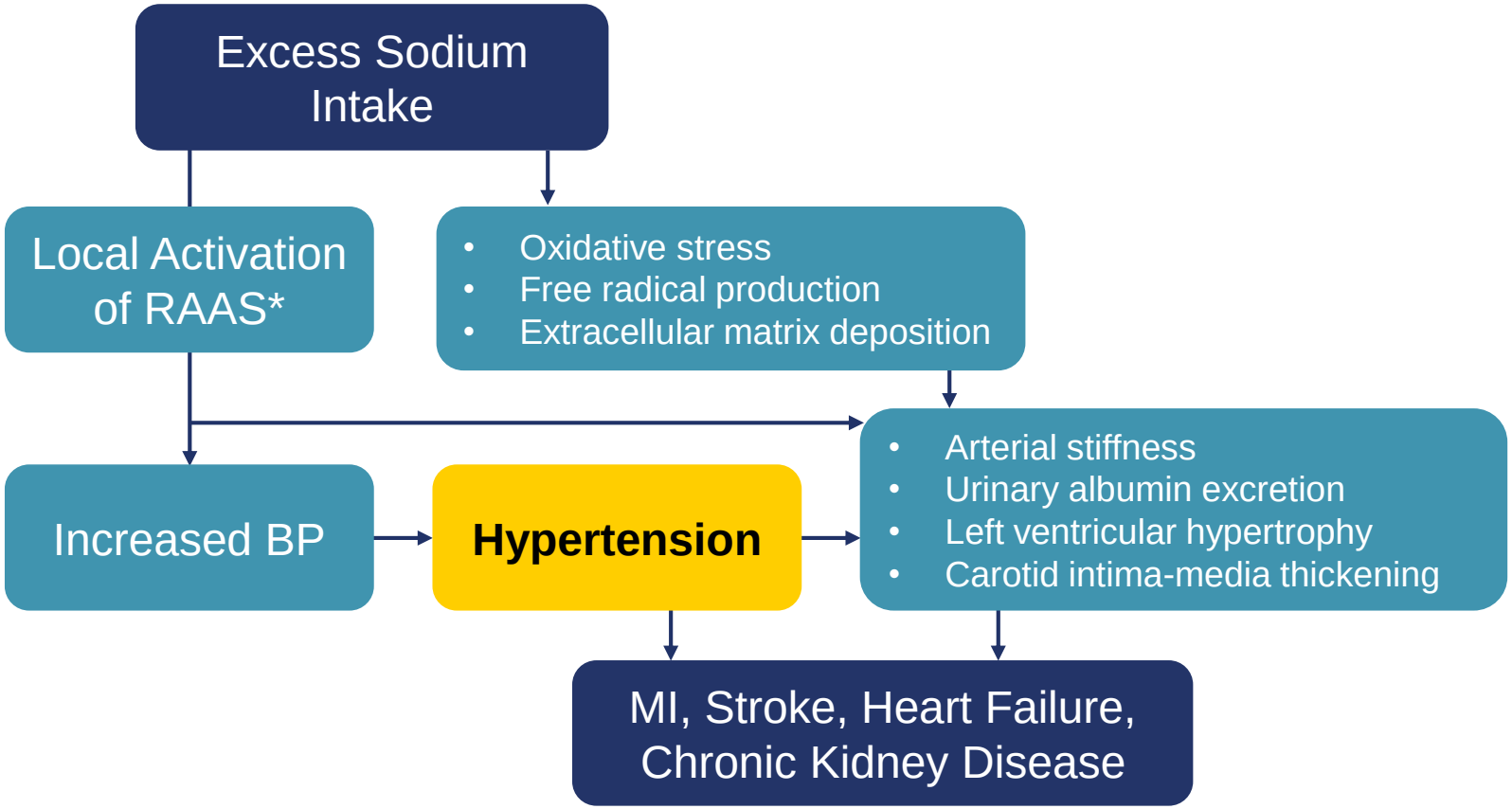
AHA Call to Action: Sodium Reduction to Prevent CV Disease, Including Stroke

- Elevated blood pressure is a leading, preventable cause of mortality and morbidity in the United States and throughout the world
- The relation of blood pressure and adverse health outcomes is direct, progressive, consistent, continuous, independent, and etiologically relevant starting at a level of 115/75 mm Hg
- A diverse body of evidence has implicated excess sodium intake in the pathogenesis of elevated blood pressure
- Independent of its effects on blood pressure, excess sodium intake adversely affects the heart, kidneys, and blood vessels
- Current intake of sodium greatly exceeds 1500 mg/day in the U.S., the upper level of intake recommended by the American Heart Association and the 2010 Dietary Guidelines Scientific Advisory Committee
- The potential public health benefits of sodium reduction are enormous

Appel L et al *Circulation* 2011; 123: 1138-1143.

Excess Sodium Intake Shown to Have a Causal Relationship With…

Hypertension and Subsequent Risk of Cardiovascular Disease



* The renin-angiotensin-aldosterone system (RAAS) has been highlighted as a potential mediator of high BP

1. Strazzullo P, et al. In: Berbari A, Mancia G, eds. *Special Issues in Hypertension*. 2012:147-56.

Effect of High Sodium Intake on Cardiovascular Outcomes

Independent of Vascular Risk Factors

- The **Northern Manhattan Study** demonstrated—sodium intake increases risk for cardiovascular outcomes, particularly stroke, independent of vascular risk factors[1]
- Research suggests that the effect of sodium on cardiovascular disease persists even after adjustment for BP and may indicate additional pathways for the impacts of sodium or other dietary factors[2]

Cardiovascular Risks From the Northern Manhattan Study[1]

	Hazard Ratio (95% CI)[a]	
Sodium Intake	Stroke	Stroke, MI, or Vascular Death
500-mg/day increase	1.17 (1.07–1.27)	1.05 (0.99–1.11)
≤1500 mg/day (reference)	**1.0**	**1.0**
1501–2300 mg/day	1.38 (0.84–2.27)	1.35 (1.00–1.82)
2301–3999 mg/day	1.32 (0.78–2.23)	1.21 (0.87–1.67)
4000–10,000 mg/day	2.59 (1.27–5.28)	1.68 (1.06–2.67)

[a]Model adjusted for demographics, behavioral risk factors, and vascular risk factors (diabetes, hypercholesterolemia, hypertension [BP ≥140/90 mm Hg, antihypertensive medication use, or the participant's self-report of hypertension], previous cardiac disease, body mass index).

The Northern Manhattan Study is a multi-ethnic urban prospective cohort study that included stroke-free individuals >40 years of age to determine stroke incidence, risk factors, and prognosis. Sodium consumption was estimated at baseline based on patient responses to a questionnaire, cardiovascular risk factors were assessed at baseline and annually thereafter, and cardiovascular events were assessed annually.

1. Gardener H, et al. *Stroke*. 2012;43(5):1200-5; 2. Committee on the Consequences of Sodium Reduction in Populations, Food and Nutrition Board, Board on Population Health and Public Health Practice, Institute of Medicine; Strom BL, et al. Washington (DC): National Academies Press (US); 2013.

Cardiovascular Effects of Reducing Sodium Intake

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Projected Effect of Dietary Salt Reductions on Future Cardiovascular Disease

Kirsten Bibbins-Domingo, Ph.D., M.D., Glenn M. Chertow, M.D., M.P.H., Pamela G. Coxson, Ph.D., Andrew Moran, M.D., James M. Lightwood, Ph.D., Mark J. Pletcher, M.D., M.P.H., and Lee Goldman, M.D., M.P.H.

Coronary Heart Disease (CHD) Policy Model*

- Computer-simulation, state-transition (Markov cohort) model of CHD prevalence in US residents ≥ 35 years of age or older
- Risk of CHD was categorized according to age, sex, SBP, antihypertensive drug use, smoking status, HDL and LDL cholesterol, diabetes status
- Disease history sub-model predicts the rate of subsequent CHD events and death from CHD stratified according to age, sex, and event history

*Authors created race specific versions of the model and extended the model to stroke using coefficients derived from the Framingham Study

Bibbins-Domingo K et al N Engl J Med 2010; 362: 590-9.

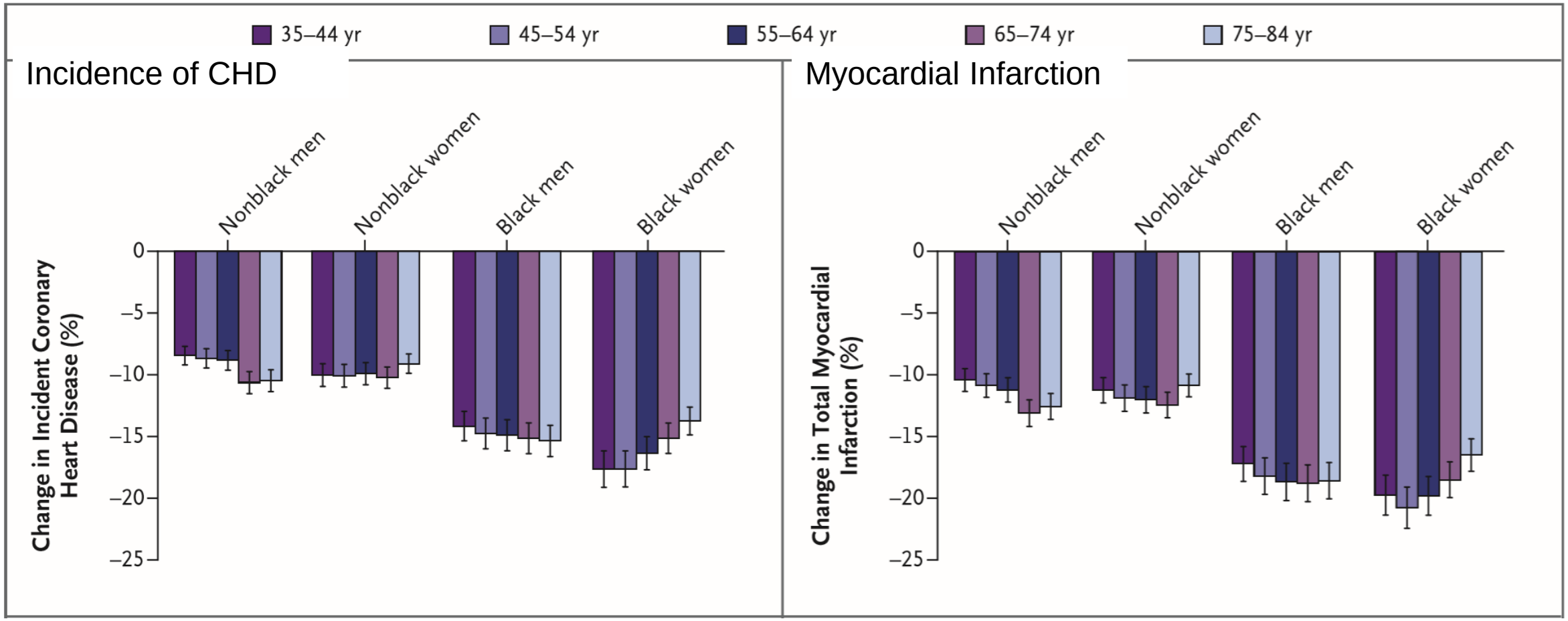
Estimated Effects of Reductions in Dietary Salt on Systolic Blood Pressure

Group	Salt Reduction, 1 g/day		Salt Reduction, 3 g/day		Reference No.
	Low Estimate of SBP Decrease	High Estimate of SBP Decrease	Low Estimate of SBP Decrease	High Estimate of SBP Decrease	
	mm Hg				
Entire U.S. population					
Persons with hypertension†	1.20	1.87	3.60	5.61	3, 15
Persons ≥65 yr old	1.20	1.87	3.60	5.61	17, 19–22
All others	0.60	1.17	1.80	3.51	3, 15
Black subpopulation					
Persons with hypertension†	1.80	3.03	5.40	9.10	3, 17, 19–22
Persons ≥65 yr old	1.20	1.87	3.60	5.61	17, 19–22
All others	1.20	1.87	3.60	5.61	17, 19–22

* SBP denotes systolic blood pressure.
† Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or use of an antihypertensive medication.

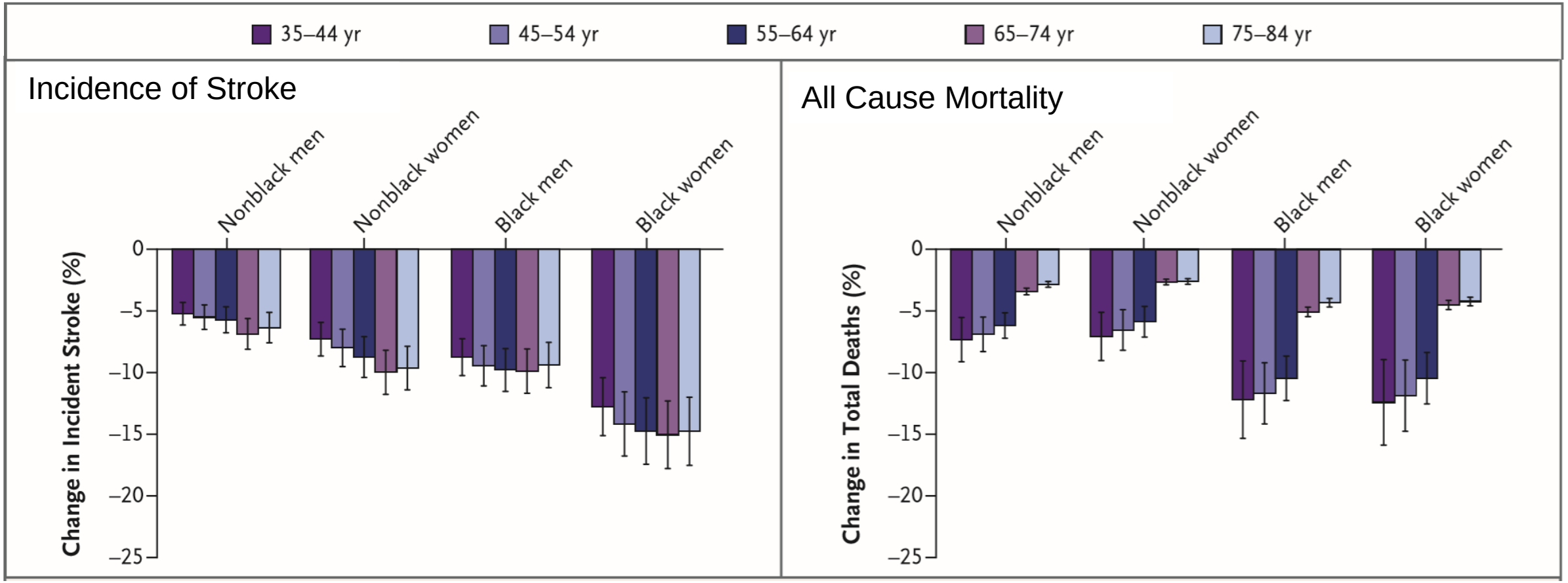
Bibbins-Domingo K et al N Engl J Med 2010; 362: 590-9.

Projected Annual Reductions in CV Events Given a 3 g Daily Reduction in Salt by Age, Gender and Race



Bibbins-Domingo K et al N Engl J Med 2010; 362: 590-9.

Projected Annual Reductions in CV Events Given a 3 g Daily Reduction in Salt by Age, Gender and Race



Bibbins-Domingo K et al N Engl J Med 2010; 362: 590-9.

Projected Effects of Reduced Sodium Intake on Risk for Cardiovascular Events and Death

Estimated benefits of population-wide reductions in dietary sodium from the Coronary Heart Disease (CHD) Policy Model[1,a]

Salt Reduction	Sodium Reduction	Change in Incidence of CHD	Change in Total MI	Change in Incidence of Stroke	Change in All-Cause Death
1 g/day	400 mg/day	−37,000 (−3.3%)	−32,000 (−4.2%)	−20,000 (−2.7%)	−28,000 (−1.4%)
2 g/day	800 mg/day	−71,500 (−6.4%)	−62,500 (−8.1%)	−40,000 (−5.3%)	−55,000 (−2.8%)
3 g/day	1200 mg/day	−110,000 (−9.6%)	−92,000 (−12.0%)	−59,000 (−7.8%)	−81,000 (−4.1%)

[a] Reduction in absolute number of events (means from Monte Carlo simulations) and percent change from expected.

- This study used the CHD Policy Model, a computer simulation of heart disease in US adults aged 35–84 years, and an extension of the model that is used to assess stroke, to estimate the benefits of population-wide reductions in dietary salt intake[1]
- Population-wide reductions in sodium intake (up to 1200 mg/day) may reduce the rates of annual cardiovascular events and death in the U.S.[1]

1. Bibbins-Domingo K, et al. *N Engl J Med*. 2010;362(7):590-9.

Sodium Intake Guidelines

Guidelines for Reductions in Sodium Intake and Projected Effects on Blood Pressure

AHA/ACC Clinical Practice Guidelines[1]

- Lowering sodium intake by at least 1000 mg/day is expected to reduce SBP in most normotensive and hypertensive individuals by 2/3 mm Hg and 5/6 mm Hg, respectively[1]

National Academies of Science, Engineering, and Medicine Dietary Reference Intakes for Sodium and Potassium[2]

- For a sodium intake range of 2300–4100 mg/day, a 1000-mg/day reduction in intake is expected to reduce chronic disease risk, as indicated by risk reduction for cardiovascular disease and hypertension, and lowering of SBP and DBP[2]
- 2300 mg/day was established as the sodium CDRR, or intake at which sodium reduction is expected to reduce chronic disease risk within an apparently healthy population[2]

1. Whelton PK, et al. *Hypertension*. 2018;71(6):e13-e115; 2. National Academies of Sciences, Engineering, and Medicine 2019. *Dietary Reference Intakes for Sodium and Potassium*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25353.

Recommended Sodium Intake in Adults

Upper Limit Ranges from 2000-2400 mg/day

Authority	Year	Target (mg/day)	Upper Limit (mg/day)
WHO[1]	2012	–	2000
Institute of Medicine[2]	2013	–	2300
DHHS/USDA[3]	2015	–	2300
Dietary Guidelines Advisory Committee[4]	2015	–	2300
FDA/USDA (Draft)[5]	2016	2300	–
AHA/ACC[6,7]	2018	1500	2400

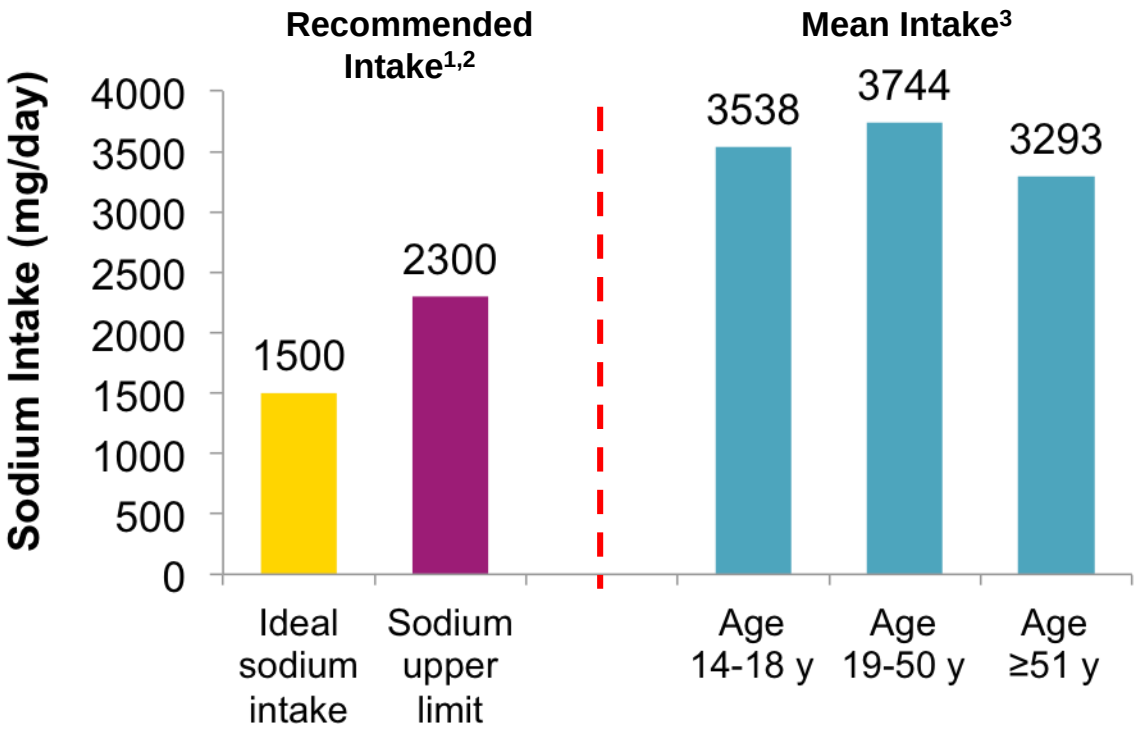
- In 2019, the National Academy of Sciences, Engineering, and Medicine established 2300 mg/day as the Chronic Disease Risk Reduction intake at which sodium reduction is expected to reduce chronic disease risk within an apparently healthy population[8]

1. WHO. Guideline: Sodium intake for adults and children. Geneva: World Health Organization (WHO). 2012. 2. Committee on the Consequences of Sodium Reduction in Populations, Food and Nutrition Board, Board on Population Health and Public Health Practice, Institute of Medicine; Strom BL, et al. Washington, DC: National Academies Press (US); 2013; 3. US Department of Health and Human Services. Food and Drug Administration Center for Food Safety and Applied Nutrition. 2016; 4. Dietary Guidelines Advisory Committee. 2015; 5. US Department of Health and Human Services and the US Department of Agriculture. 2015; 6. Eckel RH, et al. *Circulation*. 2014;129(25 suppl 2):S76-99; 7. Whelton PK, et al. *Hypertension*. 2018;71(6):e13-e115; 8. National Academies of Sciences, Engineering, and Medicine 2019. *Dietary Reference Intakes for Sodium and Potassium*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25353.

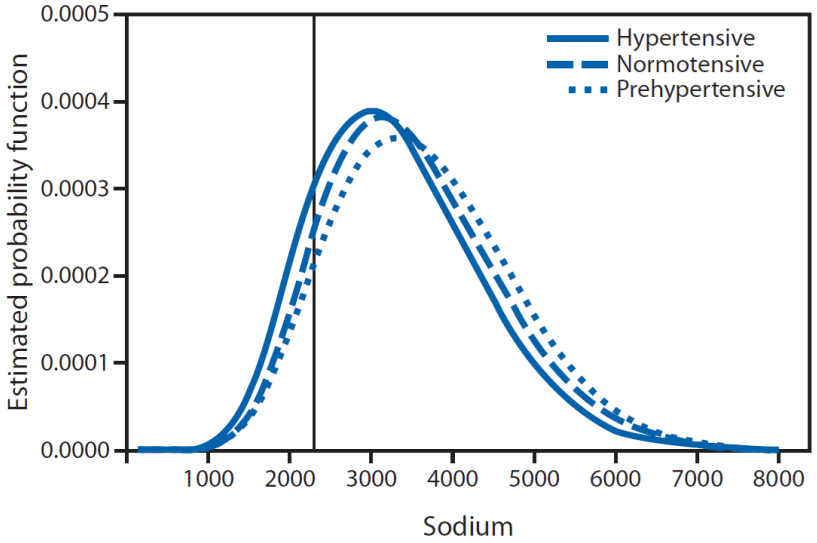
Dietary Sodium Intake Levels in the US

Adolescent and Adult Population

Recommended Versus Mean Dietary Sodium Intake (by Age)



Distribution of estimated usual intake of sodium (mg/day) among US adults, by hypertension status: National Health and Nutrition Examination Survey, 2009–2012[3]



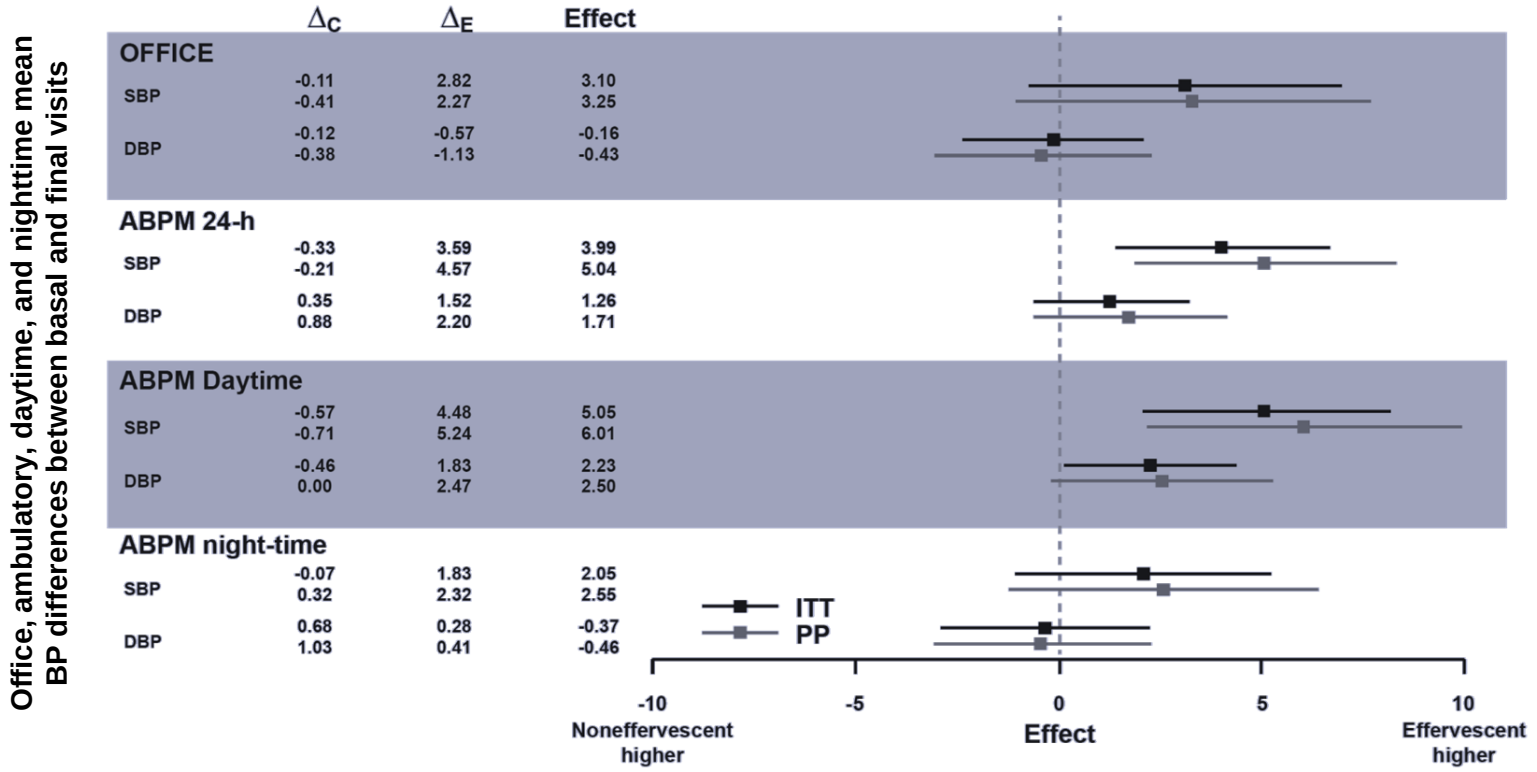
The vertical line indicates the 2015–2020 Dietary Guidelines for Americans recommendation for sodium intake (2300 mg per day for adults).

- Overall, 86% of hypertensive adults, 90% of normotensive adults, and 91% of prehypertensive adults exceeded 2300 mg per day sodium intake.

1. National Academies of Sciences, Engineering, and Medicine 2019. *Dietary Reference Intakes for Sodium and Potassium*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25353; 2. Whelton PK, et al. *Hypertension*. 2018;71(6):e13-e115; 3. Jackson SL, et al. *MMWR Morb Mortal Wkly Rep*. 2016;64(52):1393-97.

High Sodium–Containing Medications

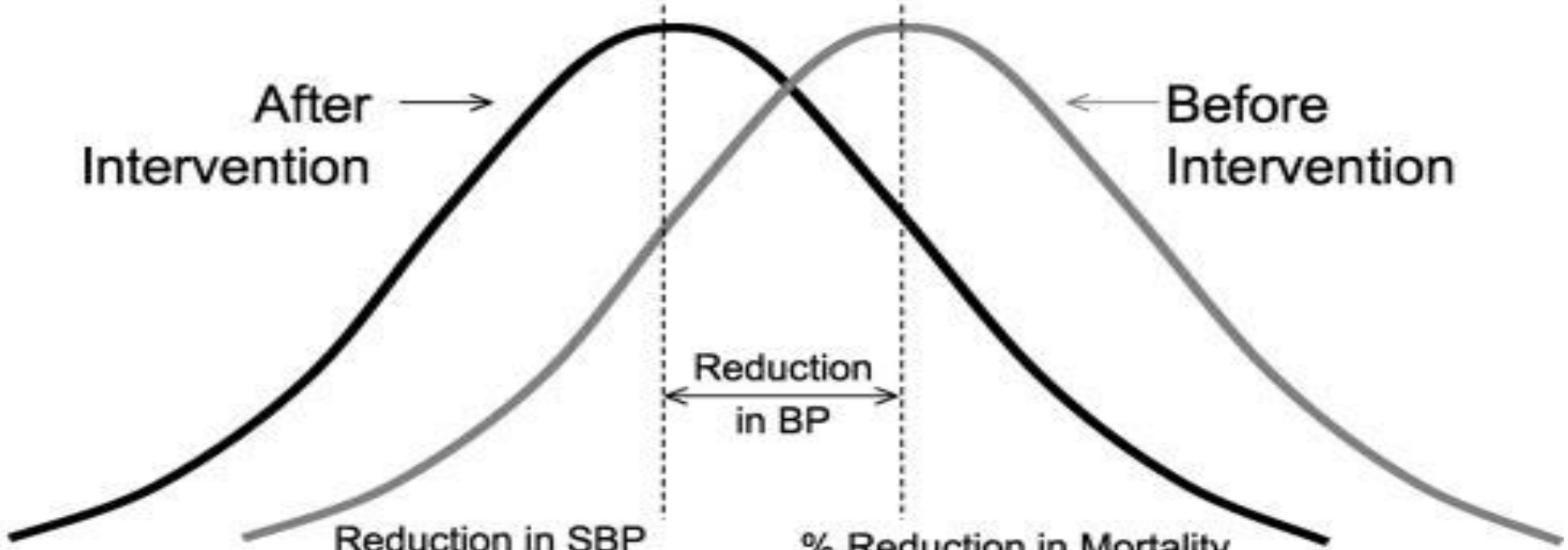
High Sodium–Containing Medications May Contribute to Elevations in Blood Pressure



- In a randomized, controlled, open, crossover study in adults with hypertension and chronic osteoarthritis, effervescent paracetamol (545 mg sodium per dose) was associated with a significant increase in overall and daytime SBP, compared with non-effervescent paracetamol (sodium-free)[1]
- In the ITT population (n=46), 24-h SBP:
  - increased by a mean of 3.59 mm Hg (95% CI, 1.39 to 5.79; *P*=0.003) with effervescent paracetamol
  - decreased by a mean of −0.33 mm Hg (95% CI, −1.78 to +1.13; *P*=0.886) with non-effervescent paracetamol
- Treatment periods were 3 weeks and separated by a washout period of 3–15 days; 1 g paracetamol was administered every 8 h

1. Benitez-Camps M, et al. *J Hypertens.* 2018;36:1656-62.

Small Reductions in Systolic BP Results in Fewer CV Events



Reduction in SBP mmHg	% Reduction in Mortality		
	Stroke	CHD	Total
2	-6	-4	-3
3	-8	-5	-4
5	-14	-9	-7

Whelton PK, et al. *JAMA.* 2002;288:1882-1888.
Adapted from *Arch Intern Med*, with additional data from Stamler R. *Hypertension.* 1991;17(SupplI):16-I20.

Consequences of ∆SBP (lower) = 3 mm Hg from Randomized Clinical Trials

- HOPE: ∆BP of 3/2 mm Hg:
  - 22% reduction in CV death, MI, or stroke (*P* <0.0001)
  - Significant reduction in all components of 1˚ endpoint
- ALLHAT doxazosin v. chlorthalidone: ∆SBP ~3 mm Hg
  - 19% reduction in stroke (*P* = 0.004)
  - 25% reduction in combined CV disease (*P* <0.001)
- ALLHAT lisinopril v. chlorthalidone: ∆SBP ~2 mm Hg
  - 15% reduction in stroke (*P* = 0.02)
  - 10% reduction in combined CV disease (*P* <0.001)

Heart Outcomes Prevention Evaluation. N Engl J Med 2000; 342: 145-153;
ALLHAT officers and coordinating center: JAMA 2002; 288: 2981-2997.

High Sodium–Containing Medications May Contribute to Adverse Cardiovascular Outcomes

Cardiovascular outcomes for sodium-containing formulations vs standard formulations from an analysis of the UK Clinical Practice Research Datalink

Outcome	Odds Ratio (95% CI)	
	Unadjusted	Adjusted[b]
Composite cardiovascular outcome[a]	1.13 (1.09–1.18)	1.16 (1.12–1.21)
Individual outcomes		
Incident nonfatal myocardial infarction	0.90 (0.85–0.96)	0.94 (0.88–1.00)
Incident nonfatal stroke	1.21 (1.15–1.28)	1.22 (1.16–1.29)
Vascular death	0.62 (0.31–1.24)	0.70 (0.31–1.59)
Hypertension	6.80 (6.41–7.21)	7.18 (6.74–7.65)
Heart failure	0.95 (0.91–1.00)	0.98 (0.93–1.04)
All-cause mortality	1.30 (1.25–1.35)	1.28 (1.23–1.33)

- In a nested case-control study, patients were prescribed at least 2 sodium-containing formulations or matched standard formulations of the same medication between January 1987 and December 2010 (mean follow-up was 7.23 years)[1]
- Exposure to sodium-containing medications was associated with significantly increased odds of adverse cardiovascular events vs standard formulations of the same medication[1]
- Of 1,292,337 patients, 61,072 experienced an incident cardiovascular event[1]

[a]Incident nonfatal myocardial infarction, incident nonfatal stroke, and vascular death.
[b]Covariates included age, sex, body mass index, smoking status, hypertension, peripheral vascular disease, angina, chronic obstructive pulmonary disease, diabetes mellitus, chronic kidney disease, migraine, heart failure, esophageal disease, and prescriptions of potassium-sparing diuretics.
1. George J, et al. *BMJ*. 2013;347:f6954.

Conclusions

- Overall, sodium intake is excessive in the US and of particular concern in those with underlying medical conditions.
- There is evidence for CV risk and untoward CV outcomes when individuals are exposed to high salt diets and high sodium containing medications
- The totality of evidence for the beneficial impact of sodium reduction on cardiovascular health is substantial
- The potential benefits of reductions in dietary sodium are greater in older persons, African-Americans and patients with heart, kidney and vascular disease.

XYWAV™ & NARCOLEPSY OVERVIEW

Robert Iannone, M.D., M.S.C.E
EVP, Research & Development

Narcolepsy Overview

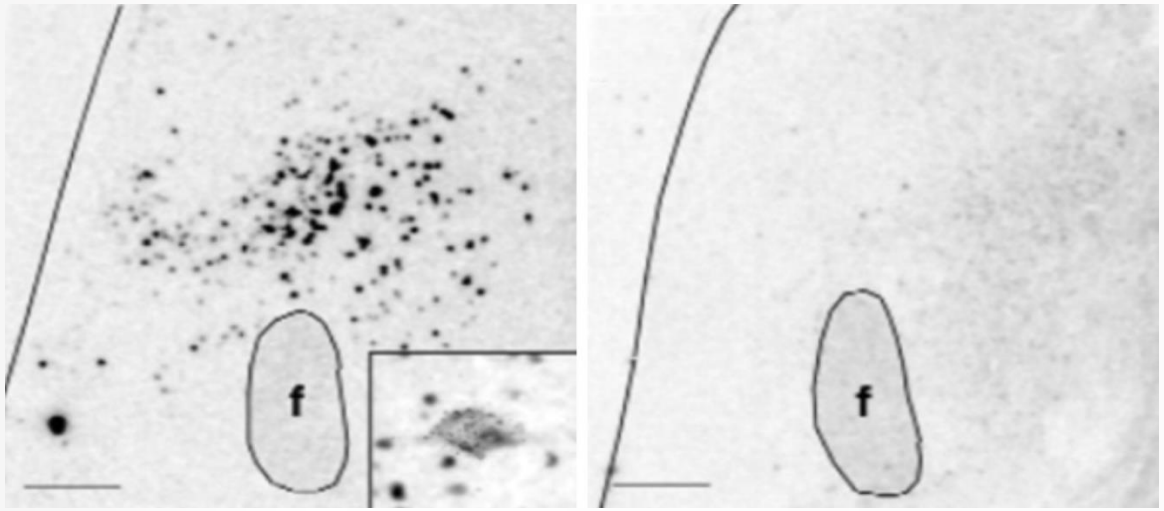
- Narcolepsy is a chronic neurologic sleep disorder[1]
  - Characterized by 5 predominant symptoms: excessive daytime sleepiness, cataplexy, disrupted nighttime sleep, sleep-related hallucinations, and sleep paralysis[2]
- No cure has been identified[1]
- Onset of symptoms typically occurs in childhood or adolescence[3,4]
- Symptoms typically warrant long-term treatment[1]
- Cardiovascular (CV) and cardio-metabolic diseases/disorders also are more common in patients with narcolepsy vs controls without narcolepsy
  - Stroke, MI, cardiac arrest and heart failure are more common in narcolepsy vs. controls[5]
  - Obesity, hypertension, diabetes, and dyslipidemia are comorbidities associated with narcolepsy[5-9]
  - Increased rate of CV diagnoses and excess mortality have also been reported[5,9]

1. Barateau L, et al. *CNS Drugs*. 2016;30(5):369-79; 2. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014; 3. Thorpy, MJ, et al. *Sleep Med*. 2014;15(5):502-7; 4. Dauvilliers Y, et al. *Neurology*. 2001;57(11):2029-33; [5] Black J, et al. Sleep Med. 2017;33:13-8. [6] Cohen A, et al. Sleep Med. 2018;43:14-8; [7] Jennum P, et al. Sleep. 2013;36(6):835-40; [8] Ohayon MM. Sleep Med. 2013;14(6):488-92; [9] Ohayon MM, et al. Sleep. 2014;37(3):439-44.

Pathophysiology of Narcolepsy

Hypocretin loss in the thalamus region[1,a]

Control



With narcolepsy

- Narcolepsy type 1 is believed to result from autoimmune destruction of hypocretin neurons[1-3]
- Although the pathophysiology of type 2 narcolepsy is less well understood, evidence suggests hypocretin dysfunction plays a role in the etiology of type 2 narcolepsy as well[3]
- In addition to stabilizing sleep-wake states,[4] hypocretin has widespread effects throughout the body and may mediate several physiologic functions, including appetite, insulin secretion, and BP[5-8]

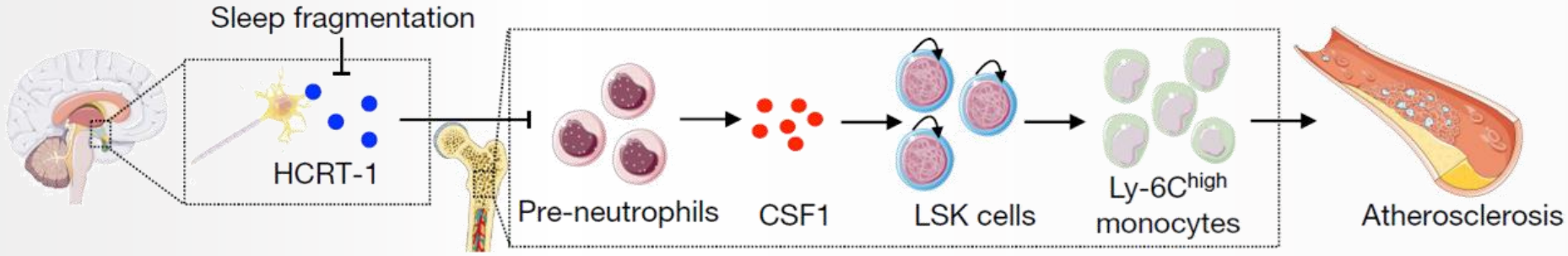
[a]Preprohypocretin mRNA in situ hybridization in the hypothalamus of controls and subjects with narcolepsy. Bar indicates 1 cm.

1. Nishino S. *Sleep Med*. 2007;8(4):373-99; 2. Barateau L, et al. *CNS Drugs*. 2016;30:369-79; 3. American Academy of Sleep Medicine. The International Classification of Sleep Disorders. 3rd ed. 2014; 4. Schwartz J, et al. *Curr Neuropharmacol*. 2008;6(4):367-78; 5. Espana R, et al. *Sleep*. 2011;34(7):845-56; 6. Herzig K, et al. *Acta Physiol (Oxf)*. 2010;198(3):199-200; 7. Li J, et al. *Br. J Pharmacol*. 2014;171(2):332-50; 8. Xu T, et al. *Cell Signal*. 2013;24(12):2413-23.

Emerging Science Suggests Relationship Between…

Hypocretin, Disrupted Nighttime Sleep, and Development of Atherosclerosis[1-4]

Model of the role of sleep in regulating hypocretin production, hematopoiesis, and atherosclerosis[1]



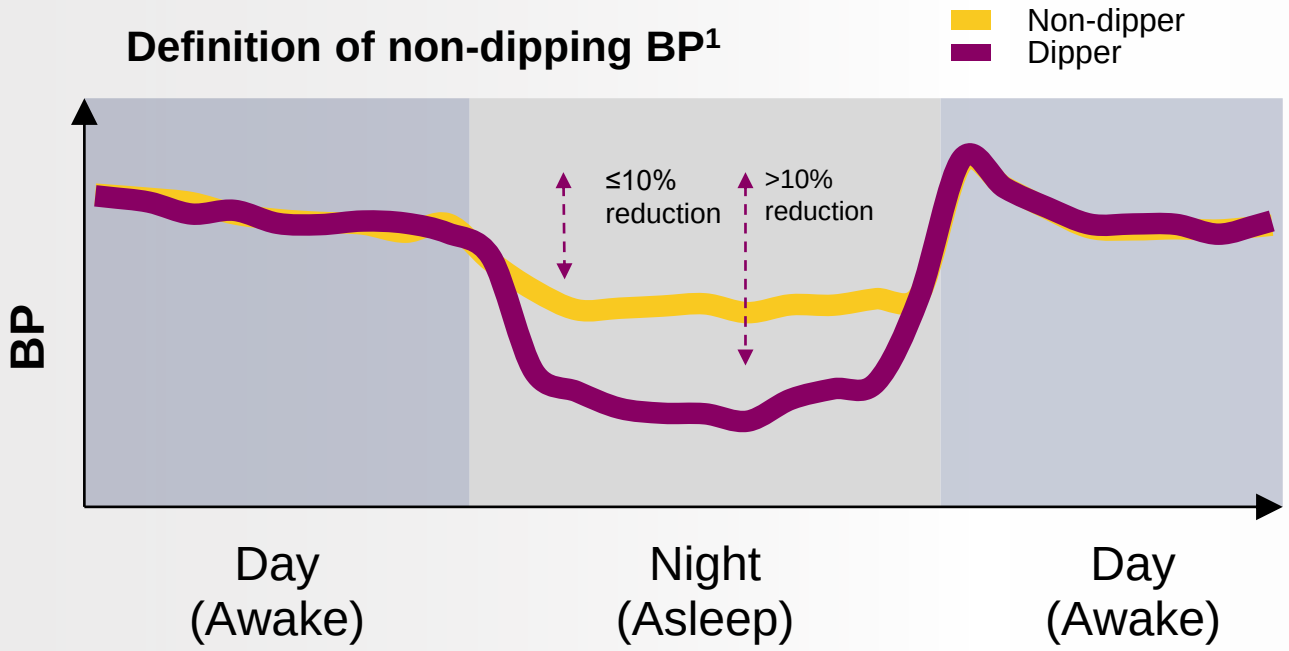
- Evidence from animal models suggests that hypocretin protects against the development of atherosclerosis due to sleep deprivation[1]
- Recent clinical research has demonstrated an association between CSF hypocretin level and severity of disrupted nighttime sleep in adult and pediatric patients with narcolepsy[2]
- Additional clinical research has demonstrated an association between disrupted nighttime sleep and blunted nocturnal BP dipping in patients with narcolepsy[3,4]

1. McAlpine CS, et al. *Nature*. 2019;566(7744):383-7; 2. Barateau L, et al. World Sleep 2019. Poster 110; 3. Grimaldi D, et al. *Sleep*. 2012;35(4):519-28; 4. Dauvilliers Y, et al. *PLoS One*. 2012;7(6):e38977.

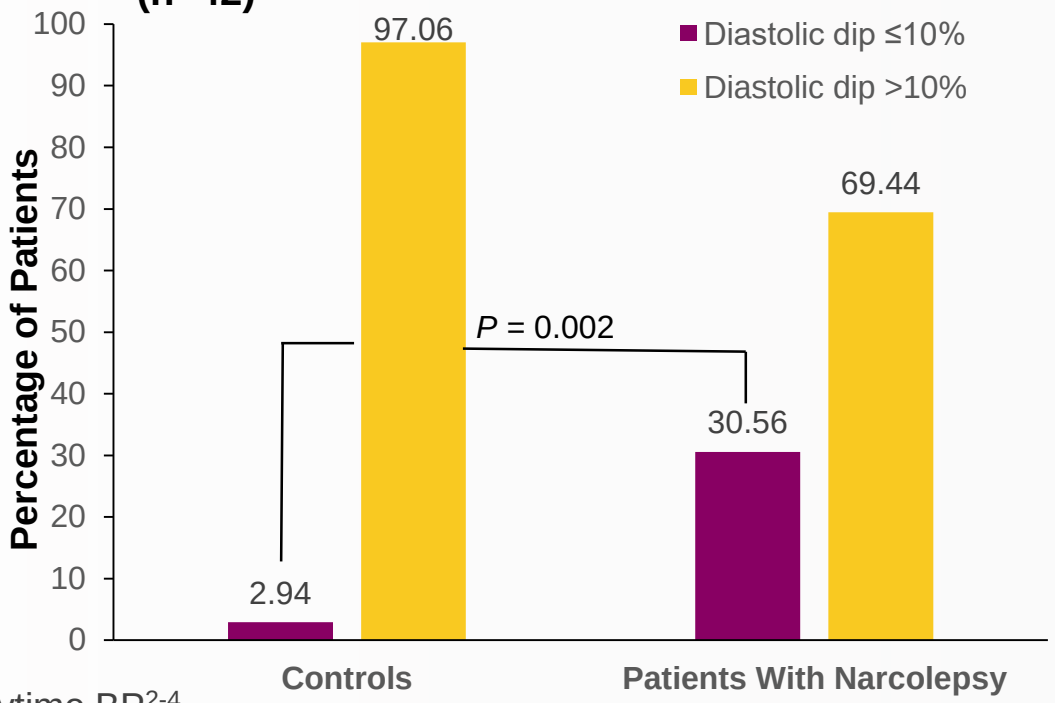
Nocturnal Blood Pressure Dipping

Non-dipping Phenotype Associated with Excess CV Risk/Mortality and is More Prevalent in Narcolepsy[5,6]

Definition of non-dipping BP[1]



Non-dipping diastolic BP profile in patients with narcolepsy with cataplexy (n=36) and in controls (n=42)[6]



- Normal physiology-BP decreases >10% to 20% at night[1]
- Non-dipping BP is classified as a decrease ≤10% during nighttime sleep[1]
- Nocturnal BP is a stronger predictor of cardiovascular outcomes than clinical or daytime BP[2-4]
- 24-hour ambulatory BP study in drug-free patients with narcolepsy with cataplexy and healthy controls demonstrated increased prevalence of blunted nocturnal dipping in patients with narcolepsy, irrespective of hypertension[4]
- Non-dipping diastolic BP was associated with REM sleep dysregulation and objective daytime sleepiness[4]

1. Kario K. *Hypertension*. 2018;71(6):997-1009; 2. Hansen TW, et al. *Hypertension*. 2011;57(1):3-10; 3. Fan HQ, et al. *J Hypertens*. 2010;28(10):2036-45; 4. Head GA. *J Hypertens*. 2017;35(3):463-5; 5. Ohkubo T, et al. *J Hypertens*. 2002;20(11):2183-9. 6. Dauvilliers Y, et al. *PLoS One*. 2012;7(6):e38977.

Cardiovascular and Cardiometabolic Comorbidities

Associated With Narcolepsy[1-5]

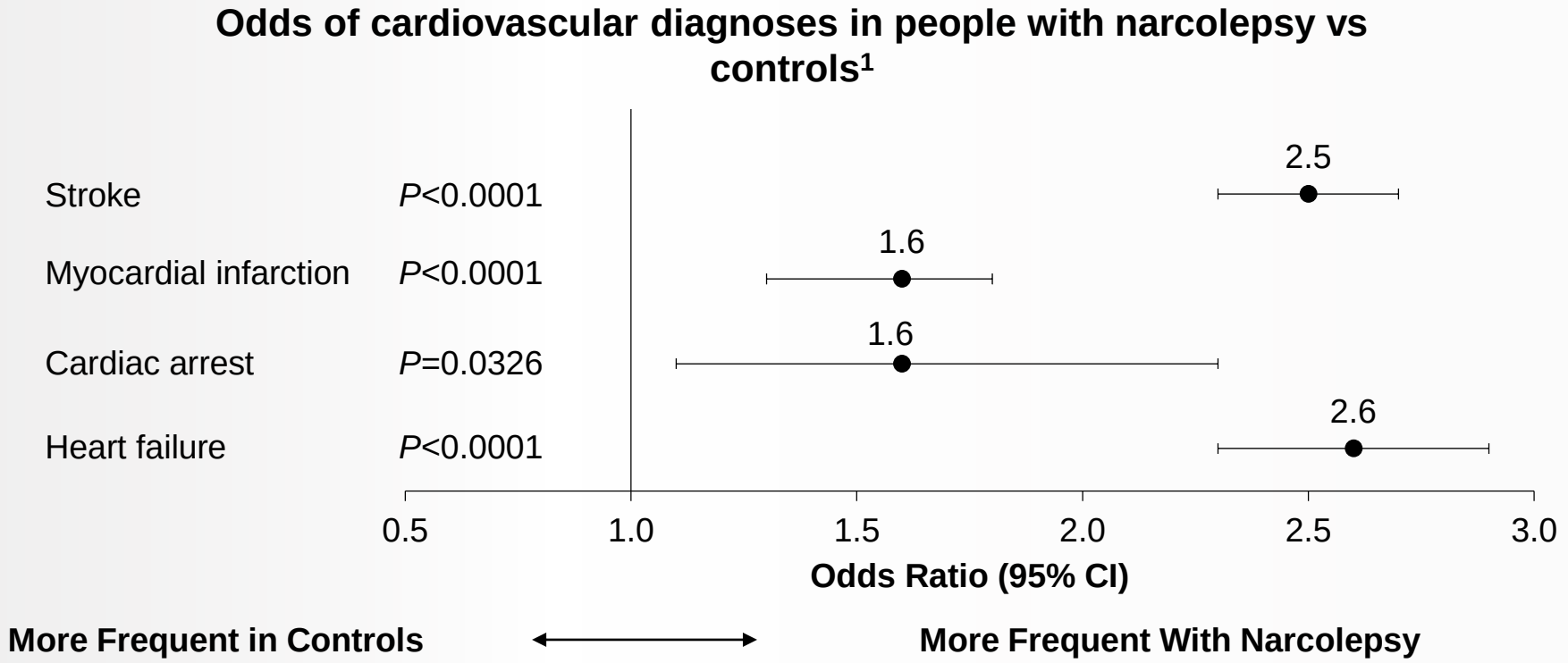
Comorbidities	Odds Ratio (95% CI)	P Value
Obesity		
Cohen et al[1]	2.07 (1.15–3.7)	0.015
Black et al[2]	2.3 (2.2–2.5)	<0.0001
Jennum et al[3]	13.4 (3.1–57.6)	<0.001
Hypertension		
Ohayon[4]	1.32 (1.02–1.70)	<0.05
Diabetes		
Black et al[2]	1.8 (1.7–1.8)	<0.0001
Jennum et al[3]	2.4 (1.2–4.7)	<0.01
Dyslipidemia		
Ohayon[4]	1.51 (1.04–2.19)	<0.05

P value for patients with narcolepsy vs matched controls. There was no adjustment for body mass or obesity.

1. Cohen A, et al. *Sleep Med*. 2018;43:14-8; 2. Black J, et al. *Sleep Med*. 2017;33:13-8; 3. Jennum P, et al. *Sleep*. 2013;36(6):835-40; 4. Ohayon MM. *Sleep Med*. 2013;14(6):488-92; 5. Ohayon MM, et al. *Sleep*. 2014;37(3):439-44.

Cardiovascular Risk in Narcolepsy is…

Increased vs. Matched Patient Controls



The BOND study used U.S. insurance claims data to analyze comorbidities in patients with narcolepsy (N=9,312) versus controls (N=46,559) matched for age, sex, geographic region, and type of insurance[1]

Figure is adapted from source article.

1. Black J, et al. *Sleep Med*. 2017;33:13-8.

FDA Approval July 21, 2020

Xywav U.S. Prescribing Information

Indication	**Xywav is a central nervous system depressant indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy**
Dosage/ Administration	*Adult Patients* • Initiate dosage at 4.5 g per night orally, divided into two doses • Titrate to effect in increments of up to 1.5 g per night per week • Recommended dosage range: 6 g to 9 g per night orally • Some patients may achieve better responses with unequal doses at bedtime and 2.5 to 4 hours later *Pediatric Patients* • The recommended starting dosage, titration regimen, and maximum total nightly dosage are based on body weight *For Patients Transitioning from Xyrem to Xywav* • Initiate at the same dose and regimen as Xyrem (gram for gram). Titrate as needed based on efficacy and tolerability

Please see the full prescribing information at www.xywav.com, including BOXED Warning and Medication Guide

NARCOLEPSY LAUNCH & COMMERCIAL LANDSCAPE

Kim Sablich
EVP & General Manager of North America

Unlocking the Potential of Xywav in Narcolepsy

Critical Success Factors Underpinning our Launch Strategy

Xywav U.S. Launch on November 2

Awareness

- Patients and HCPs understand the lifelong burden of high sodium intake
- Unbranded HCP & patient campaigns on lifelong disease and prevalence of certain comorbidities

Access

- Obtain strong payer coverage
- Patient assistance programs to help facilitate patient access at launch
- Seamless One-REMS implementation
- Expanded account level reimbursement resource

Adoption

- Strong HCP & patient branded campaigns, including media and digital presence
- Industry leading patient support
- Salesforce and account level reimbursement team readiness
- Patient and HCP branded educational programs

Experience

- Enhancing patient experience and improving persistence
- New and improved patient welcome kit
- myWAV app to enhance patient journey and ease of use + omni-channel refill
- Dedicated patient team and nurse case managers to help facilitate a positive patient journey[1]

[1] Service provided through central pharmacy

Patient Choice, Patient Voice

Narcolepsy is a Lifelong Condition Often Requiring Long-term Therapy

Patients with Narcolepsy Are at Increased Comorbid Risk

Excess Sodium Intake is Detrimental to Health

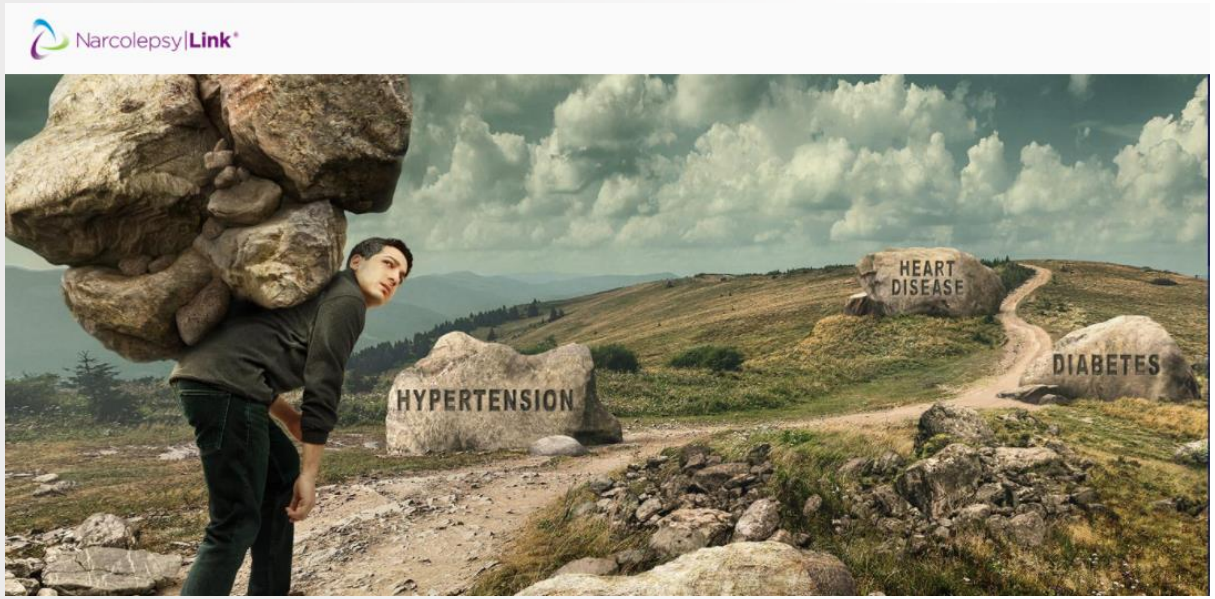
- DTC Virtual Patient Programs with KOL led patient education
- We are proudly supporting the American Heart Association's sleep disorders educational content.
- Strong engagement and collaboration with patient groups
- More Than Tired campaign – driving the need to be aware of a patient's total health

HCPs: Understanding The Impact of High Sodium Intake

Narcolepsy is a Lifelong Condition Often Requiring Long-term Therapy

Patients with Narcolepsy Are at Increased Comorbid Risk

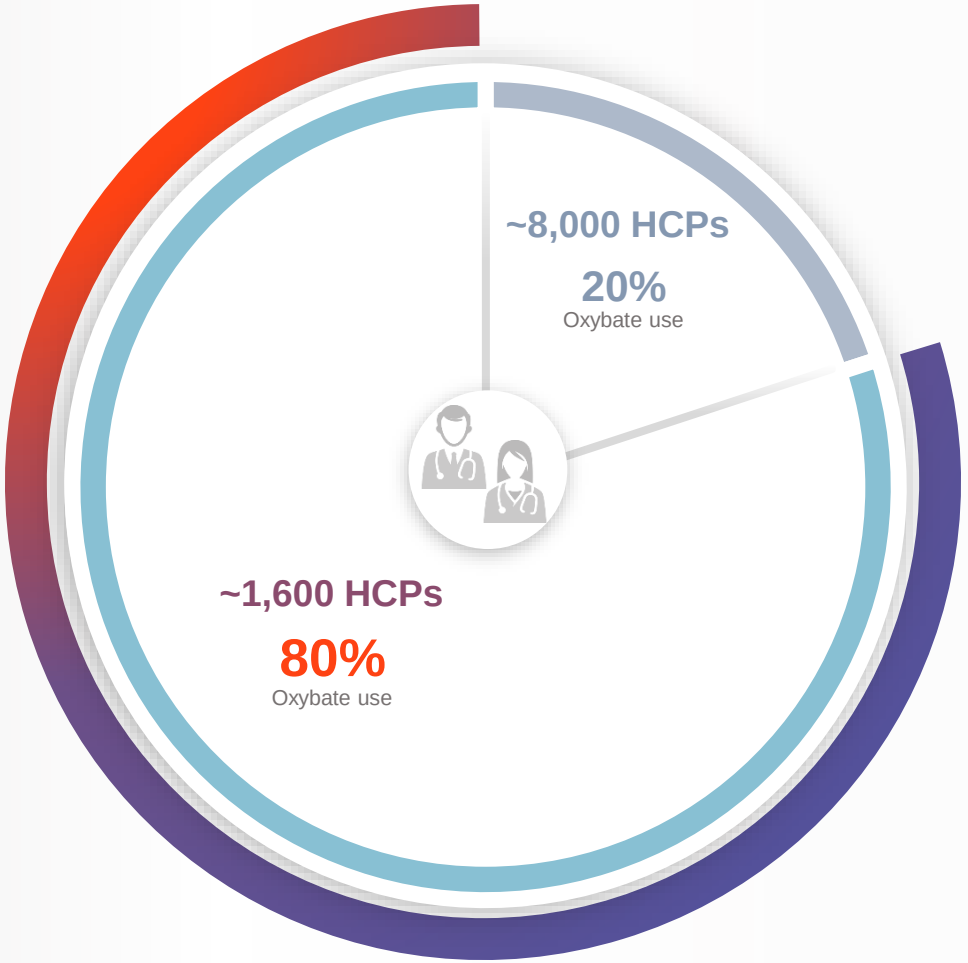
Excess Sodium Intake is Detrimental to Health



- NarcolepsyLink.com – broad educational offering including live and on-demand educational content
- Xywav pre-launch site currently active; launch site available November 2
- Field-based education and promotion
- Significant pre-launch Medical Affairs activities focused on:
  - Cardio-metabolic risk in narcolepsy
  - Label & clinical data reviews
- Extensive medical congress & publication activity

Focusing our Efforts on Top Prescribers

- Existing neuroscience salesforce of 143
- Xywav launch promotion focused on top ~1,600 HCPs covering 80%[1] of current oxybate prescriptions
- Oxybate promotion focused on Xywav
- Incentive compensation aligned to Xywav launch



- 165,000 narcolepsy patients[2]
  (estimated based on 1:2000 prevalence)
- ~75,000 drug treated
- ~15,000 average active patients on Xyrem therapy
- Meaningful number of patients not prescribed Xyrem due to sodium content concerns[2]

[1] SHA claims data from Q2'16-Q1'19 & PMR HCP segmentation Q4 2019; [2] Baumann, Basetti, Scammel, eds. Narcolepsy: Pathophysiology, Diagnosis and Treatment. Springer: NY 2011; Ohayon MM. From wakefulness to excessive sleepiness: What we know and still need to know. Sleep Medicine Reviews (2008) 12, 129-141. Based on U.S. Census Bureau population 2019 estimates of 329 million; [2] up to ~20% of existing Xyrem treated patient numbers

Industry Leading Patient Experience and Support

First-class support and patient experience to maximize the success of, and adherence to, Xywav initiation

- Enhanced Nurse Case Management, supporting patients through their first year on Xywav[1]
- Field nurse educator pilot aimed at prescribers and patients
- Omni-channel ordering & refill experience to empower Xywav patients[1]
- myWAV patient experience app in 2021[1]
- New patient welcome pack with all first time fills[1]

[1] Service provided through central pharmacy

Every Step of the Journey to Xywav is Optimized

Our account reimbursement specialists will work across service providers, HCPs and patients to ensure smooth adoption of Xywav

Central Pharmacy

Dedicated patient support team

Significant headcount resource increase

Commercial Coverage

Obtain strong commercial payer coverage over first 6 to 9 months

REMS

Joint Xywav & Xyrem REMS

Fully implemented

No re-enrollment required

Patient Assistance

Patient assistance programs to ensure broad access from launch

Key Metrics

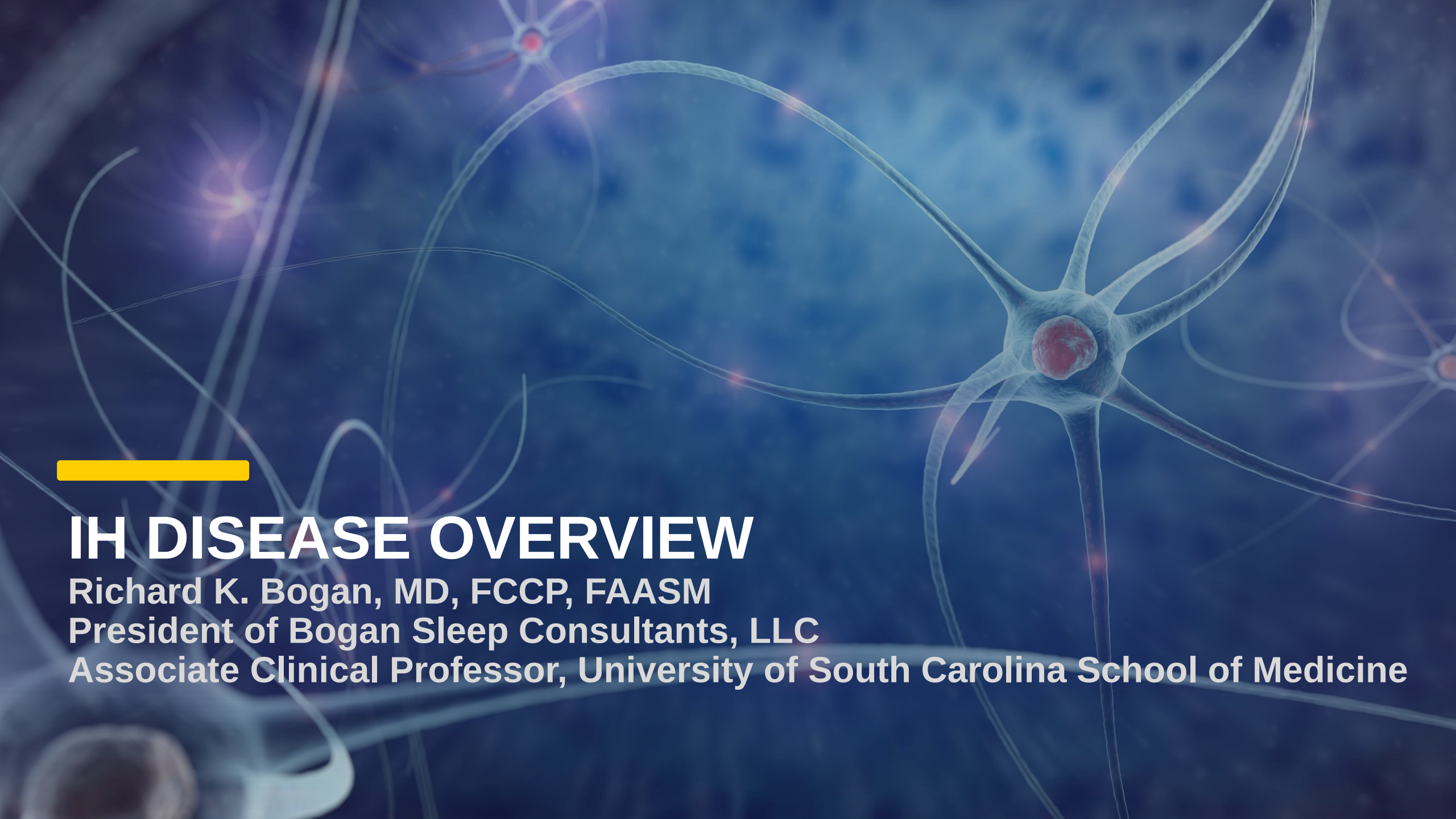
Focus on the Strong Adoption of Xywav

We expect to provide metrics reflecting access and patient uptake

Commercial Lives Covered

Adoption of Xywav Among Existing Oxybate Patients

Xywav & Xyrem Average Active Patients



IH DISEASE OVERVIEW

Richard K. Bogan, MD, FCCP, FAASM
President of Bogan Sleep Consultants, LLC
Associate Clinical Professor, University of South Carolina School of Medicine

Idiopathic Hypersomnia

- Central disorder of hypersomnolence characterized primarily by excessive daytime sleepiness (EDS)[1]
- EDS is frequently accompanied by symptoms of prolonged, unrefreshing sleep, and severe sleep inertia upon awakening[1-8]
  - Sleep inertia is defined as residual profound sleepiness upon attempts to waken
- Underlying pathophysiology not known[1,9]
- Prevalence of idiopathic hypersomnia remains unknown[1]
  - Recent claims analysis suggests a prevalence estimate of 11.3 per 100,000 persons[10]
- Incidence and prevalence are higher in females[1,9]

[1] American Academy of Sleep Medicine (AASM). International Classification of Sleep Disorders-3rd Edition (ICSD-3); Darien, IL: American Academy of Sleep Medicine. 2014;
[2] Vernet et al. *J Sleep Res*. 2010;19:525-34; [3] Roth et al. *Arch Gen Psychiatry*. 1972;26:456-62; [4] Trotti et al. *Sleep Med Clin*. 2017;12:331-44; [5] Leu-Semenescu et al. *Sleep Med*. 2016;17:38-44; [6] Kretzschmar et al. *J Sleep Res.* 2016;25:307-13; [7] Billiard et al. *Sleep Med Rev*. 2016;29:23-33; [8] Vernet et al. *Sleep.* 2009;32:753-9. [9] Leu-Semenescu et al. *Rev Neurol (Paris)*. 2017;173:32-7. [10] Acquavella et al. *J Clin Sleep Med*. 2020;16:1255-63.

Onset and Disease Course

- Onset of disease is typically before 30 years of age, and symptoms may have been present since childhood[1,2]
- Diagnostic challenges[3] may delay idiopathic hypersomnia diagnosis[2]
- Idiopathic hypersomnia is chronic in most patients, with spontaneous remission estimated to occur in 20% of patients, often after many years of symptoms[3]

1. American Academy of Sleep Medicine (AASM). International Classification of Sleep Disorders-3rd Edition (ICSD-3); Darien, IL: American Academy of Sleep Medicine. 2014;
2. Leu-Semenescu et al. *Rev Neurol (Paris)*. 2017;173:32-7; 3. Trotti et al. *Sleep Med Clin*. 2017;12:331-44.

Idiopathic Hypersomnia and Narcolepsy Symptomatology

Hypersomnolence disorders that share similar symptoms

Symptoms	Narcolepsy Type 1	Narcolepsy Type 2	Idiopathic Hypersomnia
Excess daytime sleepiness	✓	✓	✓
Sleep paralysis and hallucinations	✓	— Sometimes	— Occasionally
Cataplexy	✓	✗	✗
Difficulty staying asleep during the night	✓	— Sometimes	— Sometimes
Refreshing (restorative) night-time sleep and naps	✓	— Sometimes	— Occasionally
Sleep inertia (residual profound sleepiness upon attempts to waken)	— Occasionally	— Sometimes	✓
Long nocturnal sleep times	✗	✗	✓

Table adapted by Hypersomnia Foundation from Khan & Trotti 2015

Diagnosis of Idiopathic Hypersomnia

IH Diagnosis: ICSD-3 Criteria

A. Daily periods of irrepressible need to sleep or daytime lapses into sleep, present for at least 3 months
B. Cataplexy is absent
C. Fewer than two SOREMPs on MSLT (no SOREMP on MSLT if REM latency ≤ 15 min on nocturnal PSG)
D. At least one of the following:
    1. Mean sleep latency (MSL) ≤ 8 min on MSLT
    2. Total 24-h sleep time ≥660 min (11 hours) on 24-h PSG or by wrist actigraphy and sleep log
    (averaged over ≥ 7 days unrestricted sleep)
E. Insufficient sleep syndrome is ruled out
F. Hypersomnolence and/or MSLT findings not better explained by another condition

American Academy of Sleep Medicine. *International Classification of Sleep Disorders.* 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.

IH is Under- and Mis-Diagnosed

- Heterogeneity of disorder
- Shifting nosology
- Absence of biomarkers[1,2]
- Diagnostic testing limitations
  - MSLT test-retest reliability[3]
  - Assessing prolonged nocturnal sleep duration
    - Extended duration PSG recordings
    - Actigraphy

American Academy of Sleep Medicine (AASM). International Classification of Sleep Disorders-3rd Edition (ICSD-3); Darien, IL: American Academy of Sleep Medicine. 2014;
[1] Leu-Semenescu et al. Rev Neurol (Paris). 2017;173:32-7, [2] Billiard et al. Sleep Med Rev. 2016;29:23-33, [3] Trotti et al. J Clin Sleep Med. 2013;9:789-95

IH Disease Heterogeneity

- Two prominent phenotypes (with and without long sleep time)
- In clinical practice, different and variably severe phenotypic constellations may be encountered in individual patients

IH without long sleep time

- **Sleep attacks during the day**
- **Normal nocturnal sleep duration**
- **Differs from NT2 only by 1 SOREMP, which is an unstable biomarker**

IH with long sleep time

- **Long nocturnal sleep times**
- **High sleep efficiency**
- **Difficulty awakening**

Leu-Semenescu S et al. *Rev Neurol (Paris).* 2017;173(1-2):32-37.

IH Diagnosis Considerations

Shifting Nosology

- Initial “classical” descriptions of IH focused predominantly on increased need for sleep and prolonged nocturnal sleep
- Over time, increasing focus on daytime sleepiness or difficulty staying awake in the diagnostic schema
  - ICSD: MSLT MSL < 10 min (narcolepsy < 5 min)
  - ICSD-2: MSLT MSL ≤ 8 min (same as narcolepsy)
    - Two phenotypes (with and without long sleep time; 10-hour cut point)
  - ICSD-3: MSLT criteria unchanged; prolonged nocturnal sleep duration included as an alternative objective measure (≥ 11 hours)

ICSD-2: International Classification of Sleep Disorders: Diagnostic and Coding Manual 2. Westchester, IL: American Academy of Sleep Medicine; 2005:98-103, ICSD-3: American Academy of Sleep Medicine (AASM). International Classification of Sleep Disorders-3rd Edition (ICSD-3); Darien, IL: American Academy of Sleep Medicine. 2014.

Absence of Biomarkers

Differences from Type 1 Narcolepsy

- CSF hypocretin levels are normal
- Similar HLA DQB1*06:02 prevalence as general population
- No REM sleep instability
- Prior nosological emphasis on increased sleep efficiency not supported by meta-analysis[1]

Additional hypotheses under active investigation:

- GABA-related hypersomnolence
- Dysfunction in energy metabolic pathways
- Others – all up for debate and active area of research in the field

[1] Plante DT. *Sleep Med.* 2018;45:17-24

Diagnostic Testing Limitations

MSLT

- Multiple studies have demonstrated poor test-retest reliability in both IH and NT2[1,2,3]
- Pragmatic limitations – medications (e.g., antidepressants) may confound diagnosis[4]
- Many people with complaints of sleepiness may have MSL ≤8 minutes
  - General population[5]
  - Psychiatric disorders[6]

[1] Trotti LM et al. *J Clin Sleep Med.* 2013;9(8):789-95, [2] Lopez R et al. *Sleep.* 2017;40(12), [3] Ruoff C et al. *J Clin Sleep Med.* 2018;14(1):65-74, [4] Cairns A et al. *Sleep Med*. 2019;55:115-123, [5] Arand D. *Sleep.* 2005;28(1):123-44, [6] Plante DT. *Sleep Med Rev*. 2017;31:48-57.

PSG

Measuring Prolonged Nocturnal Sleep Duration With PSG

- No universally accepted standard protocol
- Few labs in the U.S. perform extended duration recordings of any type
- Lack of consensus regarding optimal standard protocol (32 hour protocol recently proposed)

Evangelista E et al. *Ann Neurol.* 2018;83(2):235-247.

Actigraphy

- Accelerometry-based methods only estimate sleep and wake
- Device setting parameters can have dramatic impacts on output estimates
- No established guidelines to estimate sleep time via actigraphy in IH
- Documentation of adequate sleep opportunity for ≥ 7 days is required

Cook JD et al. *J Clin Sleep Med.* 2019;15(4):597-602.

IH Treatment Paradigm

- There are no FDA approved pharmacologic agents to treat any of the symptoms of idiopathic hypersomnia (IH)[1,2]
- Stimulant medications used to treat narcolepsy are commonly used “off-label” to address excessive daytime sleepiness in patients with IH[1,2]
- Published guidelines for the assessment and treatment of IH[1,2]
  - Only grade B and C evidence-based recommendations are provided due to rarity of studies, inclusion of so few participants, and insufficient levels of evidence[1,2]
    - Recommended agents include wake promoting agents, sodium oxybate, and stimulants

[1] Evangelista E et al. *Expert Opin Inv Drugs.* 2018;27(2):187-92, [2] Lopez et al. *Rev Neurol (Paris)*. 2017;173(1-2):8-18.

Idiopathic Hypersomnia Severity Scale (IHSS)

Idiopathic Hypersomnia Severity Scale (IHSS)[1]

- Developed to assess IH symptoms, their severity, and functional consequences, in order to characterize IH burden at the time of the initial diagnostic evaluation and to monitor changes in symptom severity and functional impairment in response to treatment
- Validated clinical tool for the quantification of IH symptoms
- 14-item self-administered questionnaire that assesses:
  - Nighttime sleep symptoms and the related sleep inertia (5 items)
  - Daytime sleep symptoms and the related sleep inertia (4 items), and
  - Impaired daytime functioning due to hypersomnolence (5 items)
- Symptom frequency, intensity, and consequences are rated using a 3- or 4-point Likert scale, providing a total score that ranges from 0 to 50.
- Higher scores indicate more severe and frequent symptoms

Yves Dauvilliers, et al, Neurology 2019;92:e1754-e1762. doi:10.1212/WNL.0000000000007264

IHSS Validation[1]

- IHSS assesses all IH clinical symptoms
- Its psychometric properties and its responsiveness to treatment indicate that IHSS is a reliable tool for assessing IH symptom severity and their consequences and to detect clinically significant changes upon medication.
- IHSS can differentiate patients with IH from controls and from patients with NT1
  - IHSS can discriminate patients with IH from controls with a cutoff value of 22/50 with excellent specificity and sensitivity, and
  - From patients with NT1 with a cutoff value of 29/50 with correct sensitivity but lower specificity.
- The scores were higher in patients with IH than in controls and patients with NT1 after adjustment for age, sex, BMI, and ESS.
- IHSS can also quantify the symptom severity and related impairment after IH diagnosis, and showed good sensitivity for detecting changes in symptoms following treatment.

Yves Dauvilliers, et al, Neurology 2019;92:e1754-e1762. doi:10.1212/WNL.0000000000007264

XYWAV
PHASE 3 CLINICAL TRIAL IN IDIOPATHIC HYPERSOMNIA*

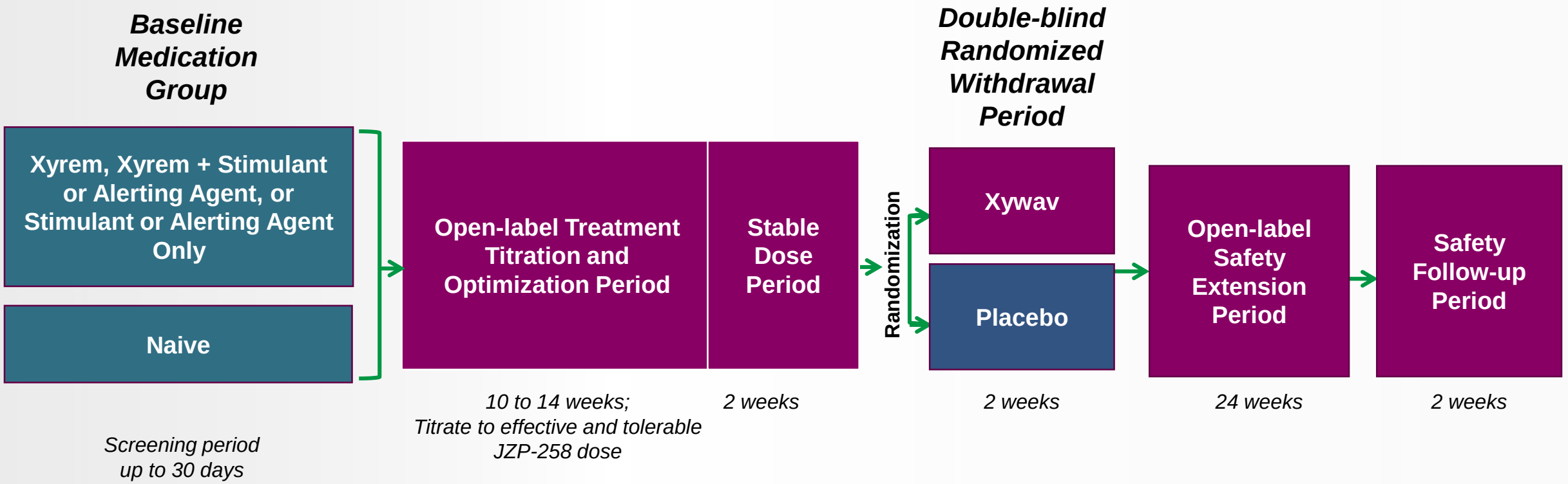
Robert Iannone, M.D., M.S.C.E
EVP, Research & Development

*This is an investigational use not approved by FDA

Phase 3 Study Design

Xywav for Idiopathic Hypersomnia*

154 adult patients were enrolled, with 115 randomized 1:1 to receive either Xywav or placebo



*This is an investigational use not approved by FDA

Phase 3 Top-Line Results

Xywav for Idiopathic Hypersomnia*

Clinically Meaningful and Highly Statistically Significant Results for Primary and Key Secondary Endpoints

Open-label Treatment Titration and Optimization Period

- Patients entering the study had EDS typical of the IH population
- All patients were treated with Xywav during this period and clinically meaningful improvements in the Epworth Sleepiness Scale (ESS) score were observed

Double-Blind Randomized Withdrawal Period

- Patients administered Xywav showed clinically meaningful maintenance of efficacy for the primary endpoint of ESS score and the key secondary endpoints of the change in Patient Global Impression of Change (PGIc) scores and Idiopathic Hypersomnia Severity Scale (IHSS)
- There was a significant worsening in patients administered placebo compared with Xywav for **ESS (p-value <0.0001), PGIc (p-value <0.0001) and IHSS (p-value <0.0001)**

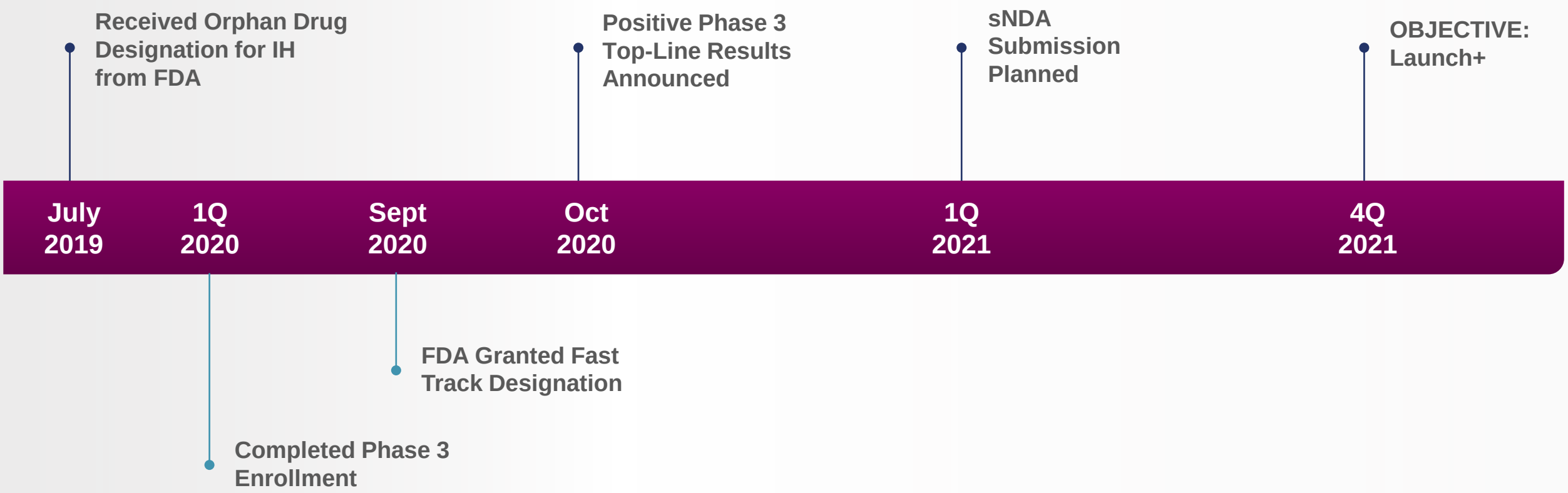
Safety Profile

- Consistent with the known safety profile of Xywav with no new safety signals observed in this patient population.

*This is an investigational use not approved by FDA

Key Events and Next Steps

Xywav for Idiopathic Hypersomnia*



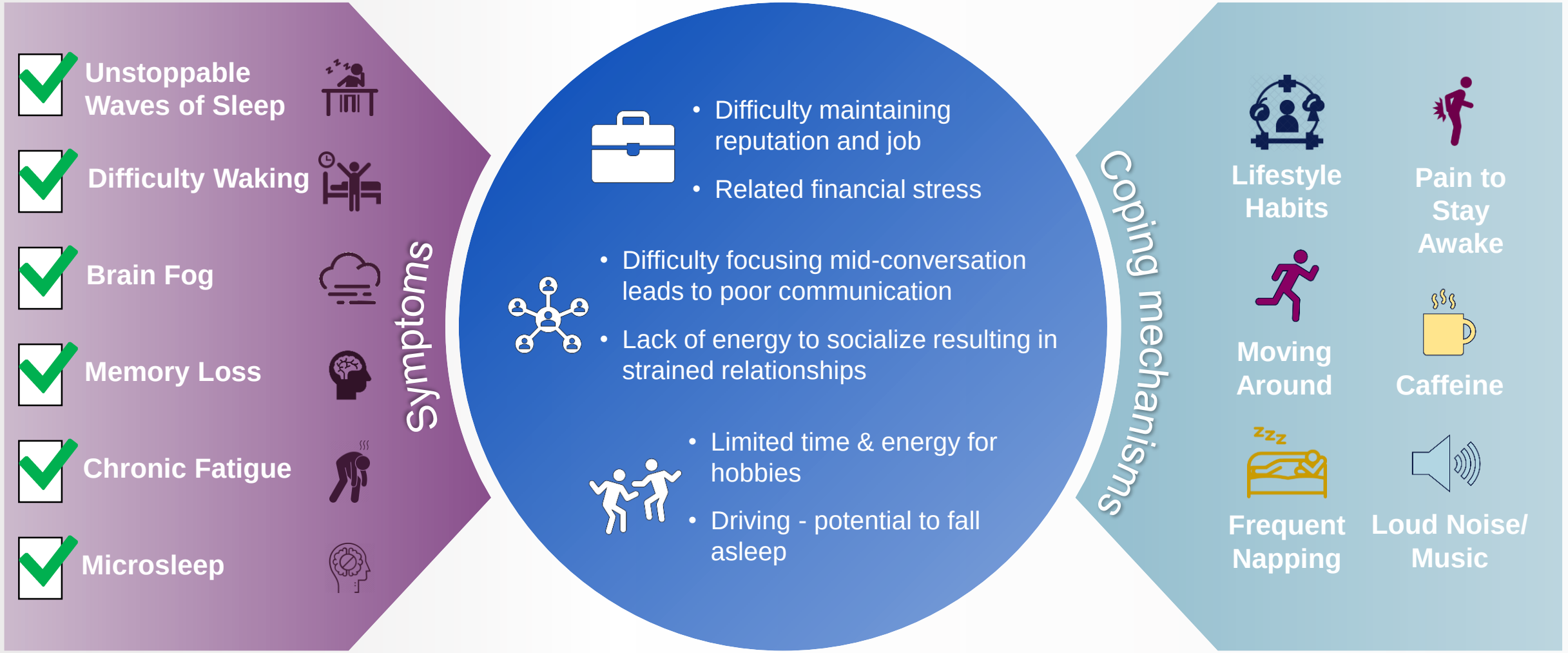
*This is an investigational use not approved by FDA
+ Post REMS implementation

IH MARKET OVERVIEW

DAN SWISHER
PRESIDENT & CHIEF OPERATING OFFICER

IH Profoundly Impacts Quality of Life

Activities of Daily Living Severely Affected



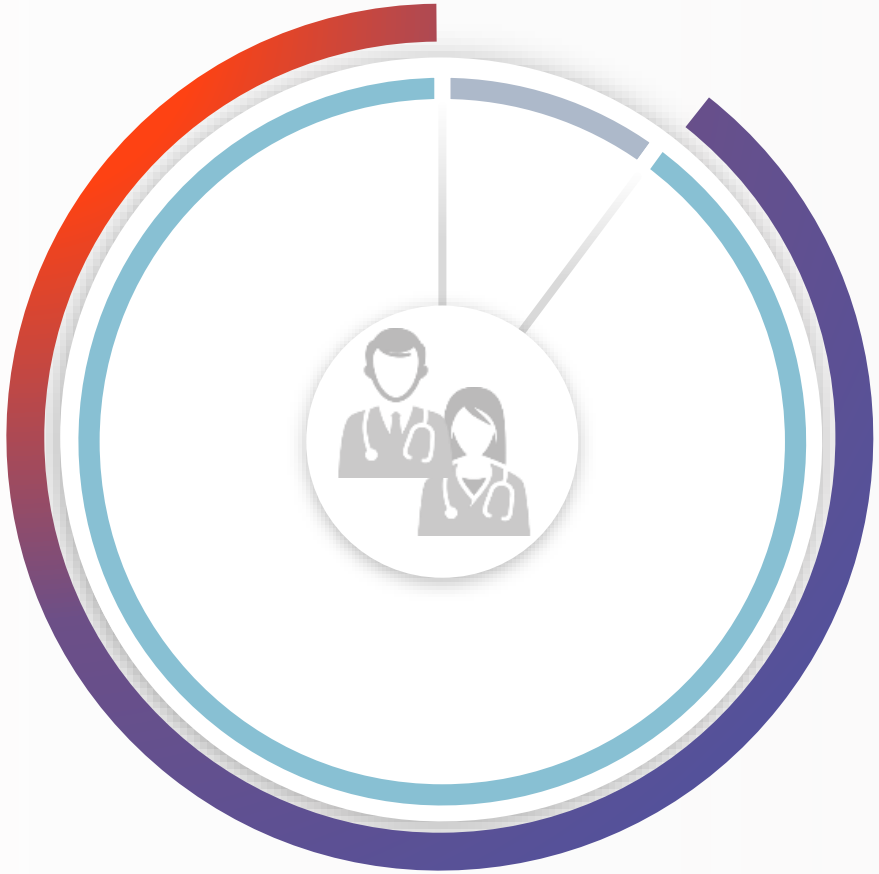
Market Characteristics

Significant and Underserved Patient Population

~37,000 diagnosed IH patients in the U.S.[1]
High likelihood of under-diagnosis

~800 physicians account for ~70% of IH diagnoses[1]

~800 physicians managing IH patients =
~90% overlap with our current call universe



[1] SHA Claims data for 60 months from Q4'14 to Q3'19

Xywav

A Major Advance in Oxybate Therapy

Xywav is a major advance for narcolepsy patients	92% less sodium than Xyrem	Individualized dosing	Targeting majority of oxybate patients on Xywav by 2023
Strong adoption	Existing oxybate patients transition at Xyrem dose, gram-for-gram	Patients unable to take Xyrem due to sodium concerns	
Seamless access to Xywav	Parity pricing	Strong payer coverage	Patient assistance programs
Idiopathic Hypersomnia Treatment	Positive top-line data October	Planned sNDA submission 1Q21	Targeting Launch 4Q21

Q&A

Sara
JZP-258 Trial Participant

APPENDIX

Boxed Warning

Xywav™ (calcium, magnesium, potassium, and sodium oxybates) oral solution

WARNING:
CENTRAL NERVOUS SYSTEM DEPRESSION and ABUSE AND MISUSE

Central Nervous System Depression
XYWAV is a CNS depressant. Clinically significant respiratory depression and obtundation may occur in patients treated with XYWAV at recommended doses *[see Warnings and Precautions (5.1, 5.4)]*. Many patients who received XYWAV during clinical trials in narcolepsy were receiving central nervous system stimulants *[see Clinical Trials (14.1)]*.

Abuse and Misuse
The active moiety of XYWAV is oxybate or gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death *[see Warnings and Precautions (5.2)].*

Because of the risks of CNS depression and abuse and misuse, XYWAV is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XYWAV and XYREM REMS *[see Warnings and Precautions (5.3)]*.

Boxed Warning

Xyrem® (sodium oxybate)

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and ABUSE AND MISUSE

Central Nervous System Depression

Xyrem (sodium oxybate) is a CNS depressant. In clinical trials at recommended doses, obtundation and clinically significant respiratory depression occurred in adult patients treated with Xyrem. Many patients who received Xyrem during clinical trials in narcolepsy were receiving central nervous system stimulants.

Abuse and Misuse

Xyrem® (sodium oxybate) is the sodium salt of gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death.

Because of the risks of CNS depression and abuse and misuse, Xyrem is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XYWAV and XYREM REMS *[see Warnings and Precautions (5.3)]*.

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Xyrem (sodium oxybate) prescribing information

Glossary

ABPM = 24-hour Ambulatory Blood Pressure Monitoring
ACC = American College of Cardiology
AHA = American Heart Association
BOND = Burden of Narcolepsy Disease
BP = Blood Pressure
CDC = Centers for Disease Control and Prevention
CDRR = (Chronic Disease Risk Reduction) thresholds
CI = Confidence Interval
CHD = Coronary Heart Disease
CNS = Central Nervous System
CSF = Cerebrospinal Fluid
CSF1= Colony-Stimulating Factor-1
CV = Cardiovascular
DBP = Diastolic Blood Pressure
DHHS = U.S. Department of Health and Human Services
DTC = Direct-to-Consumer
EDS = Excessive Daytime Sleepiness
EMA = European Medicines Agency
ESS = Epworth Sleepiness Scale
FAASM = Fellow of the American Academy of Sleep Medicine
FCCP = Fellow of the American College of Chest Physicians
FDA = U.S. Food and Drug Administration
GABA = Gamma-aminobutyric acid
GHB = Gamma Hydroxybutyrate
HCP = Health Care Provider
HCRT-1 = Hypocretin-1
HDL = High-Density Lipoproteins
HLADQB1 = Gene from Human leukocyte antigen (HLA) complex
ICSD = International Classification of Sleep Disorders
IH = Idiopathic Hypersomnia
IHSS = Idiopathic Hypersomnia Severity Scale
ITT = Intent-To-Treat
KOL = Key Opinion Leader
LDL = Low-Density Lipoproteins
LSK = Lineage (Lin)−Kit+Sca1+ Hematopoietic Progenitors
MD = Doctor of Medicine
MI = Myocardial Infarction
MSL = Mean Sleep Latency
MSLT = Multiple Sleep Latency Test
NAS = National Academies of Sciences, Engineering, and Medicine
NDA = New Drug Application
NT1 = Narcolepsy Type 1
NT2 = Narcolepsy Type 2
PGIc = Patient Global Impression of Change
PK = Pharmacokinetics
PSG = Polysomnogram
RAAS = Renin-Angiotensin-Aldosterone System
REM = Rapid Eye Movement
REMS = Risk Evaluation Mitigation Strategy
sNDA = Supplemental New Drug Application
SBP = Systolic Blood Pressure
SOREMP = Sleep-Onset REM (rapid eye movement) Period
USDA = U.S. Department of Agriculture
WHO = World Health Organization