



INVESTOR DAY | 2024

October 1, 2024 | New York City

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HARMONY
BIOSCIENCES

OPENING REMARKS

SLEEP/WAKE FRANCHISE

NEUROBEHAVIORAL FRANCHISE

EPILEPSY FRANCHISE

CLOSING REMARKS

MANAGEMENT PANEL DISCUSSION

Q&A



JEFFREY M. DAYNO, MD
President & Chief Executive Officer
Harmony Biosciences



INNOVATIVE




PATIENT-FOCUSED



CATALYST-RICH



PROFITABLE BIOTECH



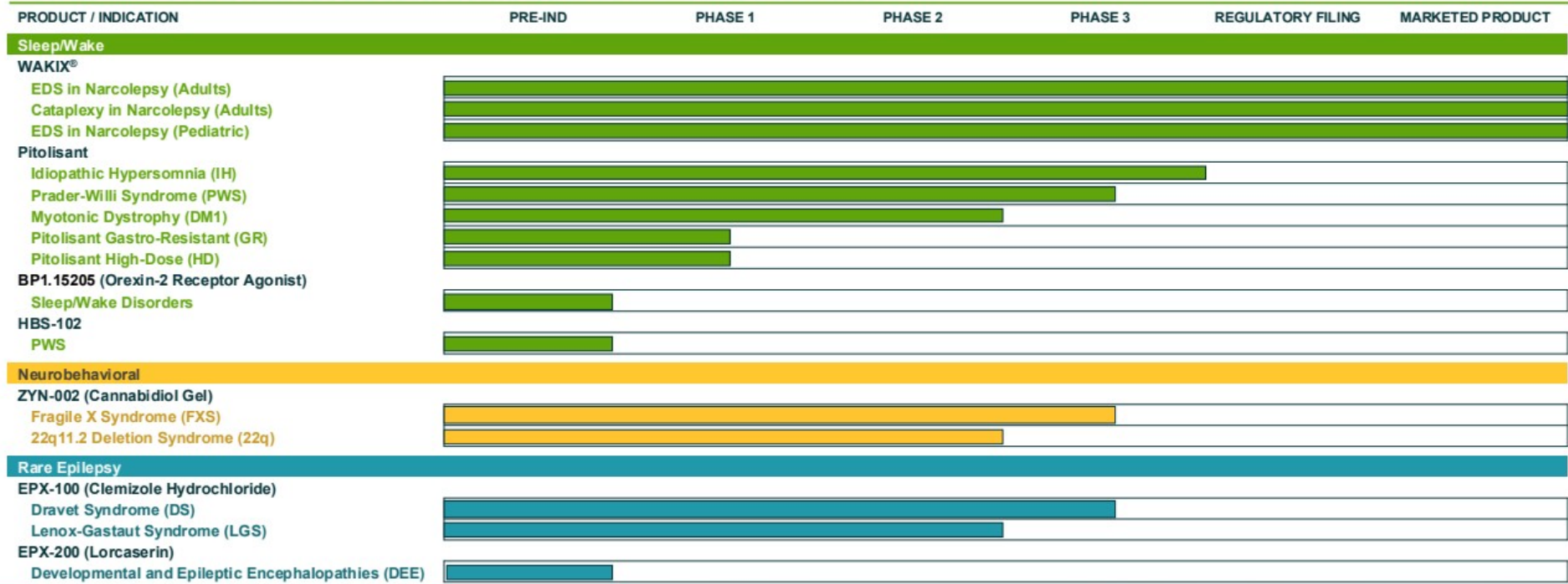
N E W R O L O G Y

Development Pipeline January 2023

PRODUCT / INDICATION	PRE-IND	PHASE 1	PHASE 2	PHASE 3	REGULATORY FILING	MARKETED PRODUCT
Sleep/Wake						
WAKIX®						
EDS in Narcolepsy (Adults)						
Cataplexy in Narcolepsy (Adults)						
Pitolisant						
Pediatric Narcolepsy						
Idiopathic Hypersomnia (IH)						
Prader-Willi Syndrome (PWS)						
Myotonic Dystrophy (DM1)						
Next Gen Formulations						
HBS-102						
PWS						

Primarily focused on sleep/wake and pitolisant

Transformation of Harmony's Pipeline



3 CNS FRANCHISES	8 ASSETS	13 DEVELOPMENT PROGRAMS	4 PHASE 3 PROGRAMS BY YEAR END
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SLEEP/ WAKE

- Compelling data; conviction in IH - sNDA on track for Q4 2024
- Next-generation formulations of pitolisant to extend franchise beyond 2040
- Potential best-in-class orexin-2 agonist (BP1.15205)

NEURO BEHAVIORAL

- ZYN-002: innovative synthetic cannabidiol (CBD)
- Pivotal Phase 3 trial in Fragile X syndrome; topline data mid-2025
- ~80,000 patients in US; no approved treatments
- On track to initiate pivotal Phase 3 trial in 22q deletion syndrome in 2025

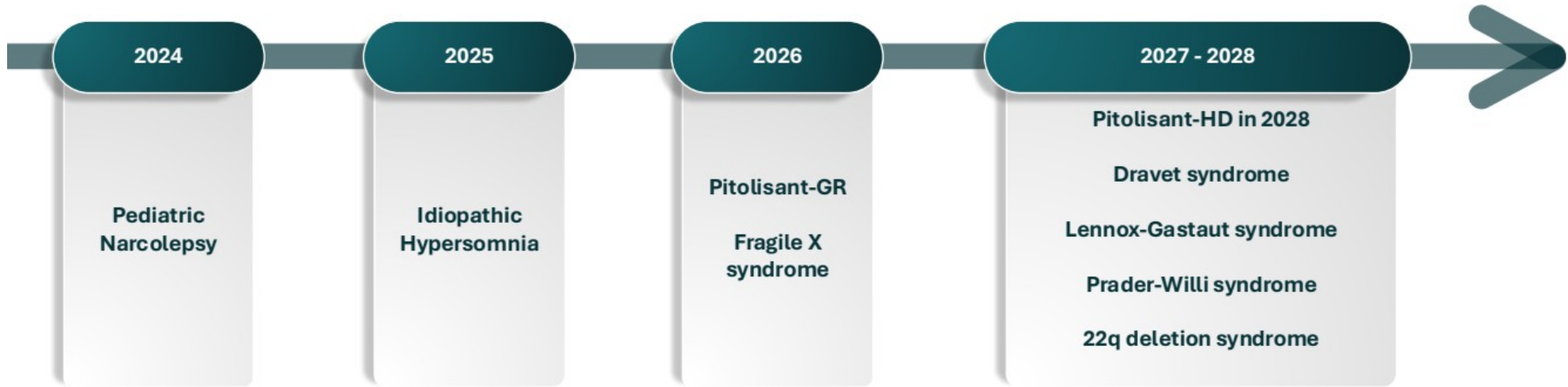
EPILEPSY

- EPX-100: validated MOA
- Pivotal registrational trial in Dravet syndrome; topline data 2026
- Pivotal Phase 3 trial in Lennox-Gastaut syndrome to initiate Q4
- ~8,000 patients in US for DS; ~40,000 patients for LGS

Innovation driving growth of the portfolio



Anticipated Delivery on Catalyst-Rich Pipeline



KEY TAKEAWAY One or more new product or indication launches each year over the next 5 years

Newrology: Building a Leading CNS Company

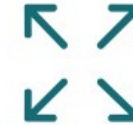
OUR FOUNDATION & PATH TO SUCCESS



Strong/durable **revenue growth for WAKIX®** in narcolepsy; **\$1B+** opportunity out to 2030



Organizational expertise and capacity to advance and deliver multiple therapeutic assets



Robust late-stage pipeline poised to deliver multi-billion-dollar revenue across **3 franchises**

Our CNS expertise and proven commercial model will be efficiently scaled to successfully launch multiple rare CNS indications

Delivering on a Promise to Patients

Our Vision

To become the leading patient-focused CNS company delivering innovative treatments to patients living with unmet medical needs



Chris
Narcolepsy Patient

Livingston
Fragile X syndrome Patient

Ciara
Dravet syndrome Patient

Potential to deliver innovative treatments to hundreds of thousands of patients

Driving Shareholder Value

\$1B+

Proven commercial product and growing

13

Development programs;
4 in Phase 3 by year end



\$3B+

Establishing leadership position in CNS

5

Anticipate 1 or more new product or indication launches each year over next 5 years

Catalyst-rich pipeline poised to deliver both near-term and long-term value creation



S L E E P / W A K E





HARMONY
BIOSCIENCES

OPENING REMARKS

SLEEP/WAKE FRANCHISE

NEUROBEHAVIORAL FRANCHISE

EPILEPSY FRANCHISE

CLOSING REMARKS

MANAGEMENT PANEL DISCUSSION

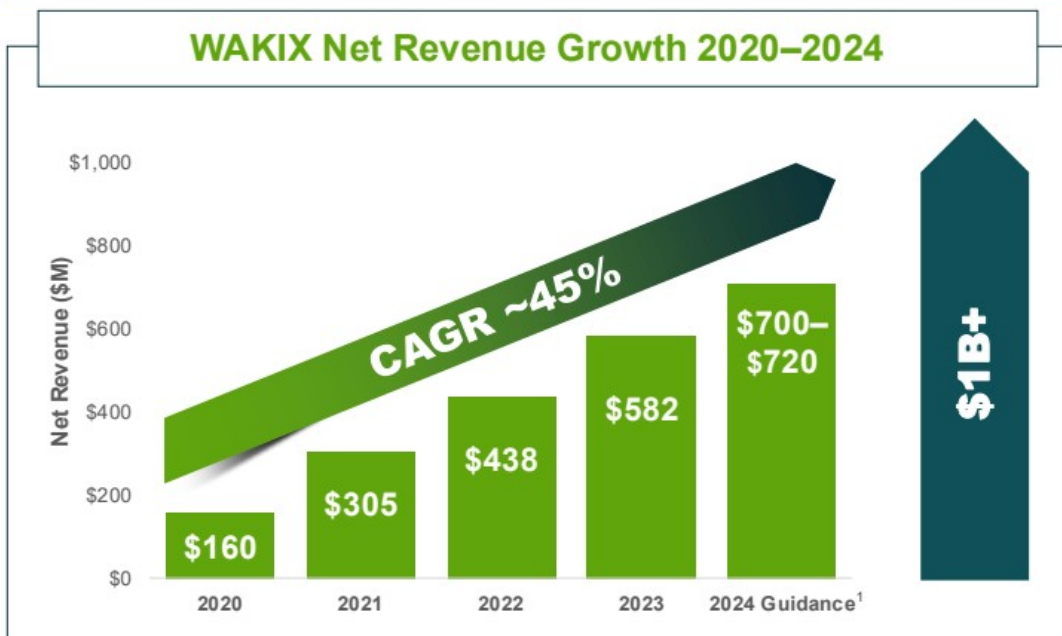
Q&A



JEFFREY DIERKS, MBA

Chief Commercial Officer
Harmony Biosciences

WAKIX[®] Is One of the Most Successful Rare/Orphan Launches With Demonstrated Durable Revenue Generation



DURABLE SALES GROWTH INTO YEAR FIVE ON THE MARKET WITH

CAGR of ~45%

REITERATES 2024 GUIDANCE:

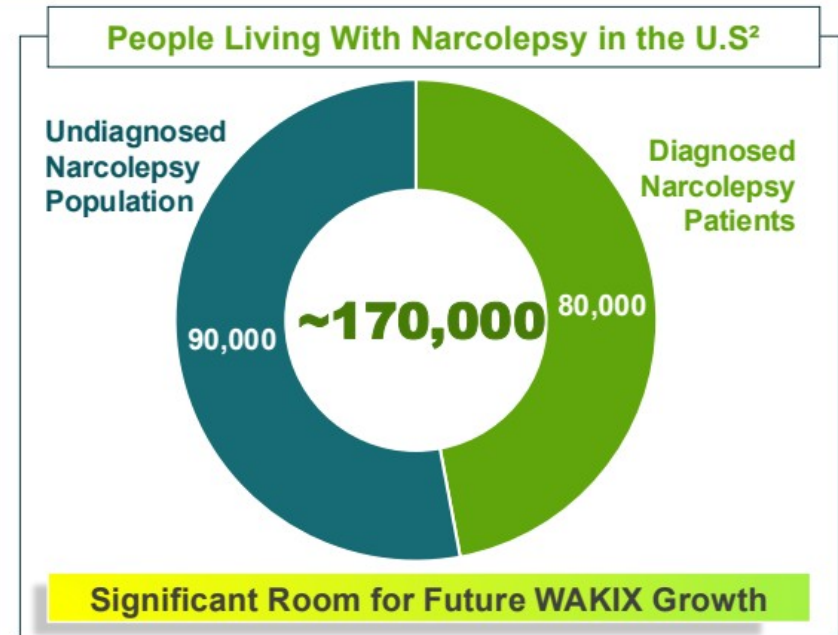
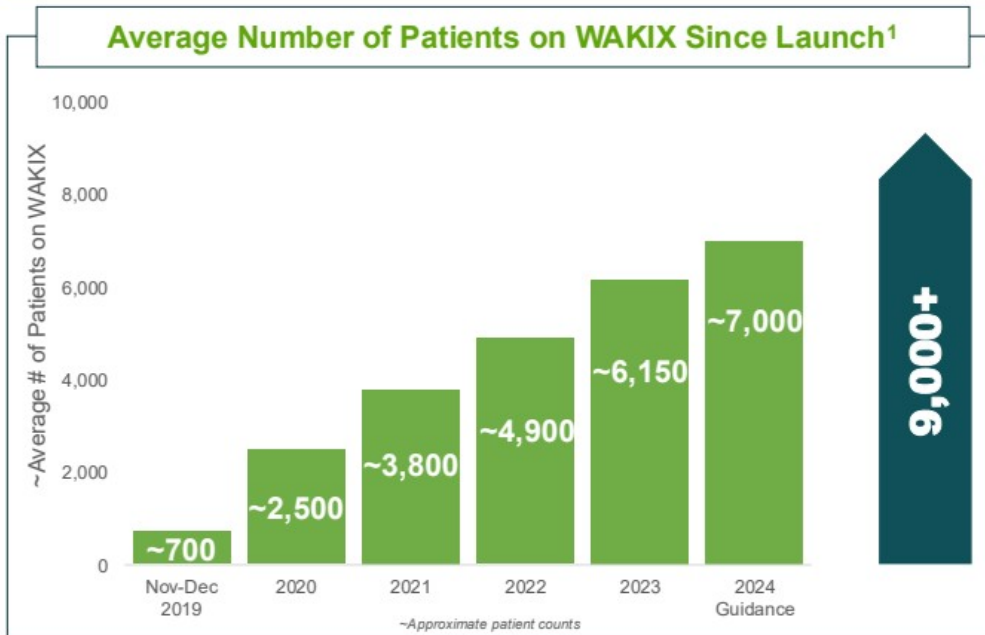
\$700–\$720M

**KEY
TAKEAWAY**

Confident in WAKIX being a potential \$1B+ opportunity in narcolepsy alone

1. Harmony Net Sales 2024 Net Sales Guidance of \$700-\$720M

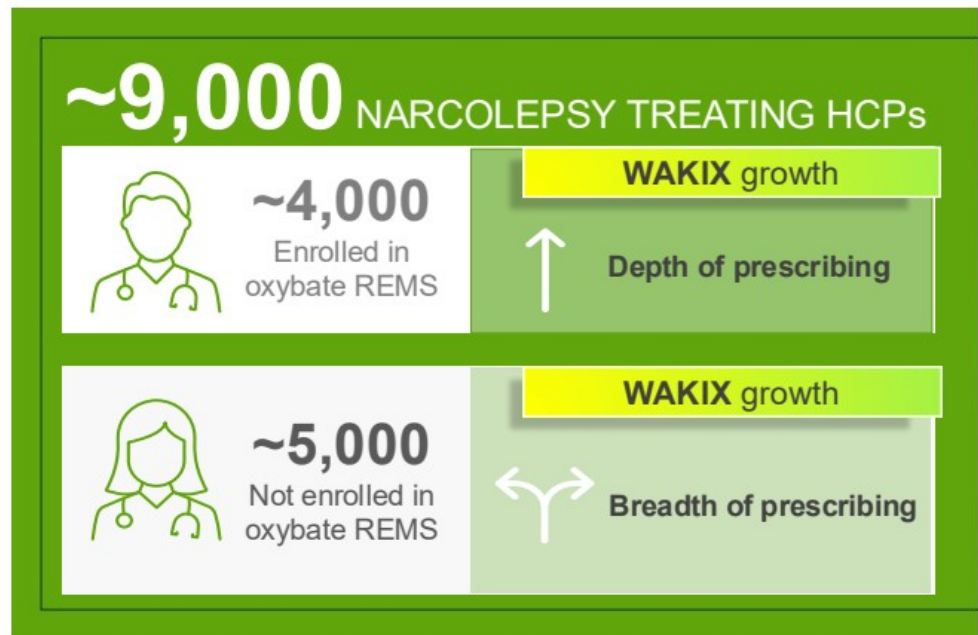
Meaningfully Differentiated Product Profile Key Driver in Strong Durable Growth in Patients on WAKIX®



KEY TAKEAWAY Strong durable patient growth, large remaining diagnosed patient opportunity

1. Net Patient Additions based on previously disclosed quarterly average number of patients on WAKIX; 2. <https://narcolepsy-network.org/> accessed Feb 2024; Harmony Biosciences, Data on file, April 2024

Unique Prescriber Dynamics Support Continued WAKIX® Growth, Opportunity for Next-Gen Pitolisant Assets in Narcolepsy



MORE UNIQUE PRESCRIBERS OF WAKIX THAN SODIUM OXYBATE

Unique feature as non-scheduled treatment is the highest performing driver and differentiator for WAKIX¹



KEY TAKEAWAY Growing prescriber base for WAKIX with access to full diagnosed patient opportunity

1. Harmony Market Research, May 2024

Core Attributes of WAKIX® Product Profile Align with Existing Unmet Needs in Narcolepsy

Top Unmet Needs in Narcolepsy

- **Non-scheduled treatment options**
- **More tolerable** treatment regimens
- **More effective** treatment options
- **Novel MOAs**
- **Once-daily dosing options**

WAKIX Product Profile*

- ✓ First and only FDA-approved **non-scheduled** treatment for narcolepsy
- ✓ **Established safety and tolerability profile**
- ✓ Approved for the **treatment of EDS or cataplexy in narcolepsy**



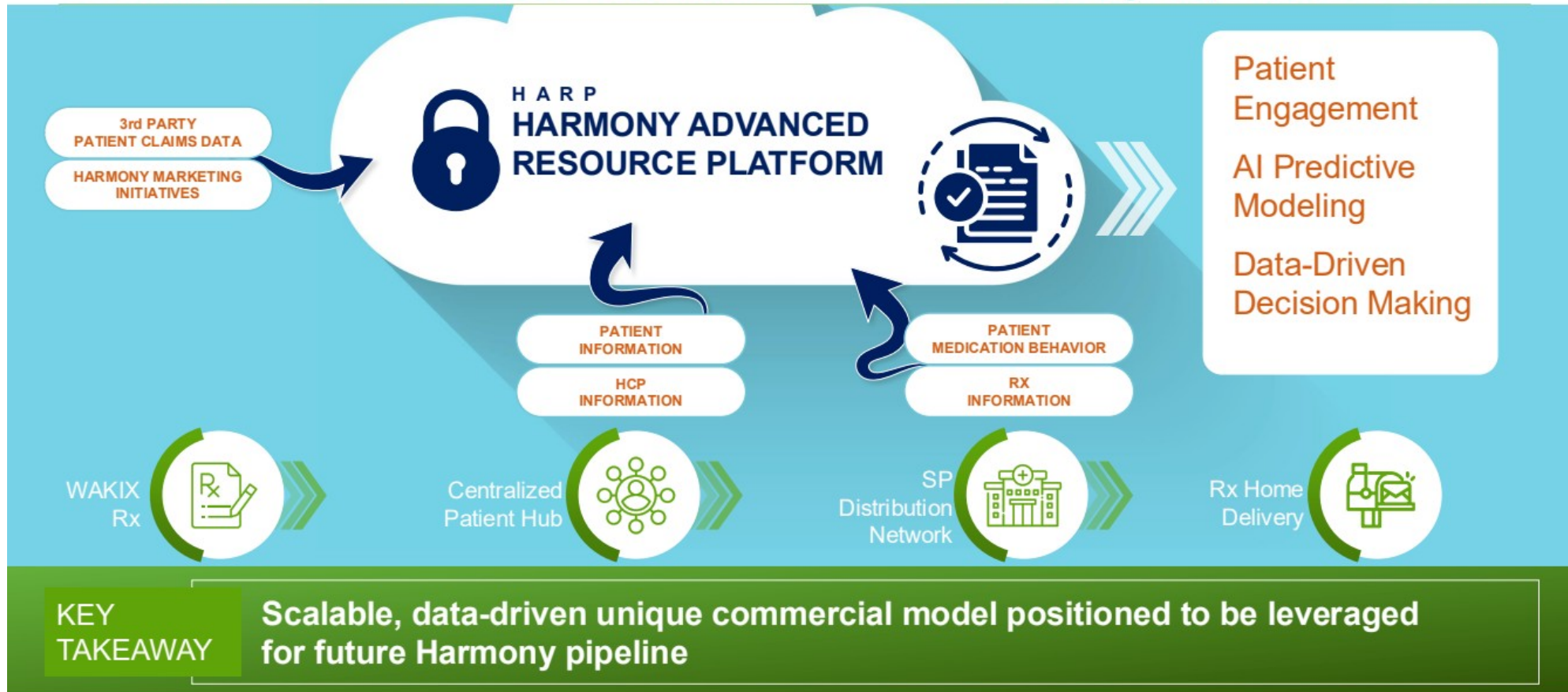
- ✓ First in class molecule with a **novel MOA**
- ✓ **Once-daily** dosing in the morning

KEY TAKEAWAY










WAKIX offers meaningfully differentiated product profile aligned to unmet needs

* Based on FDA-approved adult narcolepsy product labeling | Source: Harmony ATU, July 2018 (n=286); Versta Research, Know Narcolepsy Survey ("Know Narcolepsy"), October 2018; Unmet needs listed in descending order of importance stated by combined HCP and patient audience responses.

Unique Commercial Model Supporting WAKIX® Growth; Scalable For Next-Gen Formulations and Harmony Pipeline Assets



The Pitolisant Franchise: Patient-Centric Drug Development Building Our Leadership Position in Sleep/Wake

 Residual symptoms ¹				Higher dose, enhanced efficacy
 Report fatigue ²				Fatigue indication
 Products require titration	 Don't achieve clinical benefit	No titration	No titration	No titration
 Report GI disturbances ^{3,4}	 Cite nausea as a side effect ⁵	Gastro-resistant coating	Gastro-resistant coating	Gastro-resistant coating
 Cite frustration with side effects ⁶		Well tolerated; safety profile	Well tolerated; safety profile	Well tolerated; safety profile
 Only 1 FDA-approved treatment indicated for EDS and cataplexy		EDS and Cataplexy	EDS and Cataplexy	EDS and Cataplexy
 FDA-approved treatments are scheduled (CII – CIV)		Non-scheduled	Non-scheduled	Non-scheduled
NARCOLEPSY UNMET NEEDS		WAKIX®	Pitolisant-GR	Pitolisant-HD

1. McCullough et al. Novel treatment options in narcolepsy, Chicago Rush Memorial Center - SLEEP 2019 Abstract; 2. Droogelever et al. (2012). Severe fatigue in narcolepsy with cataplexy. Sleep, 21(2), 163-169; 3. Barateau et al., Dauvilliers, 2019; 4. Wang et al., 2023; 5. Zhan et al., 2023; 6. Postmarketing study; 6. Versta Research, Know Narcolepsy Survey ("Know Narcolepsy"), October 2018; * WAKIX attributes based on FDA-approved adult narcolepsy product labelling.

Pitolisant-HD: Viewed as a Superior Product Compared to WAKIX®, Anticipate Strong Uptake Across All Narcolepsy Patients

Physician Perception of Pitolisant-HD Target Product Profile (N=25)



Overview of Physician Feedback

- Pitolisant-HD offers significant improvements over WAKIX
- Improved efficacy addresses most pressing unmet need
- Fatigue indication could significantly increase utilization
- Anticipated high uptake of Pitolisant-HD — new, current and previous WAKIX patients

Physician Perceptions of Product Profile

Favorability vs. WAKIX

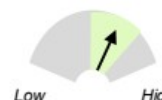
Rationale

EDS / Cataplexy



Enhanced efficacy viewed as the greatest differentiator

Improvement in Fatigue



Unique indication seen as value driver for select HCPs

Overall



KEY TAKEAWAY

Pitolisant-HD opportunity: grow the patient base, extend the pitolisant franchise

EDS: Excessive Daytime Sleepiness; HCP: Health Care Provider; HD: High-Dose. | Source: Physician Interviews; ClearView Analysis.

Favorable Market Access Landscape Outlook for Pitolisant-HD Pre- and Post-WAKIX® LOE

Management of Pitolisant-HD Pre- and Post-WAKIX LOE (N=7)

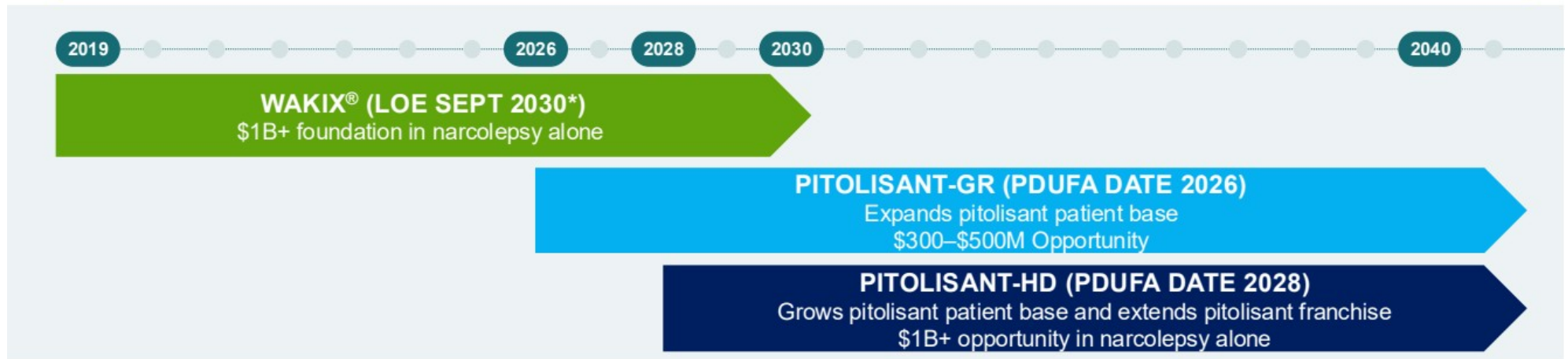
	Anticipated Management of Pitolisant-HD
PRE-WAKIX LOE	Anticipate patient access to pitolisant-HD without WAKIX step-edit ¹
POST-WAKIX LOE	
De Novo Pitolisant	Expected step through generic pitolisant ²
	Access to pitolisant-HD with fatigue validated by measurement tool used in pitolisant-HD clinical trial
Pitolisant-HD Patients	Patients with WAKIX/pitolisant experience will have access to pitolisant-HD (will not be stepped through generic pitolisant)
WAKIX Patients	
Previous WAKIX Experience	

KEY TAKEAWAY

- Anticipated access to pitolisant-HD without restrictions Pre-WAKIX LOE
- Anticipated access to pitolisant-HD for majority of patients Post-WAKIX LOE

1. Assume price parity to WAKIX; 2. Assumes generic is priced significantly below WAKIX. | GI: Gastrointestinal; HCP: Healthcare Provider; LOE: Loss of Exclusivity. Source: Payer Interviews; ClearView Analysis.

Pitolisant Franchise Poised to Drive Durable Patient and Revenue Growth to the Mid-2040s



- Two meaningfully differentiated product profiles building off WAKIX with PDUFAs prior to LOE
- Provisional patents filed out to 2044 to extend durable patient and net revenue growth
 - Pursuing other indications (IH, DM1) to drive incremental patient, net revenue growth

KEY TAKEAWAY

- Pitolisant franchise strengthens leadership position in sleep/wake
- Poised to deliver durable patient growth and significant revenue to the mid 2040s

*Based on pediatric exclusivity



HARMONY
BIOSCIENCES

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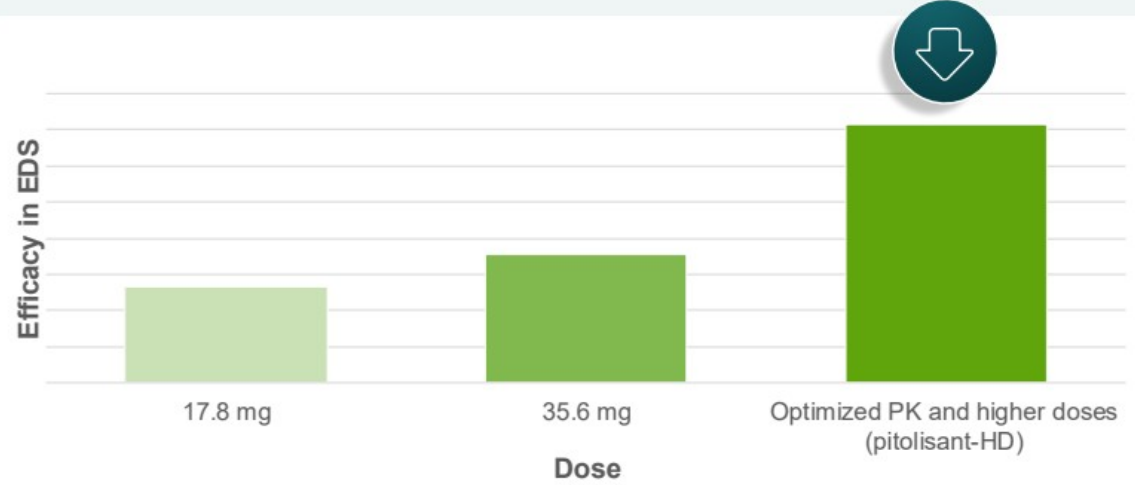
KUMAR BUDUR, MD, MS
Chief Medical & Scientific Officer
Harmony Biosciences

Why Are We Developing Pitolisant-HD?



7 to 8 out of 10 patients continue to experience EDS despite being on treatment¹

Better Efficacy at Higher Exposure of Pitolisant Addresses an Important Unmet Medical Need for Patients with Narcolepsy²



KEY TAKEAWAY Better efficacy at higher doses supported by evidence for exposure response from pitolisant clinical trials

1. McCullough et al. Novel treatments options in narcolepsy, Chicago Rush Memorial Center - SLEEP 2019 Abstract; 2. Illustrative based on pitolisant data.

Pitolisant: Generally Safe at Higher Doses

Phase 1b Safety Study

- Randomized, double-blind, placebo-controlled
- N = 15 subjects per cohort
- Assessing safety, tolerability, pharmacokinetics
- Effect on QT interval

Primary Objective

Safety and tolerability of pitolisant after 14-day multiple oral doses ranging from 60 mg/day to 180 mg/day in healthy male subjects

Initial Findings¹






- Safety profile similar to the established safety profile of WAKIX[®] at repeat doses of pitolisant up to 180 mg
- No serious AEs observed
- No new safety or tolerability issues
- Full data to be presented at upcoming scientific meeting

KEY TAKEAWAY

- Established safety up to 5X WAKIX highest labeled dose
- Safety profile similar to the established safety profile of WAKIX

1. Data on file.

Pitolisant High-Dose (HD): Differentiated Profile

	Proof Points/Development Plans	Differentiated Features
 Higher Dose	Up to 2x compared to WAKIX®	<ul style="list-style-type: none"> Better efficacy in EDS/cataplexy Higher POS for fatigue
 Optimized PK Profile	Pilot PK study	<ul style="list-style-type: none"> Higher bioavailability than WAKIX Decreased variability
 Gastro-Resistant Coating	Confirmed with dissolution assays	Designed to address GI issues
 Differentiated Indications	<ul style="list-style-type: none"> Fatigue in Narcolepsy Sleep inertia in IH EDS and Fatigue in Myotonic Dystrophy 	<ul style="list-style-type: none"> First indication for these symptoms Differentiated label
 IP	Provisional patent filed	Potential IP protection until 2044

KEY TAKEAWAY

Pitolisant-HD designed to address unmet needs with potential IP until 2044

Pitolisant-HD: Path to PDUFA



KEY
TAKEAWAY

On-track for PDUFA in 2028

Idiopathic Hypersomnia: Building Strong Benefit/Risk Proposition

IH: DISORDER WITH HIGH UNMET NEED



REAL WORLD DATA
and experience from a large clinic



FAVORABLE BENEFIT/RISK PROFILE



COMPELLING TOTALITY OF DATA FROM INTUNE STUDY
a Phase 3 pivotal study in IH



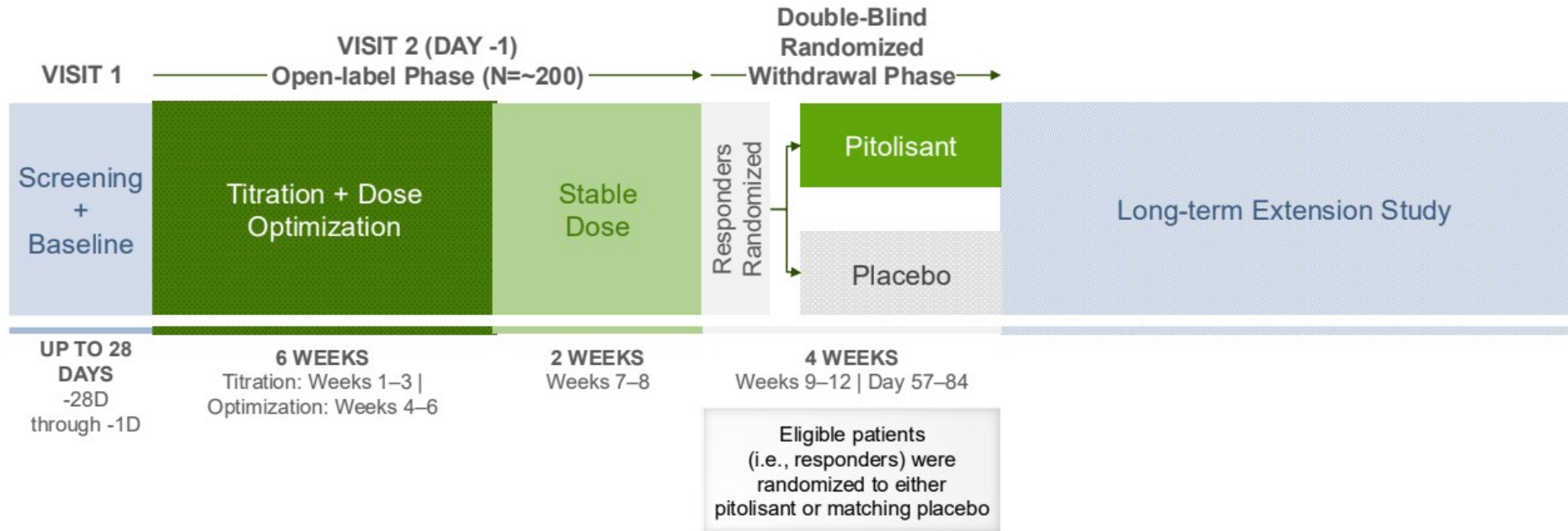
ESTABLISHED SAFETY
Non-scheduled and simple dosing regimen



KEY TAKEAWAY

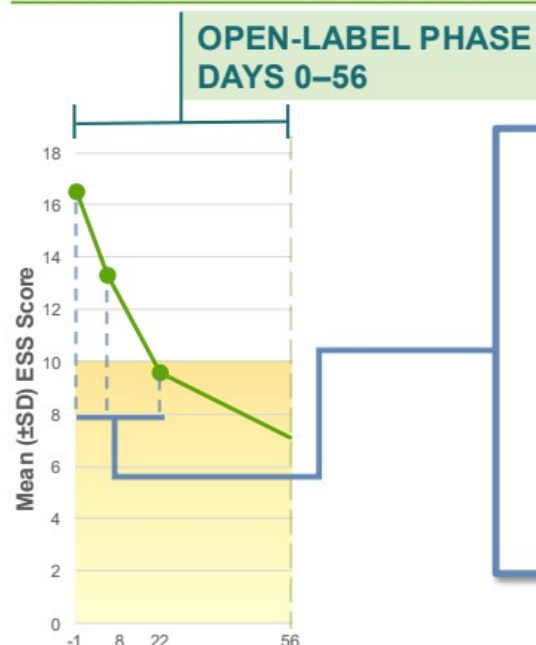
On-track for sNDA submission in 4Q 2024

Pitolisant Study Design in IH: INTUNE Study



Harmony Biosciences data on file.

Strong and Durable Improvement in EDS in Patients With IH (As Measured by ESS)



STRONG EFFICACY RESPONSE

- ~3-point decline within first week
- By day 22, mean ESS score in normal range
- Mean improvement in ESS score of 9.4 points by end of open-label phase (~5x clinically meaningful difference)
- Over response rate of 83% as defined by a 3-point improvement in ESS

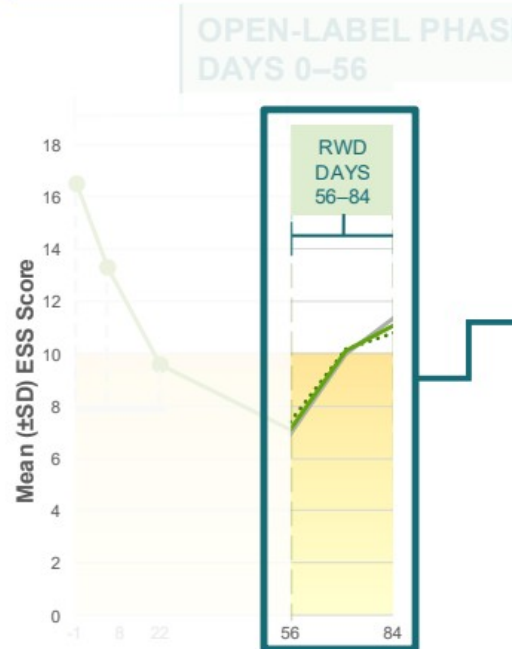
— Pitolisant

KEY
TAKEAWAY

Robust response to pitolisant during the Open-Label Phase

Harmony Biosciences data on file.

Randomized Withdrawal Period



WHAT HAPPENED DURING THE RWD PERIOD?

Persistence of efficacy in placebo arm:

- Placebo arm did not worsen as expected, even 4 weeks after the last dose of pitolisant
 - Modulation of H3 receptors and downstream effects

Outliers in pitolisant arm:

- Few outliers on pitolisant worsened and thought they were on placebo (confirmed via Exit Interviews), indicating the possibility of expectation bias
- Benign AE profile of pitolisant



KEY TAKEAWAY

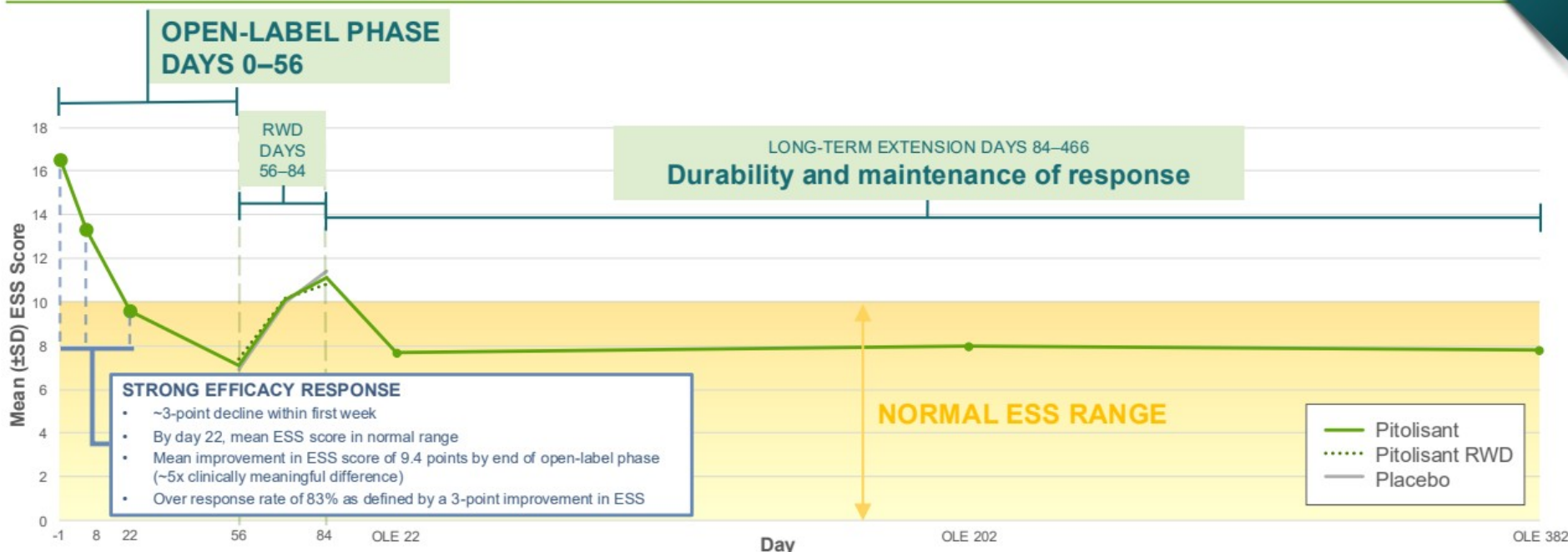
- Persistence of efficacy in placebo arm; prolonged pharmacodynamic effect
- Outliers in pitolisant arm

Harmony Biosciences data on file.

Strong and Durable Improvement in EDS in Patients With IH (As Measured by ESS)



NEW DATA



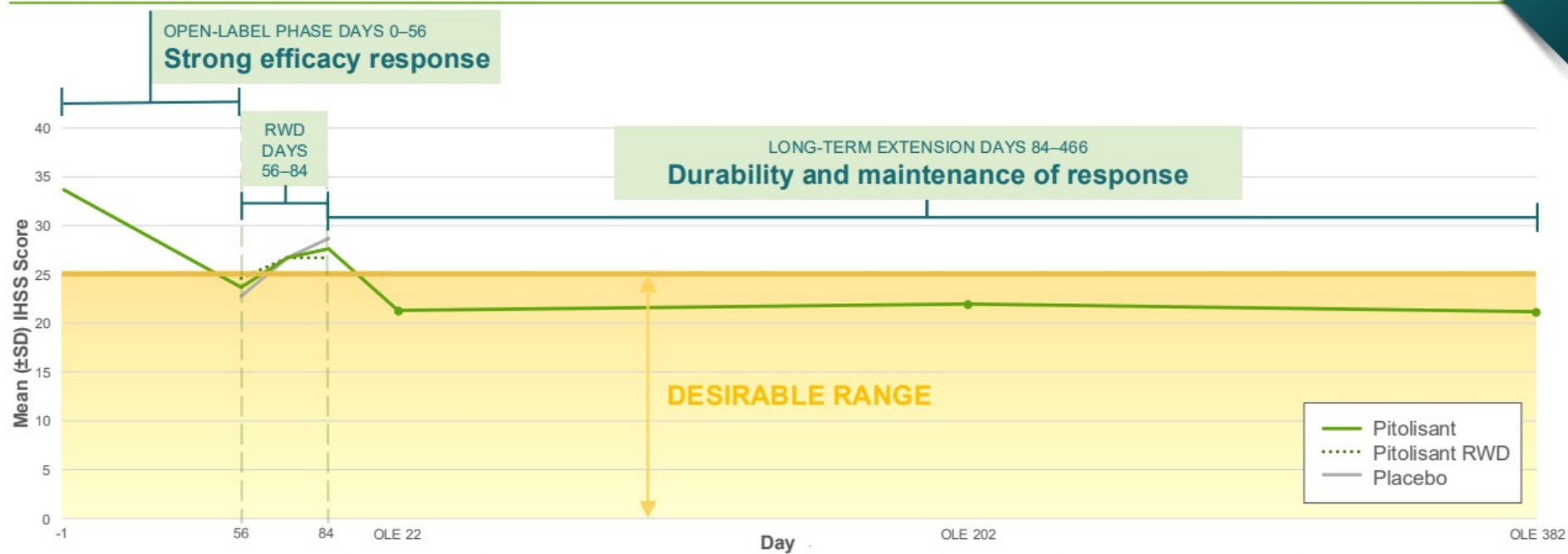
KEY TAKEAWAY The mean ESS Score stayed within the normal range throughout the long-term extension period

Harmony Biosciences data on file.

Strong and Durable Improvement in Symptoms of IH (As Measured by IHSS)



NEW DATA



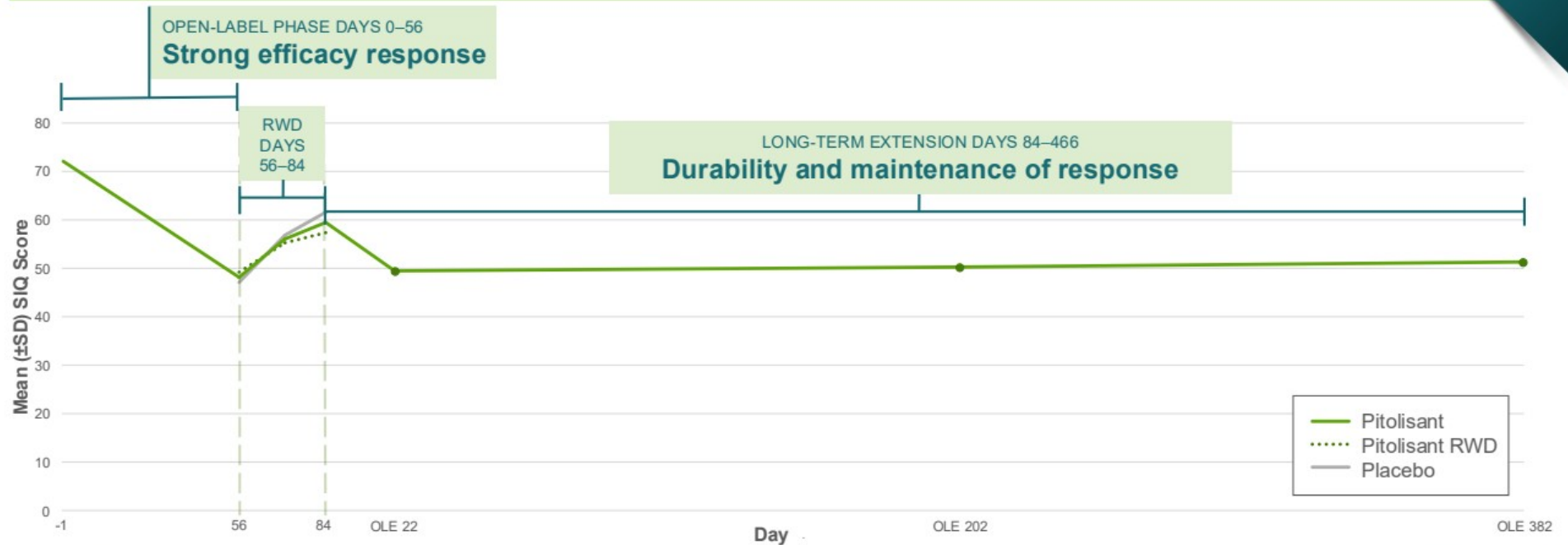
KEY TAKEAWAY The mean IHSS Score stayed within the desirable range throughout the long-term extension period

Harmony Biosciences data on file.

Strong and Durable Improvement in Sleep Inertia (As Measured by SIQ)



NEW DATA



KEY TAKEAWAY

The mean SIQ Score demonstrated sustained improvement throughout the long-term extension period

Harmony Biosciences data on file.

Pitolisant Use in Idiopathic Hypersomnia: A French Study

A real-world independent database analysis (SOMNOBANK) conducted by Yves Dauvilliers

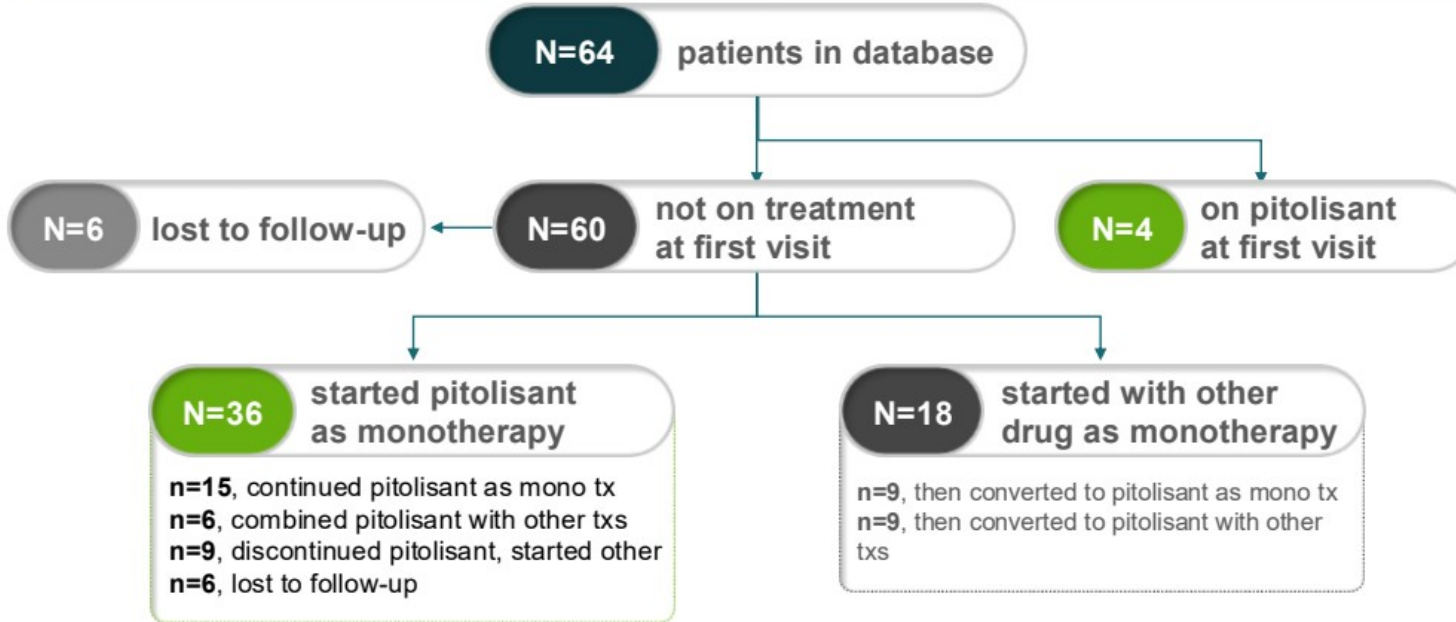


The “Somnobank” Protocol Cohort

N=64 patients with idiopathic hypersomnia treated with pitolisant between 2010–2024

314 total clinical visits were performed

SOMNOBANK Real World Database Results



TAKEAWAY

38%

24/64 pitolisant monotherapy

23%

15/64 pitolisant adjunctive treatment

61%

39/64 on pitolisant

KEY TAKEAWAY

More than 60% of IH patients experienced benefit with pitolisant

Bioprojet Compassionate Use (ATU) Study: ESS Total Score

Characteristic	
ESS Score at Baseline	
n	61
Mean (SD)	16.2 (3.80)
Mean of Post-Baseline ESS Scores	
n	27
Mean (SD)	12.3 (4.67)
Change from Baseline ESS Score to Mean of Post-Baseline ESS Scores	
n	26
Mean (SD)	-3.6* (3.80)

*Reduction of 2 points is clinically meaningful; AASM Guidelines

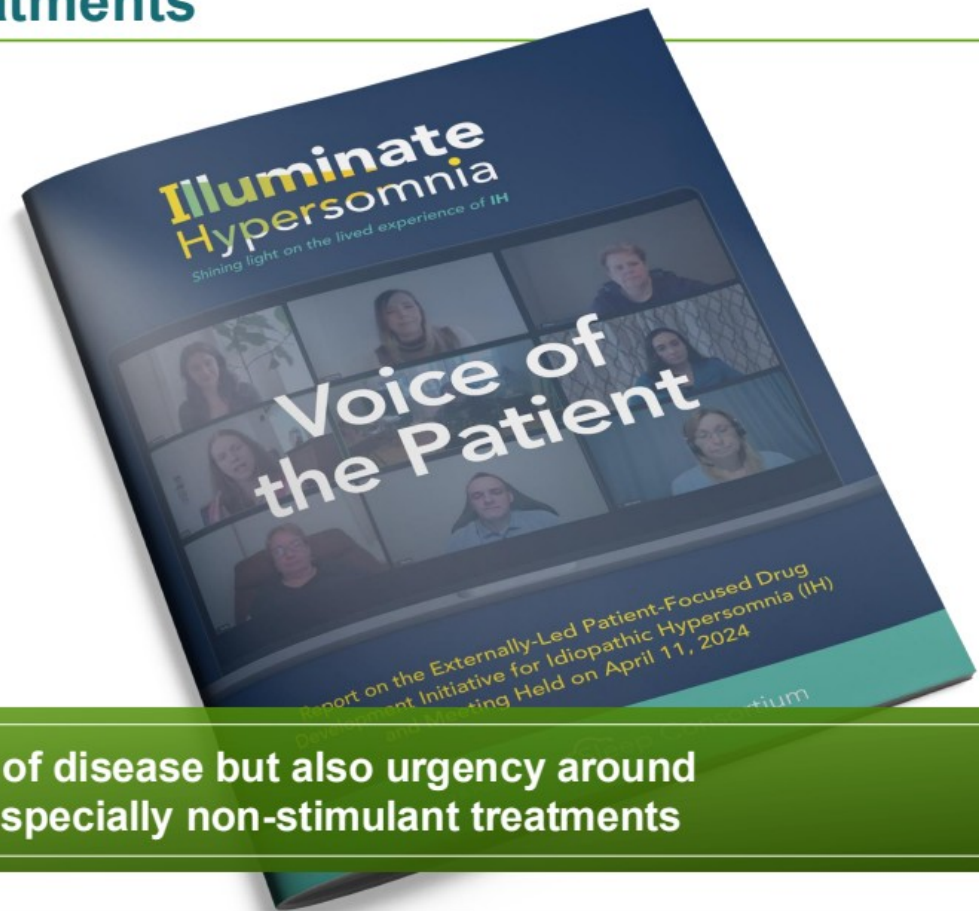
KEY TAKEAWAY

Real-world evidence in support of the efficacy of pitolisant in patients with IH

Bioprojet data on file.

Voice of the Patient Report: Highlights Patient Burden and the Need for Non-Stimulant Treatments

- Externally Led Patient-Focused Drug Development Initiative; April 2024
- Attended by FDA, Advocacy and other stakeholders
 - Need for more research and awareness
 - Desire for non-stimulant treatments
 - Frustration with current treatments
 - Hope for new treatments
- Final report: FDA input
 - Serves as reference for Agency highlighting need for new treatment options



KEY TAKEAWAY

Highlights not just the burden of disease but also urgency around the need for new treatments, especially non-stimulant treatments

Pitolisant: Strong Case for Approval Proposed in the sNDA submission for IH

sNDA SUBMISSION

ON-TRACK FOR
SUBMISSION
4Q 2024

- **TOTALITY OF DATA FROM THE PHASE 3 INTUNE STUDY**
Open-label, randomized withdrawal and long-term extension
- **REAL WORLD AND CLINICAL EXPERIENCE DATA**
- **BENEFIT / RISK PROFILE**
Non-scheduled, unique safety profile and simple dosing regimen
- **VOICE OF THE PATIENT REPORT**

BP1.15205: Potential Best-in-Class Orexin 2 (OX2R) Agonist

Next wave of
innovation in
Sleep/Wake

TEIJIN

Tokyo-based Pharma, innovator (TPM-1116)

COLLABORATION WITH PROF. YANAGISAWA

Discovered orexin receptors and implications on sleep/wake

UNIQUE STRUCTURE/CHEMICAL SCAFFOLD

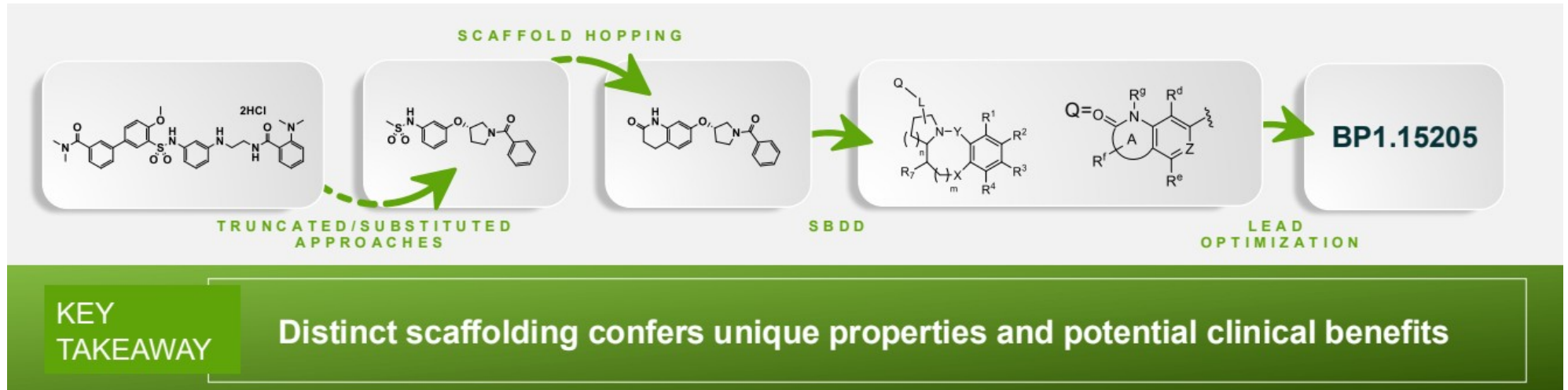
Leveraged lessons learned from other OX2R agonists

CLINICAL POTENTIAL

- Potency and selectivity
- Once-daily dosing

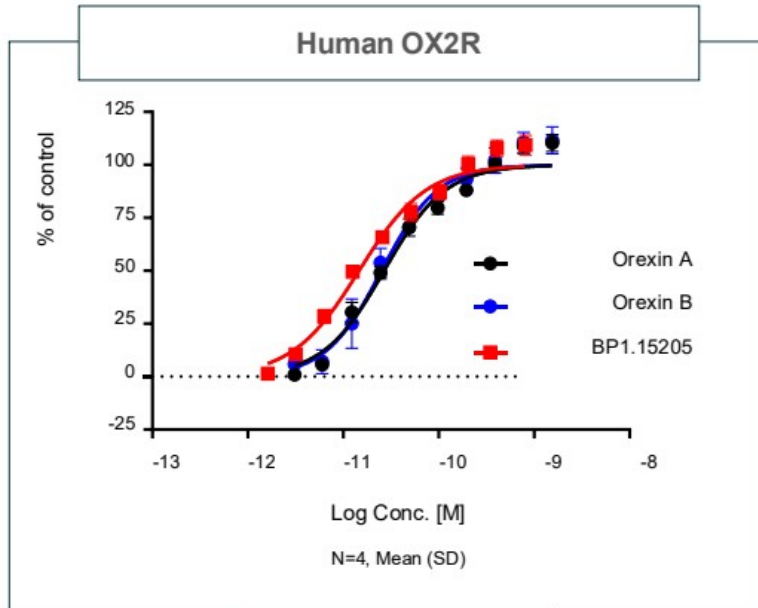
Discovery of BP1.15205: Novel Chemical Scaffolding

- Differentiated structure compared to the usual pyrrolidine sulfonamide and bicyclic moieties
- Distinct scaffolding from known ligands with drug-like properties
 - Confers unique properties and potential clinical benefits
 - Efficient and expedited synthesis



Bioprojet data on file.

In Vitro Pharmacology



- Highly potent compound which has shown concentration-dependent hOX2R agonistic activity
- Minimal inter-species difference in the agonistic activity between hOX2R, mOX2R and mkOX2R
- Greater than 600-fold selectivity for hOX2R over hOX1R
- Very high selectivity (>1,000) over more than 150 biological targets

	Human OX2R EC ₅₀ (nM)	Mouse OX2R EC ₅₀ (nM)	NHP OX2R EC ₅₀ (nM)
Orexin-A	0.027	0.041	0.047
Orexin-B	0.025	0.028	0.014
BP1.15205	0.015	0.015	0.030

KEY TAKEAWAY

High potency at OX2R demonstrated across multiple species

Bioprojet data on file.

BP1.15205: Most potent OX2R Agonist (*In Vitro* Pharmacology Data)

**NEW
DATA**

Select DMPK parameters	HRMY/BP ¹ BP1.15205	Centessa ² ORX750	Eisai ³ E2086	Takeda ⁴ TAK-861	Takeda ⁵ TAK-925	Takeda ⁴ TAK-994	Alkermes ⁶ 2680	Jazz JZP441
Potency (hOX2R, EC50)	0.015 nM	0.11 nM	2.3 nM	2.5 nM	5.5 nM	19 nM	Not reported	Not reported
Selectivity for hOX2R vs hOX1R	> 600x	9800x	> 2000x	3000x	> 5000x	Not reported	Not reported	Not reported
Dosing regimen	Potential for once-daily oral dosing	Not reported	Not reported	Twice a day dosing	IV dosing	Twice a day dosing	Once a day dosing	Not reported

KEY TAKEAWAY **The most potent orexin-2 receptor agonist (based on publicly available data)**

1. Bioprojet/Harmony data on file; 2. Lack et al., World Sleep 2023, abstract; 3. Hatanaka et al., ACNP 2022, poster; 4. Kimura et al., World Sleep 2023, abstract; 5. Yukitake et al., Pharmacol Biochem Behav. 2019, publication; 6. Clinicaltrials.gov.

BP1.15205 Clinical Potential: Novel Chemical Structure, High Potency / Good Selectivity and PK Profile

Potent on-target effects



High potency with potential efficacy in various sleep disorders and other indications



Highly desirable QD dosing



Potentially better AE profile



Potential approval in early 2030s



Potential for combination drug development:
pitolisant-HD and BP1.15205



KEY TAKEAWAY Potential best-in-class OX2R agonist with possibility for broad clinical utility; on track for IND submission mid-2025



Sleep/Wake Franchise Catalysts

- ✓ **Q4 2024** – sNDA submission for pitolisant in IH; anticipated PDUFA Q2/Q3 2025
- ✓ **Mid-2025** – IND submission for OX2R agonist (BP1.15205)
- ✓ **2026** – PDUFA for pitolisant-GR in narcolepsy
- ✓ **2028** – PDUFA for pitolisant-HD in narcolepsy



BRUCE CORSER, MD, FAASM
President and Medical Director
Intrepid Research and Sleep
Management Institute



KUMAR BUDUR, MD, MS
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Harmony Biosciences

F I R E S I D E C H A T





N E U R O B E H A V I O R A L



HARMONY
BIOSCIENCES

Neurobehavioral Franchise: Addressing a High Unmet Medical Need

ACQUISITION OF ZYNERBA BROUGHT IN ZYN-002

Innovative product profile; purely synthetic cannabidiol (CBD)



MARKET OPPORTUNITY

- ~80,000 patients in the US with FXS and similar for 22q
- Worldwide rights



LEAD PROGRAM IN FRAGILE X SYNDROME (FXS)

- Currently in Phase 3 pivotal study
- On track for topline data mid-2025
- Plan to pursue pivotal Phase 3 trial in 22q deletion syndrome (22q)

HIGH UNMET NEED

No approved treatments for both FXS and 22q



HARMONY
BIOSCIENCES

OPENING REMARKS

SLEEP/WAKE FRANCHISE

NEUROBEHAVIORAL FRANCHISE

EPILEPSY FRANCHISE

CLOSING REMARKS

MANAGEMENT PANEL DISCUSSION

Q&A



CARRIE BUCHANAN, MD

*Developmental-Behavioral Pediatrician
Greenwood Genetic Center*

Fragile X Syndrome

*The Endogenous Cannabinoid System and
the Role of CBD in Fragile X Syndrome*

Carrie Buchanan, MD

Fragile X Program Director
Greenwood Genetic Center

Oct. 1, 2024



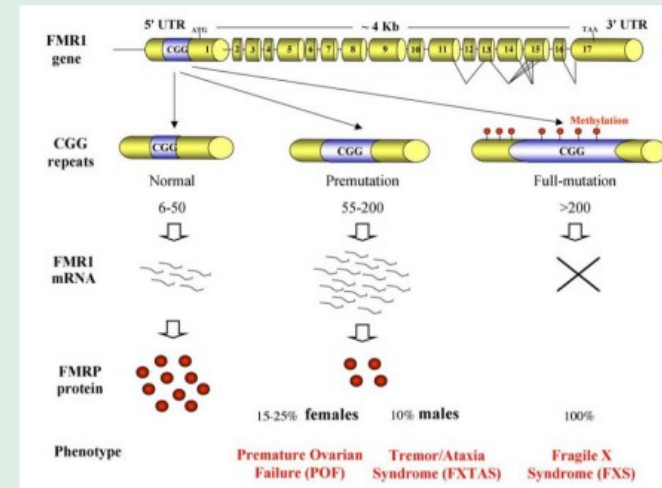
www.GGC.org

Fragile X Syndrome(FXS)

- X-linked, genetic condition
 - DNA (gene) → mRNA → Protein
 - FMR1 → FMR1 mRNA → FMRP
 - The gene (FMR1) is shut off by methylation, so the gene product (FMRP) is not made
- Caused by a CGG repeat expansion >200 repeats in the promoter region of *FMR1*
- Full mutation results in **hypermethylation** and **silencing of *FMR1* promoter** (turns off gene) and an absence or reduction of its gene product FMRP
- FMRP plays a very important role in early brain development

FMR1 = Fragile X messenger ribonucleoprotein 1 gene
 FMRP = Fragile X messenger ribonucleoprotein

CGG expansion > 200 repeats in the promoter region of *FMR1* → methylation of gene → silencing of *FMR1* promoter → absence/reduction of FMRP



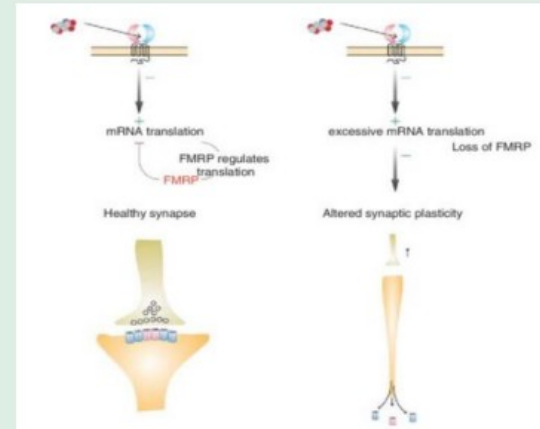
FMRP (fragile x messenger ribonucleoprotein)

Carries mRNA from the nucleus to areas of the cell where proteins are made (translation)

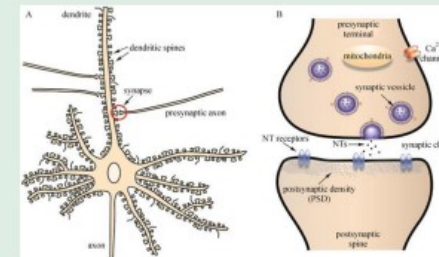
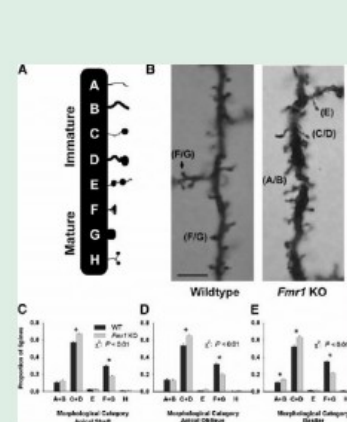
Largely repressive effect on translation (meaning, an absence of FMRP causes an over-production/abundance of many proteins)

Absence leads to dysregulation of several proteins involved in neuron formation and synaptic function

Over 1,000 known target mRNAs of FMR1



Repressive effect on translation = excessive protein production and altered synapse






Loss of FMRP results in immature dendritic spine architecture, thought to be a pruning deficit

Fragile X Syndrome (FXS)




- Neurodevelopmental disorder
- Males are more frequently affected than females, and often with higher severity (XX in females is protective)
- Most common cause of inherited intellectual disability (low IQ)
- Large impact on behavior and functional abilities
 - Daily living skills, communication, and social-emotional skills
- Most commonly known single gene cause of autism spectrum disorder (ASD)
- High levels of anxiety (social anxiety, specific phobias and generalized anxiety), social avoidance, irritability, and hyperarousal/overstimulation
 - Very common and often disabling

Fragile X syndrome
Symptoms can be found in the major categories below.




Some intelligence issues include:

 Low intelligence quotient (IQ).	 Delay of nonverbal communication.	 Problems with math.
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Some physical features include:

 A long, narrow face.	 A large forehead.	 Crossed eyes.
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Some behavioral issues, like:

 Social anxiety and shyness.	 Attention-deficit/hyperactivity disorder (ADHD).	 Poor eye contact.
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Fragile X Syndrome Behavioral Phenotype

Phenotype = observable symptoms resulting from genotype (genetics)

- poor eye contact
- social avoidance
- preference for solitary activities
- excessive shyness
- anxiety (social anxiety, generalized anxiety, specific phobias)
- hand flapping/stimming
- hand biting
- aggression
- irritability
- attention deficits
- hyperactivity
- impulsivity
- hyperarousal
- oversensitive to sensory stimuli
- autism spectrum disorder

Sensitive to sensory stimuli



Hand/finger biting



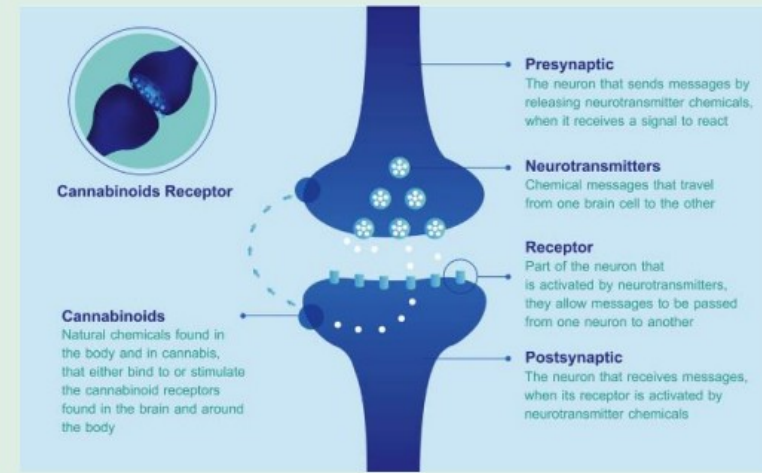
Anxiety/Irritability



Poor eye contact

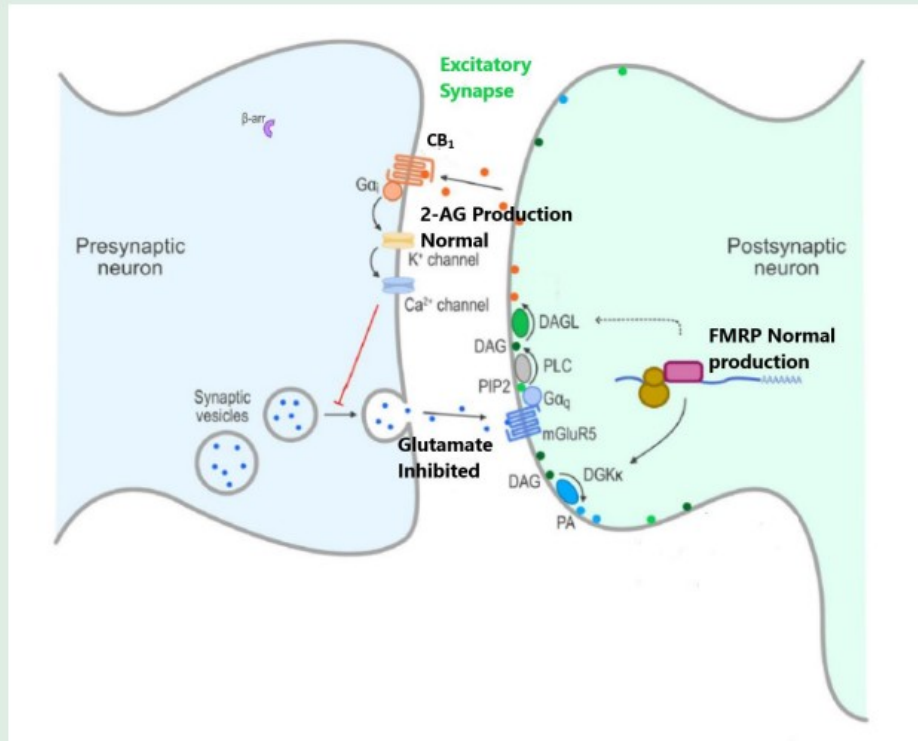
Endocannabinoid System (ECS)

- Major role in neuronal (brain) development and function:
 - Facilitates synaptic homeostasis (balance of excitatory and inhibitory neurotransmitters)
 - Neuronal plasticity (neural growth/reorganization)
- Two parts (neurotransmitters and receptor):
 - Two endocannabinoids = neurotransmitters
 - 2-AG
 - AEA
 - Cannabinoid receptor (CB1)
 - Major endocannabinoid receptor in brain
 - Present in neocortex, cerebellum, forebrain structures, basal ganglia and limbic system
 - Involved in learning, memory, executive function, social interaction, behavior and emotion



- Endo = endogenous = internal/inside the body/naturally produced
- Central role in neuronal development (development of the brain/neurons and cognitive function)
- Central role in the pathogenesis of FXS

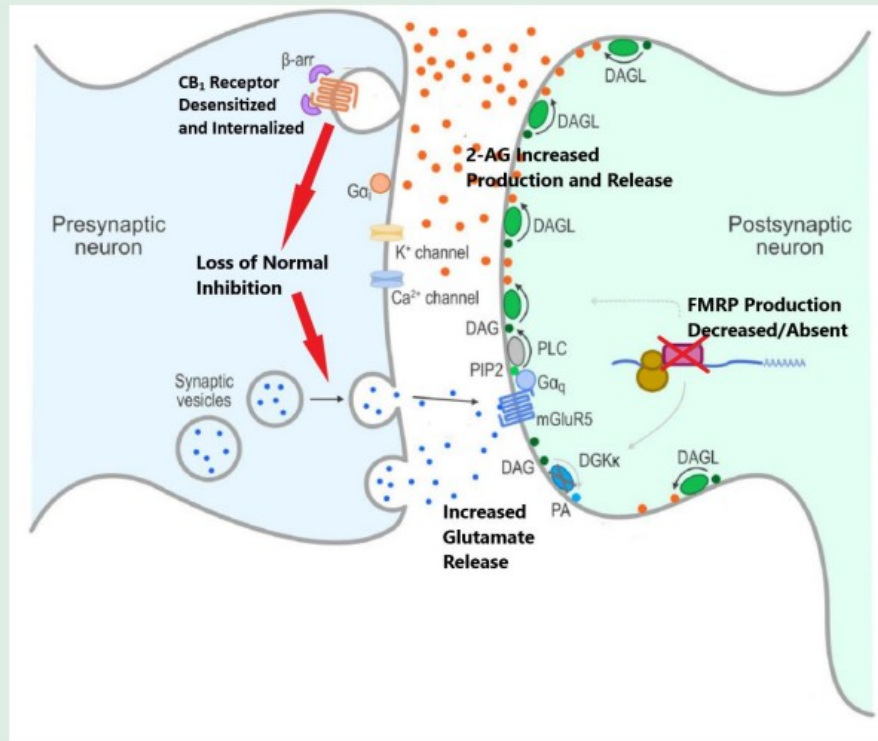
Normal Endocannabinoid System



When the *FMR1* gene functions normally, FMRP is produced at adequate levels

- 2-AG is produced normally and released and binds to the CB₁ receptor
- This inhibits glutamate release
 - Glutamate is **excitatory** so may produce symptoms like social avoidance, anxiety, and irritability
 - **Inhibition of glutamate release may prevent these**

Endocannabinoid Dysfunction in FXS

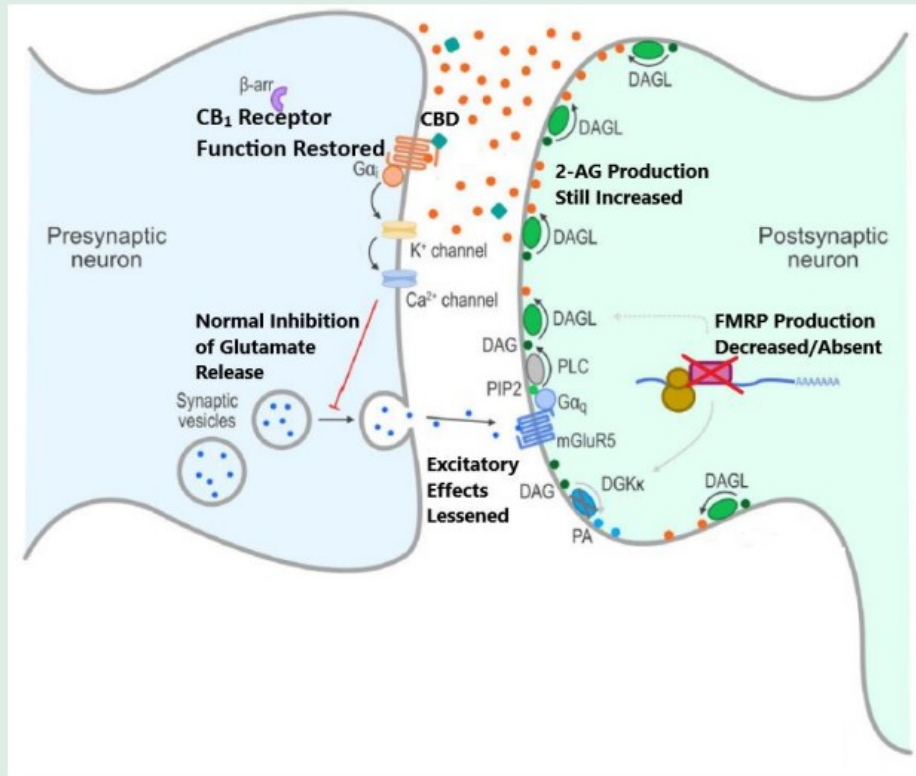


When the *FMR1* gene function is abnormal in FXS, FMRP production is decreased or absent

2-AG production and release increases

- This causes the CB₁ receptor to become desensitized and internalized
- Normal inhibition of glutamate doesn't occur
 - Excitatory glutamate is released
 - This may increase behavioral symptoms in Fragile X patients

Proposed Mechanism of Cannabidiol in Fragile X Syndrome in the ECS



CBD works to bring the endocannabinoid system closer to normal function

- 2-AG production is still increased
- FMRP production is still decreased or absent
- CBD can modulate the CB₁ receptor
 - Normal inhibition of glutamate is restored
 - Excitatory glutamate effects lessened
 - **Leads to reduction of behavioral symptoms**

Role of Endocannabinoid System and Cannabidiol Therapy in FXS

Published in the *Journal of Neurodevelopmental Disorders*

Palumbo et al.
Journal of Neurodevelopmental Disorders (2023) 15:1
<https://doi.org/10.1186/s11689-023-09475-z>

Journal of
Neurodevelopmental Disorders

REVIEW

Open Access

Role of the endocannabinoid system in fragile X syndrome: potential mechanisms for benefit from cannabidiol treatment



Joseph M. Palumbo¹, Brian F. Thomas², Dejan Budimirovic^{3,4}, Steven Siegel⁵, Flora Tassone^{6,7}, Randi Hagerman^{6,8}, Christopher Faulk⁹, Stephen O'Quinn^{1*} and Terri Sebree¹

The article can be accessed online at the *Journal of Neurodevelopmental Disorders* at <https://rdcu.be/c25fu>.
J Neurodev Disord. 2023 Jan 9;15(1):1. doi: 10.1186/s11689-023-09475-z.

- "...Multiple lines of evidence suggest a central role for the endocannabinoid system (ECS) in the neuronal development and cognitive function and in the pathogenesis of fragile X syndrome (FXS)."
- "FXS is caused by deficiency or absence of FMRP [FRM1 protein]...The absence of FMRP downregulates the ECS signaling, which has been implicated in FXS pathogenesis."
- "Consistent with these proposed mechanisms of action of cannabidiol in FXS, in the CONNECT-FX trial the transdermal cannabidiol gel, ZYN002, was associated with improvements in measures of social avoidance, irritability, and social interaction, particularly in patients who are most affected, showing $\geq 90\%$ methylation of the FMR1 gene."

CONNECT-FX Data Published in the *Journal of Neurodevelopmental Disorders*

Berry-Kravis et al.
Journal of Neurodevelopmental Disorders (2022) 14:56
<https://doi.org/10.1186/s11689-022-09466-6>

Journal of Neurodevelopmental Disorders

RESEARCH **Open Access**

A randomized, controlled trial of ZYN002 cannabidiol transdermal gel in children and adolescents with fragile X syndrome (CONNECT-FX)

Elizabeth Berry-Kravis¹, Randi Hagerman^{2,3}, Dejan Budimirovic^{4,5}, Craig Erickson⁶, Helen Heussler^{7,8}, Nicole Tartaglia⁹, Jonathan Cohen^{10,11}, Flora Tassone^{2,12}, Thomas Dobbins¹³, Elizabeth Merikle¹⁴, Terri Seebree¹⁵, Nancy Tich¹⁵, Joseph M. Palumbo¹⁵ and Stephen O'Quinn^{15*}

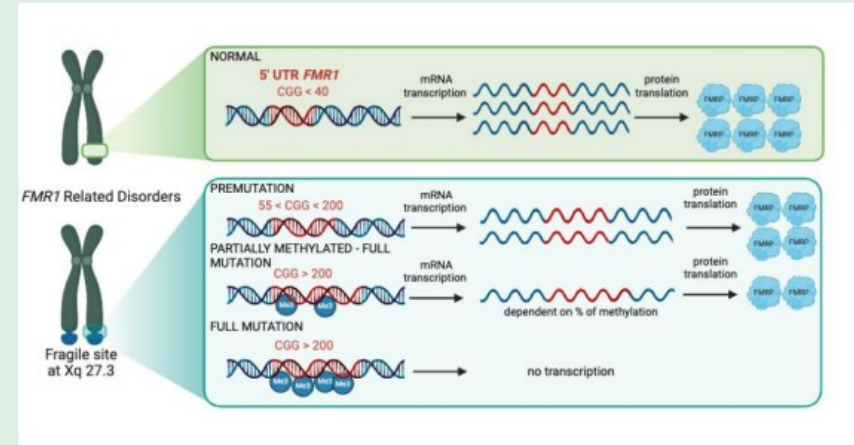


- “...ZYN002 was well tolerated in patients with FXS and demonstrated evidence of efficacy with a favorable benefit risk relationship in patients with $\geq 90\%$ methylation of the *FMR1* gene, in whom gene silencing is most likely, and the impact of FXS is typically most severe.”
- “Thus, CONNECT-FX appears to provide evidence that identifies a biologically identifiable and clinically responsive population of patients affected by FXS who are defined by both full mutation and $\geq 90\%$ methylation of the *FMR1* gene.”

The article can be accessed online at the *Journal of Neurodevelopmental Disorders* at <https://rdcu.be/c0sKz>.

Variable Methylation in the FMR1 Gene

- Healthy individuals: No methylation → normal expression and production of FMRP → normal function of the ECS
- Fragile X syndrome
 - Full mutation (over 200 CGG repeats) → full methylation (>90%) of the promoter region → complete silencing of the gene → absence of FMRP → FXS and dysregulated ECS (better response to exogenous CBD)
 - In some cases of FXS, partial methylation (<90%) occurs.
 - Full mutation (over 200 repeats) but partial methylation → variable expression of the FMR1 gene → some production of the FMRP protein → milder FXS presentation and less dysregulation of ECS (unpredictable response to exogenous CBD)



Degree of methylation affects the severity of symptoms. Individuals with partial methylation generally experience **milder cognitive, behavioral, or developmental features** compared to those with full methylation.

CONNECT-FX Trial Key Learnings: Results with complete methylation of *FMR1* gene

Consistent Improvements Observed with ZYN002 vs. Placebo in Patients with Complete Methylation

PRIMARY ENDPOINT

ABC-C_{FXS} Social Avoidance
Subscale

**40% median
improvement in
socially avoidant
behaviors
($p=0.027^*$)**

CAREGIVER-REPORTED BEHAVIOR CHANGE

Caregiver Global
Impression of Change
(ZYN002 vs Placebo)

SOCIAL INTERACTION
63% vs 37%
($p=0.005^*$)

**IRRITABLE/DISRUPTIVE
BEHAVIORS**
54% vs 33%
($p=0.027^*$)

SOCIAL AVOIDANCE/ISOLATION
58% vs 46%
($p=0.195$)

OVERALL BEHAVIOR
61% vs 46%
($p=0.100$)

CLINICIAN-REPORTED BEHAVIOR IMPROVEMENTS

Clinical Global Impression
of Improvement
(anchored)**

ANY IMPROVEMENT
ZYN002 vs placebo 50% vs 36%
($p=0.128$)

CLINICALLY MEANINGFUL BEHAVIOR IMPROVEMENTS

More Patients Achieved
Meaningful Change
(ZYN002 vs Placebo)

**SOCIAL AVOIDANCE
(≥ 3 POINTS)**
56% vs 37%
($p=0.030^*$)

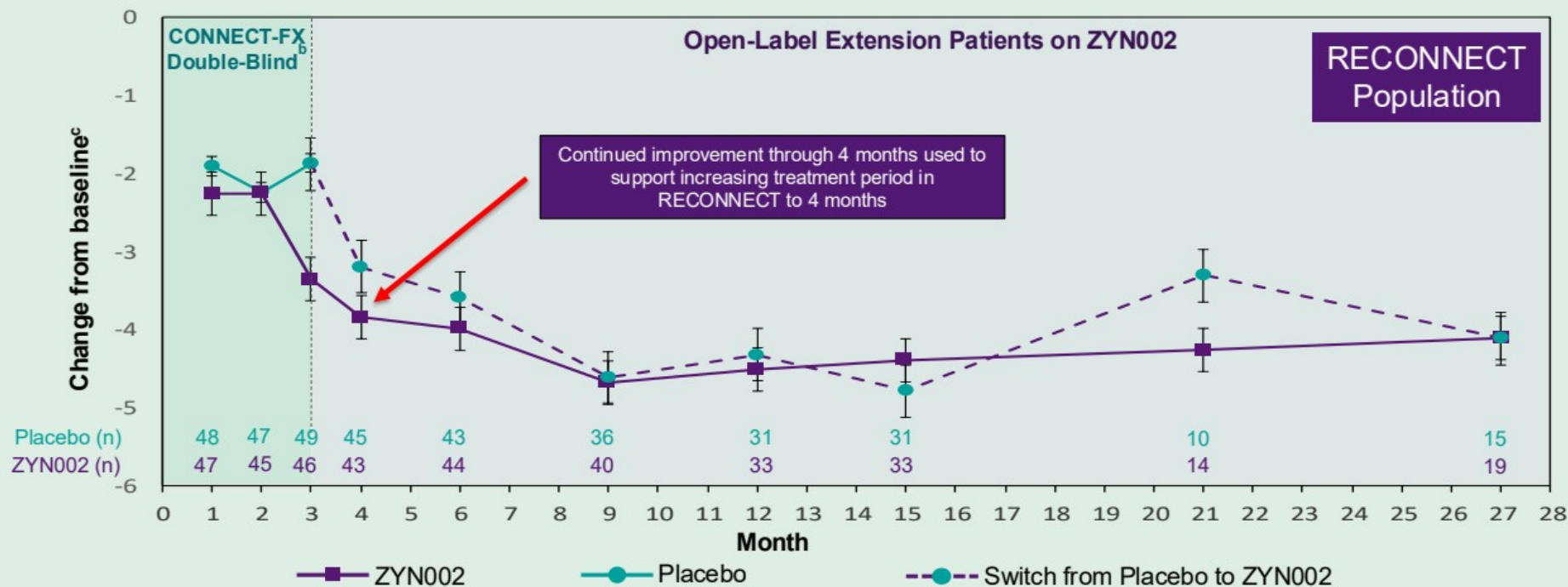
IRRITABILITY (≥ 9 POINTS)
37% vs 26%
($p=0.232$)

*Statistically significant, Not specific to Social Avoidance

Ad hoc analysis of 136 patients with complete methylation

Sustained Improvement in Patients With Complete Methylation of *FMR1*^a

Change in ABC-C_{FXS} Social Avoidance



a. Patients matching primary efficacy population in RECONNECT.

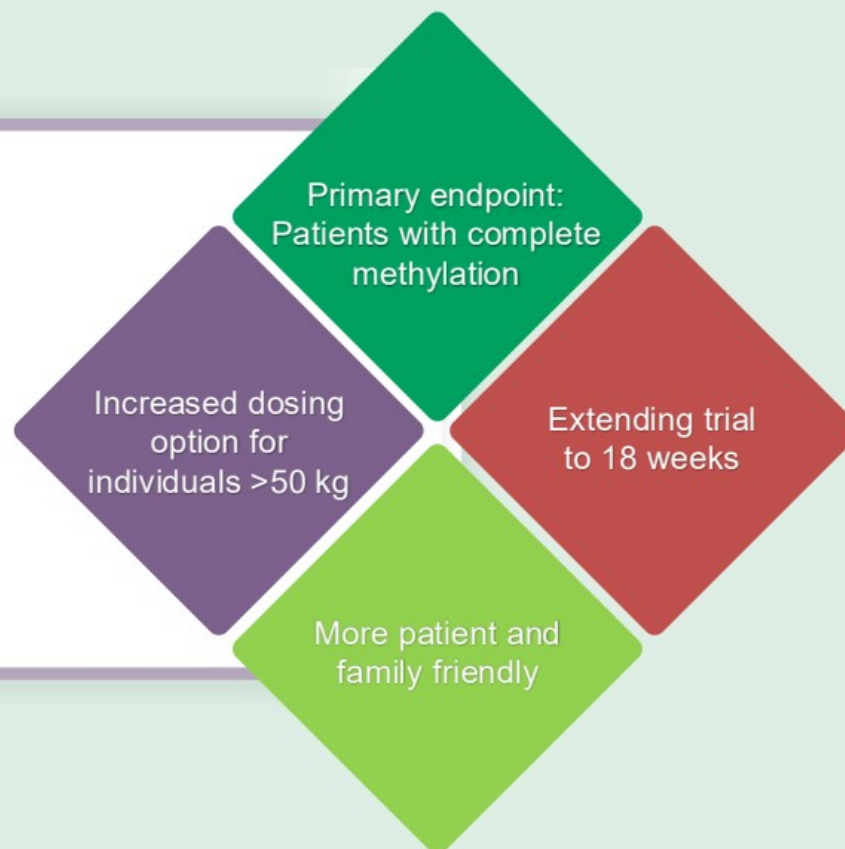
b. ZYN2-CL-016 (CONNECT-FX).

c. Least square mean \pm SE; reduction equals improvement.

Design Optimized from CONNECT-FX Trial

RECONNECT

Successful completion of Phase 3 pivotal trial expected to satisfy requirements for an NDA submission in the U.S. and a marketing authorization application in the EU.





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CLOSING REMARKS

MANAGEMENT PANEL DISCUSSION

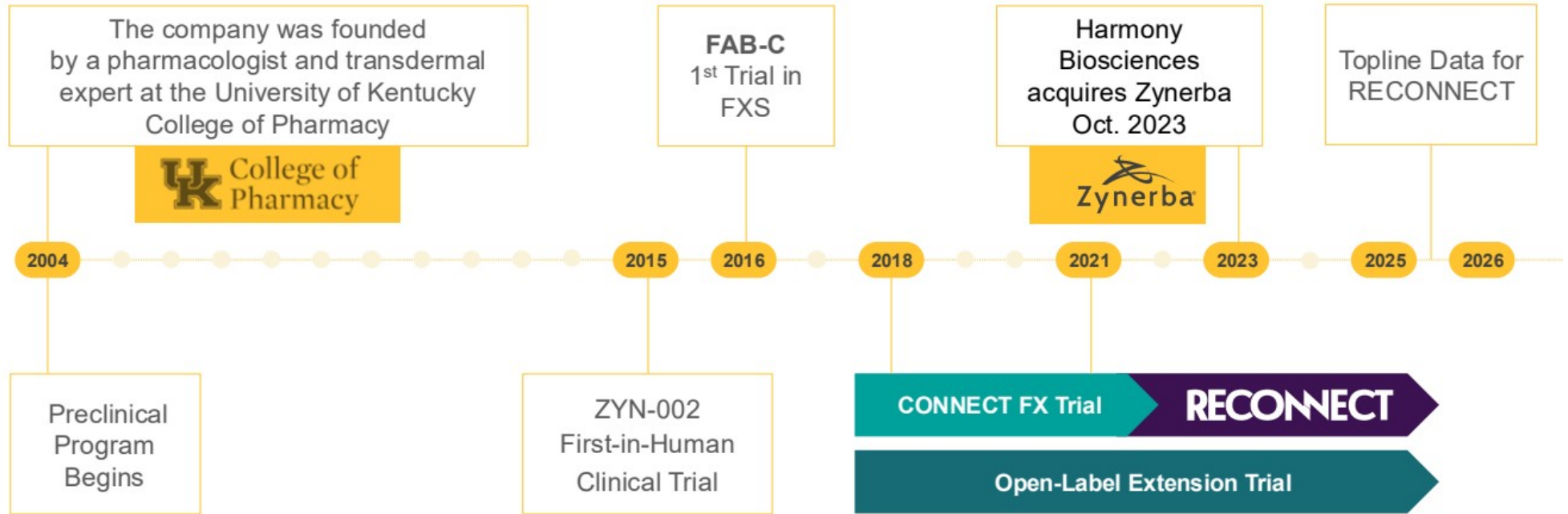
Q&A



KUMAR BUDUR, MD, MS
Chief Medical & Scientific Officer
Harmony Biosciences

The History of ZYN-002

More Than 15 Years of Research, Dedication, and Expertise

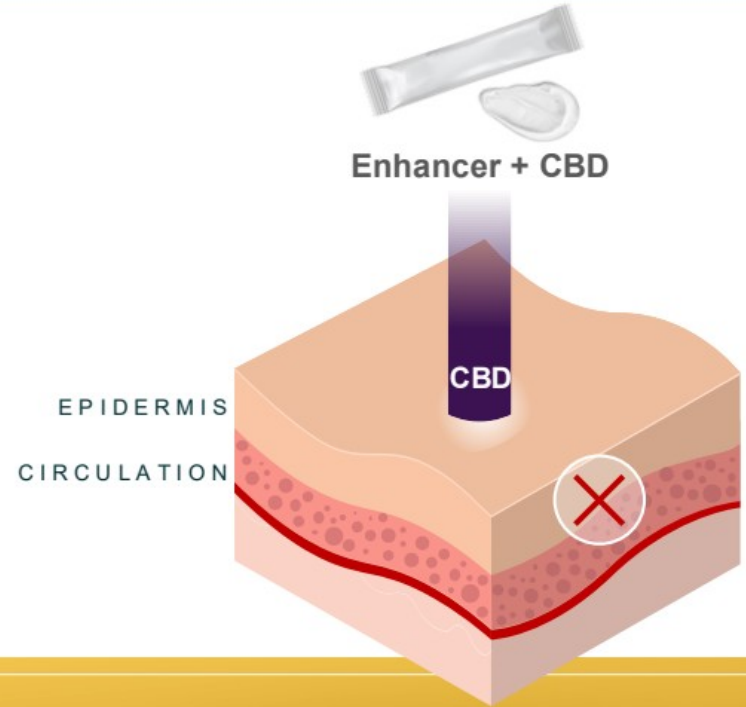


ZYN-002: Unique Product Attributes

- First and only pharmaceutically produced synthetic CBD
- Devoid of THC (no psychoactive properties)
- Patent-protected permeation enhanced gel

Transdermal delivery allows direct access into the circulation, allows for the following benefits:

- Better GI tolerability
- No first-pass metabolism in liver; minimizes potential for drug interactions or impact on LFTs
- Most common treatment related AE is “application site pain” in less than 7% of the patients.
- Some patients with FXS exposed to ZYN-002 for over 7 years!

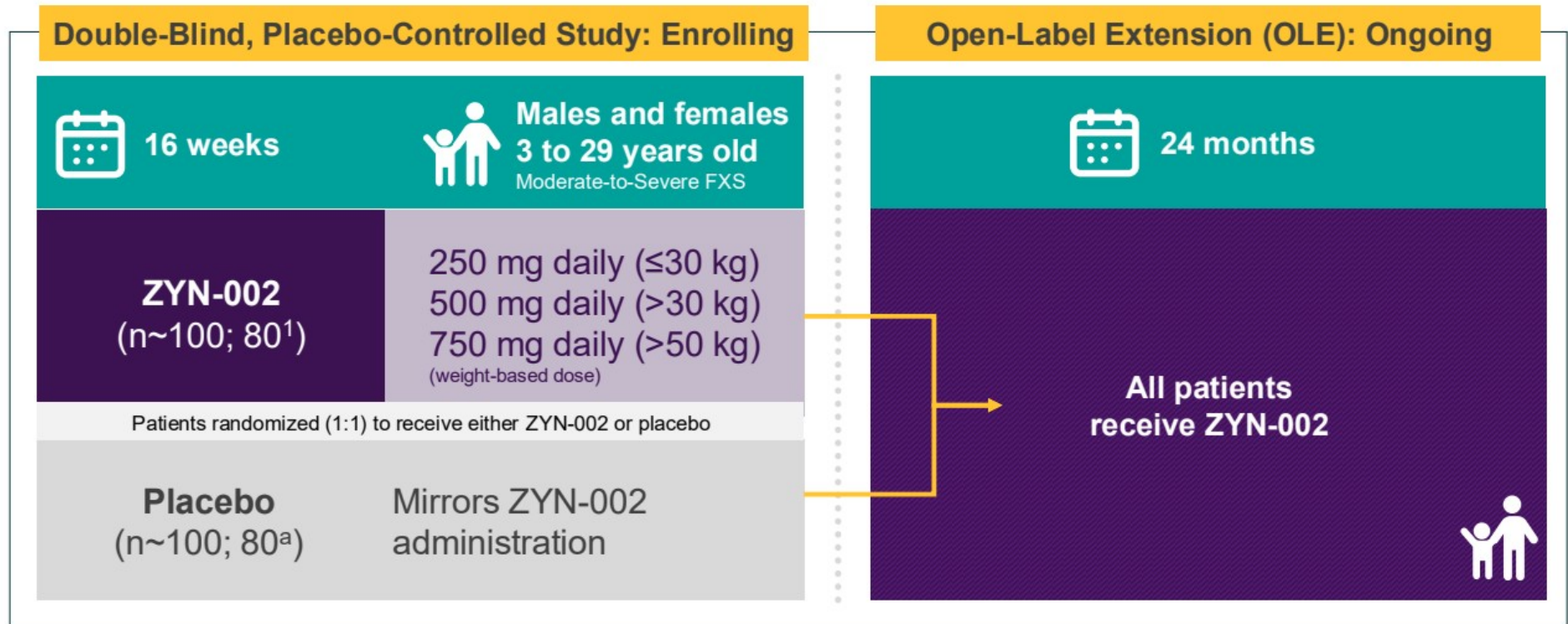


KEY TAKEAWAY

- **Unique product profile**
- **Established safety and tolerability profile: Exposure for over 7 years in FXS patients — maintenance of effect and high persistence with treatment**

Harmony Biosciences data on file.

Pivotal Phase 3 Trial in Fragile X Syndrome



1. Patients with complete methylation of FMR1 gene.

ZYN-002: Primary and Key Secondary Objectives



Primary Objective

Change from baseline to end of treatment in ABC-C_{FXS} Social Avoidance subscale in patients who have complete (100%) methylation of their *FMR1* gene

Selected Key Secondary Objectives

Change from baseline to end of treatment in:

- ABC-C_{FXS} Irritability subscale in patients who have complete methylation
- ABC-C_{FXS} Social Avoidance subscale among all randomized patients (complete and partial methylation)

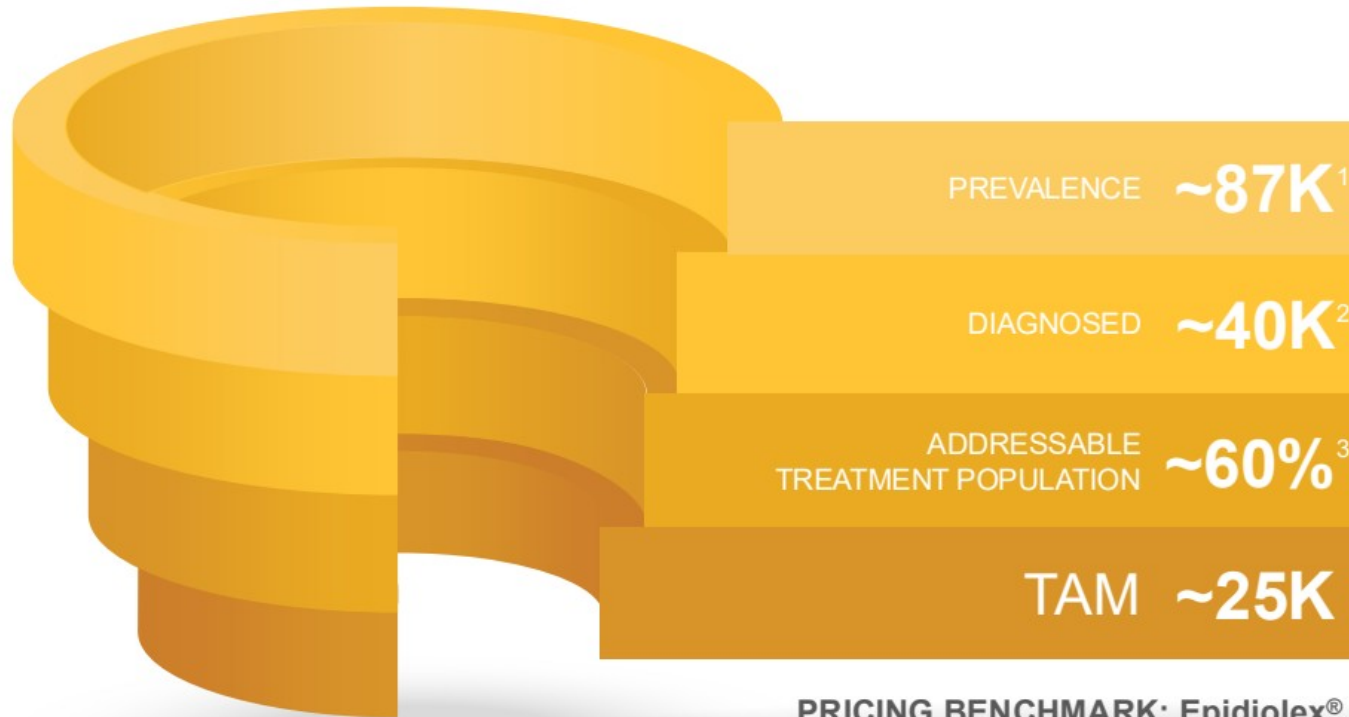
Percent of patients:

- With any improvement on the Caregiver Global Impression of Change (CaGI-C) for Social Interactions among patients with complete methylation
- Rated as improved on the Clinical Global Impression-Improvement (CGI-I) scale among patients with complete methylation

**KEY
TAKEAWAY**

Study designed to meet US and EU regulatory requirements; on track for topline data mid-2025

FXS: Total Addressable Market



- There are currently no approved therapies for the treatment of FXS
- Behavioral symptoms, especially social avoidance and irritability, significantly impact the patient and their family/ caregivers
- Patients with complete methylation demonstrate the most severe symptoms

1. National FXS Foundation; 2. Hunter 2014; 3. based on Ph2 CONNECT Trial disposition.



Neurobehavioral Franchise Catalysts

- ✓ Mid-25 – topline data in FXS
- ✓ 2H 25 – Initiate 22q pivotal Phase 3 trial
- ✓ 2026 – PDUFA for FXS



E P I L E P S Y



Epilepsy Franchise: Deliver Meaningful Treatment Options to Patients with Serious Unmet Medical Needs

ACQUISITION OF EPYGENIX

EPX-100 AND EPX-200



EPX-100:

Innovative approach to treatment of Development Epileptic Encephalopathies (DEEs) based on validated Zebra fish model

POTENTIAL FOR FAVORABLE

risk/benefit proposition



LEAD INDICATION IN DRAVET SYNDROME (DS)

Pivotal registrational study on track for topline data in 2026



ON TRACK

to initiate Phase 3 study in Lennox-Gastaut syndrome (LGS) in Q4 2024





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MANAGEMENT PANEL DISCUSSION

Q&A



SCOTT C. BARABAN, PhD
Professor of Neurological Surgery
University of California, San Francisco



References for Presentation of Rare Epilepsy Drug Discovery using Zebrafish By Scott C. Baraban, PhD

- Loscher and Schmidt, *Epilepsia* (2011)
- Baraban et al. *Nature Communications* (2013)
- Dindo and Baraban, *eNeuro* (2016)
- Griffin et al. *Frontiers in Pharmacology* (2018)
- Griffen et al. *Brain Communications* (2019)
- Baraban, *Disease Models & Mechanisms* (2021)
- Kumar et al. *eNeuro* (2016)
- Grone et al. *eNeuro* (2017)
- Dinday et al. *eNeuro* (2015)
- Griffin et al. *Brain* (2017)
- Griffin et al. *Frontiers in Pharmacology* (2020)
- Moog and Baraban, *Epilepsia Open* (2021)



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CLOSING REMARKS

MANAGEMENT PANEL DISCUSSION

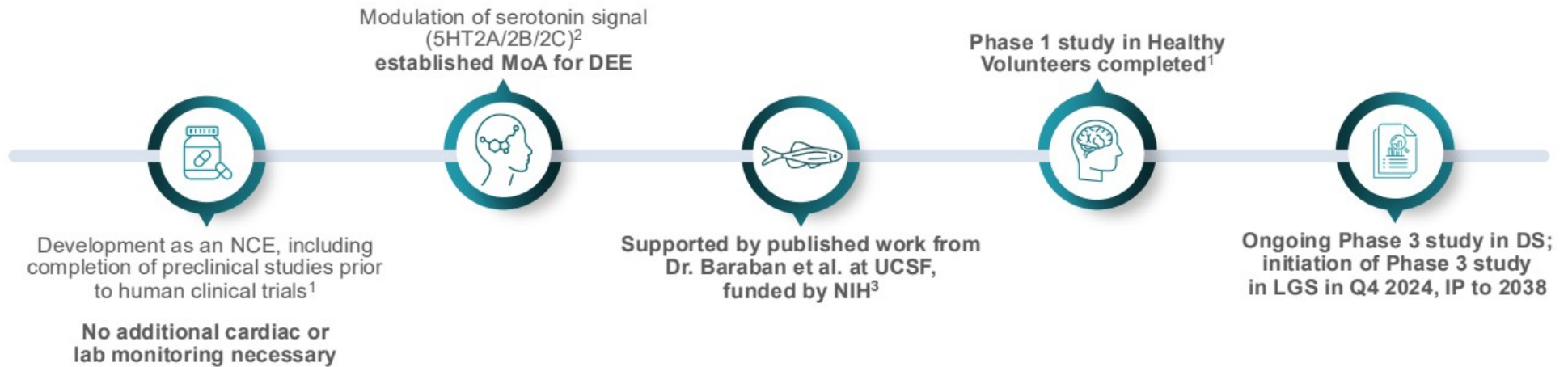
Q&A



KUMAR BUDUR, MD, MS
Chief Medical & Scientific Officer
Harmony Biosciences

EPX-100 (Clemizole HCl): Overview and Clinical Development Programs

EPX-100 or Clemizole HCl once marketed as a 1st generation antihistamine in the 1960s
Sunsetted in 1970s with the introduction of newer antihistamines — no significant post-marketing safety signals

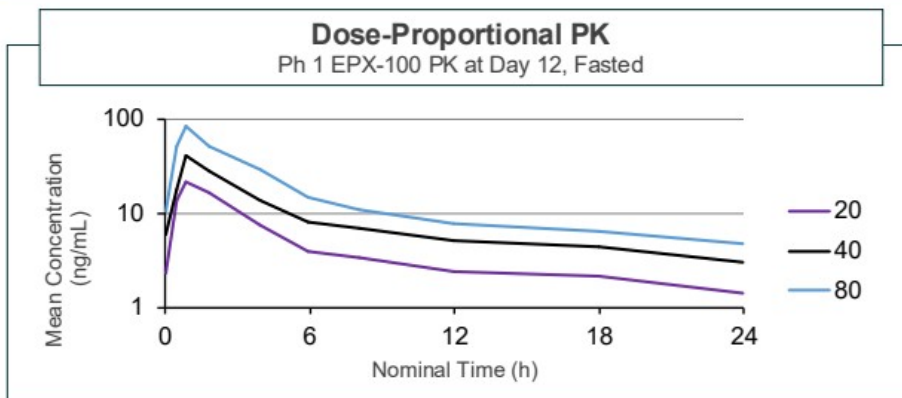


KEY TAKEAWAY

- Established MoA; potential for favorable risk/benefit profile in DEEs
- On track for topline data in DS and LGS in 2026
- EPX-100 granted ODD and RPDD for both DS and LGS

1. Harmony data on file; 2. Griffin et al Brain, 2017; 3. Baraban et al Nature Communications, 2019.

EPX-100: Generally Safe and Well Tolerated



TEAEs

(most common experienced)

of Subjects

Somnolence/drowsiness (mild)

9

Headache

2

QT prolongation*

3

* One subject on placebo and 2 subjects on EPX-100; mild, transient and self-limiting with no intervention; no symptoms reported

- ✓ Safety and pharmacokinetics of escalating single and multiple oral doses in 24 fasting, healthy subjects
- ✓ Dose-proportional PK for both EPX-100 and its main metabolite
- ✓ No apparent effects of food on PK
- ✓ Majority of the AEs were mild and self-limiting (23 mild, 4 moderate)

KEY TAKEAWAY

Generally safe and well tolerated; no need for special laboratory monitoring

Harmony Biosciences data on file.

EPX-100: Preliminary Safety and Tolerability Data Compared to Select Approved Drugs in DS and LGS

NEW
DATA

	Epidiolex ¹	Fintepla ²	EPX-100 ³
Decreased appetite	16–22%	8%	0%
Diarrhea	9–20%	6%	16%
Somnolence	23–25%	11%	12%
LFT monitoring	Required	n/a	n/a
REMS (CVD and PAH)	n/a	+	n/a
Echocardiography	n/a	Prior to initiation and every 6 months thereafter	n/a

CVD: cardiac valvular disease
PAH: pulmonary arterial hypertension

KEY TAKEAWAY

EPX-100: Preliminary safety/tolerability profile suggests no need for additional lab or cardiac monitoring; potential for favorable risk/benefit profile

1. Epidiolex PI: AEs in patients treated with Epidiolex in clinical trials; 2. Fintepla PI: MC AEs in >5% of patients and more than placebo in placebo-controlled trials; 3. Harmony Biosciences data on file.

Phase 3 Study in DS: ARGUS Study Design



Oral solution



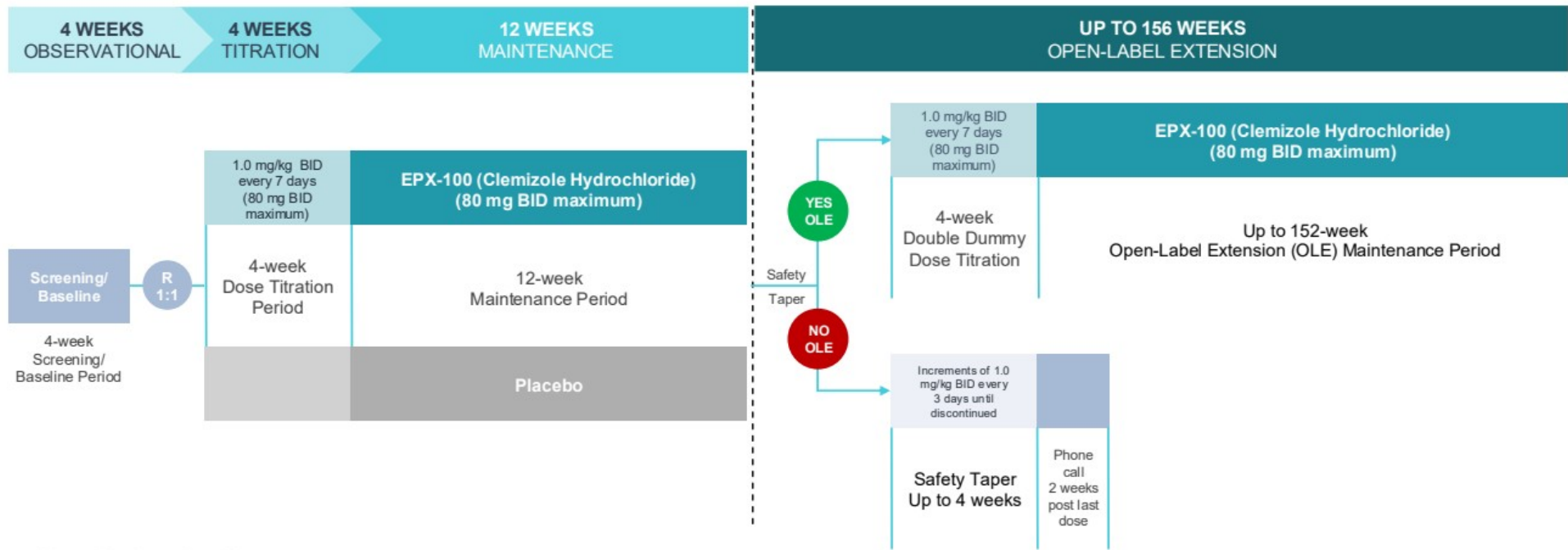
People 2 years and older



Living with DS



Active sites in US, Canada and Europe



Harmony Biosciences data on file.

ARGUS Study: Primary and Key Secondary Objectives

Primary Objective

To evaluate the efficacy of EPX-100 compared with placebo as adjunctive therapy in children and adult participants with LGS as measured by countable convulsive seizure frequency (CCSF)

Select Key Secondary Objectives

Difference between EPX-100 vs placebo in the proportion of participants with $\geq 50\%$ reduction in countable convulsive seizure frequency

Difference between EPX-100 vs Placebo per 28-day period in total countable convulsive seizure frequency

KEY TAKEAWAY

- **Well-established study design and endpoints**
- **Study designed to address the requirements for both US and EU regulatory authorities**

ARGUS Study: Status Update



● — **Actively recruiting patients in US, Canada and Europe**

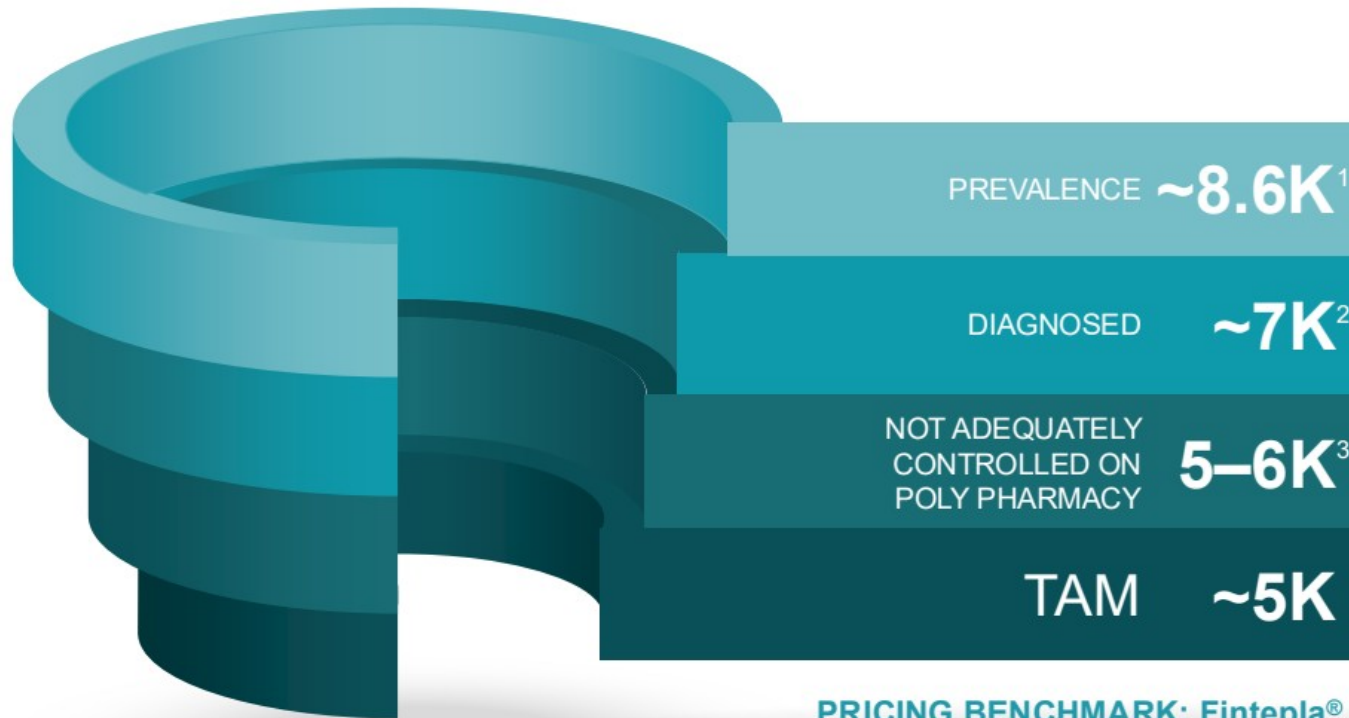
● — **Generally safe and well tolerated (data from double-blind and open-label extension study)**

Most common TEAEs occurring in >5 subjects were pyrexia, URTI, seizure, somnolence and nasopharyngitis

● — **On track for topline data in 2026**

Harmony Biosciences data on file.

Dravet Syndrome: Total Addressable Market

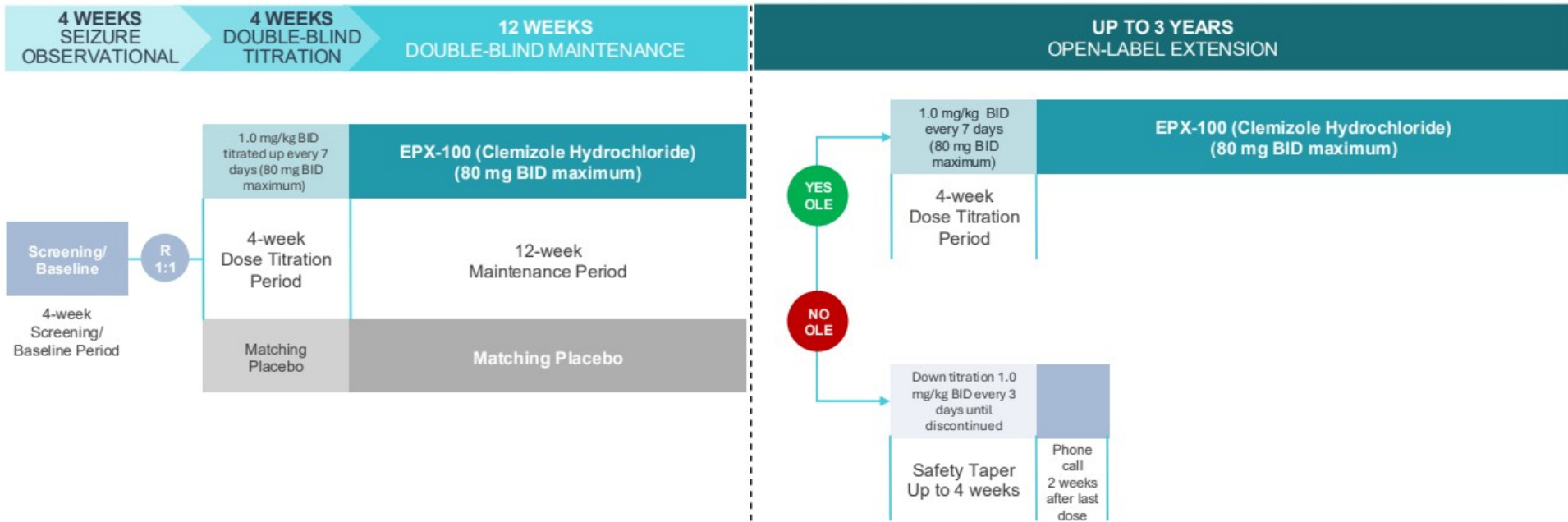


PRICING BENCHMARK: Fintepla®

- Severe refractory epilepsy not controlled even with polypharmacy
- Extreme co-morbidity/mortality if not effectively treated
- Recognized need for improved treatment options

1. Helbig 2014, Orphanet; 2. Wu 2015, medical claims data analysis and company modeling; 3. Based on KOL interviews for treatment and prescribing behavior.

EPX-100 in Lennox Gastaut Syndrome (LGS): Phase 3 Study Design



Harmony Biosciences data on file.

LGS Study: Primary and Key Secondary Objectives

Primary Objective

To evaluate the efficacy of EPX-100 compared with placebo as adjunctive therapy in children and adult participants with LGS as measured by frequency of seizures that result in drops (FSRD)

Select Key Secondary Objectives

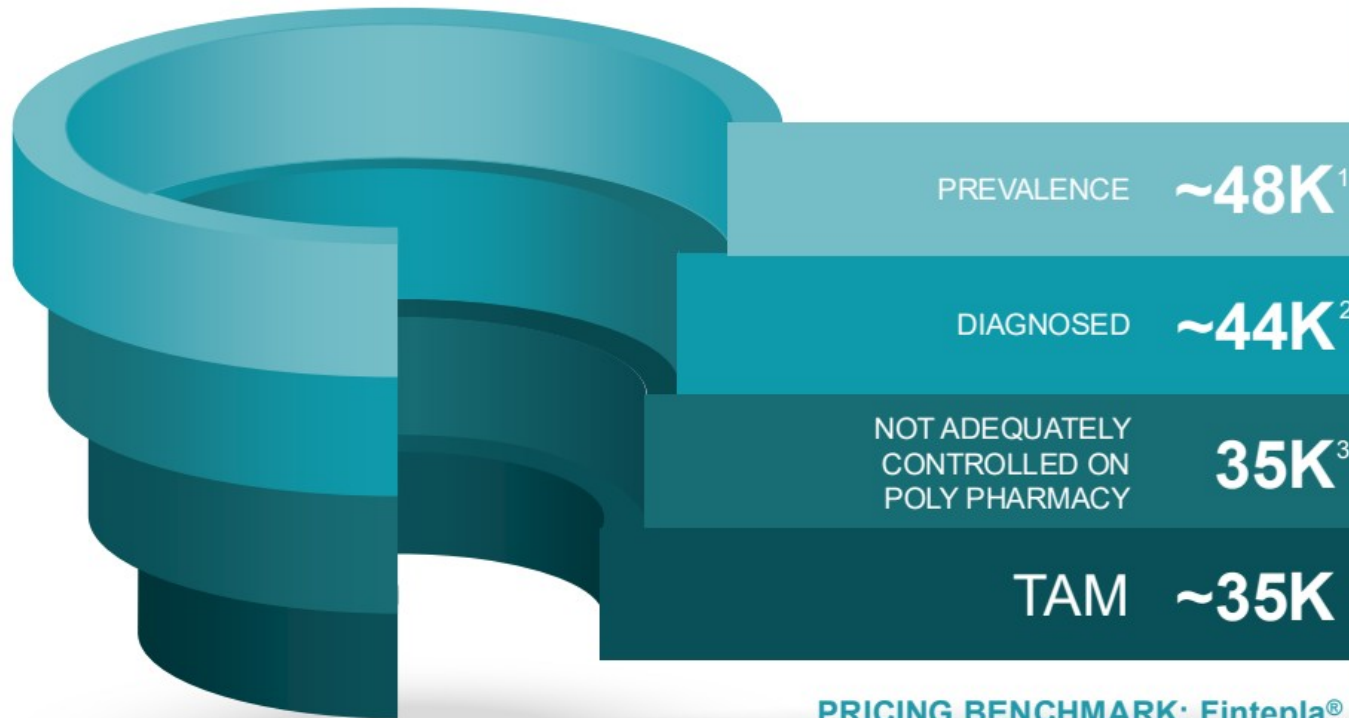
Difference between EPX-100 vs placebo in the in the proportion of participants with $\geq 50\%$ reduction in frequency of seizures that result in drops (FSRD)

Difference between EPX-100 vs Placebo per 28-day period in total countable frequency of seizures that result in drops (FSRD)

KEY TAKEAWAY

- **Well-established study design and endpoints**
- **Study designed to address the requirements for both US and EU regulatory authorities**

LGS: Total Addressable Market



PRICING BENCHMARK: Fintepla®

- Severe refractory epilepsy not controlled even with polypharmacy
- Extreme co-morbidity/mortality if not effectively treated
- Recognized need for improved treatment options

1. Lennox-Gastaut Foundation; 2. Komodo Health - medical claims data 2021-2023 and company modeling; 3. Based on KOL interviews for treatment and prescribing behavior.



Epilepsy Franchise Catalysts

- ✓ Q4 2024 – Initiate LGS pivotal Phase 3 trial
- ✓ 2H 2026 – topline data in DS
- ✓ 2H 2026 – topline data in LGS
- ✓ 2027/2028 – PDUFA for DS
- ✓ 2027/2028 – PDUFA for LGS



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Q&A



JEFFREY M. DAYNO, MD
President and Chief Executive Officer
Harmony Biosciences

DELIVER ON PROMISE TO PATIENTS

Commitment to patients

Addressing unmet medical needs

Delivering meaningful treatment options

Helping patients thrive

DELIVER STRONG VALUE TO SHAREHOLDERS

Innovative

Catalyst-rich pipeline

Profitable biotech company

Meaningful investment opportunity



P A N E L D I S C U S S I O N





JEFFREY M. DAYNO, MD
President & CEO
Harmony Biosciences



JEFFREY DIERKS, MBA
Chief Commercial Officer
Harmony Biosciences



KUMAR BUDUR, MD, MS
Chief Medical & Scientific Officer
Harmony Biosciences



SANDIP KAPADIA, CPA, MBA
CFO & Chief Administration Officer
Harmony Biosciences



Harmony is an innovative, catalyst-rich, profitable biotech company

\$1B+

Proven commercial product and growing

13

Development programs;
4 in Phase 3 by year end



\$3B+

Establishing leadership position in CNS

5

Anticipate 1 or more new product or indication launches each year over next 5 years

THANK YOU



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