

LX9211

Changing the Paradigm for
Treatment of Neuropathic Pain

Agenda

- **Overview of massive treatment gap in Neuropathic Pain** (10 mins)
Mike Exton, PhD; Director and Chief Executive Officer
- **LX9211: Potential innovative solution for DPNP** (20 mins)
Suma Gopinathan, PhD; VP, Clinical Development and LX9211 Lead
- **Expert panel discussion on the latest in Pain Management for DPNP** (45 mins)
Moderated by Craig Granowitz, MD, PhD; SVP and Chief Medical Officer
*Featuring **Dr. Rodica Pop-Busui** and **Dr. Steve Edelman***
- **Key Takeaways & 2025 Strategic Priorities** (10 mins)
Mike Exton, PhD; Director and Chief Executive Officer
- Questions and Answers (30 mins)

Overview of massive treatment gap in neuropathic pain

Mike Exton, PhD

Director and Chief Executive Officer



I have been suffering for almost 20 years with painful diabetic neuropathy that has gotten progressively worse. In addition to unrelenting pain that has limited my mobility, it is depressing that I'm unable to enjoy something as simple as playing catch with my grandson.

- Type 2 diabetes patient
with Diabetic Peripheral Neuropathic Pain (DPNP)

Neuropathic pain: A chronic condition with significant unmet need

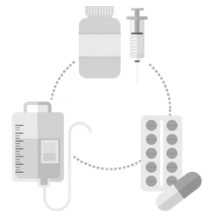
Definition

Nerve pain that occurs when the nervous system malfunctions or gets damaged¹

Causes of Neuropathic Pain (NP)



Diabetes



Chemotherapy



Multiple sclerosis



Shingles



Trauma or Amputation

Only 30%
of patients with
neuropathic pain
achieve **partial pain
management**²

1) Neuropathic pain: What it is & ways to manage it. Cleveland Clinic. (2024, May 1). <https://my.clevelandclinic.org/health/diseases/15833-neuropathic-pain>. 2) Rosenberger DC, Blechschmidt V, Timmerman H, Wolff A, Treede RD. Challenges of neuropathic pain: focus on diabetic neuropathy. J Neural Transm (Vienna). 2020 Apr;127(4):589-624. doi: 10.1007/s00702-020-02145-7. Epub 2020 Feb 8. PMID: 32036431; PMCID: PMC7148276.

Unsatisfied market with substantial impact to quality of life for patients

Significant quality of life impact



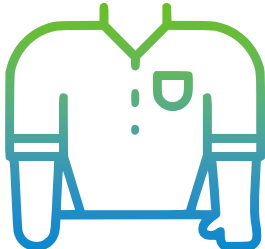
Sensation,
balance loss



Falls,
fractures



Loss of daily
function



Ulcers,
amputations



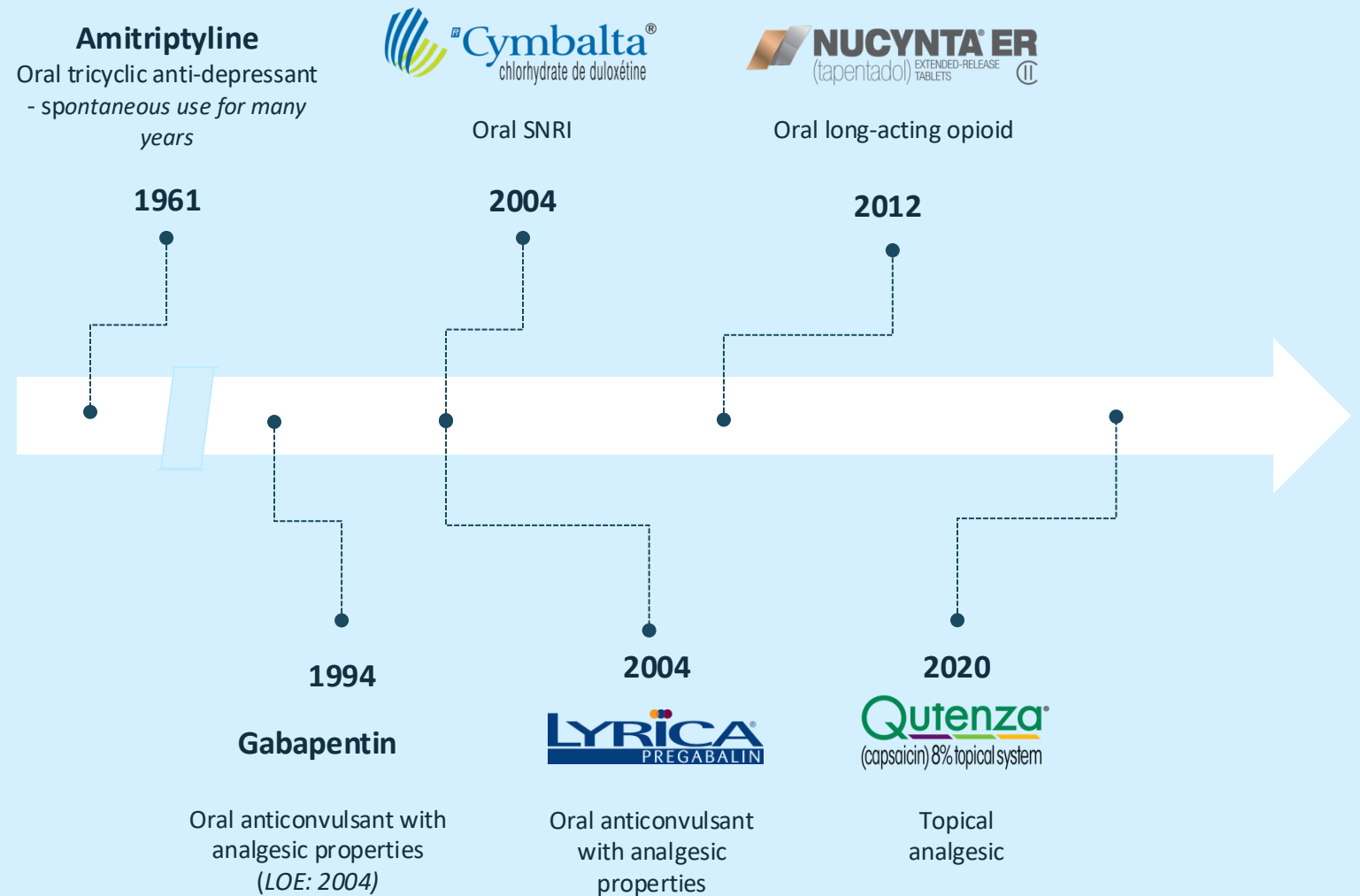
Pain,
depression



Lack of sleep

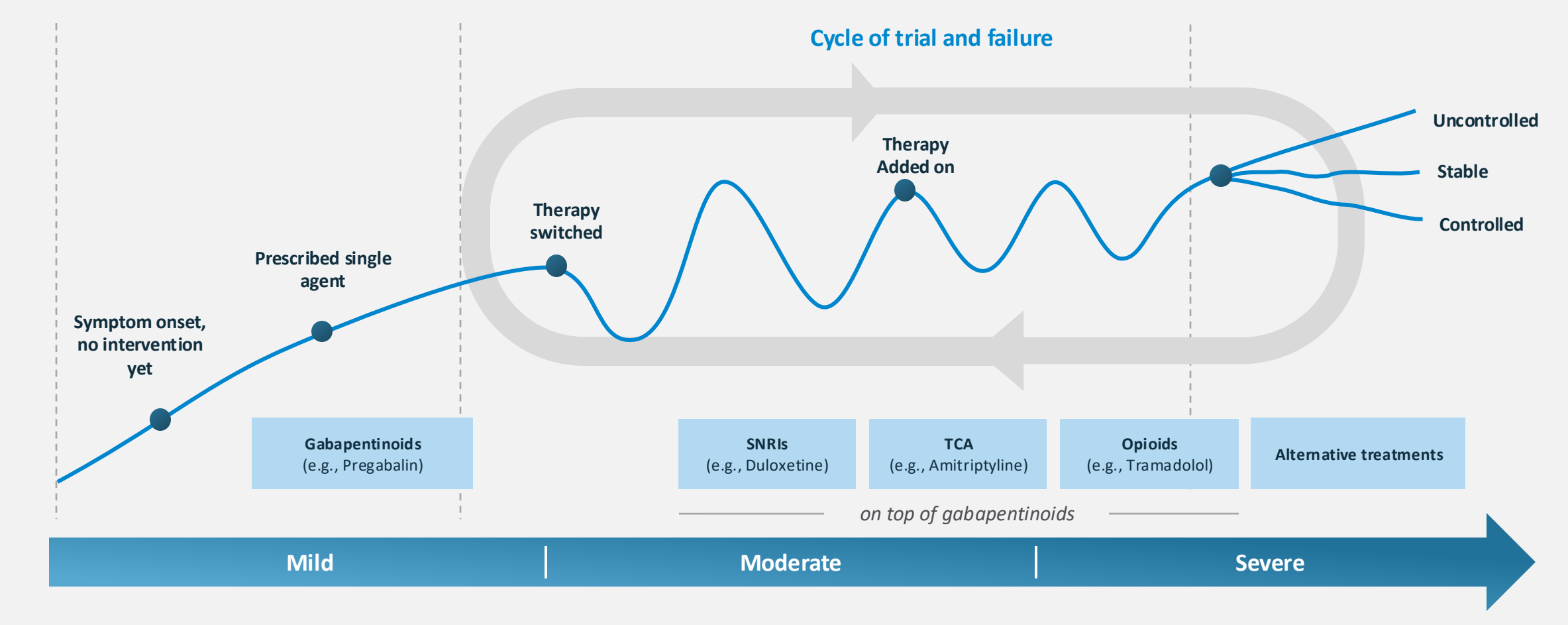


There has been **little innovation over the past 20 years**, and an intensifying need for novel and effective non-opioid therapeutic options



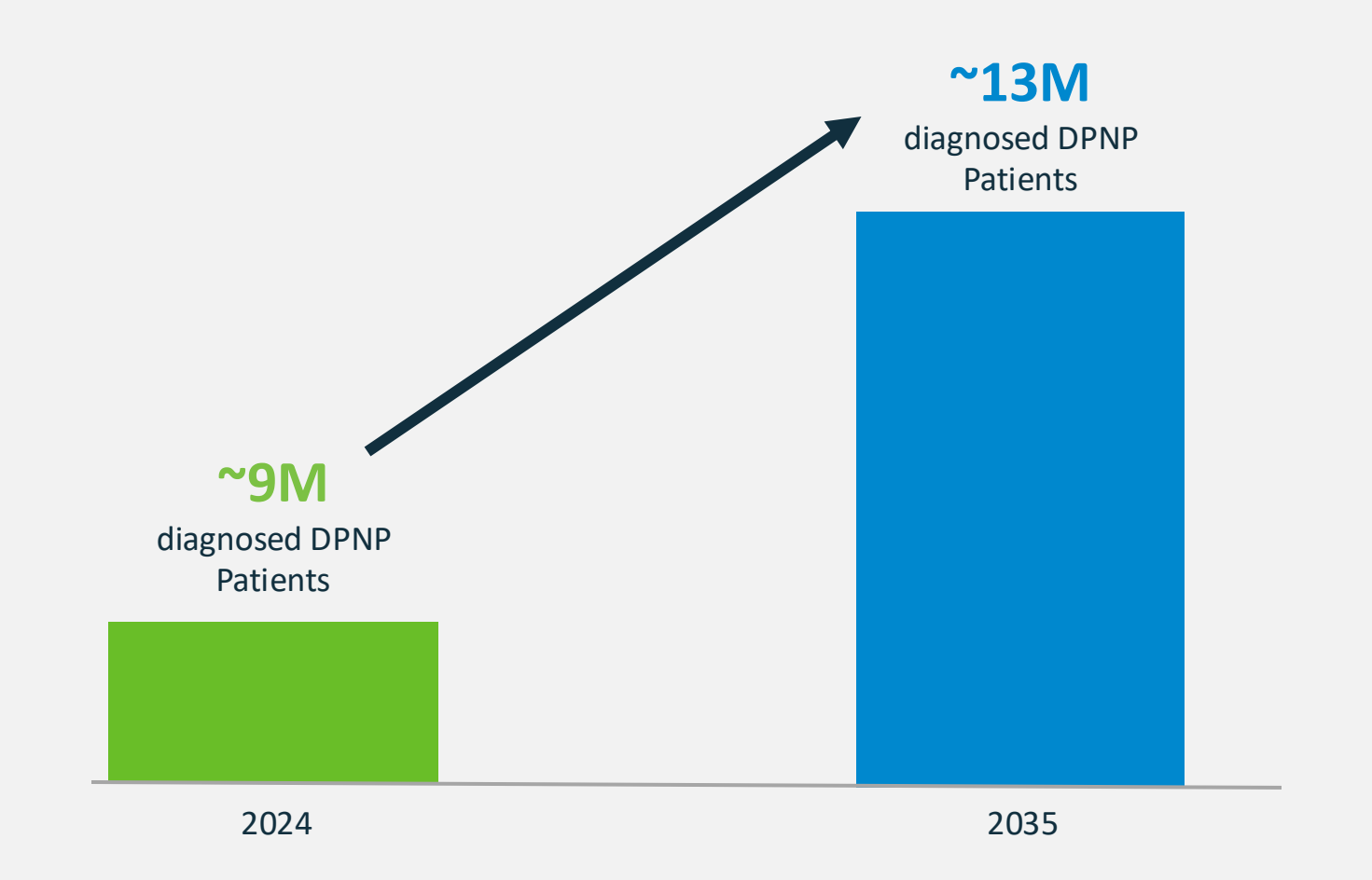
Pain management evolves from single to polypharmacy as diabetic peripheral neuropathic pain (DPNP) progresses

~60% DPNP patients treated go on to switch or add therapies¹




1) Veeva Compass data; based on internal Lexicon claims analysis

DPNP is highly prevalent and rapidly growing



 **Disease Awareness**
Investment across industry to educate on DPNP

 **Market Reinvigoration**
Educational efforts to improve standard of care in DPNP

 **Non-Opioid, Novel Options**
Introduction of new therapies with different MOAs

CDC National Diabetes Statistics Report 2024. Source: prevalence rate of DPNP in diabetics is based on primary and secondary research; Source: Clearview Analysis.

Unique potential advantages of LX9211 from our continuing clinical development program



Novel, non-opioid treatment option



Clinically and statistically significant reductions compared to placebo



Qualify dose, oral monotherapy or in combination with standard of care

LX9211: Potential innovative solution for DPNP

Suma Gopinathan, PhD

VP, Clinical Development and LX9211 Lead

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It's heartbreaking to see my husband suffering. He is often up during the night, crying out from the pain in his legs and feet, which affects the quality of life for both of us.

- First-hand account of a DPNP caregiver

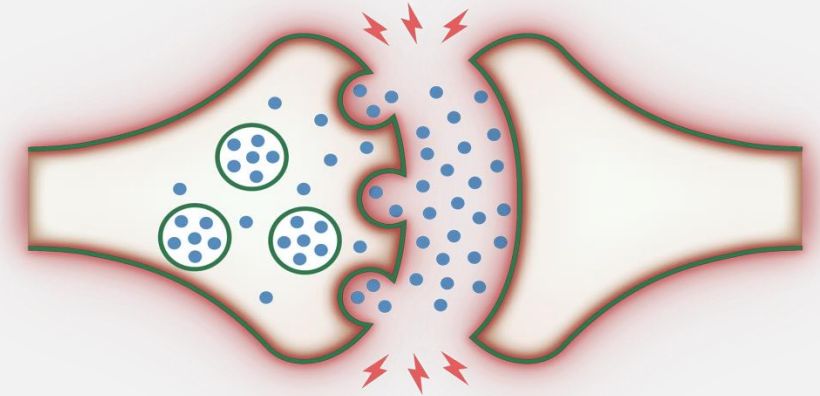
AAK1 is a novel target for neuropathic pain

Novel, non-opioid target for treating neuropathic pain

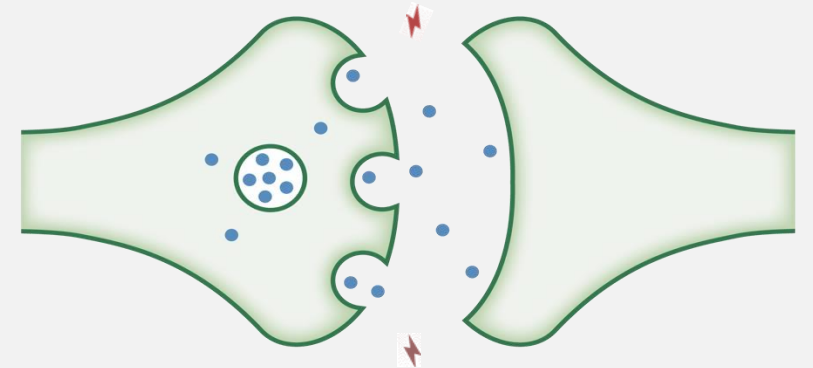
Inhibits reuptake and recycling of neurotransmitters involved in pain signaling and spasticity

Validated using a genetic knockout model, preclinical studies, and human clinical trials

Neuropathic Pain



Treatment with LX9211



AAK1: AP2-associated protein kinase 1

Broad therapeutic potential backed by data in range of neuropathies and spasticity

	Preclinical Efficacy	Clinical Proof of Concept
Neuropathic Pain		
Diabetic Peripheral Neuropathic Pain	✓	✓
Postherpetic Neuralgia	✓	✓
Chemotherapy-Induced Neuropathic Pain	✓	
Lumbosacral Radiculopathy	✓	
Multiple Sclerosis Pain	✓	
Spasticity		
Multiple Sclerosis	✓	
Spinal Cord Injury	✓	

RELIEF-DPN-1

Study Overview

Proof of concept RELIEF-**DPN-1** study in patients with DPNP

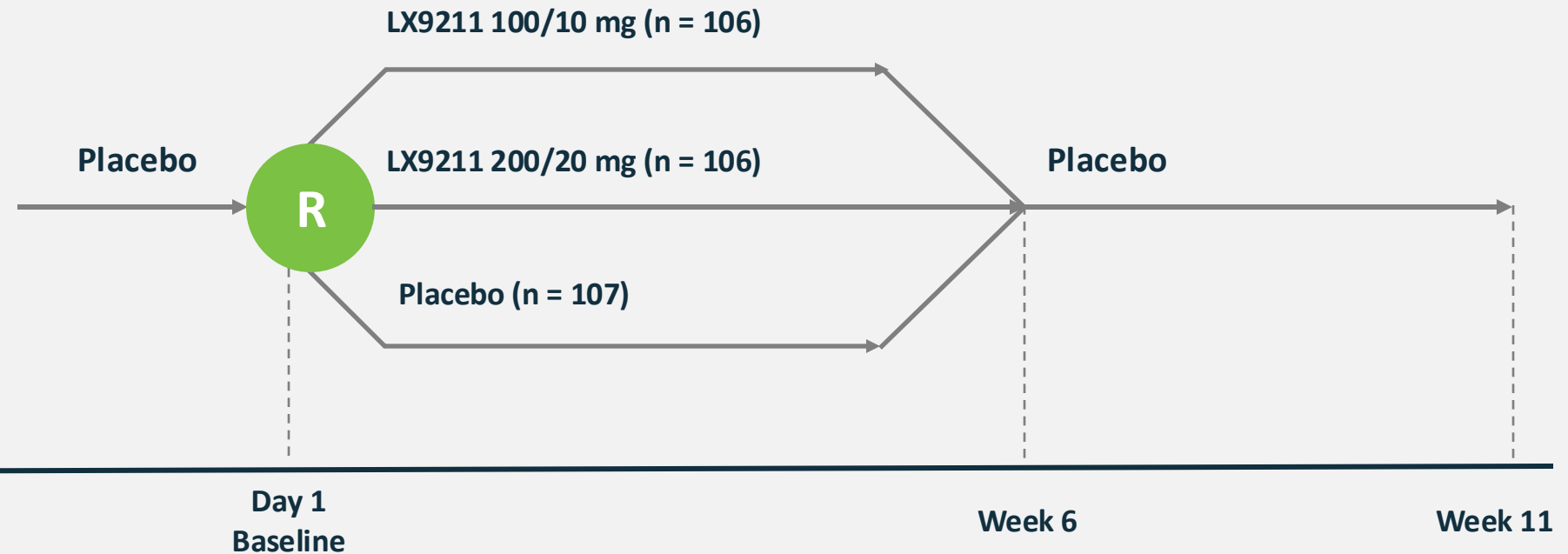
Patient Population

Run in period
2-week

Double-Blind Treatment Period
6-week

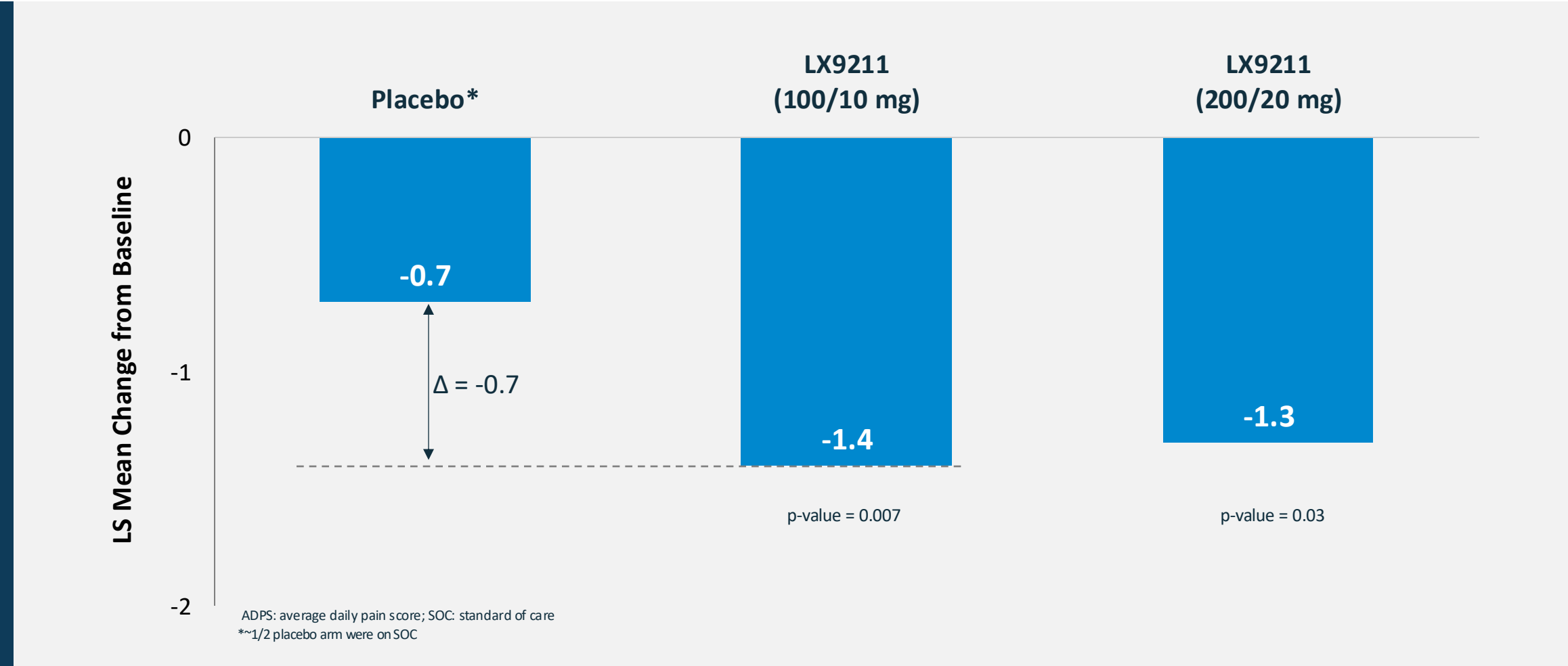
Safety Follow-up
5-week

- Patients with T1DM or T2DM
- Moderate to severe pain
- Allowed to remain on background standard of care treatment



DPNP: diabetic peripheral neuropathic pain

Meaningful and statistically significant reduction in ADPS in placebo-controlled **RELIEF-DPN-1** Phase 2 study



Most common adverse events from RELIEF-DPN1

Adverse Event	PLACEBO (N = 107) n (%)	100 mg/10 mg (N = 106) n (%)	200 mg/20 mg (N = 106) n (%)	TOTAL (N = 319) n (%)
Dizziness	2 (1.9)	16 (15.1)	29 (27.4)	47 (14.7)
Headache	4 (3.7)	9 (8.5)	10 (9.4)	23 (7.2)
Nausea	3 (2.8)	9 (8.5)	12 (11.3)	24 (7.5)

Findings were independent of other factors such as age, sex, and baseline DPNP medications used

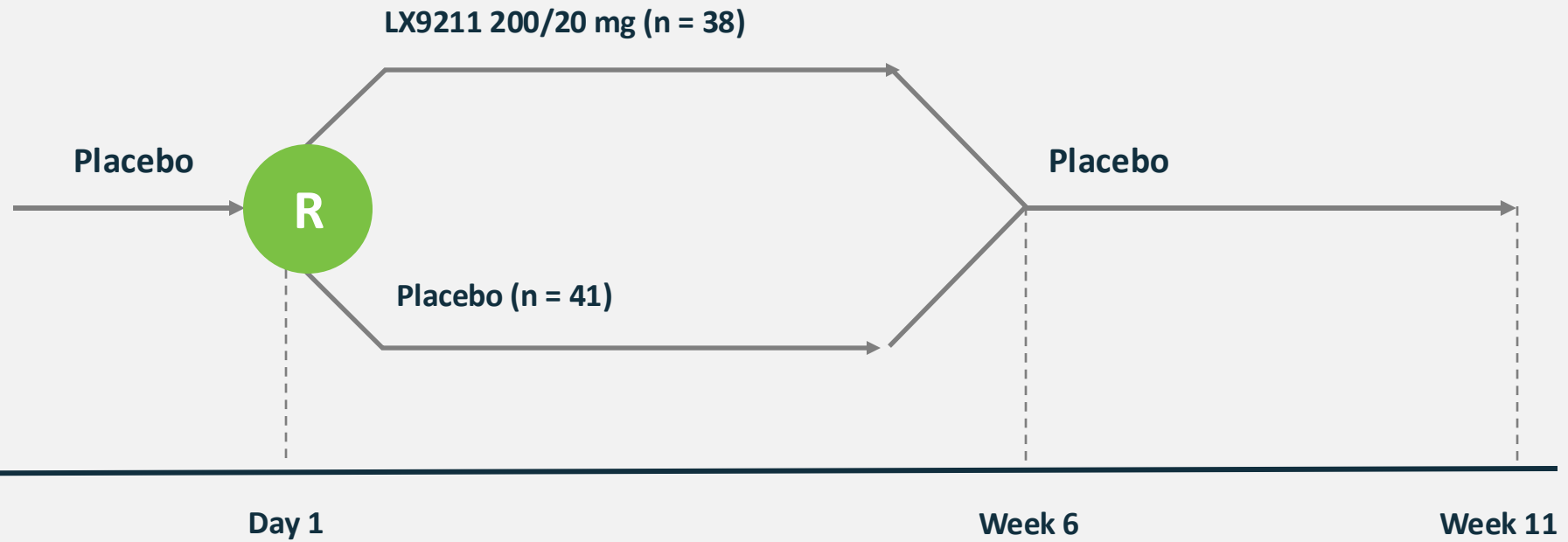
RELIEF-PHN-1

Study Overview

RELIEF-PHN-1 study design in patients with PHN

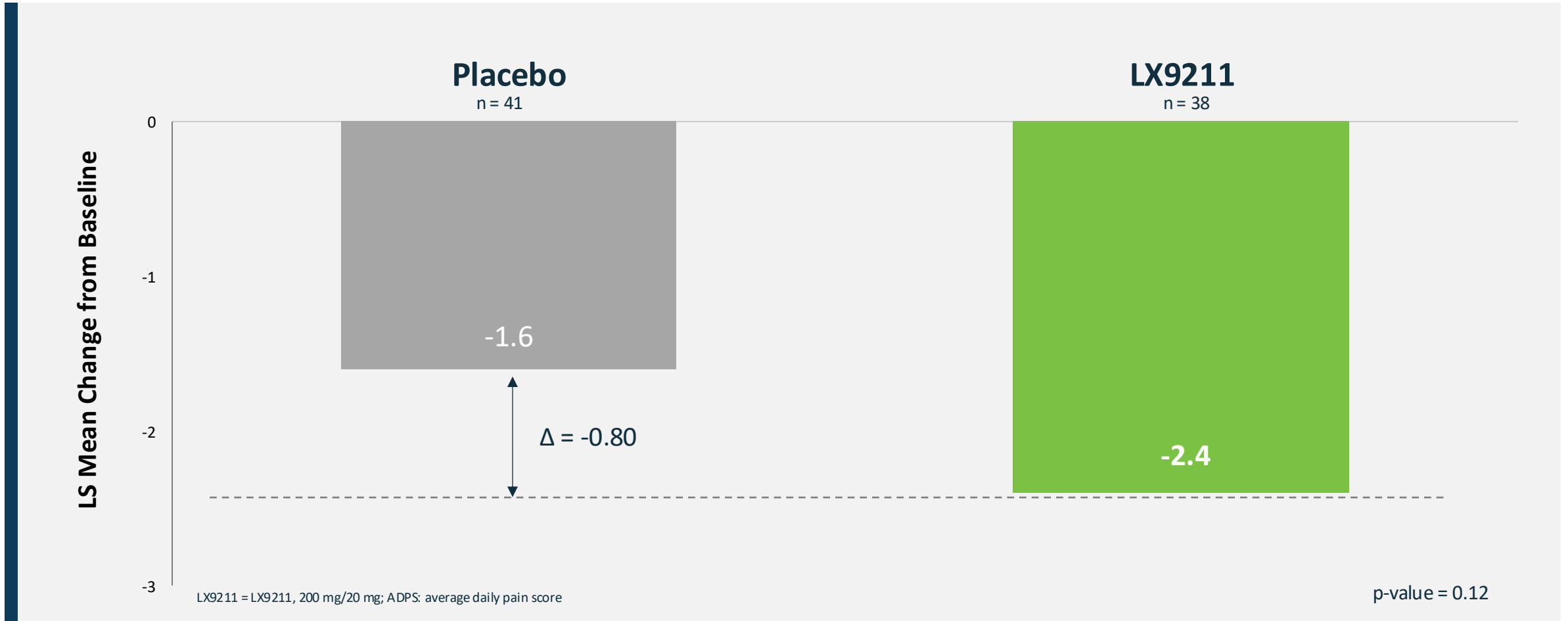


- Moderate to severe pain
- Allowed to remain on background PHN medication



PHN: Postherpetic neuralgia

Achieved proof of concept in placebo-controlled **RELIEF-PHN-1**



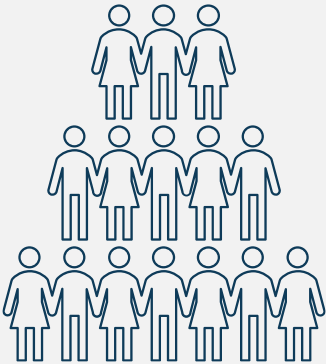
PHN: Postherpetic neuralgia

PROGRESS

Study Overview

PROGRESS study is designed to be patient-centric and powered for success

Pragmatic design led to rapid, early, and above capacity enrollment



Patient population

- Type 1 and 2
- on and off SOC



Patient selection

- Diagnosed using MNSI
- Moderate-to-severe pain



Key Design elements

- 2-week run-in
- Placebo-controlled
- No loading dose
- Training in pain reporting

MNSI: Michigan Neuropathy Screening Instrument

Goals for top-line data



Achieve similar or better efficacy



Removal of loading dose improves tolerability



Identify single dose to take into placebo-controlled Phase 3 studies



Reaffirm pragmatic design

**Target Phase 3
start in 2025**

Expert panel on the latest in pain management for DPNP

Moderated by
Craig Granowitz, MD, PhD
SVP and Chief Medical Officer

“

The first pain and the worst pain was my feet feeling like they were caught on fire, almost burning. Often, I would wake up at night and not be able to go back to sleep.

- RELIEF-DPN-1 trial patient

Objectives of today's panel discussion



**Educate on
neuropathic pain
and specifically
DPNP**



**Understand
patient journey**



**Review
the current
treatment
landscape, pros
and cons**



**Discuss clinical
trials in
neuropathic pain**

Discussion on neuropathic pain

Panelists



**Rodica Pop-Busui,
MD, PhD**

Jordan Schnitzer Chair in Diabetes |
Professor of Medicine and Division Head,
Endocrinology, Diabetes and Clinical
Nutrition | Director, Harold Schnitzer
Diabetes Center, OHSU | 2023 President for
Medicine and Science, American Diabetes
Association



Steve Edelman, MD

Professor of Medicine, the Division of
Endocrinology, Diabetes &
Metabolism at University Of California
San Diego | Veterans Affairs Medical
Center | Founder and Director Taking
Control Of Your Diabetes (TCOYD)



**Suma Gopinathan,
PhD**

VP, Clinical Development
and LX9211 Lead



**Craig Granowitz,
MD, PhD**

SVP and Chief Medical Officer

Key Takeaways

Mike Exton, PhD

Director and Chief Executive Officer

Introducing

Pilavapadin

“pill-uh-vap-uh-din”

A potential treatment for DPNP

Unique potential advantages of pilavapadin



New and Novel
no approved options for
neuropathic pain in over 2 decades



Proof of Concept
clinically and statistically significant
reductions compared to placebo



Oral Once Daily
monotherapy or in combination
with standard of care



Non-Opioid
MOA distinct from current
standard of care

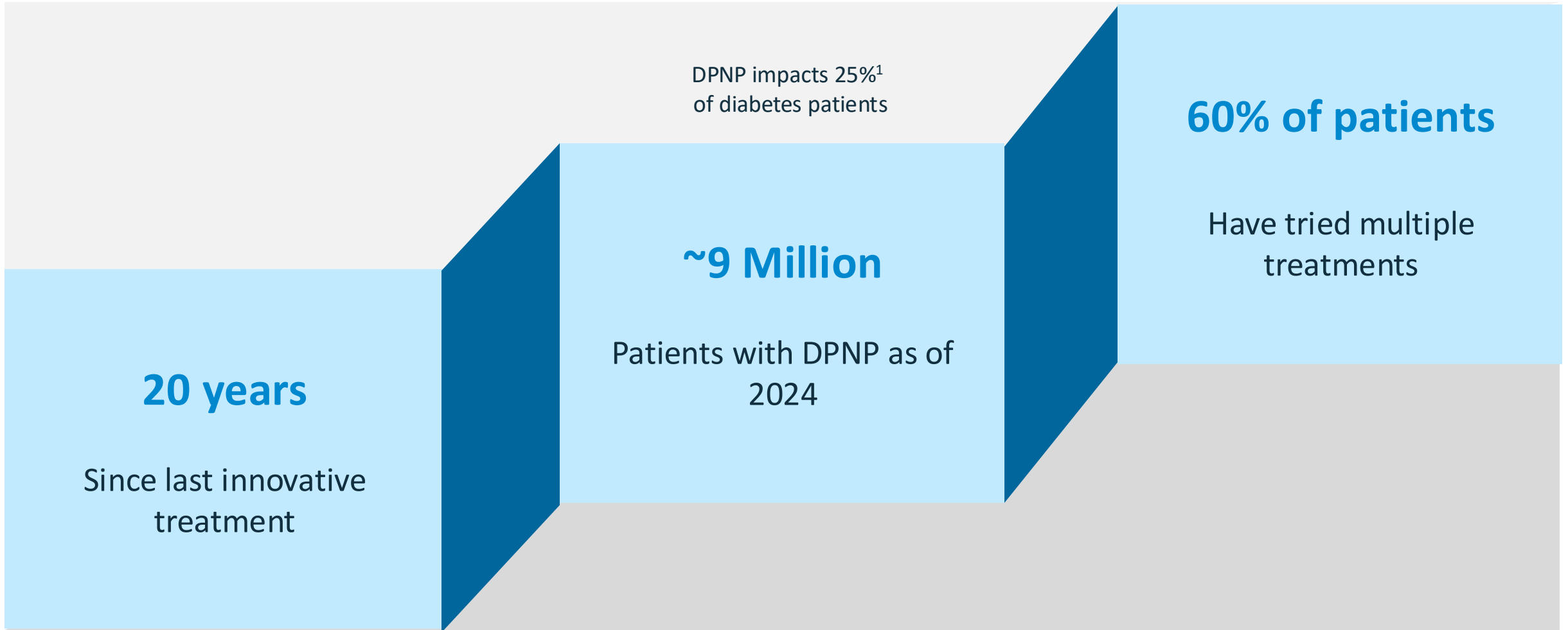


Broad Potential
including peripheral and central
neuropathic pain, and spasticity



Pragmatic Trial Design
aligned to real-life pain
management in patients

A clear need and opportunity in the DPNP treatment landscape



1) CDC National Diabetes Statistics Report 2024. Du SH, Zheng YL, Zhang YH, Wang MW, Wang XQ. The Last Decade Publications on Diabetic Peripheral Neuropathic Pain: A Bibliometric Analysis. Front Mol Neurosci. 2022 Apr 13;15:854000. doi: 10.3389/fnmol.2022.854000. PMID: 35493329; PMCID: PMC9043347. Source: prevalence rate of DPNP in diabetics is based on primary and secondary research; DPNP: diabetic peripheral neuropathic pain

2025 Year Ahead

Multiple potential catalysts for value creation in 2025



ATTRACTIVE ASSETS

- Diversified pipeline platform potential
- Partnership potential
- Earlier-stage opportunities in add'l indications



DEVELOPMENT EXPERTISE

- Clinical drug development expertise
- Adaptive, efficient trial designs
- Multiple late-stage candidates



LEAN, AGILE ORGANIZATION

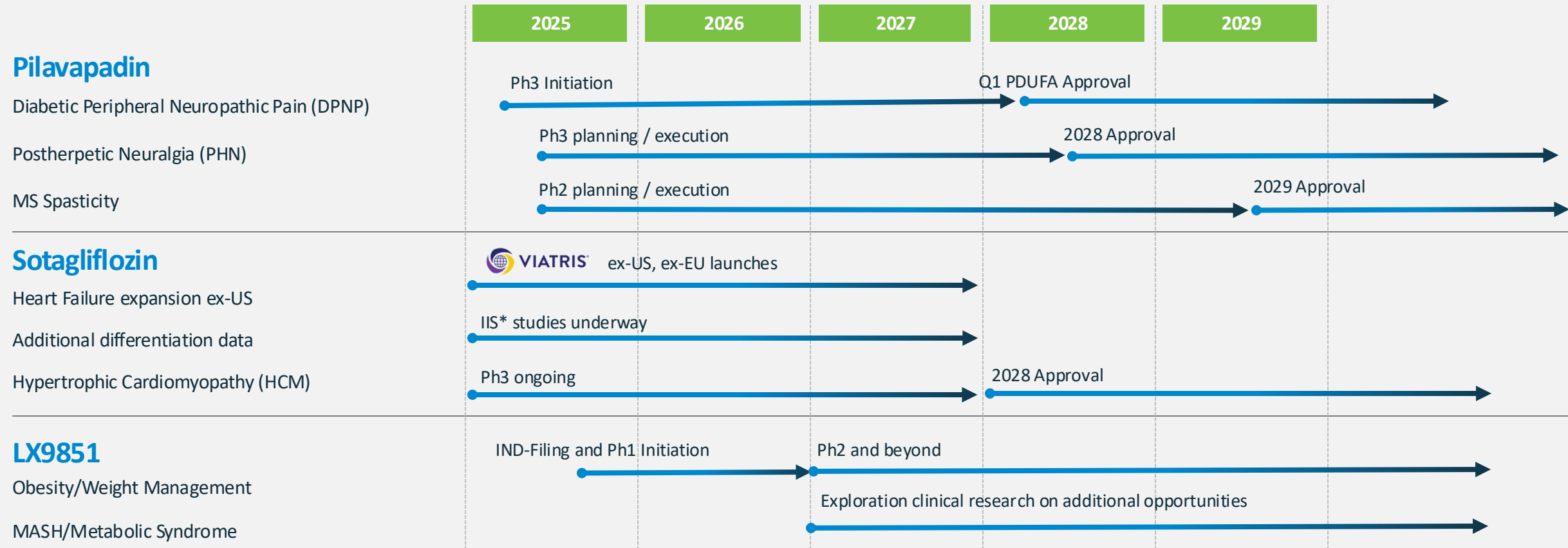
- Full focus as a development company
- Minimum viable sotagliflozin support for patient access
- Strong cash runway



NEAR-TERM CATALYSTS

- Pilavapadin Ph. 2b topline expected in 1Q
- SONATA HCM Ph. 3 enrollment underway
- Expected 2025 IND filing for LX9851

A portfolio of potential “pipelines in a pill”



Timelines are illustrative and represent potential scenarios aligned to Lexicon’s overall strategy
 * IIS: Investigator-initiated studies

Q&A



Rodica Pop-Busui, MD, PhD



Steve Edelman, MD



Mike Exton, PhD



Craig Granowitz, MD, PhD



Suma Gopinathan, PhD

Thank You