Lexicon pharmaceuticals

Corporate Presentation

November 2023

PRECISION SCIENCE. PIONEERING MEDICINE. PATIENT DRIVEN.

Forward-Looking Statements

- This presentation, including any oral presentation accompanying it, contains “forward-looking statements,” including statements about Lexicon’s strategy and operating performance and events or developments that we expect or anticipate will occur in the future, such as projections of our future results of operations or of our financial condition, the potential therapeutic and commercial potential of INPEFA® (sotagliflozin), LX9211 and our other drug programs, the success of our commercialization efforts with respect to INPEFA and any other approved products, the results of and expected timing of the completion of ongoing and future clinical trials, the expected timing and outcome of discussions with regulatory authorities regarding such trials and any applications for approval based on such trials, our other research and development efforts, and the anticipated trends in our business.
- These forward-looking statements are based on management’s current assumptions and expectations and involve risks, uncertainties and other important factors that may cause our actual results to be materially different from any future results expressed or implied by such forward-looking statements.
- Information identifying such important factors is contained in our most recent annual report on Form 10-K and quarterly reports on Form 10-Q, including the sections entitled “Risk Factors,” as well as our current reports on Form 8-K, in each case filed with the Securities and Exchange Commission.
- Lexicon undertakes no obligation to update or revise any such forward-looking statements, whether as a result of new information, future events or otherwise.

OUR MISSION

Lexicon is a biopharmaceutical company with a mission of pioneering medicines that transform patients' lives

TAKING FLIGHT – OUR STORY

Pioneering the future with a unique application of gene science, Lexicon discovers and develops innovative and precise medicines for people with serious, chronic conditions.

1. Advancing from the foundational discoveries of the Human Genome Project, Lexicon was conceived in the desire to understand the functions of those genes in mammalian physiology and behavior - and to apply that understanding to the discovery of new medicines to improve human health.

2. Lexicon embarked on the ten-year Genome5000™ project, employing knockout mice - the technology for which garnered a Nobel Prize - to systematically and genetically define the functions of approximately 5,000 genes. Using the analogy of a dictionary that gave Lexicon its name, this project brought definitions - functions - to the listing of words - genes – identified from the Human Genome Project.

3. The resulting resource provides us with unique perspective and understanding of potential therapeutic targets. We use our genetic discoveries in mammalian physiology and behavior to predict the activity of a drug targeting the protein product of that gene. Our systematic, unbiased approach provides unique insight across the genome, enabling genetically-informed drug discovery with an opportunity to open new frontiers in medicine.

Our approach to defining target proteins has so far led to the identification of more than 100 proteins with significant therapeutic potential across a range of diseases.

To date, Lexicon has advanced multiple drug candidates to human clinical trials and has conducted more than 80 clinical trials, involving tens of thousands of patients worldwide.

4. Our drug discovery efforts have yielded multiple drug candidates that have entered clinical development, and we are one of a relatively small number of companies to have brought a drug all the way to market that originated in our own laboratories, discovered by Lexicon scientists. We maintain a diverse portfolio of targets and discovery and development programs, with a focus on cardiometabolism and neuroscience.

CARDIOVASCULAR
NEUROSCIENCE
ONCOLOGY
METABOLISM
OPHTHALMOLOGY

5. This year, we are taking the next major step in our journey, bringing to market INPEFA® (sotagliflozin) for the treatment of heart failure.

6. Our unique discovery to commercialization pipeline continues to generate unique assets across diverse therapeutic areas.

The most recent of which to achieve human clinical proof-of-concept is a novel non-opioid approach to neuropathic pain, LX9211, now advancing into late stage development.

As Lexicon continues to evolve, we remain steadfast in our mission to bring new therapeutic solutions to patients in need. Our curiosity propelled us from the Human Genome Project through Genome5000™ to innovate solutions that truly impact patient lives, and our ability to deliver discoveries from within our labs all the way to market uniquely positions us for future generations of pharmaceutical innovation.

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Recently-Approved Drug and Lead Clinical Program Both Discovered Using Lexicon's Unique Approach to Gene Science

INPEFA® APPROVED FOR HEART FAILURE

- INPEFA® (sotagliflozin) is an oral drug that inhibits two proteins responsible for glucose regulation known as sodium-glucose co-transporter types 1 and 2 (SGLT1 and SGLT2)
- SGLT1 is responsible for glucose and sodium absorption in the gastrointestinal tract, and SGLT2 is responsible for glucose and sodium reabsorption by the kidney
- INPEFA has been studied in multiple patient populations encompassing heart failure, type 1 and type 2 diabetes, and chronic kidney disease in

14 PHASE 3 CLINICAL STUDIES

involving approximately 20,000 patients

LX9211 NEUROPATHIC PAIN

- LX9211 is a potent, orally delivered, selective small molecule inhibitor of adaptor-associated kinase 1 (AAK1)
- Preclinical studies of LX9211 demonstrated central nervous system penetration and reduction in pain behavior in models of neuropathic pain without affecting opiate pathways
- LX9211 has received

FAST TRACK DESIGNATION

from the U.S. Food and Drug Administration for the development in diabetic peripheral neuropathic pain

INPEFA® (sotagliflozin) for Heart Failure

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INPEFA® (sotagliflozin) Recently Approved and Commercially Launched for Treatment of Heart Failure

inpefa®
sotagliflozin tablets

INPEFA granted broad label in heart failure (HF), across full range of left ventricular ejection fraction (LVEF), including HFpEF and HFrEF, and for patients with or without diabetes

INPEFA reduced the risk of total occurrence of cardiovascular death, hospitalization for HF, and urgent HF visits by 33% compared to placebo in the SOLOIST-WHF study of worsening HF patients initiated on therapy in the hospital or promptly following discharge

Recently adopted guidelines support use of SGLT inhibitors like INPEFA in all heart failure patients, the only class of therapy recommended as foundational treatment regardless of LVEF, and specifically cite SOLOIST-WHF

Cycle of Heart Failure Hospitalizations Presents an Increasingly Costly Challenge

~6.7

million heart failure prevalence in the U.S. (in 2019)

~8.5

million heart failure prevalence in the U.S. projected by 2030

#1

cause of hospitalizations for Americans 65+ is heart failure

1.3

million hospitalizations for heart failure annually in the US

25%

of patients readmitted to hospital within 30 days

65%

of patients readmitted to hospital within a year

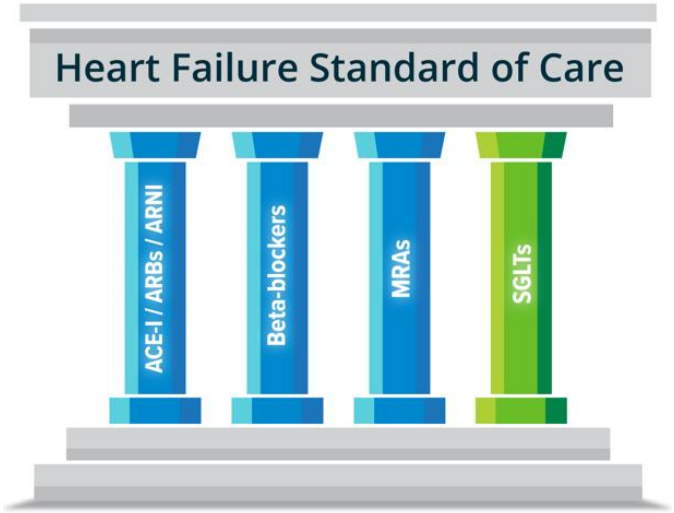
80%

of total heart failure costs are related to hospitalization

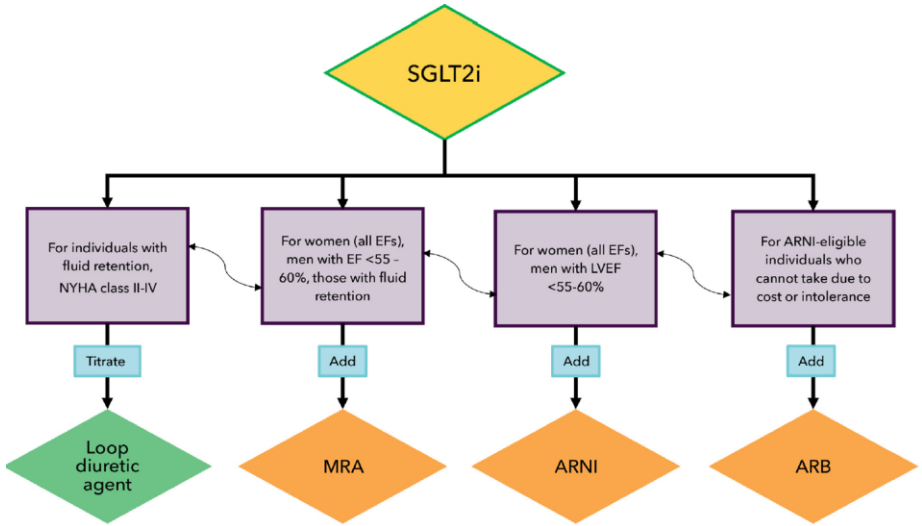
Roger VL. Epidemiology of heart failure. Circ Res. 2013.
Tsao et al. Heart Disease and Stroke Statistics—2023 Update. Circulation. January 2023.
Bozkurt B et al. Heart Failure Epidemiology and Outcomes Statistics: A Report of the Heart Failure Society of America. JCF. October 2023.
Dharmarajan et al. Diagnoses and Timing of 30-Day Readmissions after Hospitalization For Heart Failure, Acute Myocardial Infarction, or Pneumonia. JAMA. 2013.
Givertz, et al. Resource utilization and costs among patients with heart failure with reduced ejection fraction following a worsening heart failure event. ESC Heart Failure. 2021.

New Guidelines Recommend SGLT Inhibitors for all Heart Failure Patients – *Regardless of Left Ventricular Ejection Fraction*

HFrEF



HFpEF



2022

AHA/ACC/HFSA Joint Guideline for the Management of Heart Failure specifically recommend SGLT inhibitors for the prevention and treatment of heart failure

2023

ACC Expert Consensus Decision Pathway on Management of Heart Failure with Preserved Ejection Fraction recommends SGLT2i as first-line therapy in adults with HFpEF

SGLTi class is the only class recommended as foundational in treatment of heart failure regardless of ejection fraction

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Updated Guidelines and Clinical Data Are Fueling Growth of the HF-indicated SGLT Inhibitors, with Substantial Opportunity Ahead

1 of 3

inpefa®
sotagliflozin tablets

INPEFA is 1 of 3 SGLT inhibitors indicated for heart failure

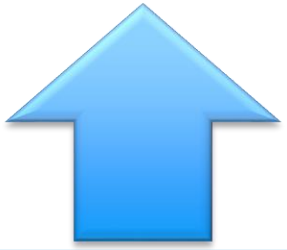
>70%

SGLT use in heart failure has grown by 73% year over year through August 2023[1]

~11%

As of August 2023, only ~1 in 10 heart failure prescriptions are for an SGLT inhibitor[2]

~40%

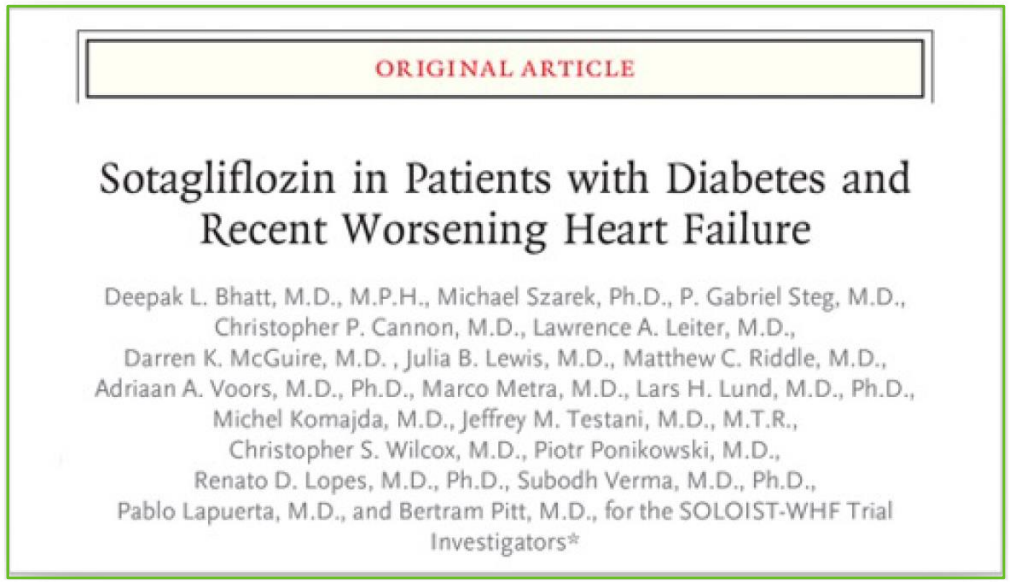


Growth of branded heart failure market from 2021 to 2022[1]

1. Based on internal Lexicon data analysis
2. Based on IQVIA prescription data

INPEFA was Studied in Two Pivotal Trials with Unique and High-risk Patient Populations

The NEW ENGLAND JOURNAL of MEDICINE



ORIGINAL ARTICLE

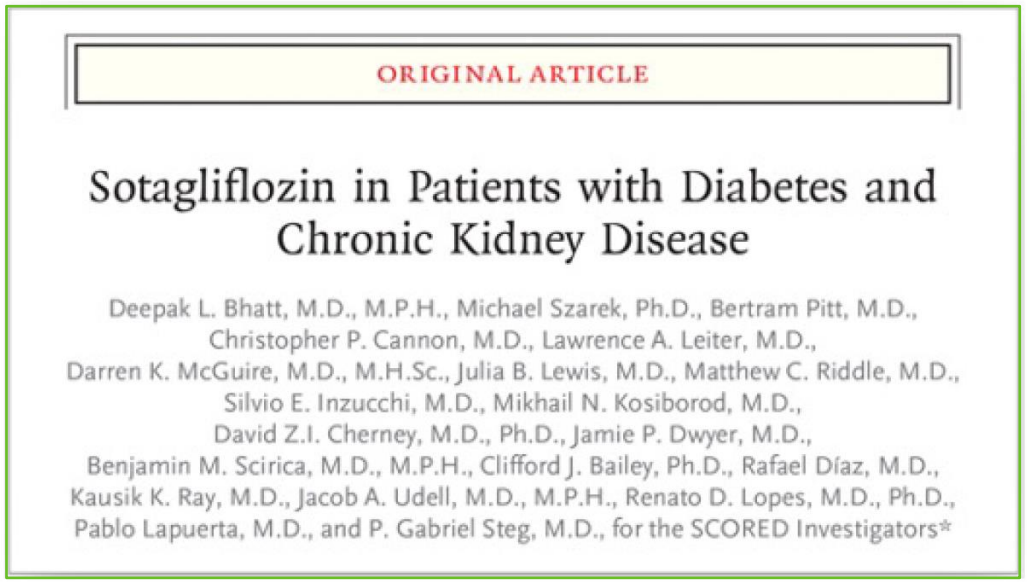
Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

Deepak L. Bhatt, M.D., M.P.H., Michael Szarek, Ph.D., P. Gabriel Steg, M.D., Christopher P. Cannon, M.D., Lawrence A. Leiter, M.D., Darren K. McGuire, M.D., Julia B. Lewis, M.D., Matthew C. Riddle, M.D., Adriaan A. Voors, M.D., Ph.D., Marco Metra, M.D., Lars H. Lund, M.D., Ph.D., Michel Komajda, M.D., Jeffrey M. Testani, M.D., M.T.R., Christopher S. Wilcox, M.D., Piotr Ponikowski, M.D., Renato D. Lopes, M.D., Ph.D., Subodh Verma, M.D., Ph.D., Pablo Lapuerta, M.D., and Bertram Pitt, M.D., for the SOLOIST-WHF Trial Investigators*

SOLOIST

1,222 Patients

The SOLOIST study evaluated the efficacy and safety of INPEFA in patients with worsening HF, regardless of EF



ORIGINAL ARTICLE

Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease

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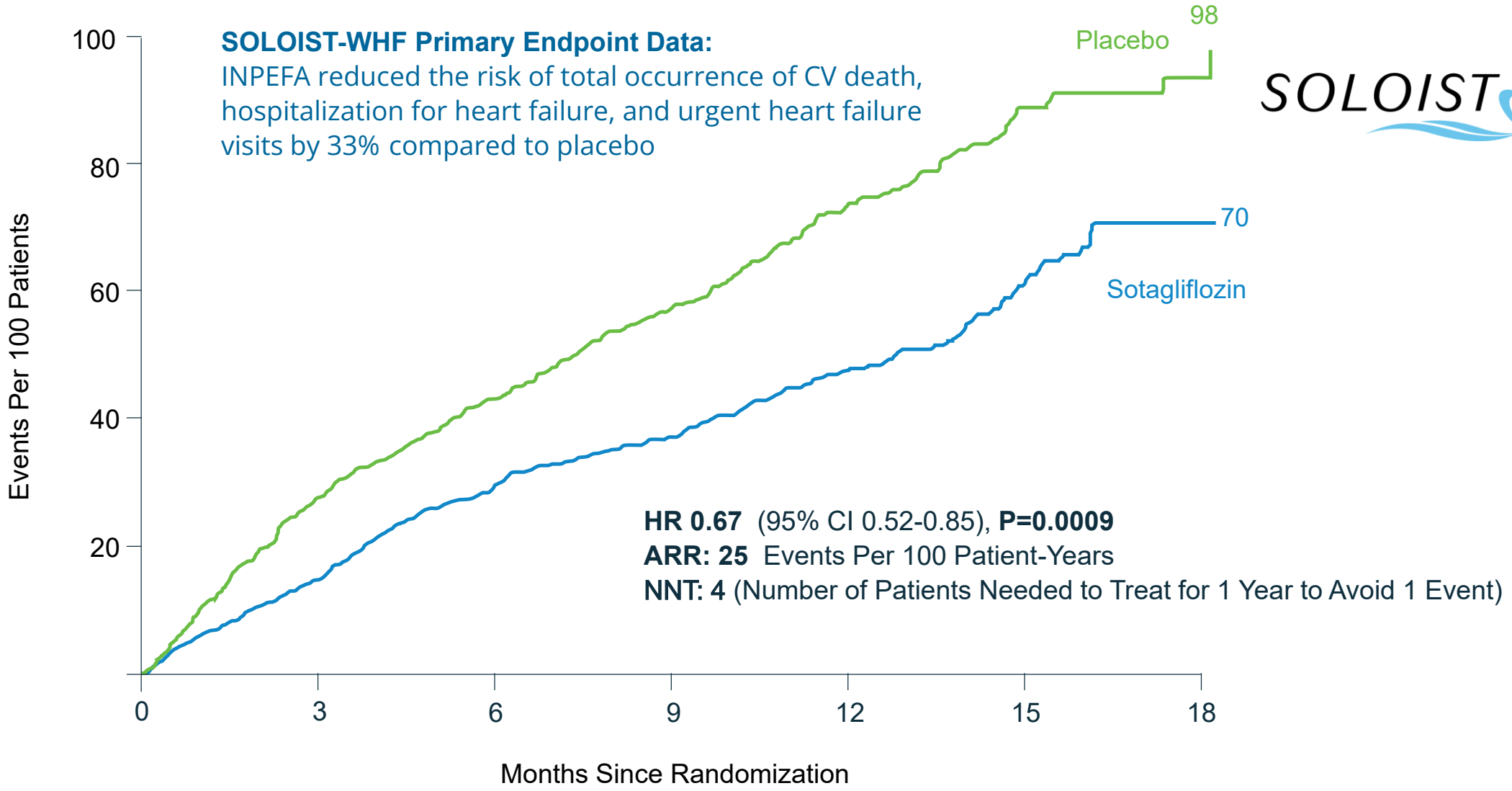
SCORED

10,584 Patients

The SCORED study evaluated INPEFA in patients with comorbidities and CV risk factors, regardless of EF

INPEFA Labeled with Reduction in CV Death and HF Events in Patients Initiated on Therapy in the Hospital or Promptly Following Discharge

SOLOIST-WHF Primary Endpoint Data:
INPEFA reduced the risk of total occurrence of CV death, hospitalization for heart failure, and urgent heart failure visits by 33% compared to placebo



SOLOIST

HR 0.67 (95% CI 0.52-0.85), **P=0.0009**
ARR: 25 Events Per 100 Patient-Years
NNT: 4 (Number of Patients Needed to Treat for 1 Year to Avoid 1 Event)

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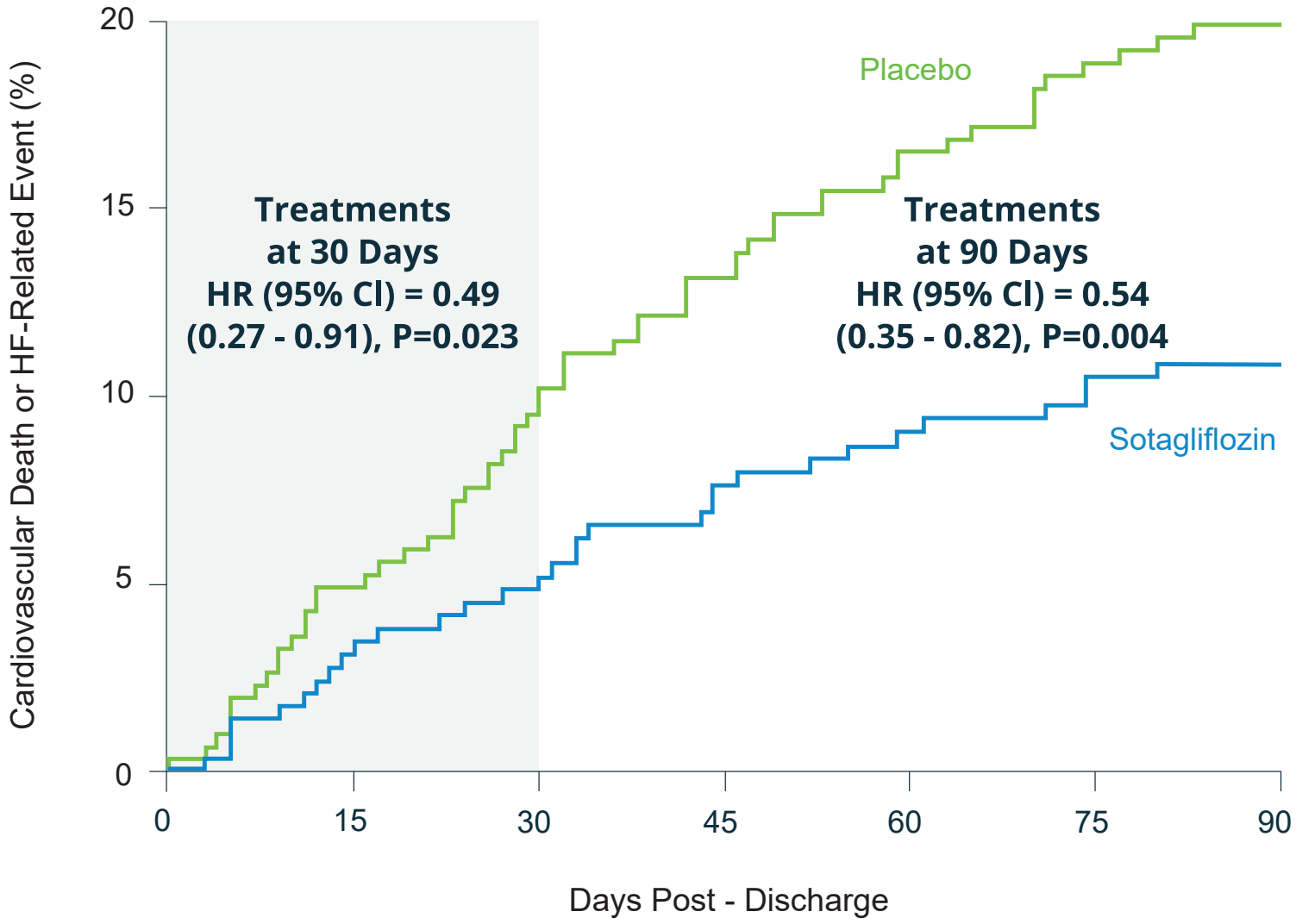
Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. N Engl J Med. 2021.

INFEFA Reduced CV Death and HF Events by 50% Over the First 30 and 90 Days Post Discharge



SOLOIST

Early effect of INPEFA demonstrated in reduction of 30-day Hospital Readmissions

Pitt B et al. AHA 2022.

INPEFA Launch Scorecard: Q3 Has Seen a Significant Ramp in Commercialization Activity and Output

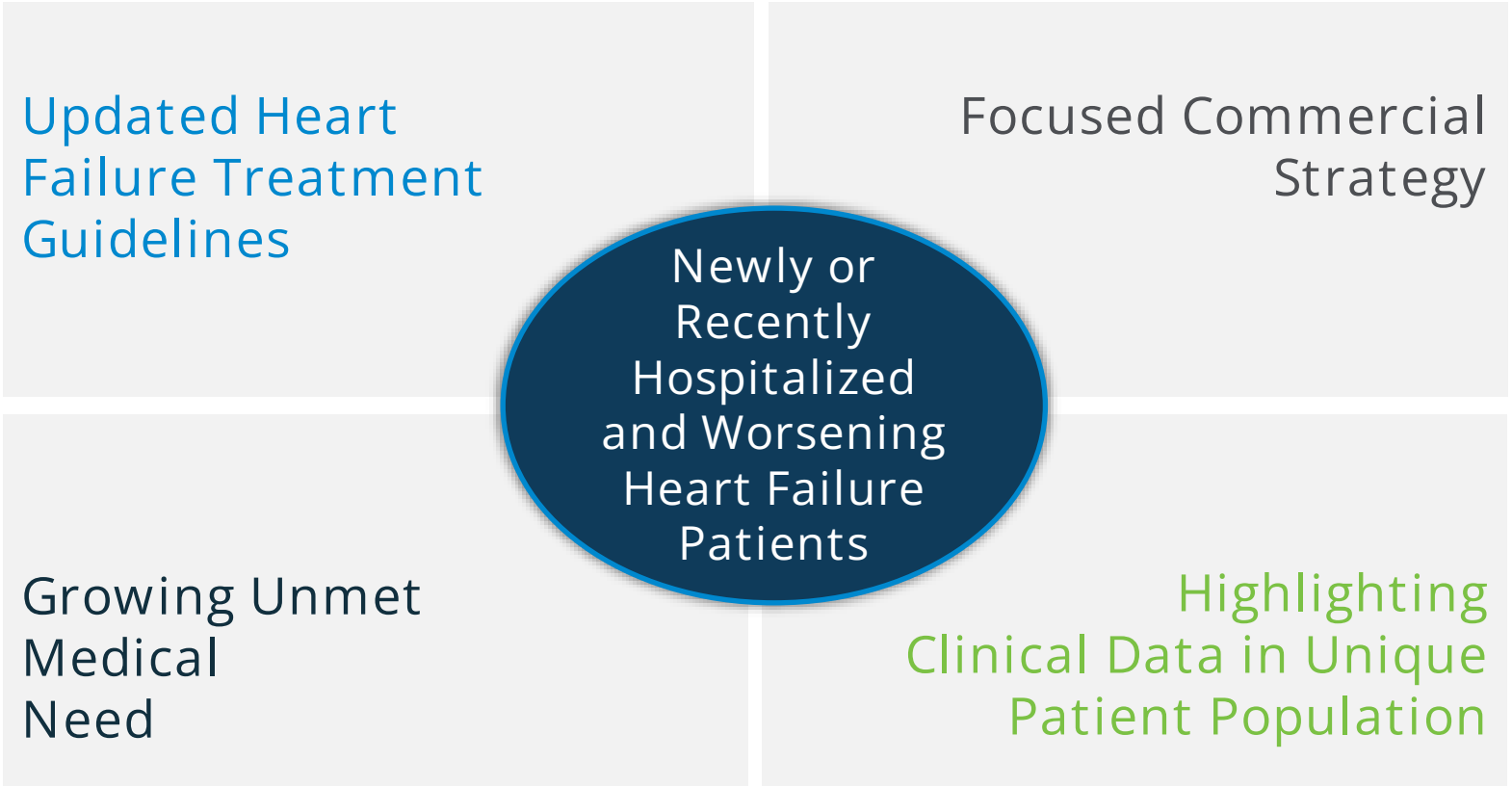
Demand Generation

- Driving awareness and broad adoption of INPEFA among prescribers who treat the most heart failure patients in the U.S.
- The number of INPEFA trialists has grown throughout Q3 and remains key strategic area of focus
- Demand, as seen through submitted claims data, has outpaced filled prescriptions as formulary access continues to build

Formulary Access

- Focused on national and regional payer plans, with all targeted plans actively engaged
- Key formulary access contracts have been executed in Q3 in both Medicare and Commercial channels with continued progress expected through Q4
- Integrated Delivery Networks (IDNs) remain a strategic focus given the uniqueness of the SOLOIST patient population and strength of INPEFA rehospitalization data

Significant Commercial Opportunity for INPEFA



02

LX9211 for Neuropathic Pain

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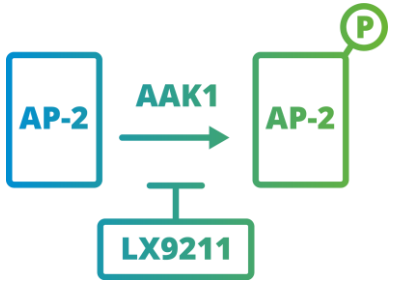
LX9211 has the Potential to Redefine the Standard of Care for Patients Suffering with DPNP – Fast Track Designation by FDA

HIGH UNMET MEDICAL NEED

- More than **20 million Americans** experience neuropathic pain
- Approximately **5 million DPNP patients** in the U.S. in 2022
- Current **standard of care does not eliminate neuropathic pain** for most patients, and many experience **undesirable side effects**

PROOF OF CONCEPT ACHIEVED

- The RELIEF-DPN-1 and RELIEF-PHN-1 studies support AAK1 inhibition as a **potential new MOA** for **multiple neuropathic pain conditions**
- Potential as the **first new MOA of significance** for neuropathic pain in **over two decades**

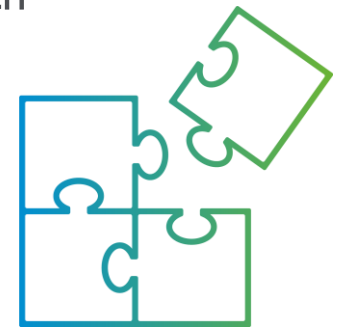


ADVANCEMENT OF CLINICAL PROGRAM

- Phase 2 studies support the **advancement** of LX9211 into late-stage development
- **FDA feedback** aligned with late-stage development plan
- **Phase 2b study commencing this year** in diabetic peripheral neuropathic pain (DPNP)

SIGNIFICANT COMMERCIAL OPPORTUNITY

- Targeting a **novel, non-opioid approach** to treat neuropathic pain
- Entry into a market with a large unmet medical need and **multibillion dollar market potential**
- Could become a **valuable future addition** to current treatment options



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Patient Data: Decision Resources Group, Landscape & Forecast Neuropathic Pain Report, June 2020
Massachusetts General Hospital. Neuropathy Overview. [Internet] 2021
Schembri, E. Are Opioids Effective in Relieving Neuropathic Pain? SN Compr. Clin. Med. 1, 30–46 (2019)
Finnerup et al. Algorithm for neuropathic pain treatment: an evidence-based proposal. Pain 2005; 118(3): 289-305

AAK1 – Adaptor-associated Protein Kinase 1

AAK1 is a Novel Target for Neuropathic Pain

AAK1: AP2-associated protein kinase 1

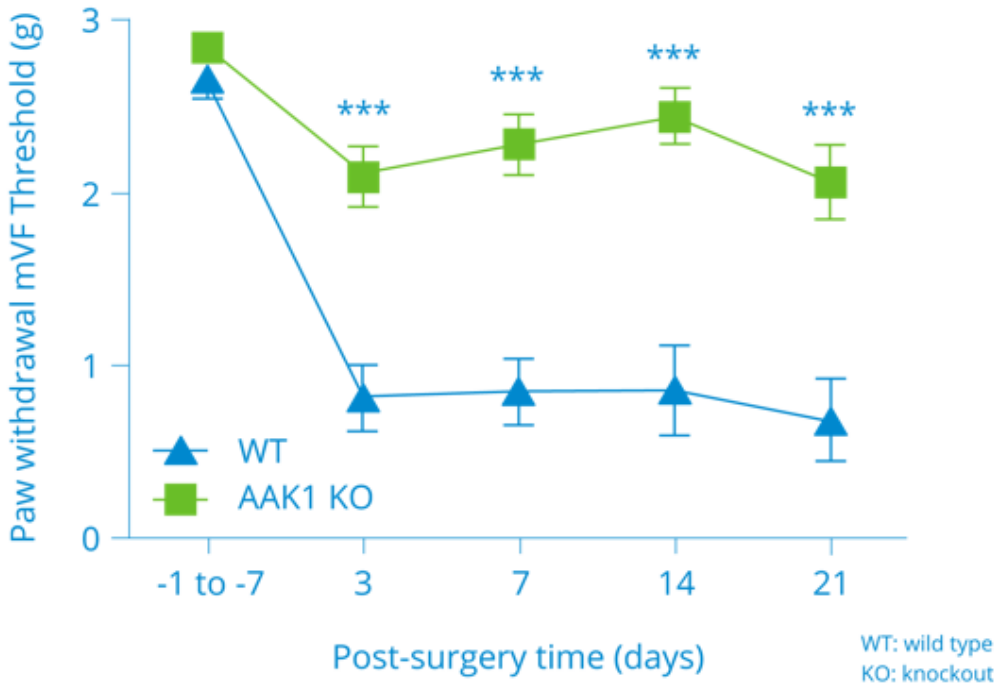
- AAK1 regulates clathrin-mediated endocytosis
- AAK1 knockout mice were resistant to development of neuropathic pain
- Mechanism of action:
  - does not involve the opioid pathway
  - involves the α2 adrenergic receptor pathway

LX9211 is a potent, highly-selective, small molecule inhibitor of the novel target, AAK1

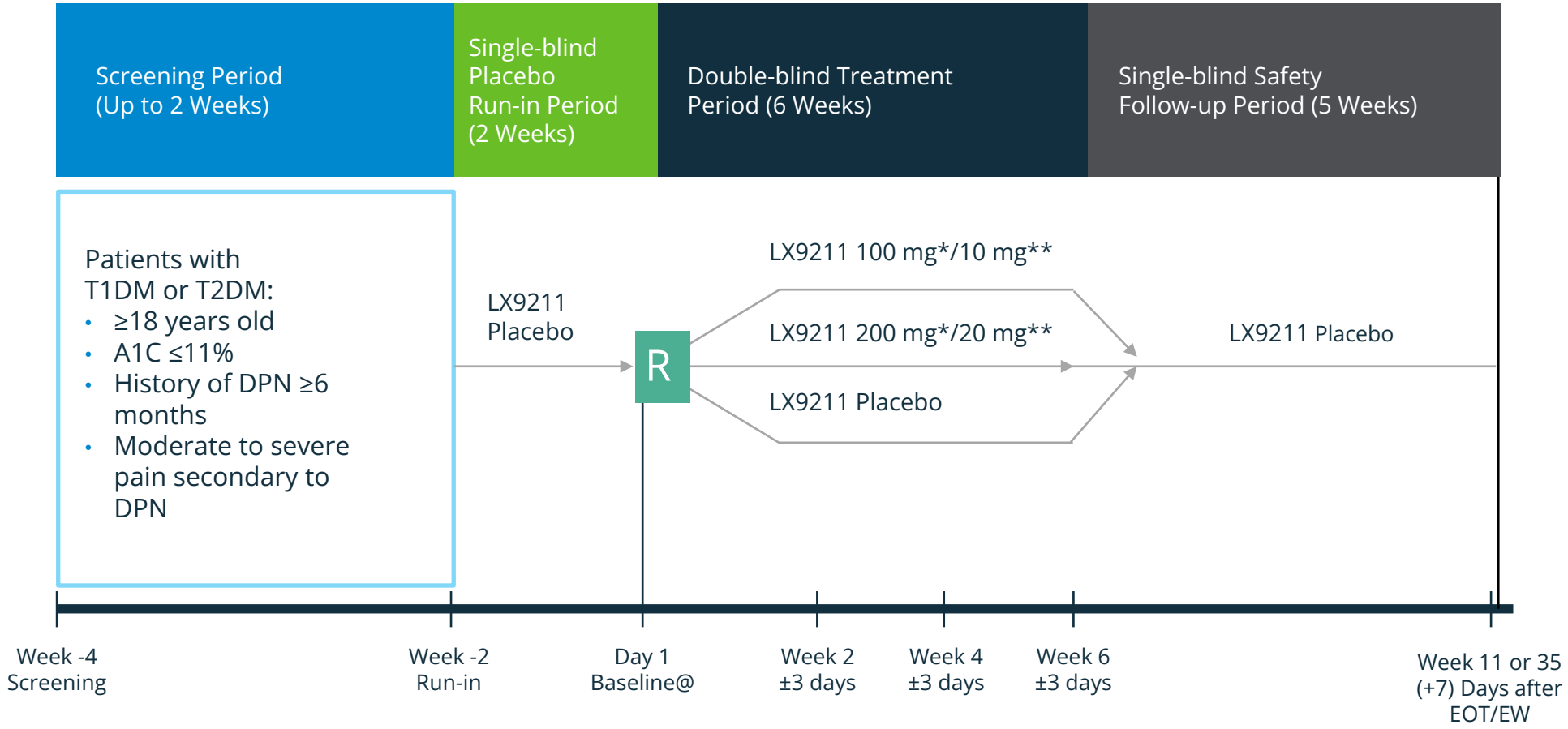
Advancing into late-stage development

AAK1 Knockout Mice

Spinal Nerve Ligation Model



RELIEF-DPN-1: Efficacy, Safety, and PK of LX9211 in Patients with Diabetic Peripheral Neuropathic Pain (DPNP)

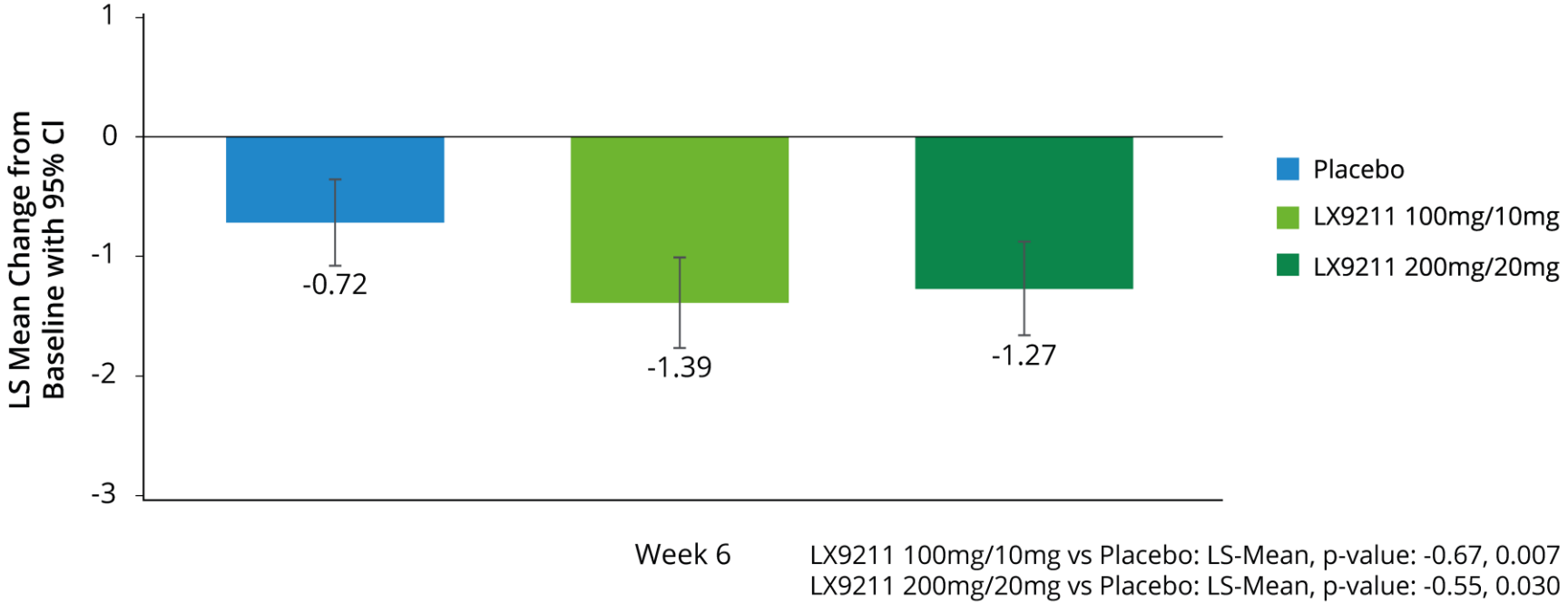


R = randomization
EOT = end of treatment
EW = early withdrawal

* Loading Dose (Day 1)
** Maintenance Dose (Day 2 – Week 11 Visit)
@ Day 1 may occur up to 2 weeks plus 3 days after start of the Run-in period

LX9211 Achieved the Primary Endpoint in RELIEF-DPN-1

Statistically significant reduction in average daily pain score (ADPS) at Week 6 compared to placebo in the low dose arm with results that plateaued in the high dose arm



Effect on ADPS consistent across age, sex, use of baseline DPNP medications, and baseline pain score

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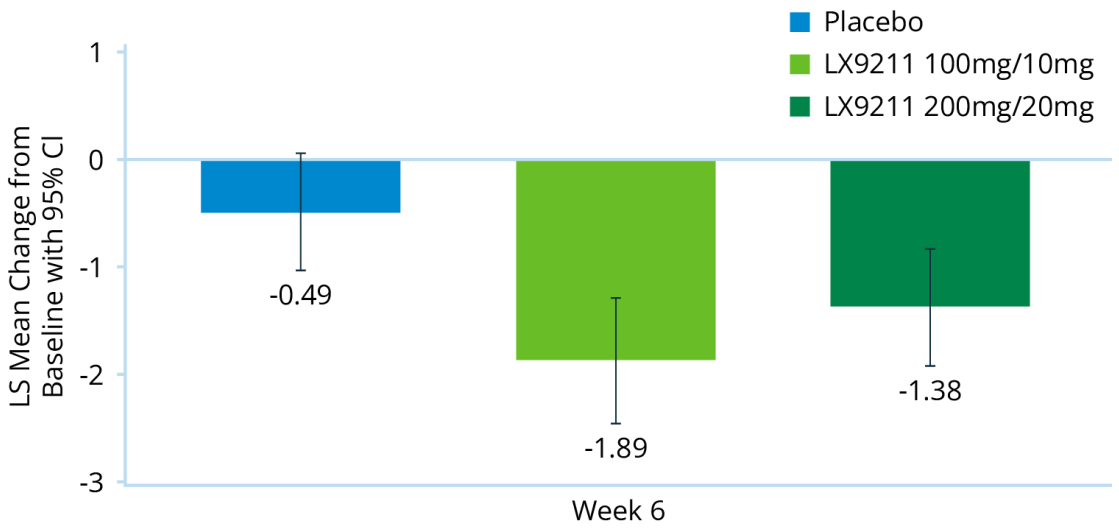
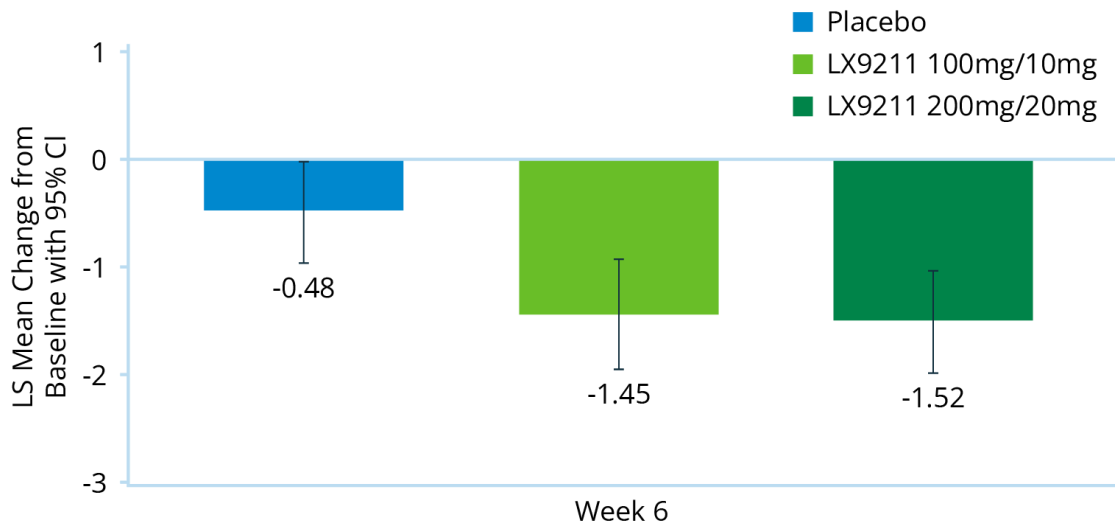
Significant Benefits Demonstrated in Both Burning Pain and On Pain Interference with Sleep

LS MEAN CHANGE FROM BASELINE IN BURNING PAIN



LX9211 100mg/10mg vs Placebo: LS-Mean, p-value: -1.40, <.001
LX9211 200mg/20mg vs Placebo: LS-Mean, p-value: 0.89, 0.017

LS MEAN CHANGE FROM BASELINE IN INTERFERENCE IN SLEEP



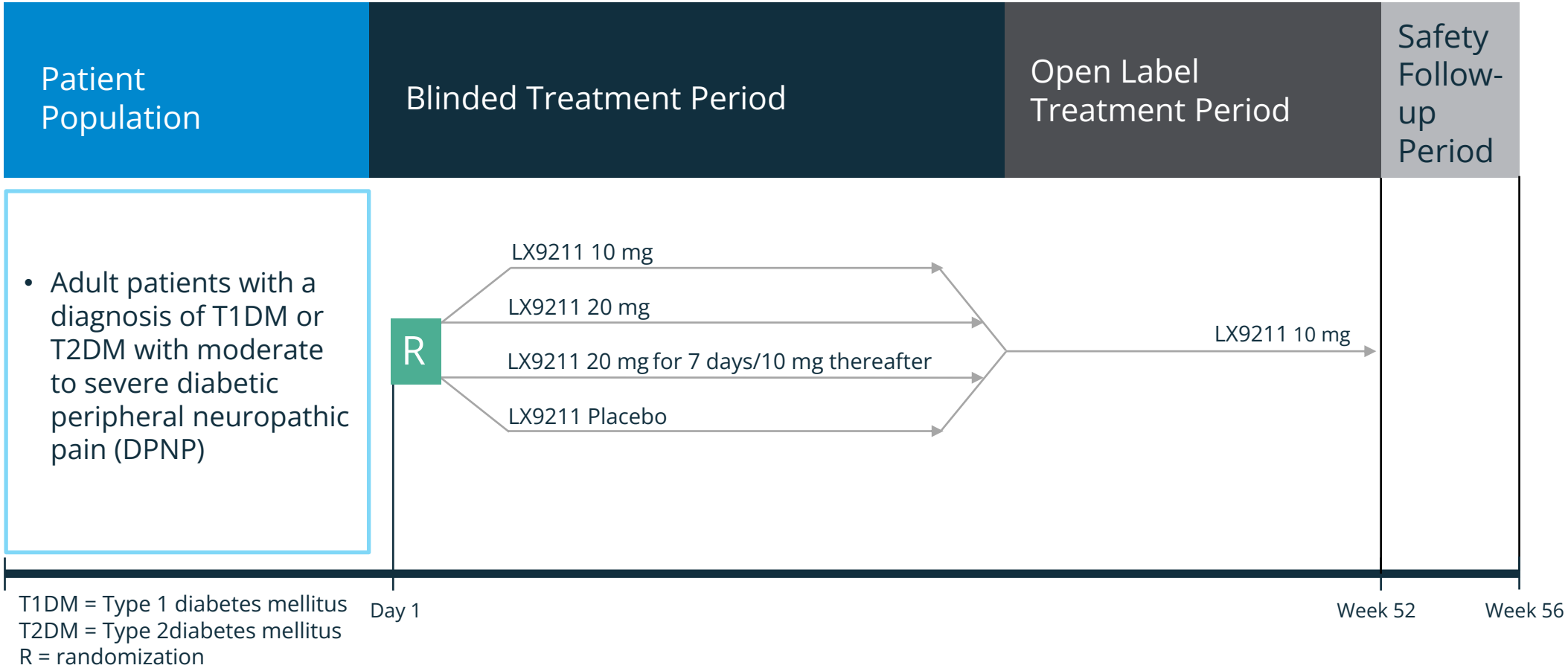
LX9211 100mg/10mg vs Placebo: LS-Mean, p-value: -0.96, 0.005
LX9211 200mg/20mg vs Placebo: LS-Mean, p-value: -1.04, 0.002

LX9211 Advancing into Late-stage Development in DPNP

- DPNP represents the largest market opportunity indication within neuropathic pain
- FDA feedback obtained in Q2 2023 and has been adapted into the development plan
  - Average Daily Pain Score (ADPS) will continue to be the primary endpoint of the studies
- Planned clinical program optimizes opportunities for success, time and efficiency in satisfying regulatory requirements for approval
- The first late-stage development study, named PROGRESS, will:
  - Provide dose optimization data to inform Phase 3 pivotal study design
  - Include a long-term extension to satisfy ICH exposure requirements which will run in parallel with Phase 3

The PROGRESS Study will enable more efficient Phase 3 study execution and de-risk investment, while maintaining overall development program cost and timelines

The PROGRESS Study – Patient Enrollment Will Begin in December, First Data Read-out Expected in Q2 '25



Study Enrollment: ~400 patients, ~100 patients per arm

03

Financial Information and Q3 Summary

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Q3 2023 Financial Summary

	As of Sept 30, 2023	As of Dec 31, 2022
Cash, cash equivalents and short-term investments	$218.4M	$138.4M
Total assets	$276.5M	$194.3M
Long-term debt	$99.3M	$48.6M

Loan facility with Oxford Finance provides up to $50 million in additional borrowing capacity designed primarily to support the commercial launch of INPEFA in heart failure, should it be needed.

	Q3 2023	Q3 2022
Total revenues	$0.16M	$0.039M
Operating expenses		
R&D[1]	$17.6M	$10.6M
SG&A[1]	$32.2M	$12.6M
Total operating expenses	$49.8M	$23.1M
Net loss	($50.5M)	($23.4M)
Net loss per common share	($0.21)	($0.13)

Full Year Expense Guidance	2023
Operating Expenses	
R&D	$60M - $70M
SG&A	$110M - $120M
Total operating expenses	$170M - $190M
Non-cash Expenses[2]	$17M-$18M

1. Includes stock-based compensation expenses
2. Non-cash expenses, consisting primarily of stock-based comp, with ~$2mm in depreciation and amortization

Lexicon Q3 2023: Meaningful Progress and Growth of INPEFA Coupled with Significant Advancement of LX9211 Program

Launch of INPEFA into large and fast-growing heart failure market

- INPEFA granted a broad label across full range of left ventricular ejection fraction, incorporating unique data from SOLOIST focused on patients recently hospitalized for heart failure
- First full quarter after launch has shown meaningful increases in both demand and filled scripts
- Market access coverage has improved through Q3 with additional plans expected to be added in Q4 2023

LX9211 moves into late-stage development for DPNP – FDA Fast Track

- Supported by data from Phase 2 proof-of-concept studies in both diabetic peripheral neuropathic pain (DPNP) and post-herpetic neuralgia (PHN)
- First patient enrollment expected for Phase 2b PROGRESS study in early December, initiating full, late-stage development program for DPNP
- Potential to be the first major drug innovation in many years in large, underserved neuropathic pain market

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Thank You

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