Lexicon pharmaceuticals

Corporate Presentation

March 2024

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.
- This presentation shall not constitute an offer to sell or the solicitation of an offer to buy these securities, nor shall there be any sale of these securities in any state or jurisdiction in which such offer, solicitation, or sale would be unlawful prior to registration or qualification under the securities laws of any such state or jurisdiction.

Lexicon's Evolution from a Unique Foundation in Mammalian Genetics

As Lexicon continues to evolve, we remain steadfast in our mission to bring new therapeutic solutions to patients in need.

Advancing from the foundational discoveries of the Human Genome Project...

Lexicon embarked on the ten-year Genome5000™ project, to systematically define the functions of approximately 5,000 genes in mammalian physiology and behavior, enabling prediction of the activity of a drug targeting the protein product of that gene.

The resulting resource provides us with unique perspective and understanding of potential therapeutic targets, enabling genetically-informed drug discovery.

CARDIOVASCULAR
METABOLISM
NEUROSCIENCE

Our efforts have yielded multiple drug candidates, two of which we have brought all the way to market.

And we maintain a diverse portfolio of targets and programs.

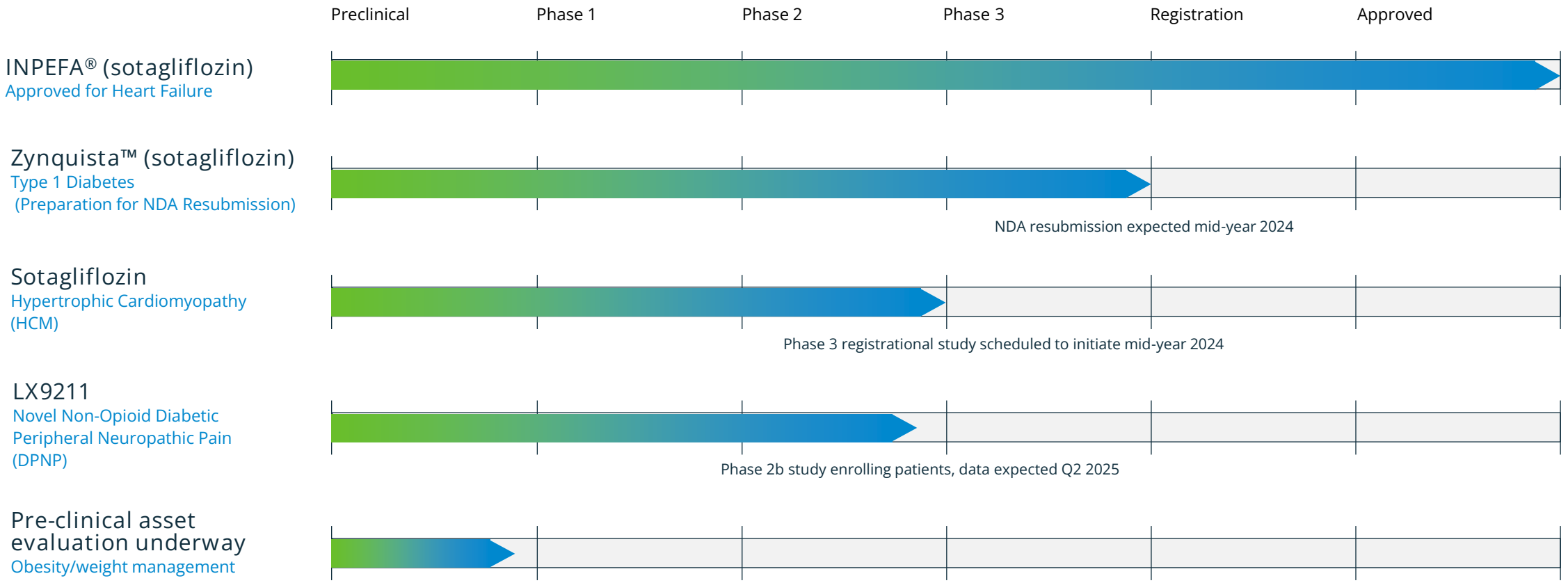
inpefa
sotagliflozin tablets

In 2023 we took the next major step in our journey, bringing to market INPEFA® (sotagliflozin) for the treatment of heart failure.

Also from our discovery engine, a novel non-opioid approach to neuropathic pain, LX9211, has advanced into late-stage development. And we are preparing an NDA resubmission for sotagliflozin in type 1 diabetes with chronic kidney disease.

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.

Lexicon – Leveraging Scientific Platform and Expertise to Build Strong Pipeline Opportunities for Growth and Partnership



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

inpefa®
sotagliflozin tablets

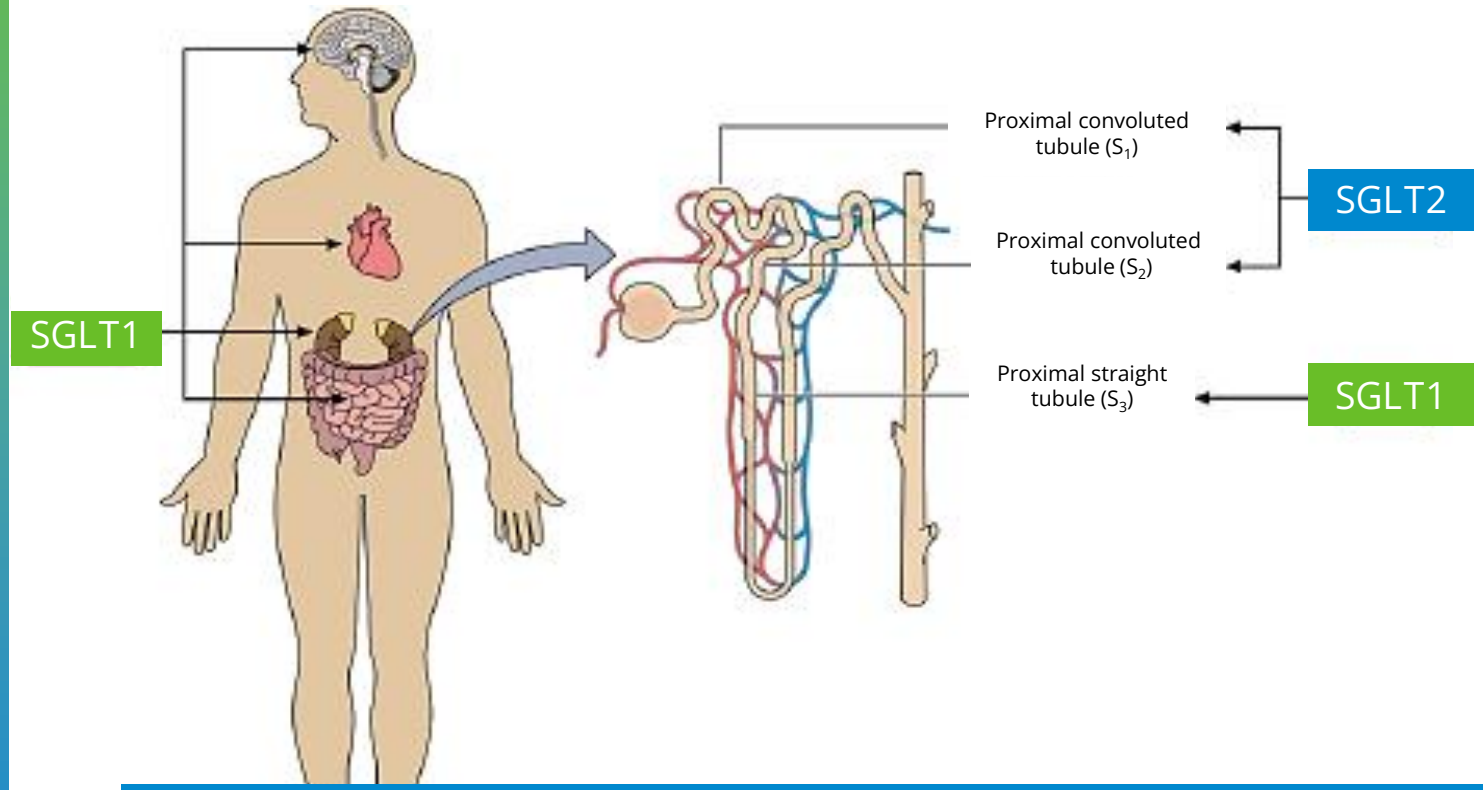
INPEFA granted broad label in heart failure (HF), across full range of left ventricular ejection fraction (LVEF), including HFpEF and HFrEF, and for patients with or without diabetes

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

Sotagliflozin Inhibits Two Targets With Important Cardiometabolic Profiles

Sotagliflozin is an oral inhibitor of sodium-glucose cotransporters -1 (SGLT1) and -2 (SGLT2), responsible for absorption (or reabsorption) of sodium and glucose



SGLT2 is expressed in the kidney, where it reabsorbs 90% of filtered glucose

SGLT1 is the primary transporter for absorption of glucose and galactose in the GI tract

Lexicon's Genome5000 program identified SGLT1 and SGLT2 as compelling cardiometabolic targets and provided evidence of benefit of inhibiting SGLT1 in addition to SGLT2

INPEFA is the only SGLT inhibitor with SGLT 1 inhibition uniquely recognized in its label

Elevations of SGLT1 and SGLT2 are Separately Associated with Heart Failure and Other Cardiometabolic Diseases

Left ventricle:

- Heart failure[1-4]
- Dilated cardiomyopathy[1]
- Ischemic heart disease with/without type 2 diabetes[1-3]
- Diabetic cardiomyopathy[3,4]

Small intestine:

- Type 2 diabetes[5]

Kidney:

- Diabetic nephropathy[6]
- Heart failure[7,a]

[a]Rat coronary artery ligation model of heart failure.

1. Sayour AA et al. *Cardiovasc Diabetol*. 2020;19(1):159. doi:10.1186/s12933-020-01141-1 2. Di Franco A et al. *Int J Cardiol.* 2017;243:86-90. doi:10.1016/j.ijcard.2017.05.032
3. Banerjee SK et al. *Cardiovasc Res.* 2009;84(1):111-118. doi:10.1093/cvr/cvp190 02537 4. Lambert R et al. *J Am Heart Assoc*. 2015;4:e002183 doi:10.1161/JAHA.115.002183
5. Dyer J et al. *Am J Physiol Gastrointest Liver Physiol*. 2002;282:G241–248. doi: 10.1152/ajpgi.00310.2001 6. Wang XX et al. *J Biol Chem*. 2017;292(13):5335-5348. doi:10.1074/jbc.M117.779520
7. Katsurada K et al. *Circ Heart Fail*. 2021;14(12):e008365. doi:10.1161/CIRCHEARTFAILURE.121.008365. 8. Seidelmann SB et al. *J Am Coll Cardiol*. 2018;72(15):1763-1773. doi:10.1016/j.jacc.2018.07.061

Human Genetics Provides Further Support for SGLT1 as a Target for Heart Failure and Cardiometabolic Disease

SGLT1 elevated in

Left ventricle
- Heart failure[1-4]
- Dilated cardiomyopathy[1]
- Ischemic heart disease with/without type 2 diabetes[1-3]
- Diabetic cardiomyopathy[3,4]

Small intestine
- Type 2 diabetes[5]

SGLT2 elevated in

Kidney
- Diabetic nephropathy[6]
- Heart failure[7,a]

Naturally-Occurring SGLT1 Reduced Function Variant[8]

	Adjusted HR (95% CI)	*P* Value
Incident diabetes	0.81 (0.69–0.94)	0.006
Heart failure	0.74 (0.60–0.91)	0.0046
Risk of HF or death	0.80 (0.71–0.90)	0.00089

[a]Rat coronary artery ligation model of heart failure.

1. Sayour AA et al. *Cardiovasc Diabetol*. 2020;19(1):159. doi:10.1186/s12933-020-01141-1 2. Di Franco A et al. *Int J Cardiol.* 2017;243:86-90. doi:10.1016/j.ijcard.2017.05.032
3. Banerjee SK et al. *Cardiovasc Res.* 2009;84(1):111-118. doi:10.1093/cvr/cvp190 02537 4. Lambert R et al. *J Am Heart Assoc*. 2015;4:e002183 doi:10.1161/JAHA.115.002183
5. Dyer J et al. *Am J Physiol Gastrointest Liver Physiol*. 2002;282:G241–248. doi: 10.1152/ajpgi.00310.2001 6. Wang XX et al. *J Biol Chem*. 2017;292(13):5335-5348. doi:10.1074/jbc.M117.779520
7. Katsurada K et al. *Circ Heart Fail*. 2021;14(12):e008365. doi:10.1161/CIRCHEARTFAILURE.121.008365. 8. Seidelmann SB et al. *J Am Coll Cardiol*. 2018;72(15):1763-1773. doi:10.1016/j.jacc.2018.07.061

01

Zynquista™ (sotagliflozin) for Type 1 Diabetes

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Type 1 Diabetes: Substantial Opportunity in Area of High Unmet Medical Need – Up to $1B Opportunity

Type 1 diabetes is a form of diabetes mellitus with complete insulin deficiency due to destruction of beta cells in the pancreas

Clinical results suggest that sotagliflozin provides:

- Glycemic control on top of optimized insulin
- Reduction in body weight
- Reduction in blood pressure
- Improvement in time-in-range
- Reduction in risk of hypoglycemia

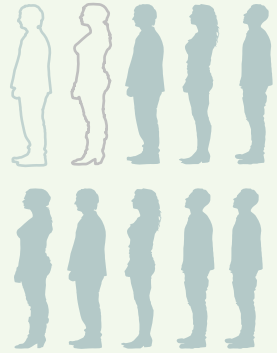
US EPIDEMIOLOGY

1.7M adults with T1D[1]

21% have Chronic Kidney Disease[2]

42% with high blood pressure*[3]

66% are obese or overweight for patients >25 years[4]



UNMET NEEDS DESPITE INSULIN THERAPY

>79% A1C >7%[3]

85%+ Confirmed Hypoglycemia**[5]

5-8% DKA[6]

~50% A1C >8%[3]

13%+ Severe Hypoglycemia**[5]

Average 12hrs Spent out of target glycemic range each day despite optimal insulin therapy[7]

*Lexicon's projection

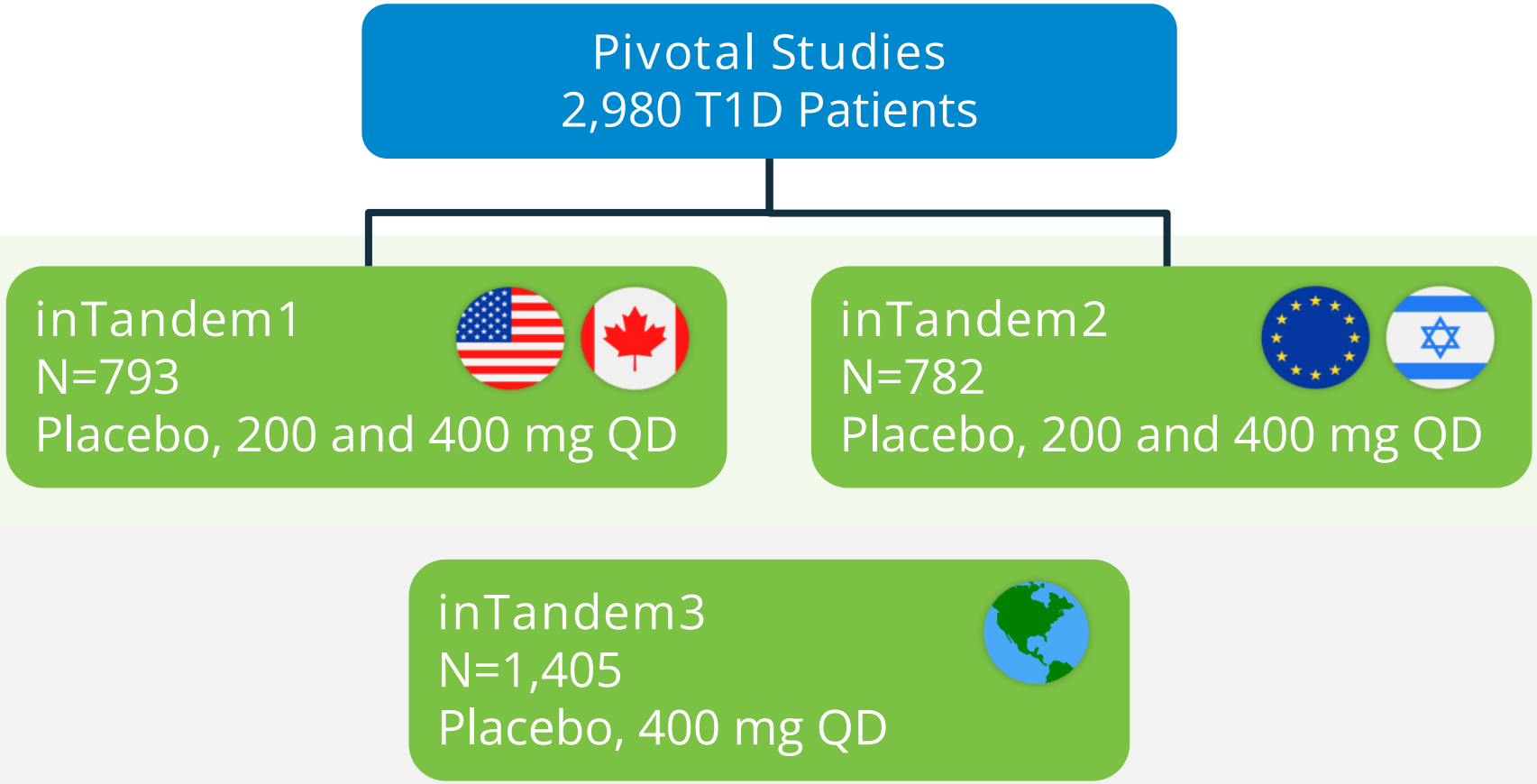
1. Centers for Disease Control and Prevention National Diabetes Statistics Report (2021 Estimates); 2. Rossing P. et al. *Diabetes* 2023; 3. T1D Exchange Registry Data; 4. Miller *et al.* 2015; 5. Cariou B, et al. 2015 ; 6. Weinstock *et al.* 2013; 7. Danne *et al.* 2019; *Based on the latest definition of hypertension: SBP ≥130 or DBP ≥80

Following FDA Feedback, Lexicon is Preparing to Resubmit NDA for Type 1 Diabetes with CKD

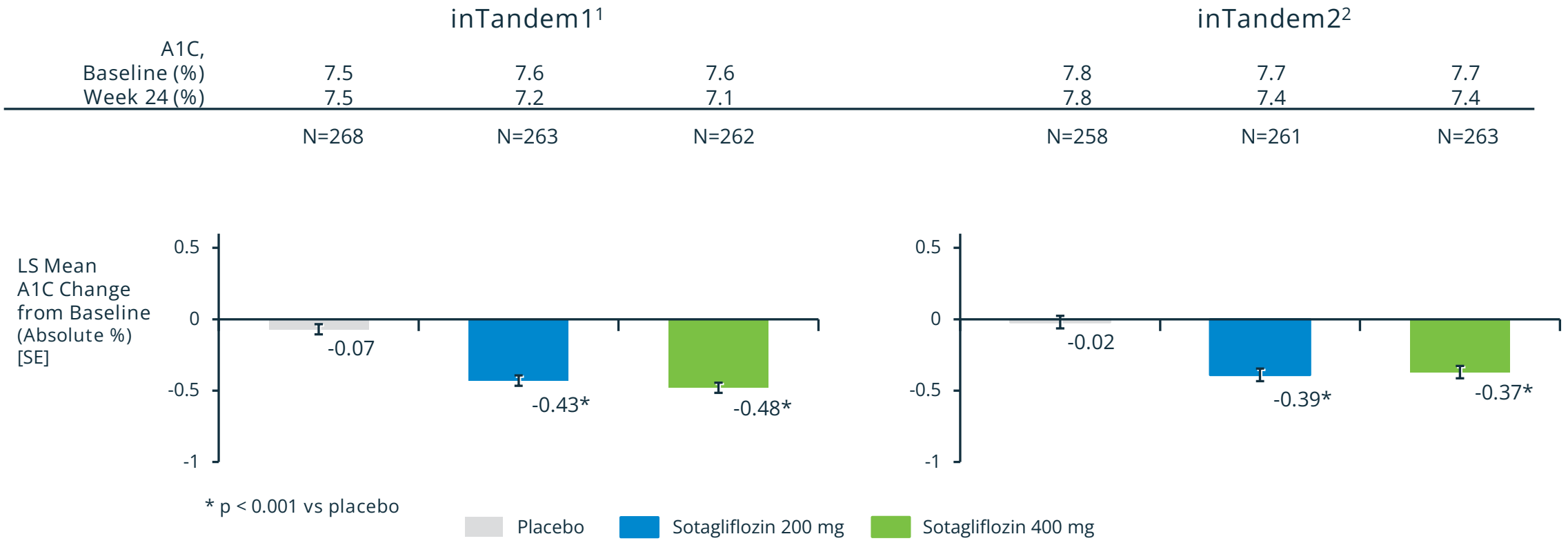
- Sotagliflozin studied in largest-ever Phase 3 program for an oral agent in T1D
- Since FDA filing for T1D, significant data has been generated demonstrating benefits of sotagliflozin in heart failure, MACE, and kidney protection
- Studies support that people with CKD need better glycemic control to prevent disease progression
- Significant unmet need exists for better treatments options for people with T1D and CKD
- Following feedback from FDA, we are pursuing regulatory approval in a population where we believe the benefit/risk is the greatest for treatment with sotagliflozin

Proposed Indication: Zynquista (sotagliflozin) is indicated as an adjunct to insulin therapy to improve glycemic control for adults with type 1 diabetes mellitus and chronic kidney disease.

Largest-Ever Phase 3 Program for an Oral Anti-Diabetic Agent in Type 1 Diabetes



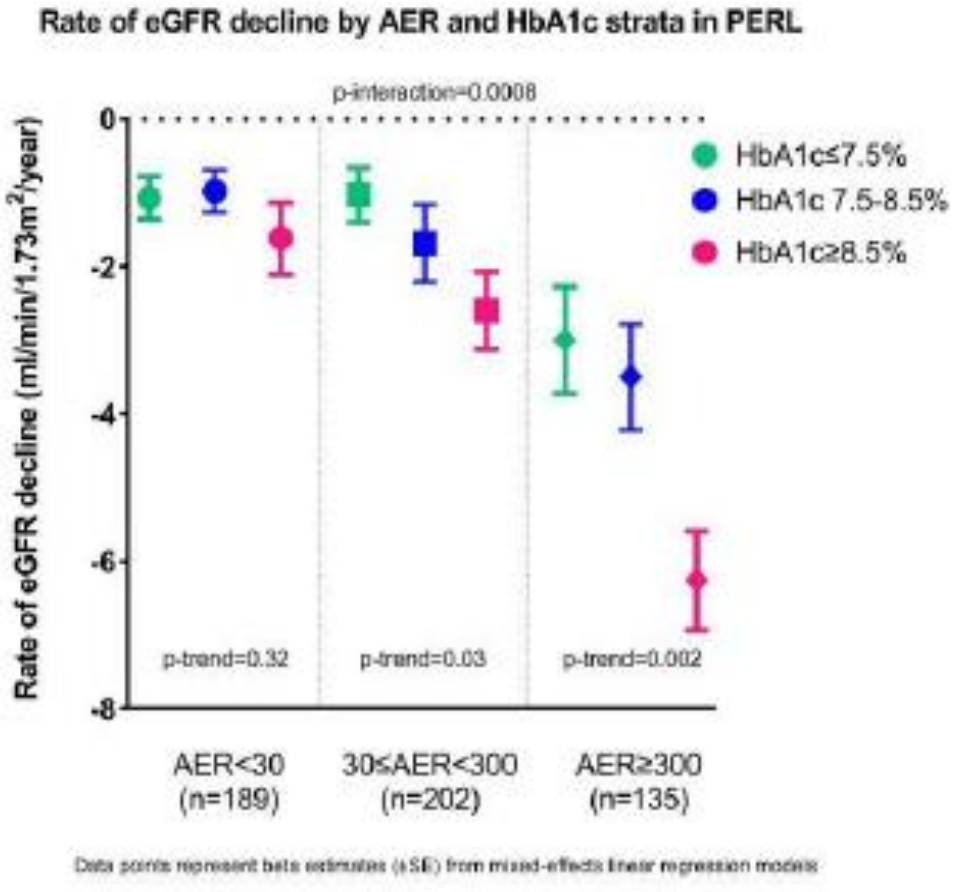
Sotagliflozin Achieved Primary Endpoint, Significantly Improving A1C on Top of Optimized Insulin



1. Buse et al. Diabetes Care 2018;41:1970-1980. DOI.org/10.2337/dc18-0343
2. Danne et al. Diabetes Care 2018;41:1981-1990. DOI.org/10.2337/dc18-0342

Better Glycemic Control is Particularly Important for People with T1D Who Have Chronic Kidney Disease (CKD)

Higher Glucose in People with T1D is Associated with More Rapid Progression of Chronic Kidney Disease



Shah HS et al. J Clin Endocrinol Metab. Published online ahead of print January 23, 2024. DOI.org/10.1210/clinem/dgae044

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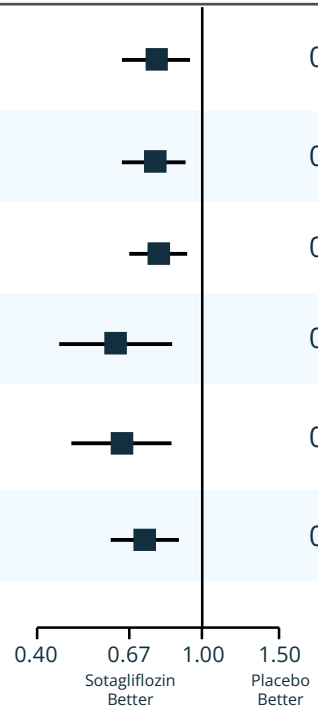
SCORED Data in Type 2 Diabetes Patients Shows Evidence of Reduction in Progression of CKD

Endpoint	Sotagliflozin n/N (%)	Placebo n/N (%)	HR (95% CI)	p-value
eGFR ↓ 57%, ESKD, renal or CV death	215 (4.1)	273 (5.2)	0.78 (0.65, 0.93)	0.0061
eGFR ↓ 50%, ESKD, renal or CV death	239 (4.5)	306 (5.8)	0.77 (0.65, 0.91)	0.0023
eGFR ↓ 40%, ESKD, renal or CV death	342 (6.5)	428 (8.1)	0.79 (0.68, 0.91)	0.0010
eGFR ↓ 57%, ESKD, renal death	67 (1.3)	107 (2.0)	0.62 (0.46, 0.84)	0.0021
eGFR ↓ 50%, ESKD, renal death	92 (1.7)	141 (2.7)	0.64 (0.49, 0.83)	0.0008
eGFR ↓ 40%, ESKD, renal death	199 (3.8)	269 (5.1)	0.73 (0.61, 0.87)	0.0007



Note: eGFR declines needed to be sustained for ≥30 days or at last assessment; ESKD = eGFR <15 mL/min/1.73m^2 for ≥30 days or at last assessment, dialysis for ≥90 days, or renal transplant.

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Sridhar VS. Clin J Am Soc Nephrol. Online ahead of print January 26, 2024. | DOI: 10.2215/CJN.0000000000000414.

Sotagliflozin Achieved Consistent Glycemic Control Benefits in T1D Population with CKD, with Similar Safety on Key Measures

Pooled Data from inTandem1 and inTandem2

A. Entire Cohort

Change in HbA1c (%) from Baseline to Week 24	LSM DIFF (95% CI)	P-value
Sotagliflozin 200mg	-0.36 (-0.44, -0.29)	<.001
Sotagliflozin 400mg	-0.38 (-0.45, -0.31)	<.001

B. CKD Cohort

Change in HbA1c (%) from Baseline to Week 24	LSM DIFF (95% CI)	P-value
Sotagliflozin 200mg	-0.35 (-0.56, -0.14)	0.001
Sotagliflozin 400mg	-0.32 (-0.53, -0.10)	0.004

	Entire Cohort			CKD Cohort		
	Placebo N=526	Sotagliflozin 200mg N=524	Sotagliflozin 400mg N=525	Placebo N=76	Sotagliflozin 200mg N=85	Sotagliflozin 400mg N=76
Severe hypoglycemia, n (%)	39 (7.4)	30 (5.7)	23 (4.4)	13 (17.1)	6 (7.1)	3 (3.9)
DKA, n (%)	1 (0.2)	15 (2.9)	20 (3.8)	1 (1.3)	4 (4.7)	2 (2.6)

Sridhar VS et al. Efficacy and safety of sotagliflozin in patients with type 1 diabetes and chronic kidney disease. 2023 American Society of Nephrology Annual Meeting Poster presentation.
Buse et al. Diabetes Care 2018;41:1970-1980. DOI.org/10.2337/dc18-0343
Danne et al. Diabetes Care 2018;41:1981-1990. DOI.org/10.2337/dc18-0342

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Sotagliflozin Offers Important Potential Benefits for People with Type 1 Diabetes with CKD

People with T1D and poor glucose control have greater progression to CKD

Improving A1C in people with T1D is associated with reduced risk of CKD progression

People with T1D and CKD have been shown to have similar glycemic control with sotagliflozin compared to the entire T1D cohort in the inTandem trials

Sotagliflozin reduced the risk of CKD progression in people with type 2 diabetes (T2D) in SCORED study

Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. *N Engl J Med*. Feb 10 2000;342(6):381-389. doi:10.1056/NEJM200002103420603
Perkins BA, Bebu I, de Boer IH, et al. *Diabetes Care*. May 2019;42(5):883-890. doi:10.2337/dc18-2062
de Boer IH, Sun W, Cleary PA, et al. *N Engl J Med*. Dec 22 2011;365(25):2366-2376. doi:10.1056/NEJMoa1111732
DCCT/EDIC Research Group. *Lancet Diabetes Endocrinol*. Oct 2014;2(10):793-800. doi:10.1016/s2213-8587(14)70155-x
Skupien J et al. *J Am Soc Nephrol*. Dec 2014;25(12):2916-2925. doi:10.1681/ASN.2013091002
Bhatt DL et al. New Engl J Med. 2021;384:129-139. DOI: 10.1056/NEJMoa2030186
Sridhar VS et al. Clin J Am Soc Nephrol. Online ahead of print January 26, 2024. | DOI: 10.2215/CJN.0000000000000414.
Sridhar VS et al. Efficacy and safety of sotagliflozin in patients with type 1 diabetes and chronic kidney disease. 2023 American Society of Nephrology Annual Meeting Poster presentation.
Davies MJ et al. Sotagliflozin in patients with type 1 diabetes and chronic kidney disease: A subanalysis of inTandem 3. 2024 Advanced Technology & Treatments for Diabetes e-Poster presentation.

02

INPEFA® (sotagliflozin) for Heart Failure and Expansion Opportunities in Cardiovascular Medicine

Lexicon pharmaceuticals

Heart Failure represents a Substantial and Growing Public Health Problem, with High Patient Burden and Costs Driven by Repeat Hospitalizations

~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 admissions to hospital for Americans 65+

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.

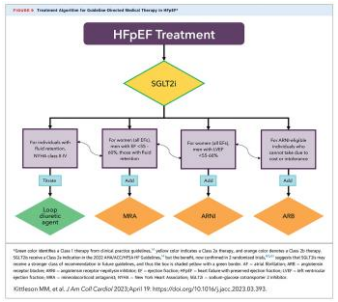
Heart Failure is a Large and Fast-Growing Market with the SGLT Class – including INPEFA – Positioned for Significant Growth

SGLT1&2

inpefa® sotagliflozin tablets

1 of 3 SGLT inhibitors indicated for heart failure – and the only that inhibits SGLT1

1 of 3



SGLTs are recommended foundation of HF treatment in guidelines and ACC consensus

~11%

Despite guideline endorsement SGLT inhibitors[2] account for only ~11% of HF Rx's

>70%

Strong Growth of SGLT use in heart failure[1] is expected to further accelerate

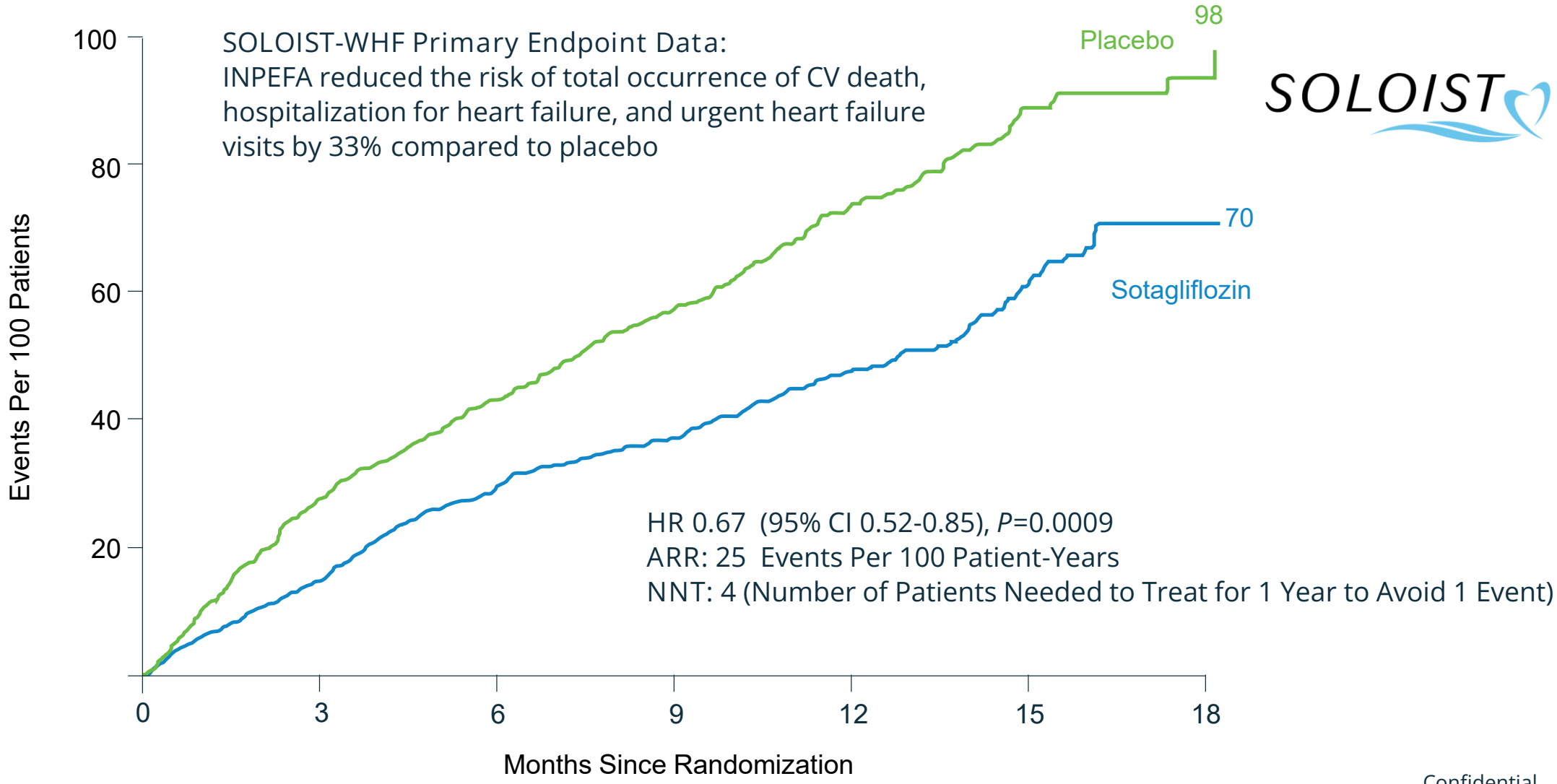
~$9.3B

Anticipated size of US Heart Failure Market by 2030 (14.3% CAGR[3])

1. Based on IQVIA prescription data for HF (MAT Oct 2023 vs. MAT Oct 2022
2. Based on IQVIA prescription data for HF (Oct 2023)
3. Grandview Research - Congestive Heart Failure Drugs Market Size Report, 2030

INPEFA is the *First* and *Only* SGLT Inhibitor Labeled with a Reduction of CV Death and HF Events in Patients Initiated on Therapy in the Hospital or Promptly Following Discharge

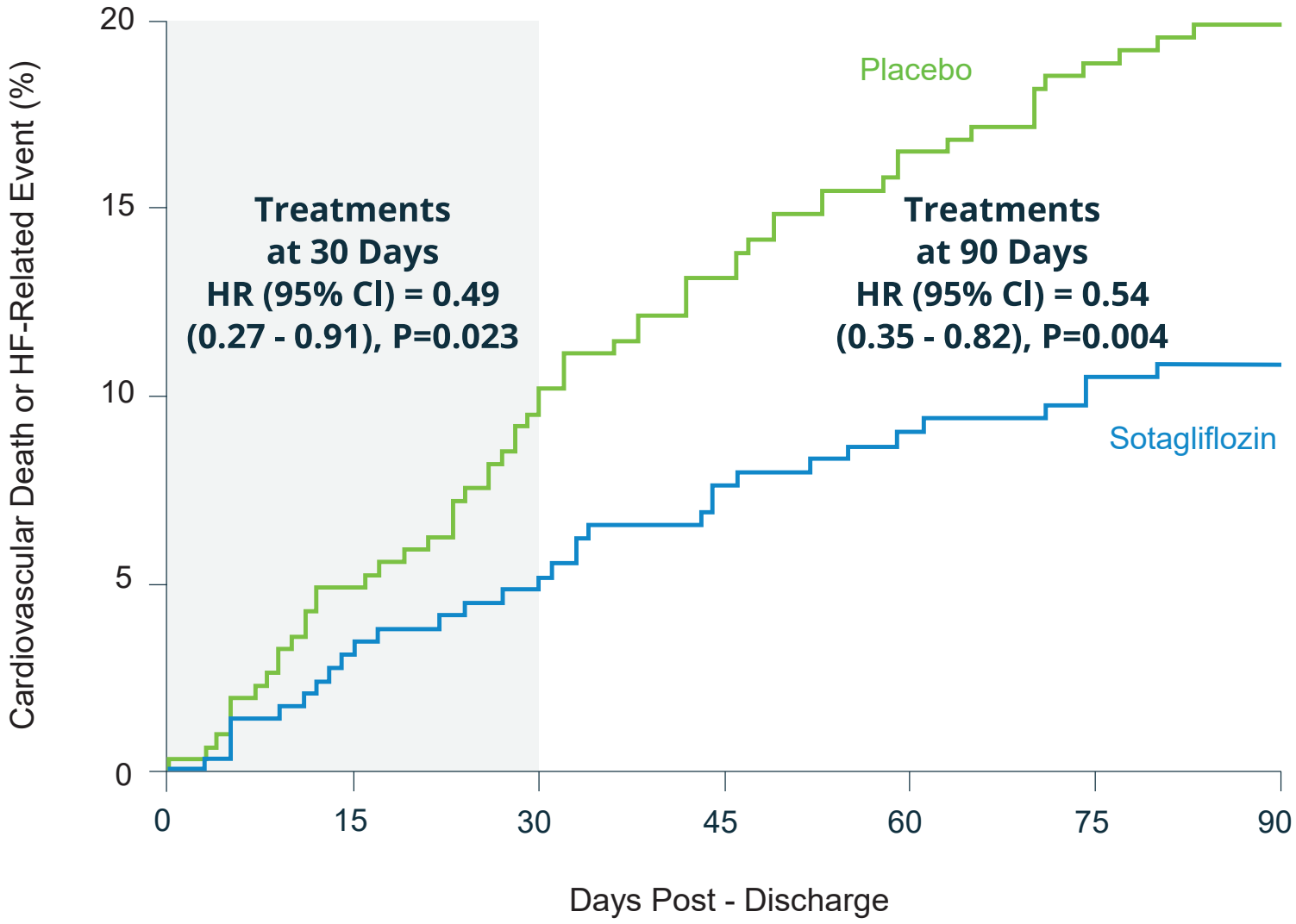
SOLOIST-WHF Primary Endpoint Data:
INPEFA reduced the risk of total occurrence of CV death, hospitalization for heart failure, and urgent heart failure visits by 33% compared to placebo



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)

Bhatt DL et al. New Engl J Med. 2021;384:117-128. DOI: 10.1056/NEJMoa2030183

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

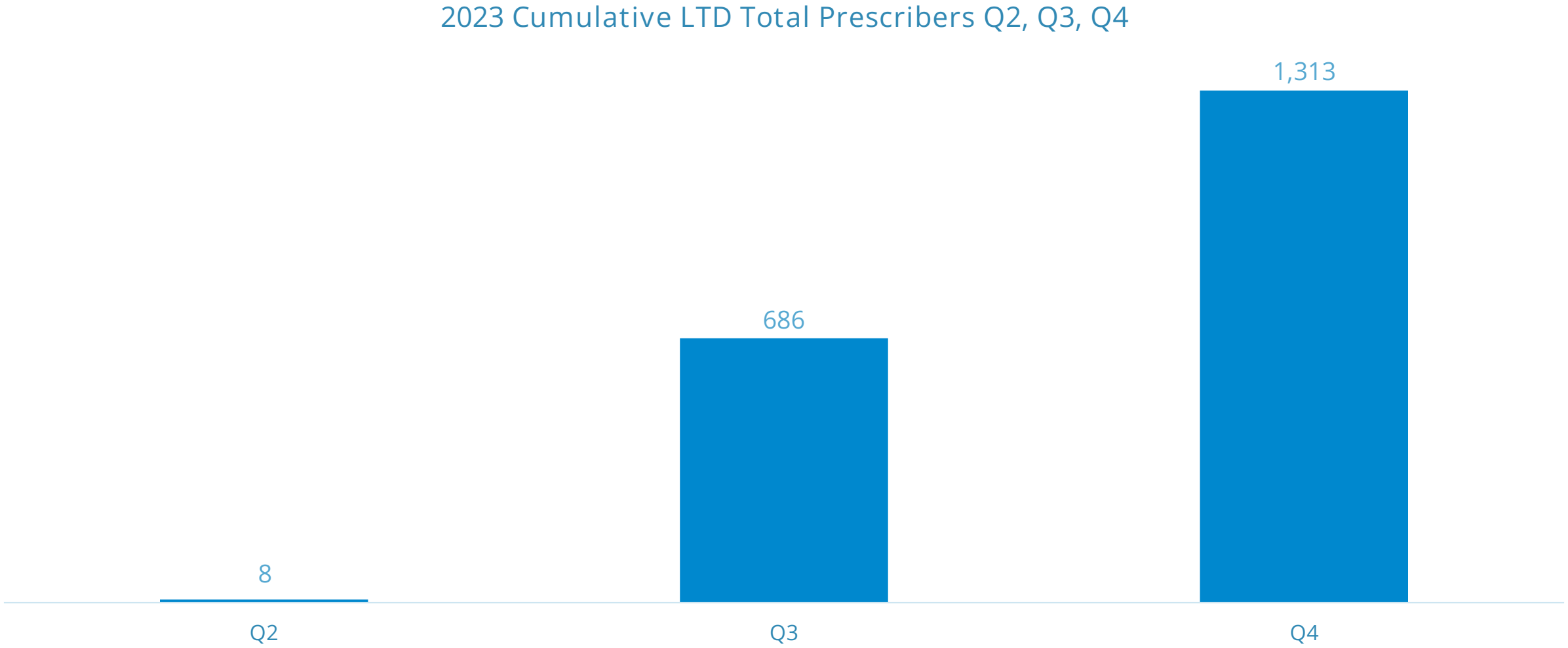


SOLOIST

INPEFA is the *Only* SGLT Inhibitor to Demonstrate a Significant Reduction in 30-day Hospital Readmissions

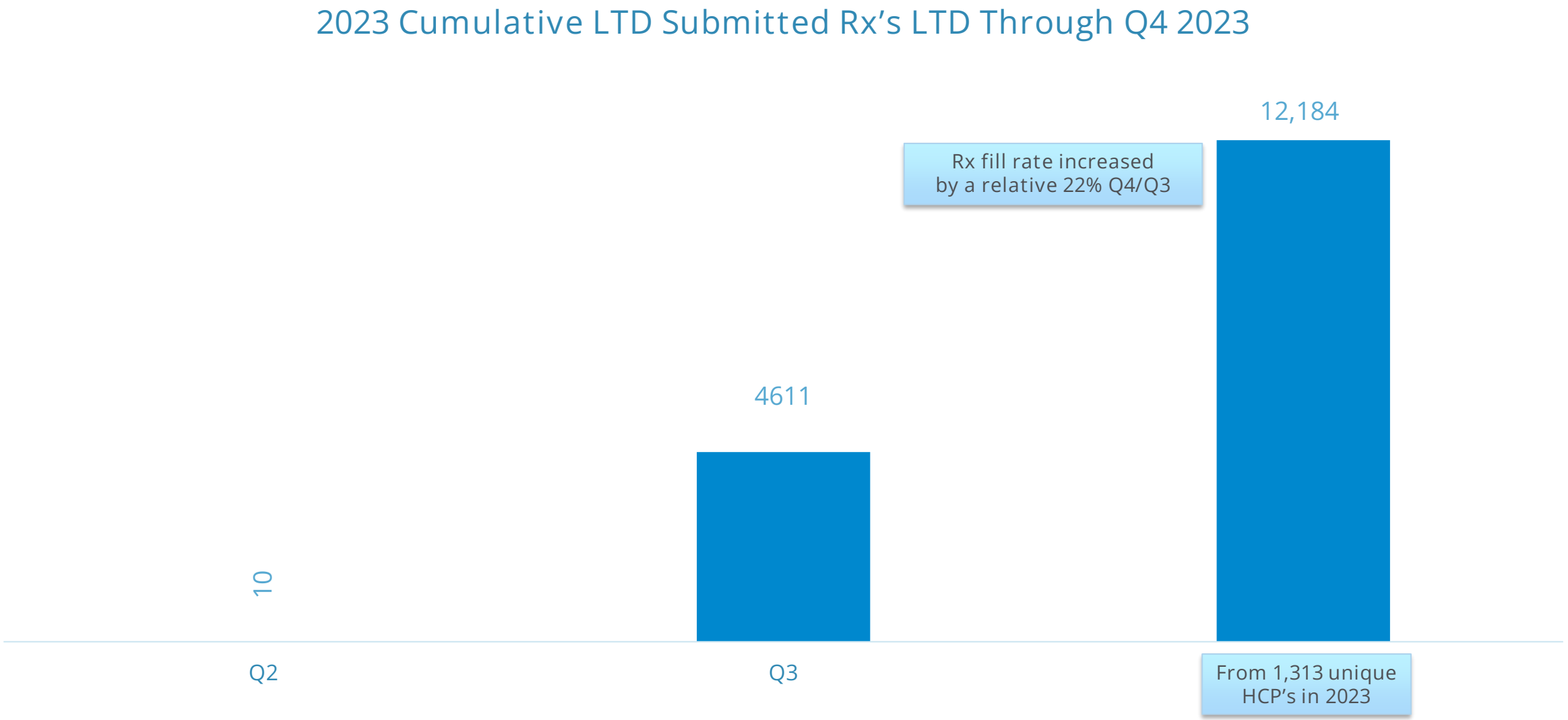
Pitt B et al. J Am Coll Cardiol HF. 2023;11:879-889. DOI.org/10/1016/j.jchf.2023.05.026

INPEFA 2023 LTD Total Prescribers have Continued to Expand throughout Q4 to 1,313 from 686 in Q3 *(91% growth QoQ)*



Source: Filled Rx data through Q4 2023 LTD. Company estimated from multiple Rx sources.

Submitted Rx's have continued to accelerate through Q4 demonstrating broadening adoption of INPEFA *(64% growth QoQ)*



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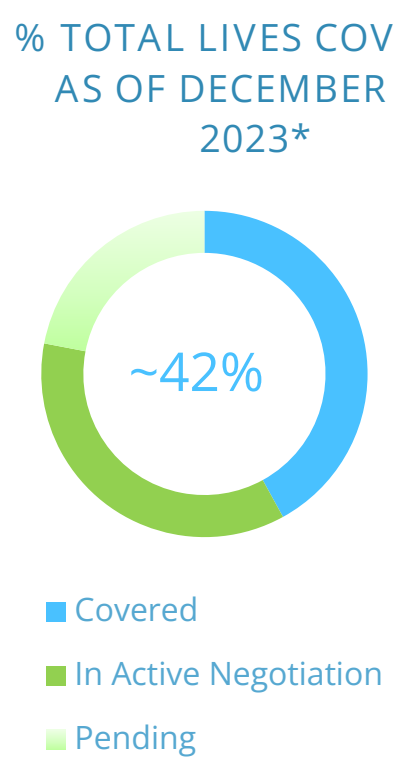
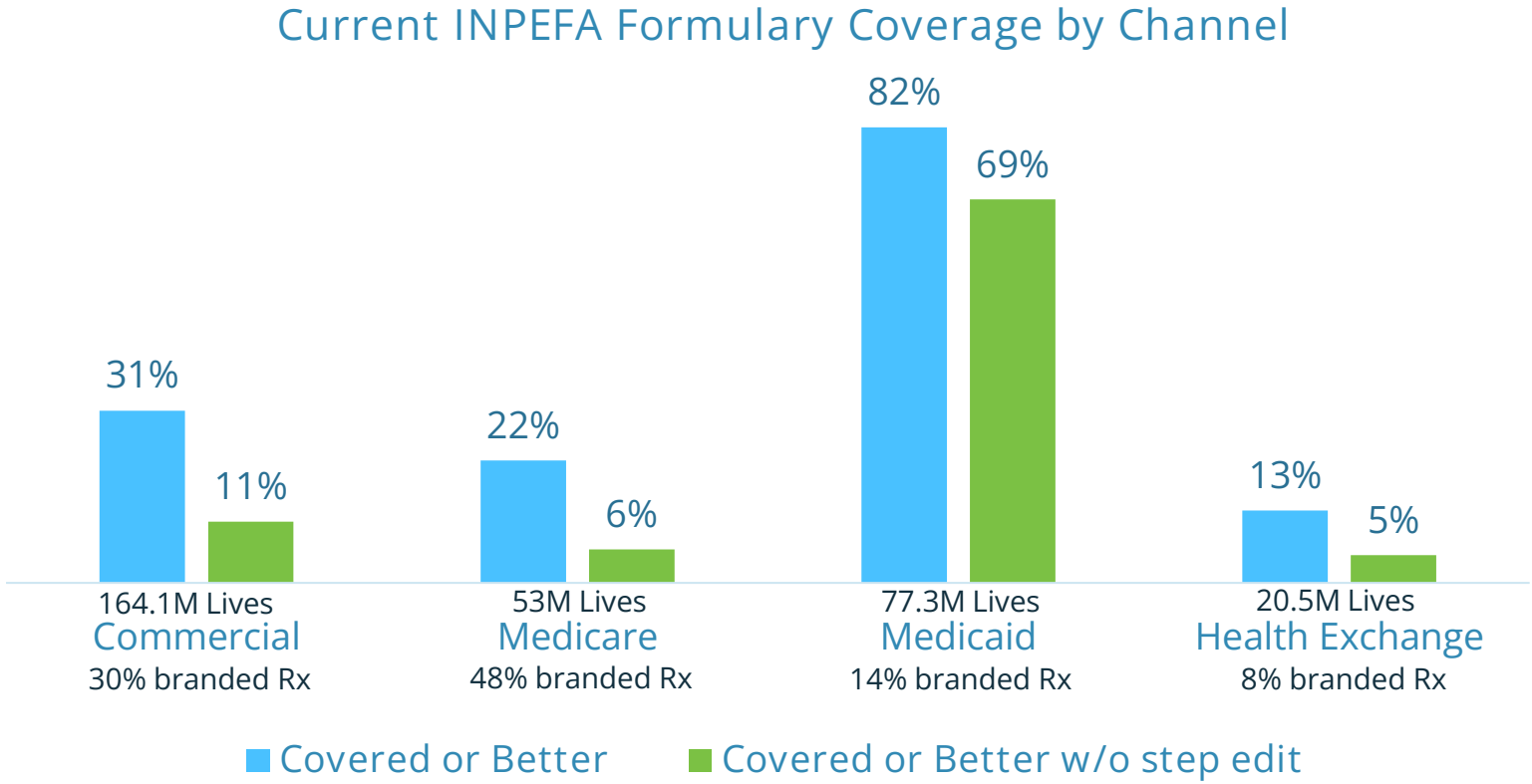
*Submitted Rx's through Q4 2023. Company estimated from multiple claims & Rx sources.

INPEFA Coverage Continued to Expand Through Q4 2023

Expected Expansion from Current Coverage and Reduction of Utilization Management Expected to Open Opportunity for Accelerating Growth in 2H 2024





We expect both to substantially increase Commercial and Medicare coverage in 2024 and to significantly eliminate step edits by contracting for both new and existing coverage, consistent with our INPEFA access strategy

Source: MMIT Analytics & Landscape

Expected Expansion of Coverage Would Build on Early Successes Already Achieved with Key Plans in Q3 and Q4 2023

Selected Accounts Current Market Access Status		
Plan Name/Formulary	Channel	Effective Date
CVS/Aetna EQWP	Medicare	12/1/2023
Express Scripts – Premier Access	Medicare	11/1/2023
Express Scripts – Premier Performance	Medicare	11/1/2023
Express Scripts – High Performance	Commercial	11/1/2023
Express Scripts – Basic Formulary	Commercial	11/1/2023
Blue Cross Blue Shield of Michigan – Optum	Commercial	10/1/2023
Procare	Commercial	10/1/2023
Emisar – Select Standard	Commercial	10/1/2023

What Customers are Telling Us about INPEFA

- Product Promise: The INPEFA product promise resonates strongly with Cardiologists in helping patients to feel better by improving symptoms while reducing events
- Product Differentiation: INPEFA can benefit from SGLT inhibitor class growth while also differentiating given its unique clinical profile
- Clinical Data: INPEFA's data from both SOLOIST-WHF and SCORED are seen as highly compelling, especially the NNT of 4 from the SOLOIST-WHF trial
- Patient Type: Respondents consistently view INPEFA as a drug for all heart failure patients given strength of clinical data vs. other SGLTs across the HF spectrum
- GDMT: Approaches to implementing GDMT vary widely and INPEFA has opportunity to increase awareness & adoption of the latest guidelines while delivering unique promotional messages

Life-Cycle Management Opportunity for Sotagliflozin in HCM

Hypertrophic Cardiomyopathy (HCM)

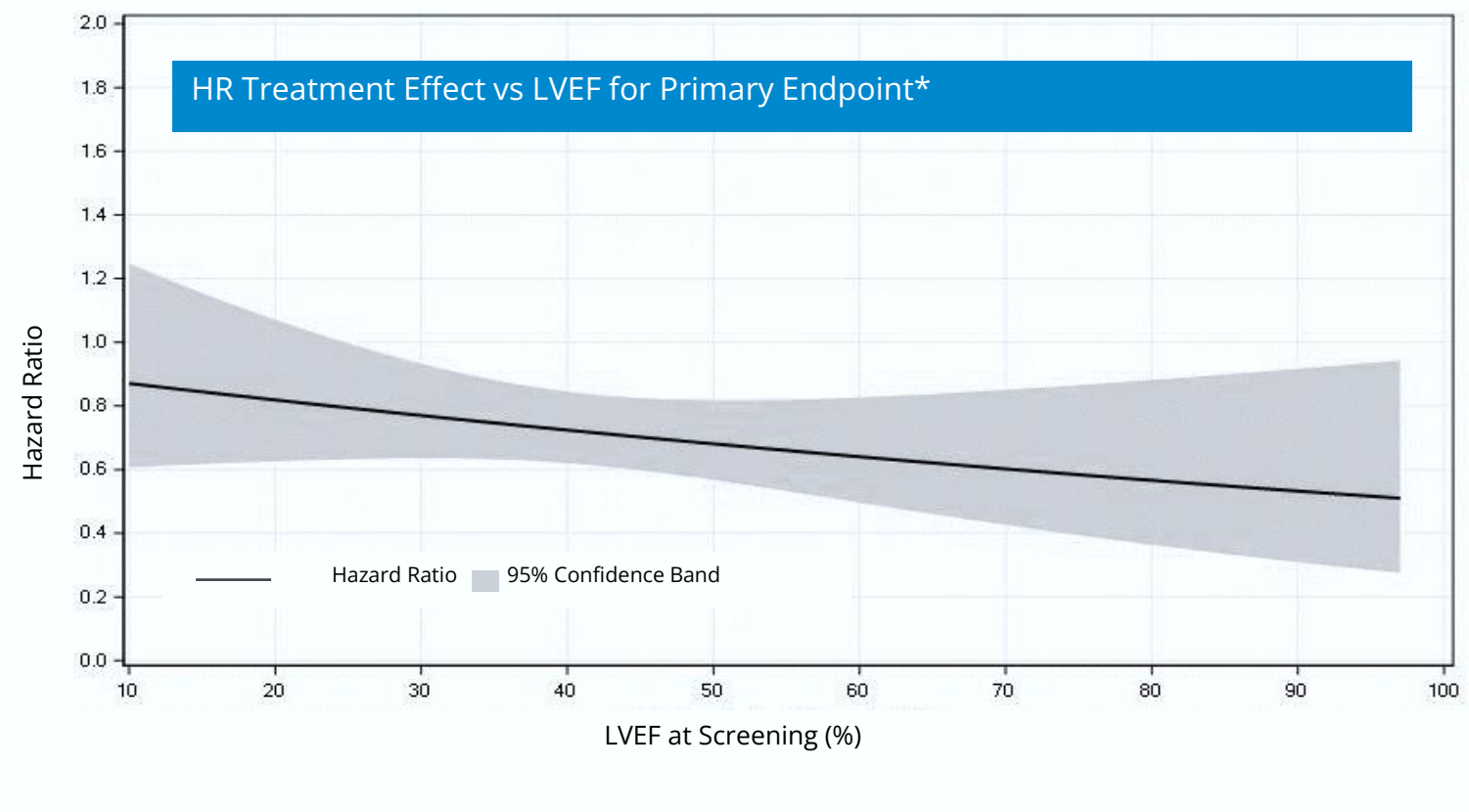
- Indication with strong scientific rationale and that would be unique to sotagliflozin among SGLT inhibitors
- Significant market opportunity with limited existing treatments:
  - Estimated ~1 million patients in the U.S. *
  - Adjacent to and some overlap with heart failure (HFpEF)
- FDA feedback supports potential for INPEFA sNDA for HCM based on single successful Phase 3 study:
  - Potential to support broad indication encompassing both obstructive and non-obstructive HCM
  - Use alone or in combination with other therapies (including CMIs)

Extended IP Protection for INPEFA Offers Runway for High Value Label Expansion Opportunities

*CVrg Market Strategies Heart Failure 2021 – 2030 pg 41. **US Hypertrophic Cardiomyopathy Projections, 2021–2030.** Estimated total (diagnosed and undiagnosed) HCM prevalence Based on the Cardia Study https://pubmed.ncbi.nlm.nih.gov/7641357/ .

Sotagliflozin's Efficacy Data Across LVEF is Compelling for Heart Failure… And Points to Potential Life-Cycle Management Opportunity in HCM

Treatment effect of sotagliflozin was observed in SOLOIST and SCORED patients, regardless of LVEF



- Pooled analysis of all patients from SOLOIST-WHF and patients from SCORED with a history of heart failure
- Hazard ratio and 95% confidence band for the primary endpoint: Total CV death, HHF, and urgent HF visit

CV = cardiovascular; HF = heart failure; HHF = hospitalization for heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction; HCM = Hypertrophic cardiomyopathy.

Bhatt DL et al. 2021 American College of Cardiology Virtual Presentation.
Data on file Lexicon Pharmaceuticals, Inc.
Bhatt DL et al. New Engl J Med. 2021;384:117-128. DOI: 10.1056/NEJMoa2030183
Bhatt DL et al. New Engl J Med. 2021;384:129-139. DOI: 10.1056/NEJMoa2030186

SCORED Data in Patients with Left Ventricular Hypertrophy without Hypertension Offer Perspective on Potential Application in Patients with HCM

Sotagliflozin Reduces the Risk of Cardiovascular Events in Patients With Left Ventricular Hypertrophy Without Hypertension: A Post Hoc Analysis From SCORED

Primary and selected CV endpoints in patients with reported LVH and no reported hypertension*

	SOTAGLIFLOZIN (N = 217) Events/100 PY	PLACEBO (N = 201) Events/100 PY	HR (95% CI)
CV death and HF-related events (HHF and UVHF)	5.2	9.5	0.40 (0.17, 0.92)
3-point MACE	3.1	5.3	0.52 (0.21, 1.28)
3-point MACE + HHF	5.5	10.2	0.46 (0.21, 0.99)

*LVH reported in CVRF Q and Hypertension was based on Medical History

- In a sensitivity analysis removing patients with reported aortic stenosis (n = 1) or any patient with uncontrolled hypertension per CVRF Q (n = 56), the results are comparable to those in Table 2.

- Cohort shares phenotypic and physiological traits of patients with HCM and may include undiagnosed cases of HCM.
- Results provide insights into the potential efficacy of sotagliflozin in patients with HCM.

Davies et al. 2023 Heart Failure Society of America Annual Scientific Meeting ePoster.

Confidential

FDA Feedback Supports Potential for Sotagliflozin sNDA for HCM

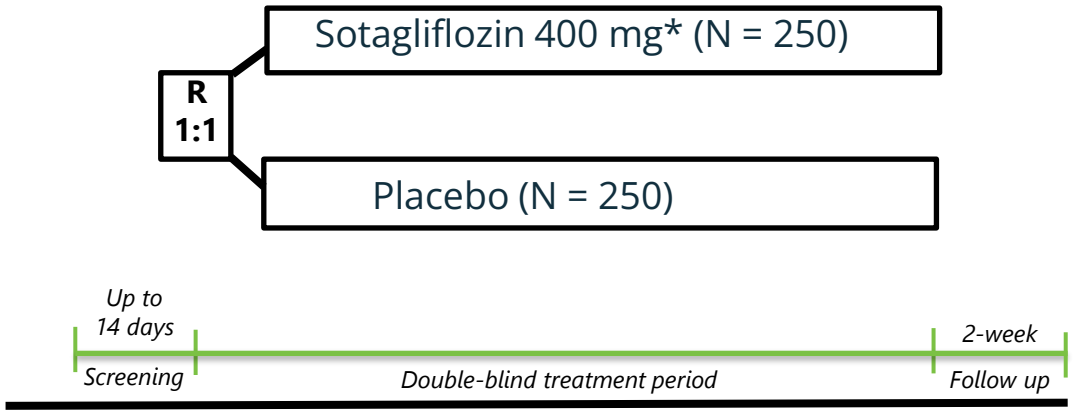
Based on Single Successful Phase 3 Study with KCCQ Primary Endpoint

Primary endpoint: Change from baseline in KCCQ Clinical Summary Scale (CSS) score

Proposed indication: INPEFA is indicated to improve symptoms and physical limitations in adults with symptomatic hypertrophic cardiomyopathy

Placebo-controlled trial at 135 sites in 22 countries (N = 500)

- Adults with HCM (o/no)
- LVOT gradient per HCM type:
  - oHCM ≥30 mm Hg at rest OR with Valsalva maneuver
  - nHCM <30 mm Hg at rest AND with Valsalva maneuver
- KCCQ23 CSS <85
- NYHA Class II or III
- LVEF ≥50%



**For patients not tolerating treatment, sotagliflozin (and matching placebo) down-titrated to 200 mg starting at Week 4.*

O = obstructive; NO = non-obstructive; LVOT = left ventricular outflow tract; NYHA = New York Heart Association; KCCQ = Kansas City Cardiomyopathy Questionnaire; R = randomization.

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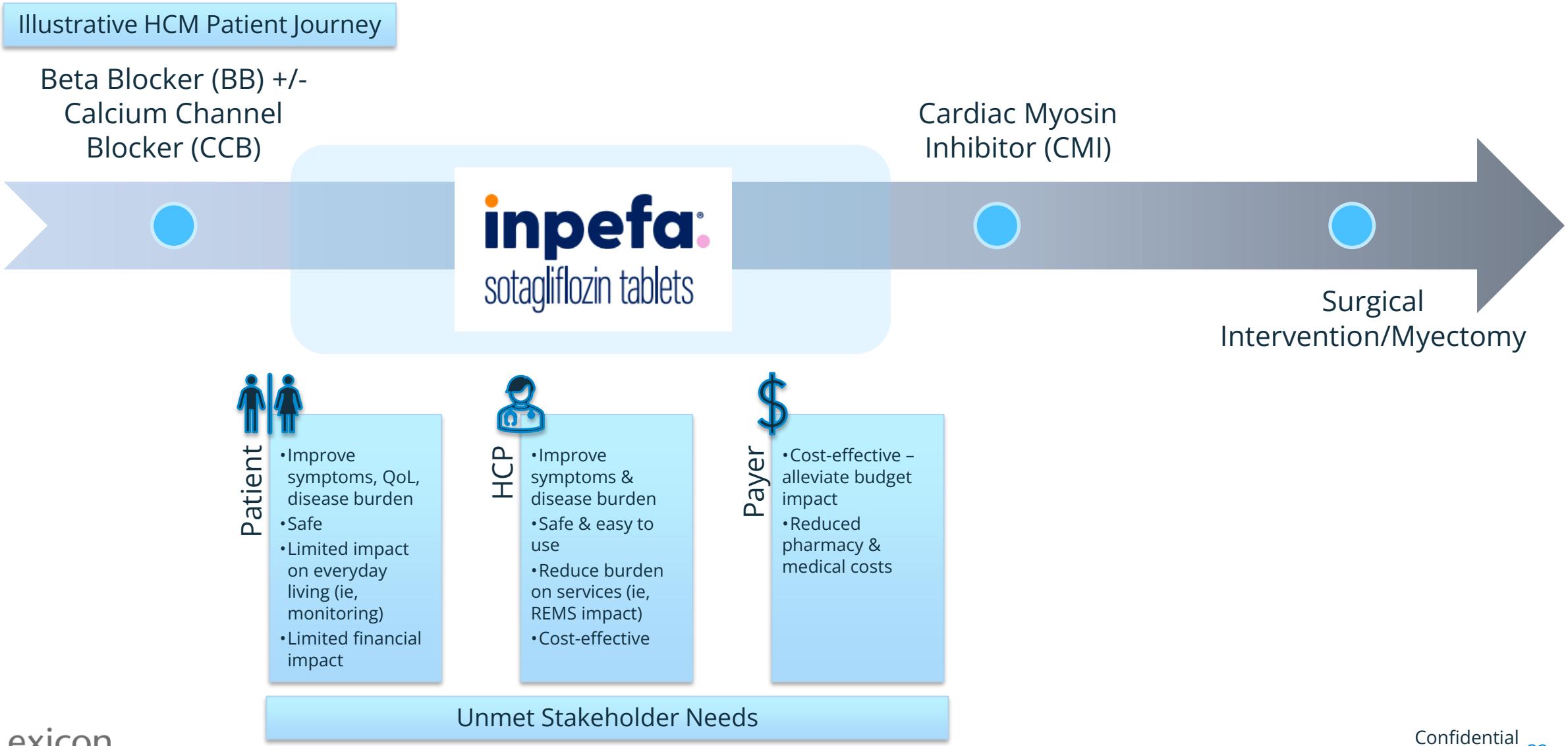
Study start-up activities ongoing, planned initiation mid-year 2024

Despite Recent Advances for the Treatment of HCM, Significant Opportunities and Stakeholder Needs Remain as Disease Progresses



03

LX9211 for Neuropathic Pain

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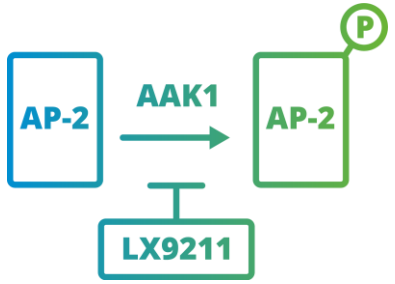
LX9211 has the Potential to Redefine the Standard of Care for Patients Suffering with DPNP – Fast Track Designation by FDA

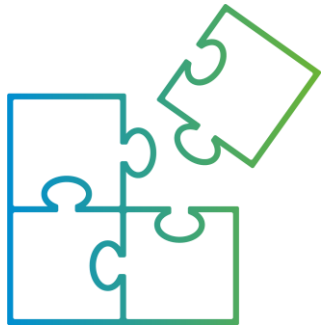
HIGH UNMET MEDICAL NEED

PROOF OF CONCEPT ACHIEVED



LATE-STAGE CLINICAL DEVELOPMENT UNDERWAY

POTENTIAL FOR SIGNIFICANT COMMERCIAL OPPORTUNITY

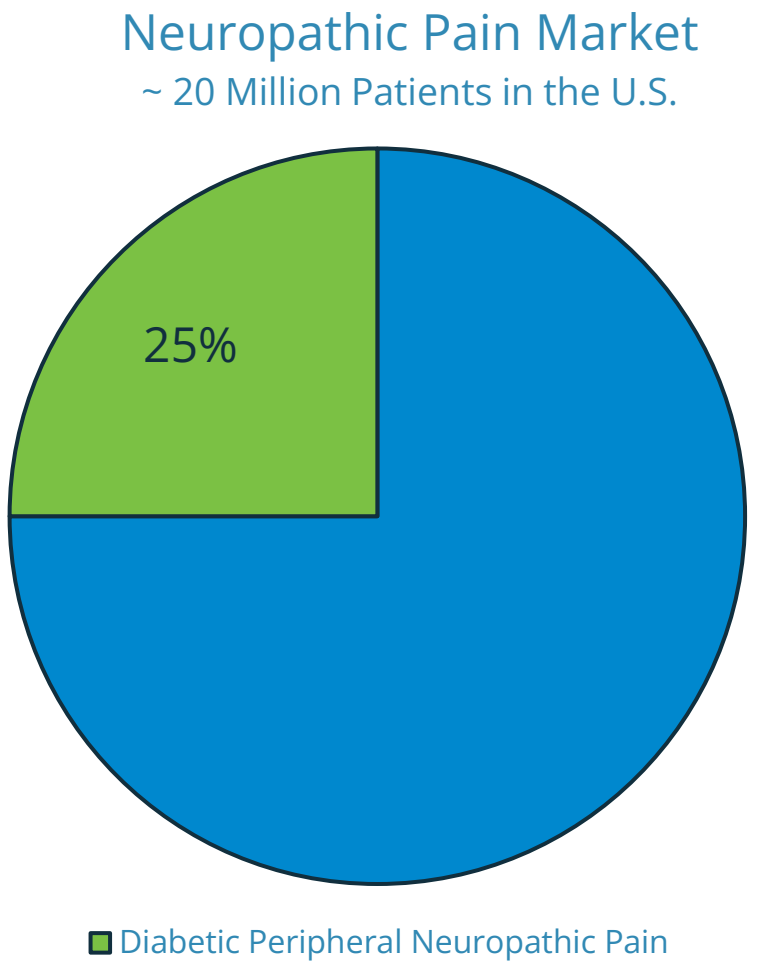


Patient Data: Decision Resources Group, Landscape & Forecast Neuropathic Pain Report, June 2020
Massachusetts General Hospital. Neuropathy Overview. [Internet] 2021
Schembri, E. Are Opioids Effective in Relieving Neuropathic Pain? SN Compr. Clin. Med. 1, 30–46 (2019)
Finnerup et al. Algorithm for neuropathic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

AAK1 – Adaptor-associated Protein Kinase 1

DPNP represents a Potentially Significant Commercial Opportunity with High Unmet Medical Need

- 20 million+ Americans experience neuropathic pain
  - Approximately 5 million DPNP patients in the U.S.
- Current standard of care does not eliminate neuropathic pain for most patients, and many experience undesirable side effects
- LX9211 and AAK1 inhibition represent a novel, non-opioid approach to treat neuropathic pain, with an opportunity to be the first drug with a new mechanism of action approved in neuropathic pain in over two decades
- First-to-market potential in large, multibillion dollar market



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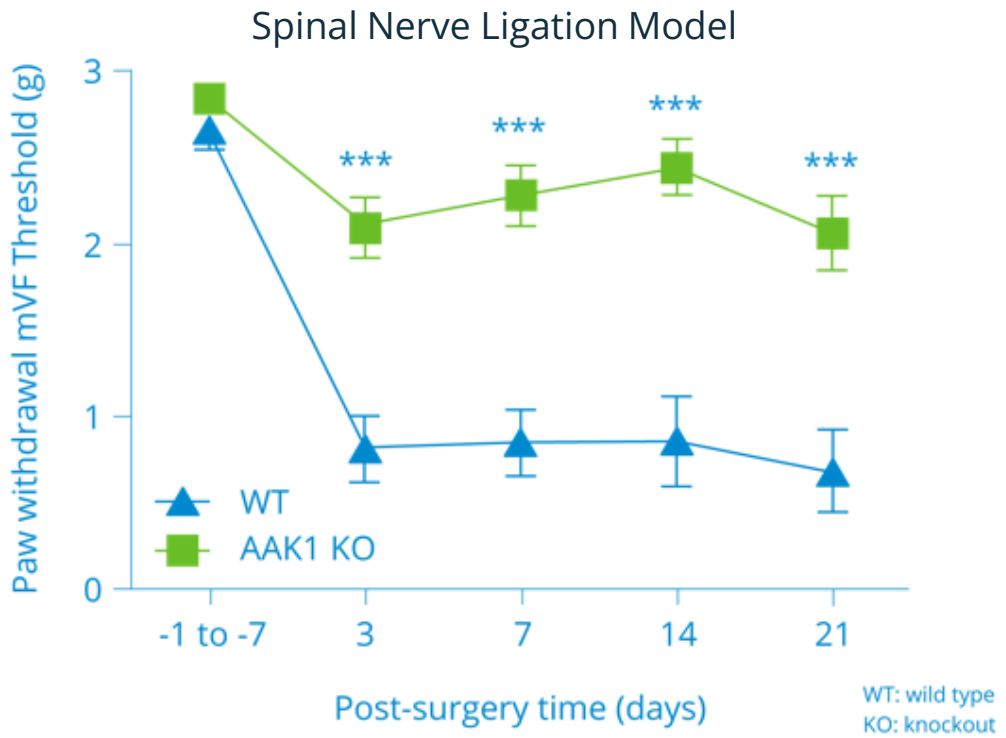
Finnerup et al. Algorithm for neuropathic pain treatment: an evidence-based proposal. Pain 2005; 118(3): 289-305

Lexicon Identified AAK1 as the Most Compelling Target for Neuropathic Pain among the Nearly 5,000 Targets Evaluated in the Genome5000 Program

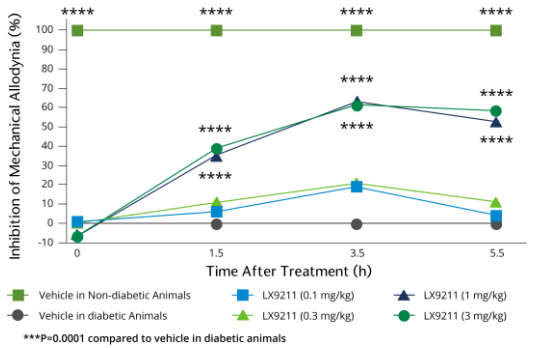
Genetic Knockouts of AAK1 Demonstrated Resistance to Neuropathic Pain



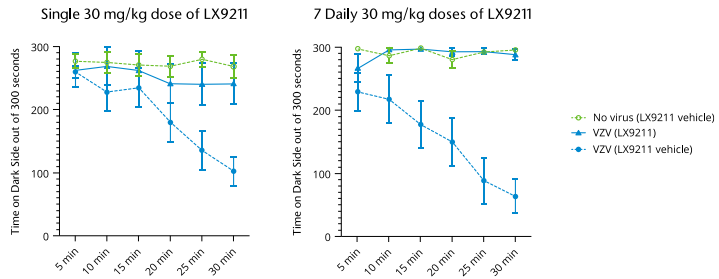
Genome5000 Supported Selection of AAK1 over Other Putative Targets with Less Compelling Profiles for Neuropathic Pain

Among the targets evaluated – and left unselected for further discovery efforts in neuropathic pain based on their profiles – were multiple voltage-gated sodium channels, including:
SCN3A (Na_v 1.3)
SCN9A (Na_v 1.7)
SCN10A (Na_v 1.8)
SCN11A (Na_v 1.9)

LX9211 Demonstrated Benefits in Multiple Preclinical Models of Neuropathic Pain



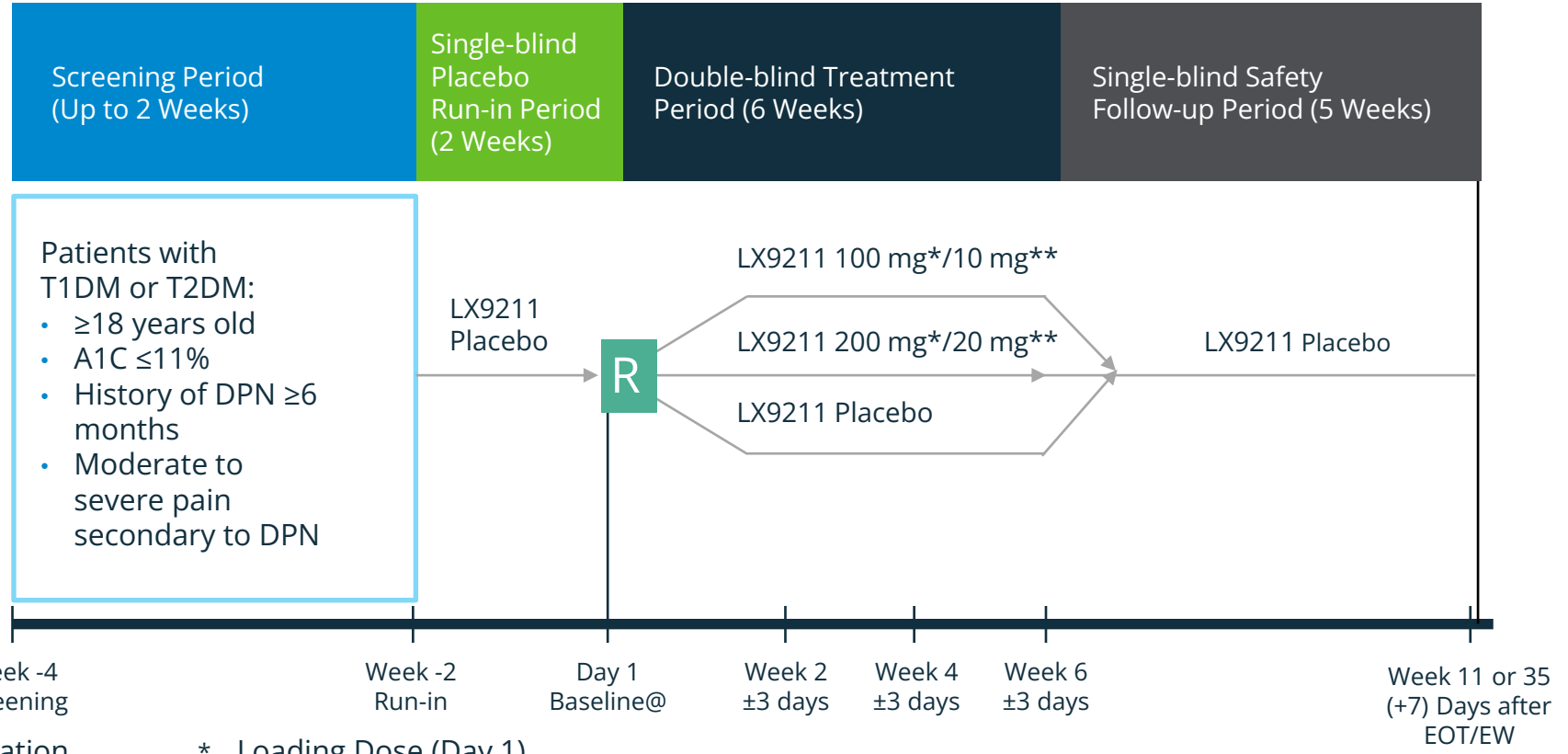
LX9211 reduced neuropathic pain in the streptozotocin (STZ)-induced painful diabetic neuropathy (PDN) model in rats



LX9211 reduced neuropathic pain in varicella-zoster virus (VZV) model of post-herpetic neuralgia (PHN) in rats

Phase 2 Study of LX9211 in Diabetic Peripheral Neuropathic Pain was Designed to Demonstrate Effect Versus Placebo

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



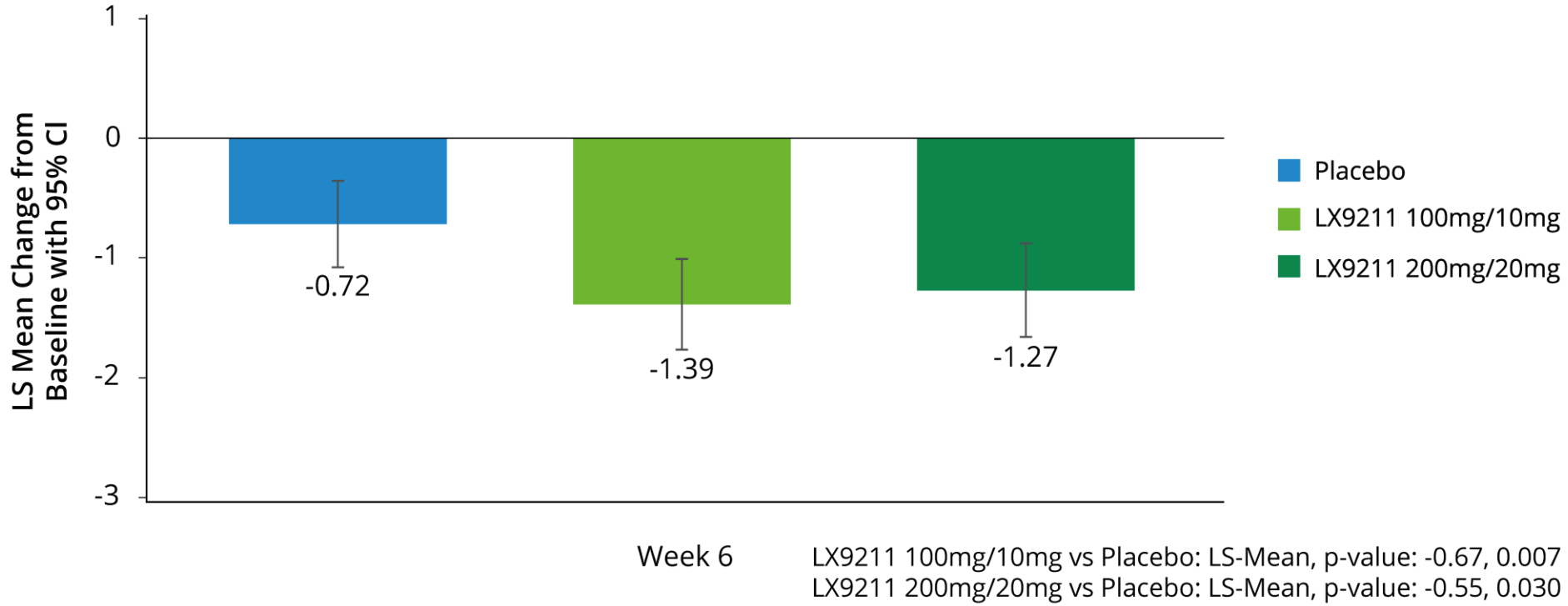
R = randomization
EOT = end of treatment
EW = early withdrawal

* 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

Study design permitted patients to maintain one stable-dose DPNP therapy (gabapentin, pregabalin or duloxetine) without being forced to withdraw from therapies that, although inadequate, may be providing benefit – aligning with how new DPNP drugs are likely to be used in practice

LX9211 Achieved the Primary Endpoint in RELIEF-DPN-1

Clinically and 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



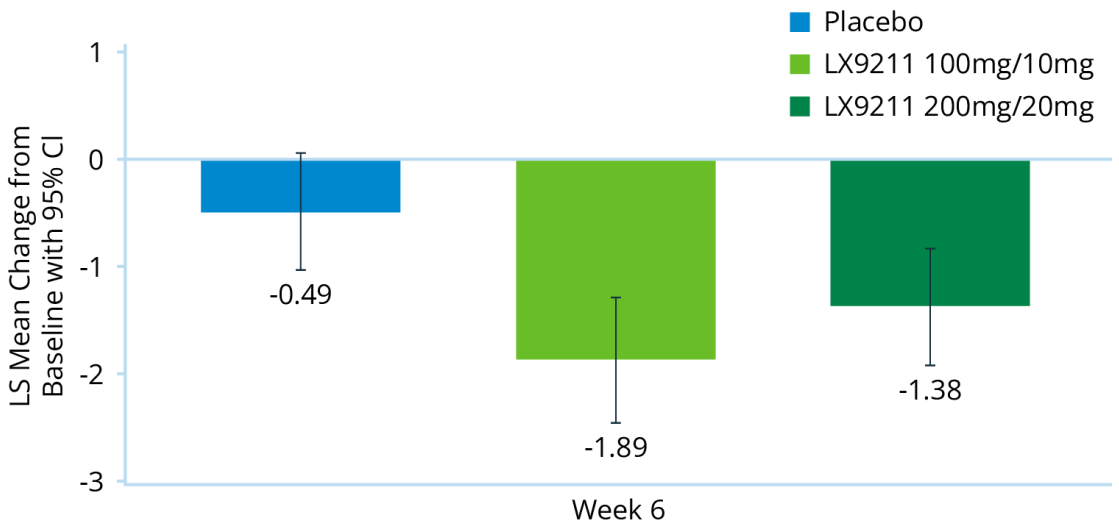
Effect on ADPS consistent across age, sex, use of baseline DPNP medications, and baseline pain score

**Relief DPN-1 permitted continued use of stable-dose standard of care therapy, with 55% of patients in placebo arm on gabapentin, pregabalin or duloxetine*

Significant and Clinically Meaningful Benefits Demonstrated in Both Burning Pain and Pain Interference with Sleep

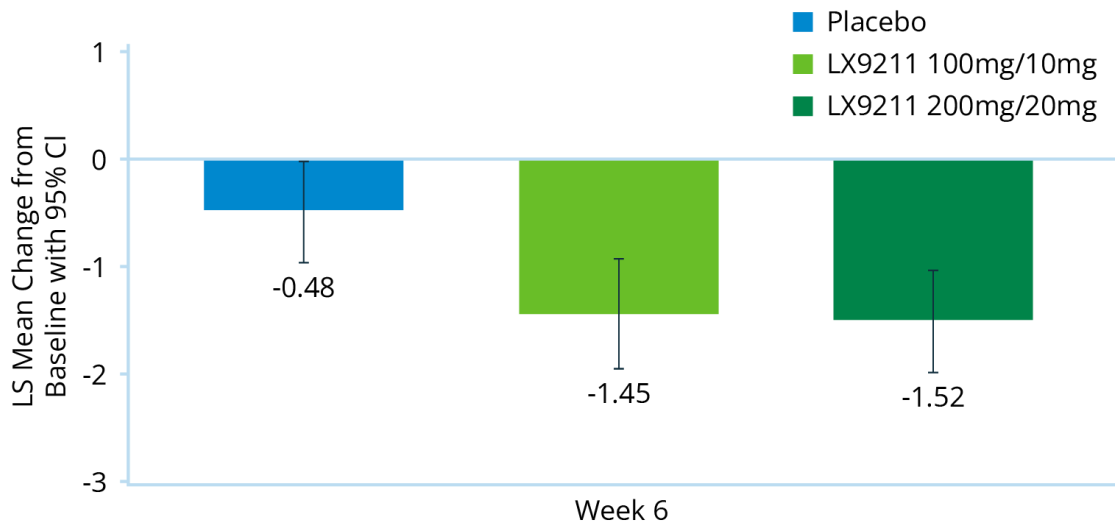
Both are commonly reported challenges experienced by DPNP patients

LS MEAN CHANGE FROM BASELINE IN BURNING PAIN



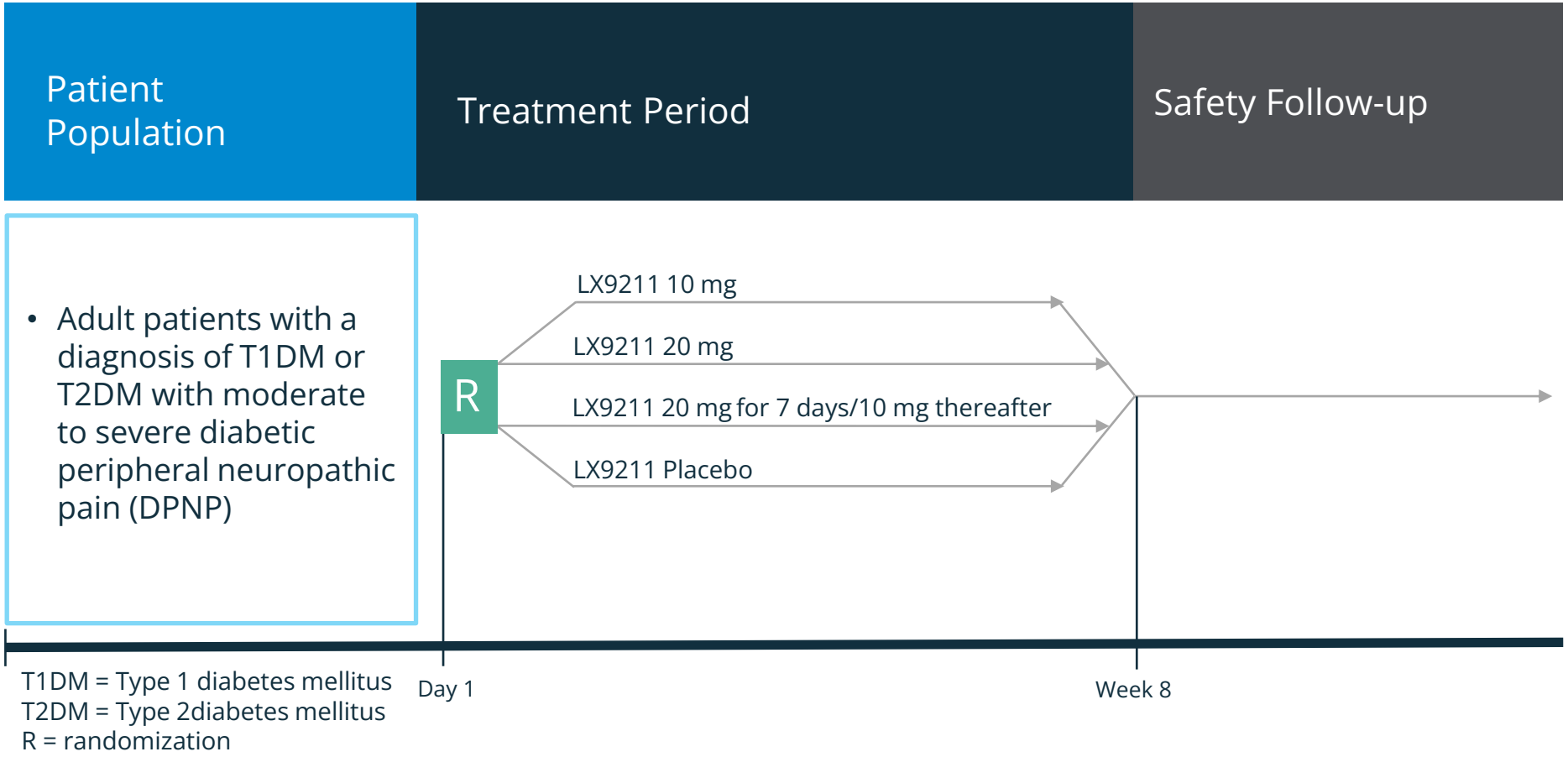
LX9211 100mg/10mg vs Placebo: LS-Mean, p-value: -1.40, <.001
LX9211 200mg/20mg vs Placebo: LS-Mean, p-value: 0.89, 0.017

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

PROGRESS Phase 2b Study – Patient Enrollment Underway, First Topline Data Read-out Expected in Q2 '25



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

LX9211 Has Entered Late-stage Development for DPNP

- Potential first-to-market opportunity with very few novel treatments in development for DPNP or neuropathic pain generally
- DPNP represents the largest and fastest growing neuropathic pain market opportunity
- FDA feedback obtained in Q2 2023 and has been adapted into the development plan
- Program has been optimized for probability of success, time and efficiency
- PROGRESS study will inform Phase 3 pivotal study design
- Topline data anticipated in Q2 2025

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

04

Summary and 2024 Areas of Focus

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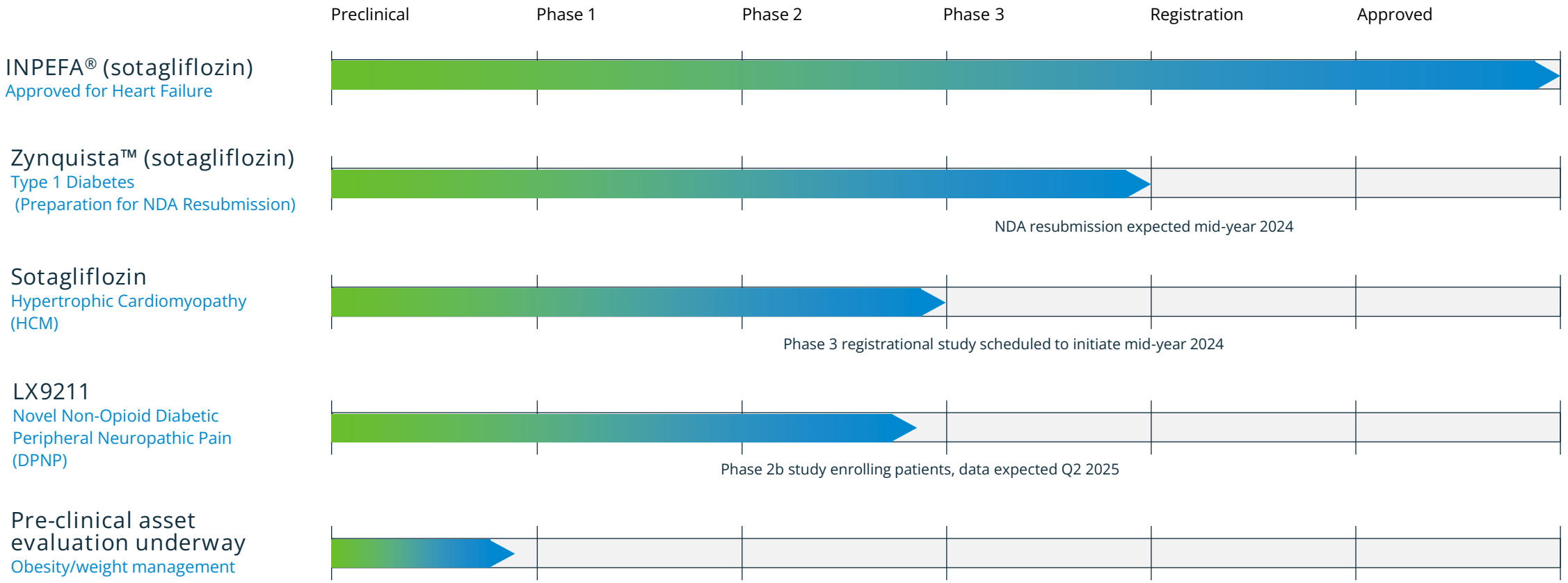
Lexicon in 2024 – Key Business Objectives

Further Accelerate Launch of INPEFA for Heart Failure

Resubmit NDA for T1D with CKD & Advance LX9211 for DPNP

Progress Opportunities for Partnership, Growth and Expansion

Lexicon – Leveraging Scientific Platform and Expertise to Build Strong Pipeline Opportunities for Growth and Partnership



04

Financial Summary & Upcoming Catalysts

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Q4 2023 Financial Summary

	As of Dec 31, 2023	As of Dec 31, 2022
Cash, cash equivalents and short-term investments	$170.0M	$138.4M
Total assets	$229.4M	$194.3M
Long-term debt	$99.5M	$48.6M

	Q4 2023	Q4 2022
Total revenues	$0.67M	$0.00M
Operating expenses		
R&D[1]	$14.8M	$14.0M
SG&A[1]	$32.6M	$16.3M
Total operating expenses	$47.4M	$30.3M
Net loss	($48.2M)	($30.5M)
Net loss per common share	($0.20)	($0.16)

Completion of Private Placement in March 2024 Increasing Cash and Investments by Net Proceeds of ~$242 Million

1. Includes stock-based compensation expenses

Planned Catalyst Calendar 2024 – 2025

	Key Program	Planned Catalyst 2024 – 2025
INPEFA & Sotagliflozin	INPEFA Heart Failure	Launch inflection in back half of 2024
	Hypertrophic Cardiomyopathy	Phase 3 study commencement mid-2024
	Type 1 Diabetes with Chronic Kidney Disease	Resubmit NDA mid-2024; 6 month review anticipated
LX9211	Diabetic Peripheral Neuropathic Pain	Enrollment completion 2024; Top line data Q2 2025 Potential partnership opportunity
Preclinical Oral Small Molecule	Obesity & Weight Management	Publicly identify target 1H 2024, commence IND enabling studies and file IND

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Thank You

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