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VX-548 PHASE 2 RESULTS IN PAINFUL DIABETIC PERIPHERAL NEUROPATHY

DECEMBER 13, 2023

SAFE HARBOR STATEMENT

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, statements regarding our expectations for our pain program, our plans to develop a new class of medicines with a superior profile to existing therapies for peripheral neuropathic pain (PNP), our plans to secure a broad PNP label, expectations to have Phase 3 acute pain results in early 2024, plans for our Phase 2 study evaluating VX-548 in LSR, including plans to enroll patients in this study, plans to advance VX-548 in PNP into pivotal development in 2024, our plans to engage with regulators, our beliefs that there is a large commercial opportunity for VX-548 that is addressable with a specialty model, our plans to develop a portfolio of first-in-class and best-in-class medicines for pain, including NaV1.8 inhibitors, NaV1.7 inhibitors and potential combinations of NaV1.8 and NaV1.7 inhibitors, commercial potential in moderate-to-severe acute pain. While Vertex believes the forward-looking statements contained in this presentation are accurate, these forward-looking statements represent the company's beliefs only as of the date of this presentation and there are a number of risks and uncertainties that could cause actual events or results to differ materially from those expressed or implied by such forward-looking statements. Those risks and uncertainties include, among other things, that data from preclinical testing or clinical trials, especially if based on a limited number of patients, may not be indicative of final results, that patient enrollment in our trials may be delayed, that actual patient populations able to participate in our trials or eligible for our products may be smaller than anticipated, that we may not be able to achieve a broad label for VX-548, that data from the company's development programs may not be available on expected timelines, or at all, and may not support registration or further development of its potential medicines due to safety, efficacy or other reasons, and other risks listed under “Risk Factors” in Vertex's annual report filed with the Securities and Exchange Commission (SEC) and available through the company's website at www.vrtx.com and on the SEC’s website at www.sec.gov. You should not place undue reliance on these statements, or the scientific data presented. Vertex disclaims any obligation to update the information contained in this presentation as new information becomes available.

SIGNIFICANT UNMET NEED IN ACUTE AND PERIPHERAL NEUROPATHIC PAIN

- Over 90 million patients in the U.S. treated for acute or neuropathic pain annually
- Existing therapies have significant limitations
- VRTX's approach targets the underlying causal human biology
  - $Na_V1.8$ and $Na_V1.7$ are validated targets for pain
  - Selectively inhibiting $Na_V1.8$/$Na_V1.7$ could reduce the transmission of pain signals in peripheral sensory neurons
- VX-548 is a selective $Na_V1.8$ inhibitor:
  - On track for Phase 3 results in **Acute Pain** in early 2024
  - In **Peripheral Neuropathic Pain (PNP):**
    - Completed Phase 2 in Diabetic Peripheral Neuropathy (DPN)
    - Initiated Phase 2 in Lumbosacral Radiculopathy (LSR)
- Large commercial opportunity addressable with specialty model

VX-548: POSITIVE RESULTS IN PHASE 2 STUDY IN DIABETIC PERIPHERAL NEUROPATHY (DPN)

Results support aspiration to target Nav1.8 and transform the treatment of peripheral neuropathic pain (PNP)

PNP program goals

- Develop a new class of medicines with a superior profile to existing therapies in PNP
- Secure broad PNP label

DPN Phase 2 study goals

- Establish proof-of-concept of the safety and efficacy of VX-548 over 12 weeks of treatment in DPN
- Further establish proof-of-concept of the safety and efficacy of the NaV1.8 inhibitor class in the chronic setting

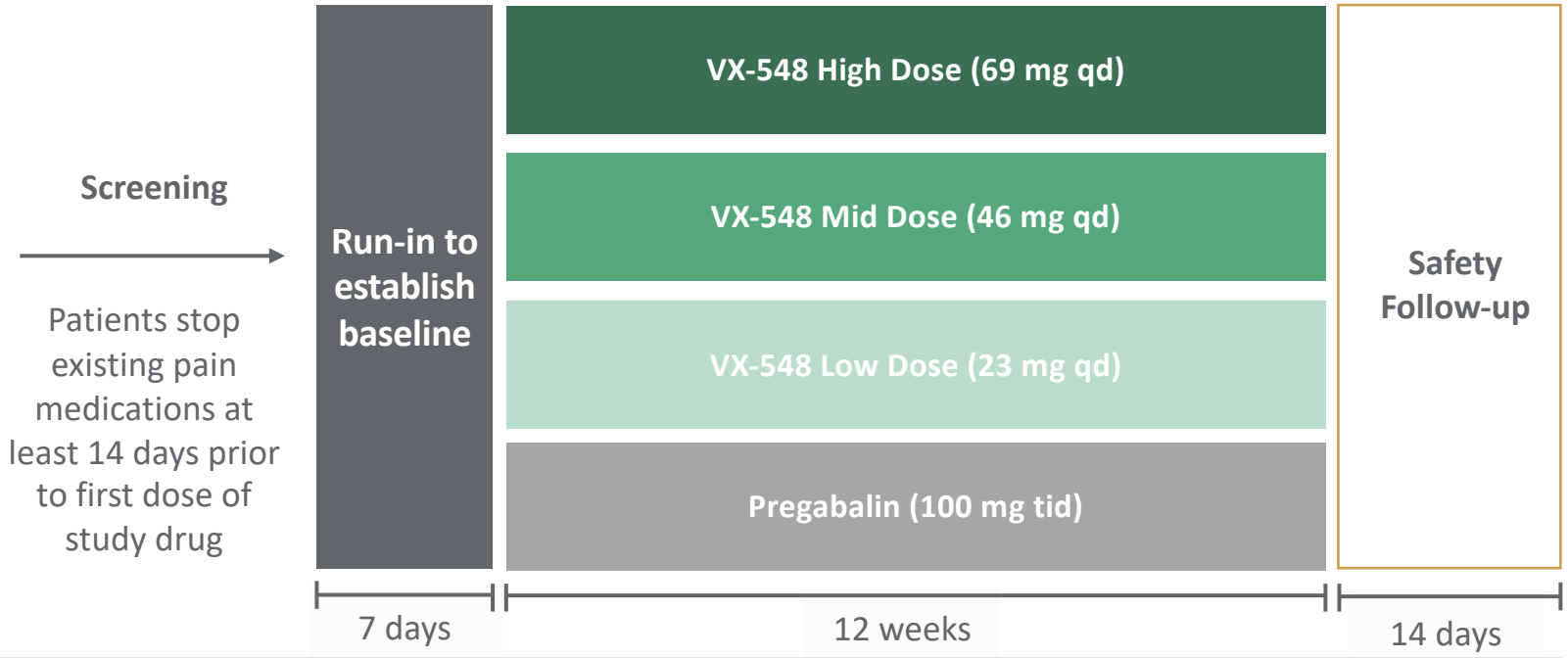
DPN Phase 2 results

- **Primary endpoint**: statistically significant and clinically meaningful reduction from baseline in weekly average pain scores across all VX-548 doses tested
- Favorable **safety and tolerability** profile for 12 weeks
- VX-548 exposure in three dose groups overlapping, and at the high end of the therapeutic range

VX-548 PHASE 2 STUDY IN PAINFUL DIABETIC PERIPHERAL NEUROPATHY

VX-548 PHASE 2 DPN STUDY DESIGN

Phase 2, randomized, double-blind, active-controlled, dose-ranging study to evaluate safety and efficacy of VX-548 in patients with DPN



N=192 patients*, randomized 2:2:1:2 VX-548 High, VX-548 Mid, VX-548 Low, Pregabalin. Treatment naïve and treatment experienced patients were randomized after a 7-day run-in period to establish baseline. Existing pain medications (except acetaminophen 500 mg) were stopped at least 14 days prior to first dose of study drug.

Key inclusion criteria: patients with diabetes mellitus type 1 or type 2, ages 18 to 80; bilateral pain in lower extremities due to DPN for at least 1 year; moderate to severe pain at baseline

Key exclusion criteria: painful neuropathy other than DPN

- **Primary endpoint:** Change from baseline in the weekly average of daily pain intensity on a numeric pain rating scale (NPRS) at week 12
- Secondary and other endpoints were assessed
- Study not designed or powered for comparisons between VX-548 arms or between VX-548 and pregabalin
- In order to maintain blinding in the study, patients discontinued if CrCl<60 mL/min across all arms
  - Pregabalin is renally cleared; per label, dose adjustment needed if CrCl<60 mL/min

*192 patients enrolled in the trial, 173 were evaluated for efficacy. Due to non-compliance with taking VX-548 at one clinical trial site with 19 enrolled patients, data from this site was included in the safety analyses, but not in the efficacy analyses.
Qd = once a day, tid = three times a day; 100 mg tid is the maximum recommended daily dose of pregabalin for DPN

PRIMARY ENDPOINT: TREATMENT WITH VX-548 SHOWED STATISTICALLY SIGNIFICANT & CLINICALLY MEANINGFUL PAIN RELIEF IN PATIENTS WITH DPN

Baseline NPRS:

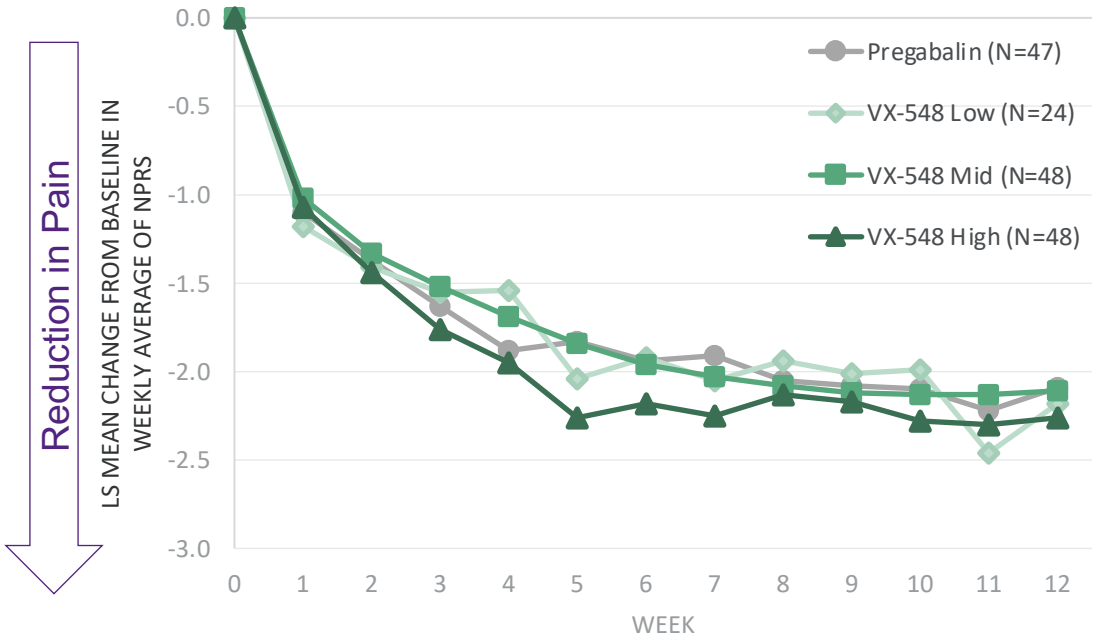
	Pregabalin 100mg TID N=47	**VX-548** Low Dose N=24	**VX-548** Mid Dose N=48	**VX-548** High Dose N=48
Mean (SD)	5.98 (1.28)	5.70 (1.32)	5.88 (0.97)	5.79 (1.22)

PRIMARY END POINT: Within group, change from baseline, in the weekly average of daily pain intensity on NPRS at week 12

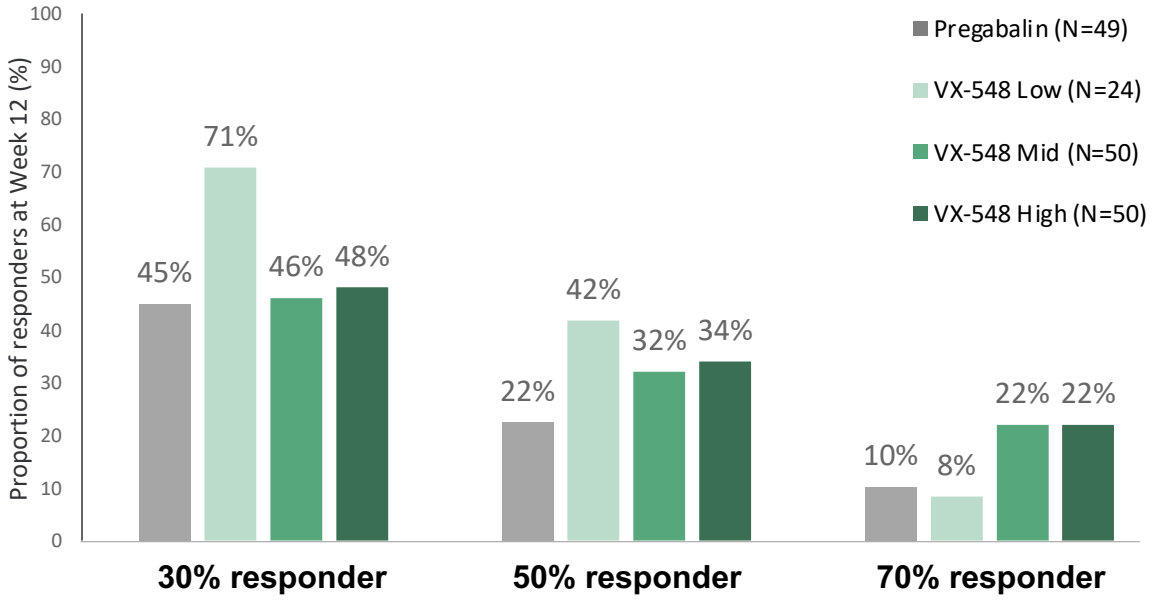
	Pregabalin 100mg TID N=47	**VX-548** Low Dose N=24	**VX-548** Mid Dose N=48	**VX-548** High Dose N=48
LS Mean (SE)	**-2.09** (0.29)	**-2.18** (0.39)	**-2.11** (0.28)	**-2.26** (0.28)
95% CI	(-2.65, -1.52)	(-2.94, -1.41)	(-2.67, -1.55)	(-2.82, -1.70)
P value	<0.0001	<0.0001	<0.0001	<0.0001

LS Mean = least square mean, SD = standard deviation, SE = standard error, CI = confidence interval

PRE-SPECIFIED ADDITIONAL ENDPOINTS INDICATE IMPROVED PAIN SCORES FOR PATIENTS TREATED WITH VX-548



Sustained reductions in pain throughout the treatment period for all VX-548 arms



With VX-548, more than 30% of patients achieved ≥50% reduction, more than 20% of patients in the mid- and high-dose groups achieved ≥70% reduction in pain scores

The pregabalin arm serves as a reference. Study was not designed or powered for comparisons between the VX-548 arms or between VX-548 and pregabalin.

VX-548 WAS GENERALLY WELL TOLERATED AT ALL DOSES STUDIED

All Study Arms

No SAEs related to VX-548* or pregabalin

VX-548 Arms

The majority of AEs were mild or moderate

14.5% related AEs
(all three VX-548 arms combined)

Pregabalin Arm

The majority of AEs were mild or moderate

27.8% related AEs

The pregabalin reference arm experienced AEs consistent with pregabalin's label

** One death in the mid-dose VX-548 group was due to atherosclerotic cardiovascular disease and was assessed as NOT related to VX-548.*

TREATMENT EMERGENT ADVERSE EVENTS (TEAE) IN ≥ 2 PATIENTS IN ANY TREATMENT ARM

	Pregabalin N = 54 n (%)	VX-548 Low Dose N = 28 n (%)	VX-548 Mid Dose N = 55 n (%)	VX-548 High Dose N = 55 n (%)	Total VX-548 N = 138 n (%)
Subjects with any TEAEs	20 (37.0)	14 (50.0)	21 (38.2)	31 (56.4)	66 (47.8)
CrCL decrease	1 (1.9)	0	1 (1.8)	6 (10.9)	7 (5.1)
Headache	2 (3.7)	0	3 (5.5)	1 (1.8)	4 (2.9)
Diarrhea	0	1 (3.6)	2 (3.6)	1 (1.8)	4 (2.9)
Nausea	0	0	1 (1.8)	2 (3.6)	3 (2.2)
Fatigue	1 (1.9)	1 (3.6)	0	2 (3.6)	3 (2.2)
Constipation	1 (1.9)	0	2 (3.6)	1 (1.8)	3 (2.2)
Somnolence	2 (3.7)	1 (3.6)	2 (3.6)	0	3 (2.2)
Back pain	0	3 (10.7)	0	0	3 (2.2)
Cellulitis	0	0	0	2 (3.6)	2 (1.4)
GERD	0	0	0	2 (3.6)	2 (1.4)
Pain in extremity	0	0	0	2 (3.6)	2 (1.4)
Type 2 diabetes mellitus	0	0	0	2 (3.6)	2 (1.4)
Lipase increased	2 (3.7)	0	0	1 (1.8)	1 (0.7)
Dizziness	5 (9.3)	0	1 (1.8)	0	1 (0.7)
Oedema peripheral	3 (5.6)	1 (3.6)	0	0	1 (0.7)
Weight increased	4 (7.4)	0	0	0	0

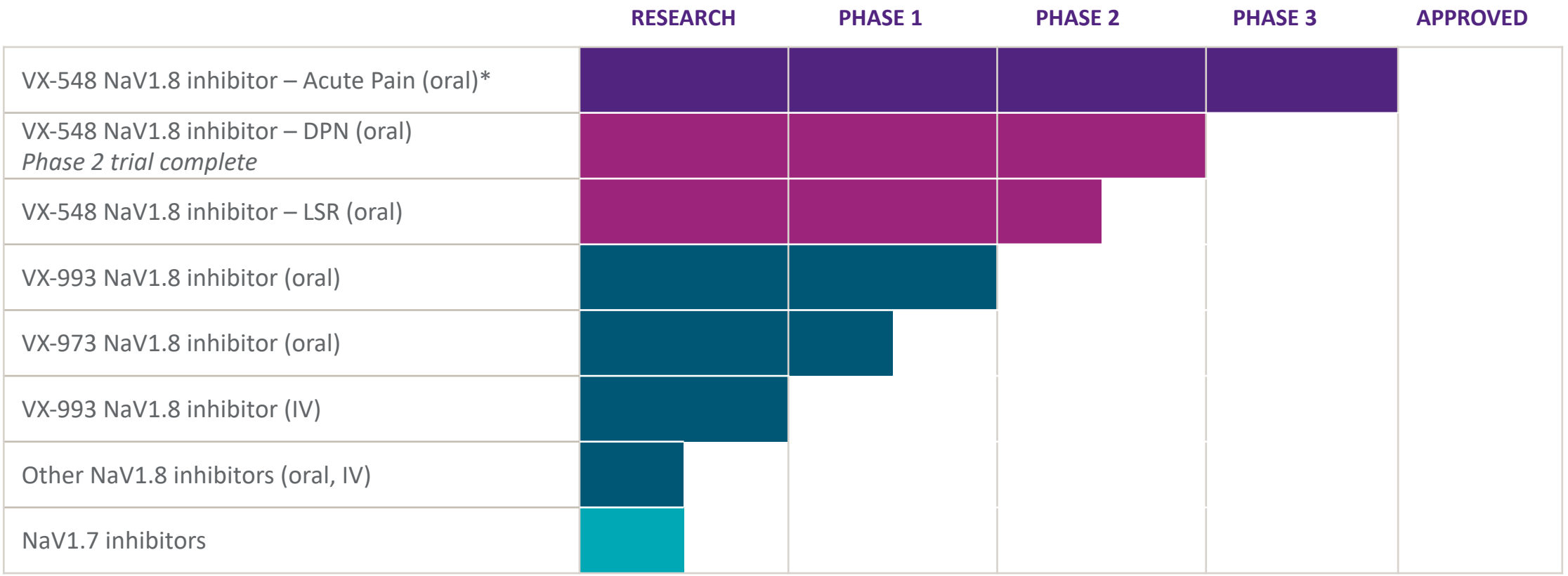
RELATED TEAE IN ≥ 2 PATIENTS IN ANY TREATMENT ARM

	Pregabalin N = 54 n (%)	VX-548 Low Dose N = 28 n (%)	VX-548 Mid Dose N = 55 n (%)	VX-548 High Dose N = 55 n (%)	Total VX-548 N = 138 n (%)
Subjects with any related TEAEs	15 (27.8)	6 (21.4)	7 (12.7)	7 (12.7)	20 (14.5)
Diarrhea	0	1 (3.6)	2 (3.6)	0	3 (2.2)
Weight increased	3 (5.6)	0	0	0	0
Headache	2 (3.7)	0	1 (1.8)	1 (1.8)	2 (1.4)
Dizziness	4 (7.4)	0	0	0	0
Somnolence	2 (3.7)	1 (3.6)	1 (1.8)	0	2 (1.4)

TEAE = treatment emergent adverse event

VERTEX IS COMMITTED TO TRANSFORMING THE TREATMENT OF PAIN

BROAD AND DEEP PIPELINE TO MAINTAIN LEADERSHIP IN MULTIPLE PAIN STATES



IV: intravenous

** Dosing in the Phase 3 program in Acute Pain has completed.*

SUMMARY: POSITIVE PHASE 2 RESULTS WITH VX-548 IN PAINFUL DIABETIC PERIPHERAL NEUROPATHY

Growing body of evidence supporting the promise of NaV1.8 inhibitors for pain, the first potential new class of pain medicines in over two decades

- ❑ MoA targets the underlying causal human biology
- ❑ Non-opioid class that acts in the peripheral nervous system
- ❑ Six out of six positive Phase 2 studies with Vertex selective NaV1.8 inhibitors

Phase 2 DPN results are first demonstration of VX-548 safety & efficacy in a chronic pain condition

- ❑ Statistically significant and clinically meaningful reduction from baseline in weekly average pain scores at 12 weeks
- ❑ Favorable safety and tolerability profile

Immediate next steps in PNP

- ❑ Enroll Phase 2 study of VX-548 in painful LSR
- ❑ Engage in End of Phase 2 meeting with regulators
- ❑ Advance VX-548 into pivotal development in 2024

Mid- and long-term goals in pain

- ❑ Develop a portfolio of first-in-class and best-in-class medicines for pain: NaV1.8 inhibitors, NaV1.7 inhibitors, and potential combinations of NaV1.8 and NaV1.7 inhibitors
- ❑ Secure broad PNP label

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VERTEX PHARMACEUTICALS

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