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SUZETRIGINE (VX-548) PHASE 2 RESULTS IN PAINFUL LUMBOSACRAL RADICULOPATHY

DECEMBER 19, 2024

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This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, statements regarding the anticipated benefits of suzetrigine as a treatment for patients with LSR, beliefs that Vertex can demonstrate success in a Phase 3 study of suzetrigine for patients with LSR, including beliefs that trial design may better control for the placebo effect, plans to advance to Phase 3 pending regulatory discussions focused on acceptance of novel study design and requirements to broaden beyond DPN indication, expectations for the LSR patient population in the U.S., expectations for securing a broad PNP label, Vertex's commitment to transforming the treatment of pain, and plans to continue advancing the next wave of NaV1.8 and NaV1.7 inhibitors. 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 the company's pain programs may not support registration or further development of its potential medicines due to safety, efficacy or other reasons, that discussions with regulators may have different outcomes than the company anticipates, that the company may be unable to successfully commercialize suzetrigine as a treatment for pain 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.

SUZETRIGINE PHASE 2 STUDY IN PAINFUL LUMBOSACRAL RADICULOPATHY (LSR): KEY POINTS

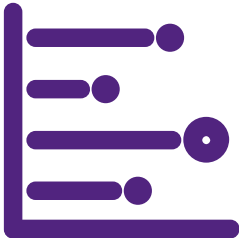
- Suzetrigine Phase 2 LSR study **met its primary endpoint**: -2.02 within-group change from baseline in NPRS scores at week 12
  - **Statistically significant and clinically meaningful** reduction in NPRS scores
  - Clearly an **active drug**, with **meaningful treatment effect** across pain studies
  - However, **treatment curves did not separate**; placebo effect: -1.98 within-group change in NPRS to week 12
- Suzetrigine was **well tolerated with a lower AE rate than the placebo arm**, adding to the safety profile
- Vertex **believes we can demonstrate success in a Phase 3** study in LSR given:
  1. The suzetrigine **treatment effect was robust and consistent** with prior studies
  2. Insights from post hoc analyses regarding **site variability and placebo effect**
  3. Our belief that we **can better control for the placebo effect** with innovation in clinical trial design
- **Advancing to Phase 3 pending regulatory discussions**, focused on
  1. Study design optimization to manage the placebo effect
  2. FDA requirements to broaden beyond a diabetic peripheral neuropathy (DPN) indication
- Committed to **transforming the treatment of pain with innovations in $Na_V1.8/Na_V1.7$ research *and* clinical trial design**

NPRS = numeric pain rating scale, AE = adverse event.
Suzetrigine is *an investigational medicine* for acute and peripheral neuropathic pain, including lumbosacral radiculopathy.

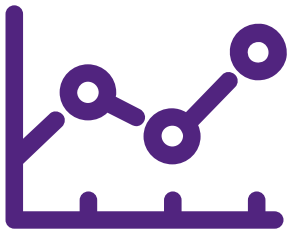
HIGH UNMET NEED AND LIMITED CLINICAL TRIAL EXPERIENCE CREATE SIGNIFICANT OPPORTUNITY IN LSR

>4 million LSR patients in the U.S.

No approved therapies specifically indicated for LSR



- Limited LSR studies:*
  - ~10 published Phase 2 randomized placebo-controlled trials in LSR
  - No studies with $Na_V1.8$ pain signal inhibitors
  - No Phase 3 study ever completed in LSR



No defined standard for meaningful between-group difference of change in NPRS

*Defined as studies of systemic therapies, does not include devices or procedures

SUZETRIGINE PHASE 2 STUDY DESIGNED TO UNDERSTAND PERFORMANCE OF SELECTIVE NAV1.8 PAIN SIGNAL INHIBITOR AND PLACEBO IN LSR

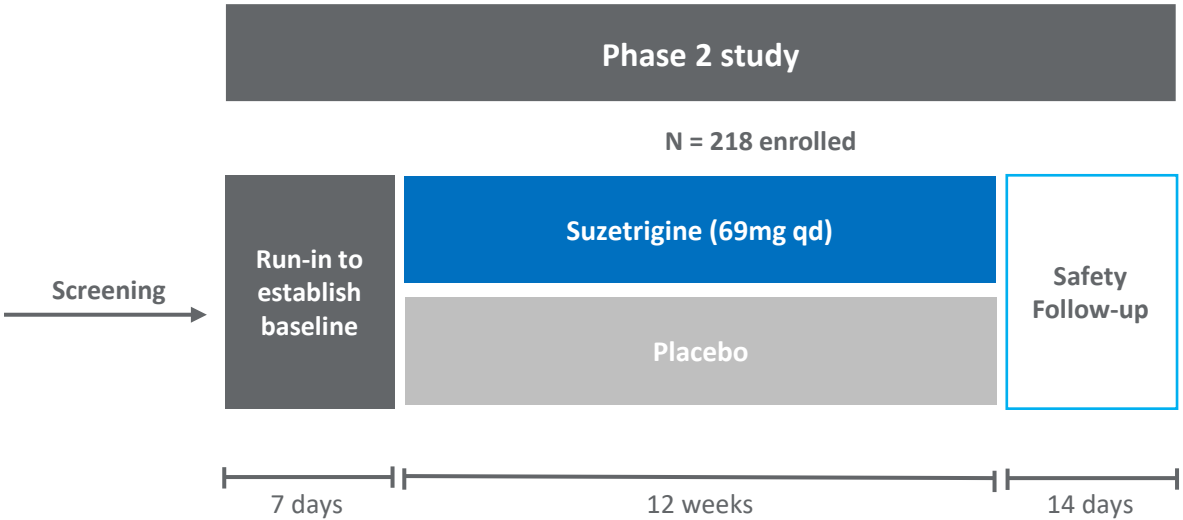
Study goals

1. Evaluate the magnitude of the treatment effect with suzetrigine, the first selective $Na_V1.8$ pain signal inhibitor to be studied in LSR
2. Evaluate the effect of placebo in patients with LSR
3. Assess safety and tolerability over 12 weeks of treatment

Translate these learnings into next steps for suzetrigine in LSR

SUZETRIGINE PHASE 2 LSR STUDY DESIGN

Phase 2, randomized, double-blind, placebo-controlled study in patients with painful LSR lasting over 3 months



Primary Endpoint:

- Within-group change from baseline in the weekly average of daily leg pain intensity on the NPRS at week 12

Secondary Endpoints:

- Within-group change from baseline in the weekly average of the daily sleep interference scale (DSIS) at week 12;
- Safety and tolerability

N=218 patients*, randomized 1:1 suzetrigine vs. placebo, enrolled across 38 sites. Patients were randomized after a 7-day run-in period to establish baseline. Pain medications, except stable over-the-counter doses of ibuprofen (up to 1600 mg/24-hour) or naproxen (up to 440 mg/24-hour), were stopped at least 14 days prior to first dose. Acetaminophen (up to 500 mg every 4 to 6 hours, as needed) was allowed during the run-in period and throughout the study.

Key inclusion criteria: patients with painful lumbosacral radiculopathy lasting over 3 months, ages 18 to 70; moderate-to-severe pain (NPRS≥4 and <10).

Key exclusion criteria: painful neuropathy other than LSR, history of prior lumbar spine surgery.

*202 patients evaluated for efficacy. One site with 15 patients excluded from the efficacy analysis, due to non-compliance. One patient was randomized but not dosed. All patients dosed were included in the safety analysis.

DEMOGRAPHICS AND BASELINE CHARACTERISTICS GENERALLY BALANCED

		Suzetrigine N = 102	Placebo N = 100
Demographics	Age in years, Mean (SD)	53.4 (11.2)	50.9 (12.7)
	Female, %	59.8%	63.0%
	Race, % White Black or African American Asian Other	 74.5% 21.6% 1.0% 2.9%	 69.0% 27.0% 1.0% 3.0%
Baseline Characteristics	BMI in kg/m^2, Mean (SD)	30.0 (5.5)	29.3 (5.2)
	Years since LSR diagnosis, Mean (SD)	5.2 (6.5)	7.3 (8.8)
	Back Pain associated with LSR, %	92.2%	89.0%
	Baseline NSAID use, %*	43.1%	42.0%
	Dermatome with pain, % L4 L5 S1	23.5% 27.5% 49.0%	24.0% 31.0% 45.0%
	Baseline Weekly average of NPRS, Mean (SD)	6.33 (1.22)	6.05 (1.07)
	Baseline Weekly average of NPRS category, % <7 ≥7	67.6% 32.4%	78.0% 22.0%

*Note: Acetaminophen, up to 500 mg every 4 to 6 hours, as needed, was allowed during the run-in period and as rescue throughout the study. Acetaminophen use was balanced in both arms.

PRIMARY ENDPOINT: TREATMENT WITH SUZETRIGINE SHOWED STATISTICALLY SIGNIFICANT & CLINICALLY MEANINGFUL REDUCTION IN LEG PAIN INTENSITY

Baseline leg pain intensity (NPRS score)

	Suzetrigine 69 mg QD N=102	**Placebo** N=100
Mean (SD)	6.33 (1.22)	6.05 (1.07)

PRIMARY END POINT: Within group change from baseline in the weekly average of daily leg pain intensity on NPRS at week 12; study not powered or designed for between group comparison

	Suzetrigine 69 mg QD N=102	**Placebo** N=100
LS Mean	**-2.02**	**-1.98**
95% CI	(-2.40, -1.64)	(-2.36, -1.60)
P value	*<0.0001*	*<0.0001*

NPRS = numeric pain rating scale, LS Mean = least square mean, SD = standard deviation, CI = confidence interval

SUZETRIGINE WAS WELL TOLERATED

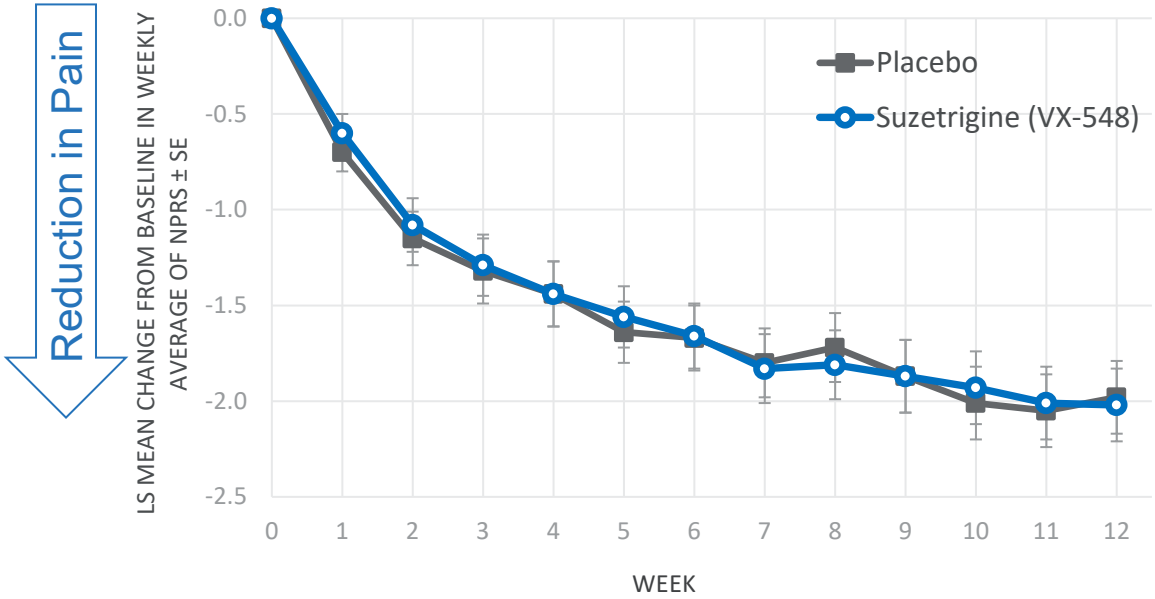
	Suzetrigine N = 109 n (%)	Placebo N = 108 n (%)
Subjects with any AEs	**25 (22.9)**	**35 (32.4)**
Subjects with AEs by strongest relationship		
Not related	16 (14.7)	20 (18.5)
Unlikely related	1 (0.9)	6 (5.6)
Possibly related	6 (5.5)	8 (7.4)
Related	2 (1.8)	1 (0.9)
Subjects with AEs by maximum severity		
Grade 1/Mild	15 (13.8)	17 (15.7)
Grade 2/Moderate	10 (9.2)	17 (15.7)
Grade 3/Severe	0	1 (0.9)
Grade 4/Life-threatening	0	0
Grade 5/Death	0	0
Subjects with serious AEs	1 (0.9)	2 (1.9)
Subjects with AEs leading to treatment discontinuation	0	1 (0.9)
Subjects with AEs leading to death	0	0

All AEs in subjects who received suzetrigine were mild or moderate; no related SAEs; no clinically significant trends or patterns in labs, ECGs, or vital signs

AE = adverse event, ECG = electrocardiogram

LEG PAIN INTENSITY DECLINED FOR PATIENTS TREATED WITH SUZETRIGINE OVER 12 WEEKS

Placebo had similar response



- Results for secondary and other endpoints were consistent with the primary endpoint

VERTEX INTERPRETATION

1) Suzetrigine is **active in LSR**

- Statistically significant improvement
- Clinically meaningful ≥2 point reduction
- Consistent magnitude of pain reduction for both
  - VRTX $Na_V1.8$ inhibitors in neuropathic pain
  - medicines approved for neuropathic pain

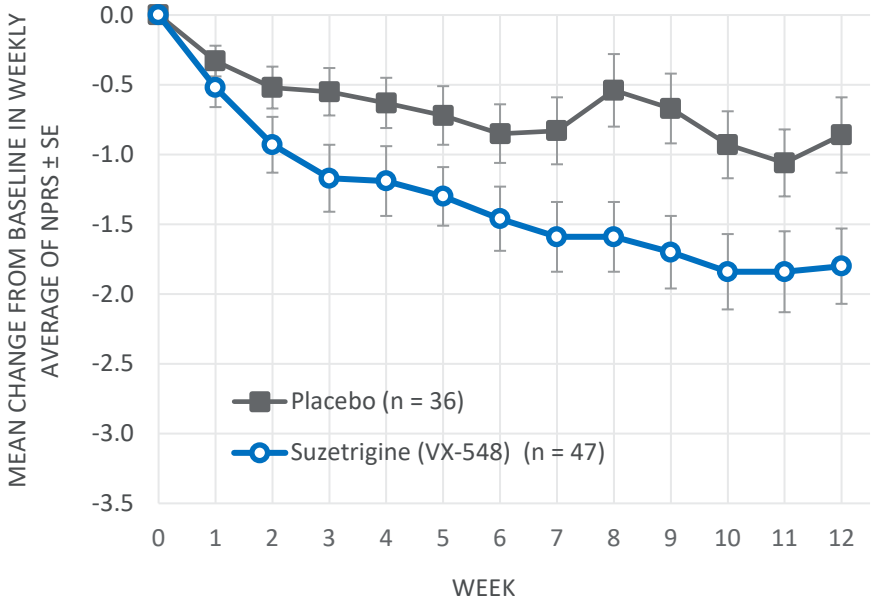
2) Placebo response of **equal magnitude** to suzetrigine in this study

- High overall placebo response
- High site-to-site variability in placebo response

HYPOTHESIS: The high placebo response was driven by some sites, leading to lack of separation of suzetrigine and placebo curves

TO EVALUATE THIS HYPOTHESIS, POST HOC ANALYSES WERE CONDUCTED OF SITES WITH LOWER PLACEBO RESPONSE

Post hoc analysis of leg pain intensity over time at sites with lower placebo response



Sites that had either no placebo patients or no suzetrigine patients are excluded.

- Post hoc analyses were conducted to evaluate the placebo response, which varied across sites, a known issue in pain studies
- Approximately 40% of the clinical trial sites had a lower placebo response
- Analyses of the primary and other endpoints *at these sites* showed **suzetrigine arm within-group reduction in pain was consistent with the overall study and had greater separation from the placebo arm**
- As such, we believe that innovation in clinical trial design could allow us to control for the placebo response and separate the treatment effect of suzetrigine from placebo

VERTEX IS COMMITTED TO TRANSFORMING THE TREATMENT OF PAIN WITH INNOVATIONS IN $NA_V1.8/NA_V1.7$ RESEARCH *AND* PAIN CLINICAL TRIAL DESIGN:

LSR TAKEAWAYS AND NEXT STEPS

EFFICACY:

- Suzetrigine met its primary endpoint with a **clinically meaningful and statistically significant** reduction in pain scores in LSR
- Suzetrigine is an active drug: **magnitude of the treatment effect was consistent** with our experience with selective $Na_V1.8$ pain signal inhibitors and the overall treatment effect in the field of neuropathic pain
- Placebo effect in this study was high and **treatment curves did not separate**

SAFETY:

- Today's results **add to the body of evidence on the well tolerated safety profile** of suzetrigine and the selective $Na_V1.8$ pain signal inhibitor class

NEXT STEPS:

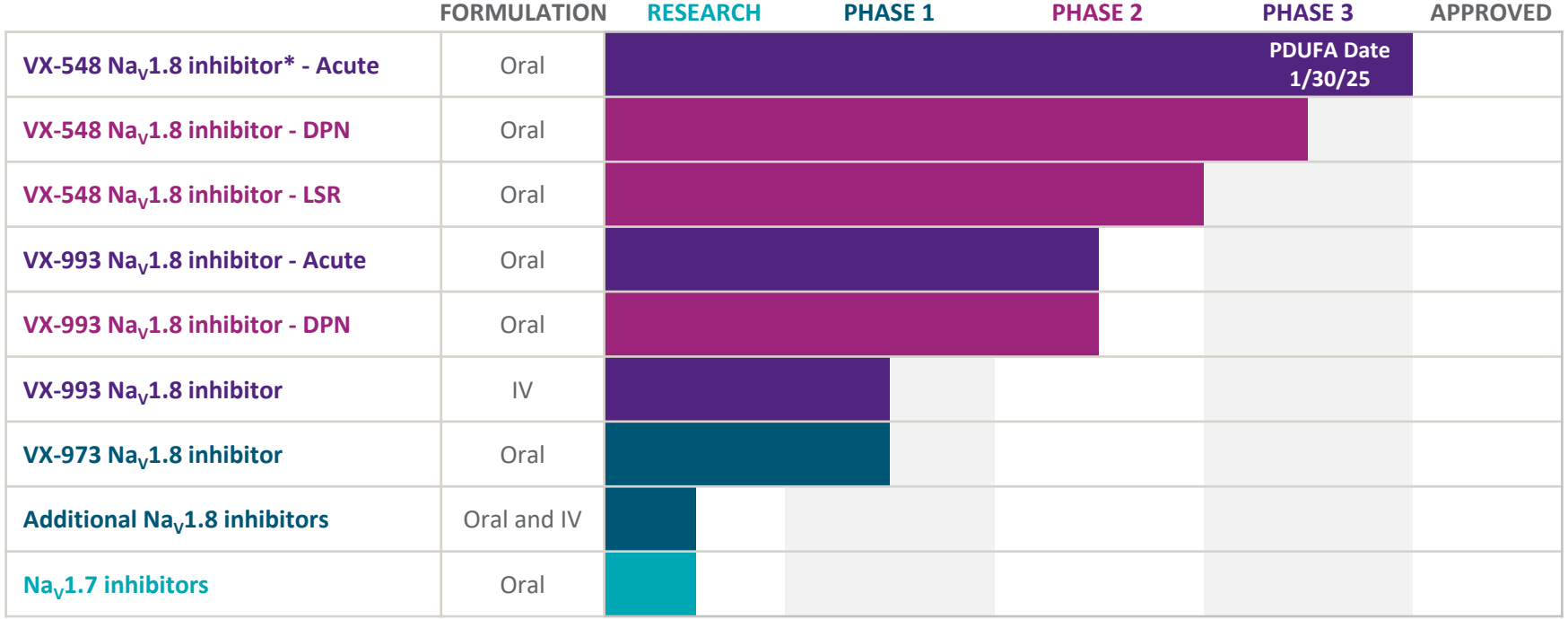
- **Move into Phase 3**, pending regulatory discussions focused on 1) acceptance of novel study design and 2) requirements to broaden beyond DPN indication

OUTLOOK FOR PHASE 3 SUZETRIGINE LSR SUCCESS DRIVEN BY:

- **Robust and consistent treatment effect** with suzetrigine
- **Insights from post hoc analyses** regarding site variability and placebo effect
- Potential for **innovative clinical trial design** to better control for placebo effect

VERTEX IS COMMITTED TO INNOVATING TO TRANSFORM THE TREATMENT OF PAIN

Serial innovation, broad/deep pipeline for leadership in multiple pain states



DPN: diabetic peripheral neuropathy; LSR: lumbosacral radiculopathy; IV: intravenous.
All molecules are investigational for acute and peripheral neuropathic pain.

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