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SUZETRIGINE (VX-548) ASA UPDATE

OCTOBER 20, 2024

AGENDA

Introduction

Susie Lisa, CFA, Senior Vice President, Investor Relations, Vertex

Phase 3 Results of Suzetrigine

Todd Bertoch, M.D., Diplomat of the American Board of Anesthesiology, CEO of CenExel JBR Clinical Research

Real-World Perspective on Acute Pain Management

Ashraf Habib, M.D., Professor of Anesthesiology, Professor of Obstetrics and Gynecology, Chief of Division of Women's Anesthesiology, Duke University Hospital

Commercial Opportunity in Acute Pain

Duncan McKechnie, Senior Vice President, Head of North America Commercial, Vertex

Questions & Answers

Dr. Bertoch, Dr. Habib, Duncan McKechnie, joined by additional Vertex executives including Charlie Wagner, Executive Vice President and Chief Financial Officer and Paul Negulescu, Senior Vice President, Disease Area Executive for Pain, Research Leadership Team

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, Vertex's expectations that suzetrigine inhibits pain signals with no addictive potential as a monotherapy and as part of a multimodal therapy, expectations that suzetrigine could fundamentally reshape the treatment of acute pain, beliefs about the commercial potential for suzetrigine as a treatment for acute pain, plans to continue to engage with federal and state policymakers, plans for our commercial launch readiness for suzetrigine, and expectations with respect to our chronic pain program, including plans to pursue multiple indications for suzetrigine in chronic 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 the company's development programs may not support registration or further development of its potential medicines due to safety, efficacy or other reasons, that we may be unable to successfully commercialize suzetrigine as a treatment for acute 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.

Randomized, Placebo-Controlled, Phase 3 Trials of Suzetrigine, a Non-Opioid, Pain Signal Inhibitor for Treatment of Acute Pain After Abdominoplasty or Bunionectomy

Todd Bertoch[1], Dominick D'Aunno[2], Jessica McCoun[3], Daneshvari Solanki[4], Louise Taber[5], Joshua Urban[6], Jessica Oswald[7,8], Matthew Swisher[8], Simon Tian[9], Xiaopeng Miao[9], Darin J Correll[9], Paul Negulescu[9], Carmen Bozic[9], Scott Weiner[10]

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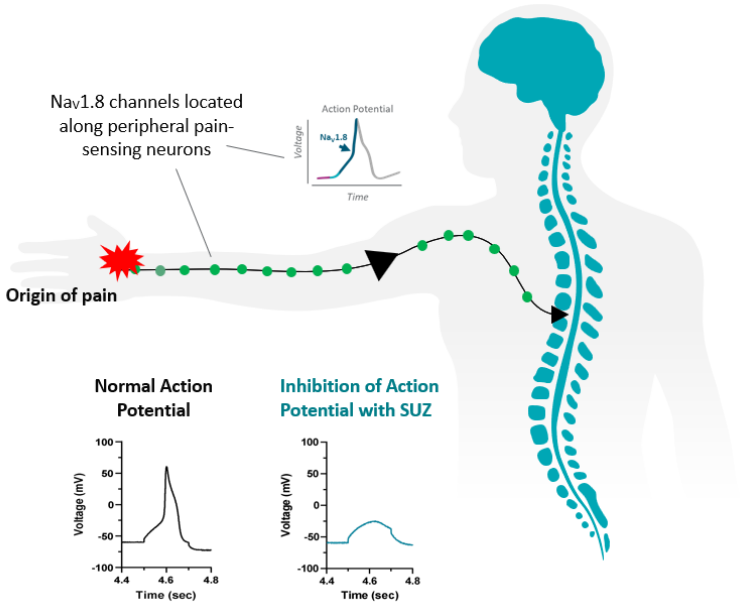
the ANESTHESIOLOGY® annual meeting
American Society of Anesthesiologists®

Todd Bertoch, M.D. Disclosure

Consultant: Vertex Pharmaceuticals

Selectively Targeting Peripheral $Na_V1.8$ Channels With Suzetrigine Inhibits Pain Signals With No Addictive Potential



$Na_V1.8$

- **Therapeutic target** for pain management
- Critical role in transmitting nociceptive signals; **selectively expressed on peripheral nociceptors** and within dorsal root ganglia
- **Not expressed in the brain;** therefore, not associated with addiction

Suzetrigine

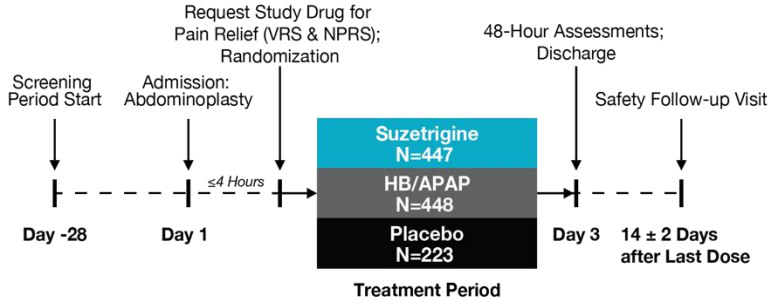
- **Oral, small molecule** that is potent and highly selective for $Na_V1.8$
- A **selective pain signal inhibitor** with no addictive potential

Suzetrigine, a non-opioid, non-addictive, selective pain signal inhibitor, holds the promise to be the first treatment for moderate-to-severe acute pain in a new pharmacologic class in over two decades.

$Na_V1.8$: voltage-gated sodium channel 1.8

Largest Phase 3 Randomized, Controlled Trials in Established Models of Acute Pain

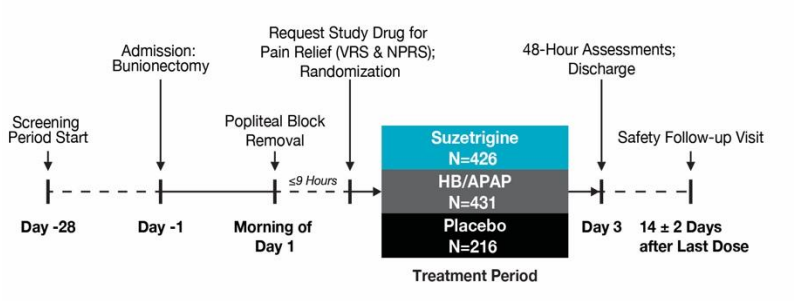
NAVIGATE 2: Abdominoplasty (N=1118)



Study Design

- **Suzetrigine tablets:** 100-mg then 50-mg every 12 hours administered orally
- **HB/APAP capsules:** 5-mg/325-mg every 6 hours administered orally
- **Rescue medication:** ibuprofen was permitted, if needed, for pain relief, as is conventional in trials of acute pain with an opioid comparator

NAVIGATE 1: Bunionectomy (N=1073)



Key Eligibility Criteria

- **Age:** 18 to 80 years
- **Reported pain:** moderate or severe on the VRS and ≥4 on the NPRS within 4 hours after abdominoplasty or 9 hours after removal of the popliteal sciatic nerve block (with ropivacaine) after a bunionectomy

HB/APAP: hydrocodone bitartrate/acetaminophen; **N:** number of participants in the analysis set; **NPRS:** numeric pain rating scale; **VRS:** verbal categorical rating scale

Primary and Key Secondary Efficacy Endpoints for NAVIGATE 1 and NAVIGATE 2 Trials

Primary Efficacy Endpoint

- SPID48 for suzetrigine compared to placebo

Key Secondary Efficacy Endpoints

- SPID48 for suzetrigine compared to HB/APAP
- Time to ≥2-point reduction in NPRS from baseline for suzetrigine compared to placebo (i.e., time to clinically meaningful pain relief)

Analysis of the Primary and Key Secondary Endpoints

- **Pre-specified analysis with imputation of NPRS** scores after ibuprofen rescue for 6 hours using the pre-rescue score to assess the efficacy of suzetrigine as a **monotherapy** compared to placebo.
- **Ad hoc analysis without imputation of NPRS** scores after ibuprofen rescue to assess the efficacy of suzetrigine *plus* ibuprofen (if used) compared to placebo *plus* ibuprofen (if used), which is representative of **multimodal treatment.**

HB/APAP: hydrocodone bitartrate/acetaminophen; **NPRS:** numeric pain rating scale; **VRS:** verbal categorical rating scale; **SPID48:** time-weighted sum of the pain intensity difference as recorded on the NPRS from 0 to 48 hours

Demographics & Baseline Characteristics Were Balanced Within Each Trial; Greater Baseline Pain in the Abdominoplasty Trial Than the Bunionectomy Trial

	Abdominoplasty				Bunionectomy			
	Suzetrigine N = 447	HB/APAP N = 448	Placebo N = 223	Total N = 1118	Suzetrigine N = 426	HB/APAP N = 431	Placebo N = 216	Total N = 1073
Age (years), mean (SD)	41.5 (9.1)	42.1 (8.7)	41.5 (8.5)	41.8 (8.8)	47.7 (13.3)	48.3 (12.6)	48.1 (13.5)	48.0 (13.1)
Sex, n (%)								
Female	437 (97.8)	441 (98.4)	220 (98.7)	1098 (98.2)	366 (85.9)	359 (83.3)	187 (86.6)	912 (85.0)
Male	10 (2.2)	7 (1.6)	3 (1.3)	20 (1.8)	60 (14.1)	72 (16.7)	29 (13.4)	161 (15.0)
Race, n (%)								
White	307 (68.7)	316 (70.5)	155 (69.5)	778 (69.6)	285 (66.9)	314 (72.9)	160 (74.1)	759 (70.7)
Black or African American	123 (27.5)	114 (25.4)	62 (27.8)	299 (26.7)	116 (27.2)	96 (22.3)	48 (22.2)	260 (24.2)
Other*	17 (3.8)	18 (4.0)	6 (2.7)	41 (3.7)	25 (5.9)	21 (4.9)	8 (3.7)	54 (5.0)
BMI (kg/m^2), mean (SD)	29.21 (4.06)	29.38 (4.37)	29.58 (4.20)	29.35 (4.21)	28.10 (4.93)	28.07 (4.82)	28.29 (4.77)	28.13 (4.85)
NPRS, mean (SD)	7.3 (1.7)	7.4 (1.7)	7.5 (1.7)	7.4 (1.7)	6.7 (1.8)	6.8 (1.9)	6.8 (1.8)	6.8 (1.8)
NPRS category, n (%)								
<8	227 (50.8)	229 (51.1)	111 (49.8)	567 (50.7)	274 (64.3)	274 (63.6)	143 (66.2)	691 (64.4)
≥8	220 (49.2)	219 (48.9)	112 (50.2)	551 (49.3)	152 (35.7)	157 (36.4)	73 (33.8)	382 (35.6)
VRS, n (%)								
Moderate	266 (59.5)	262 (58.5)	127 (57.0)	655 (58.6)	291 (68.3)	279 (64.7)	147 (68.1)	717 (66.8)
Severe	181 (40.5)	186 (41.5)	96 (43.0)	463 (41.4)	135 (31.7)	152 (35.3)	69 (31.9)	356 (33.2)

Table includes participants who were randomized and received at least one dose of study drug. Participants were analyzed according to their randomized treatment.

* "Other" category includes Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, Multiracial, or Missing

BMI: body mass index; **HB/APAP:** hydrocodone bitartrate/acetaminophen; **N:** number of participants in the analysis set; **n:** number of participants; **NPRS:** Numeric Pain Rating Scale; **SD:** standard deviation; **VRS:** Verbal Categorical Rating Scale

Suzetrigine Showed Statistically Significant Superior Efficacy in Pain Reduction Compared to Placebo as Measured by SPID48

Primary Endpoint was Met in Both Trials

	Abdominoplasty		Bunionectomy	
Primary Endpoint: SPID48 Compared to Placebo	**Suzetrigine N=447**	**Placebo N=223**	**Suzetrigine N=426**	**Placebo N=216**
With Rescue Imputation (monotherapy)				
LS mean (SE)	118.4 (4.3)	70.1 (6.1)	99.9 (4.5)	70.6 (6.3)
LS mean difference from placebo	48.4	--	29.3	--
95% CI	(33.6, 63.1)	--	(14.0, 44.6)	--
P value versus placebo	<0.0001	--	0.0002	--
Without Rescue Imputation (representative of multimodal therapy in real-world setting)				
LS mean (SE)	153.0 (4.5)	105.4 (6.4)	128.8 (4.7)	100.1 (6.6)
LS mean difference from placebo	47.7	--	28.8	--
95% CI	(32.4, 62.9)	--	(12.9, 44.6)	--
Nominal *P* value versus placebo*	<0.0001	--	0.0004	--

Table includes participants who were randomized and received at least one dose of study drug. Participants were analyzed according to their randomized treatment.
*Analyses for SPID48 compared to placebo without rescue imputation are ad hoc; therefore, *P* values are nominal.

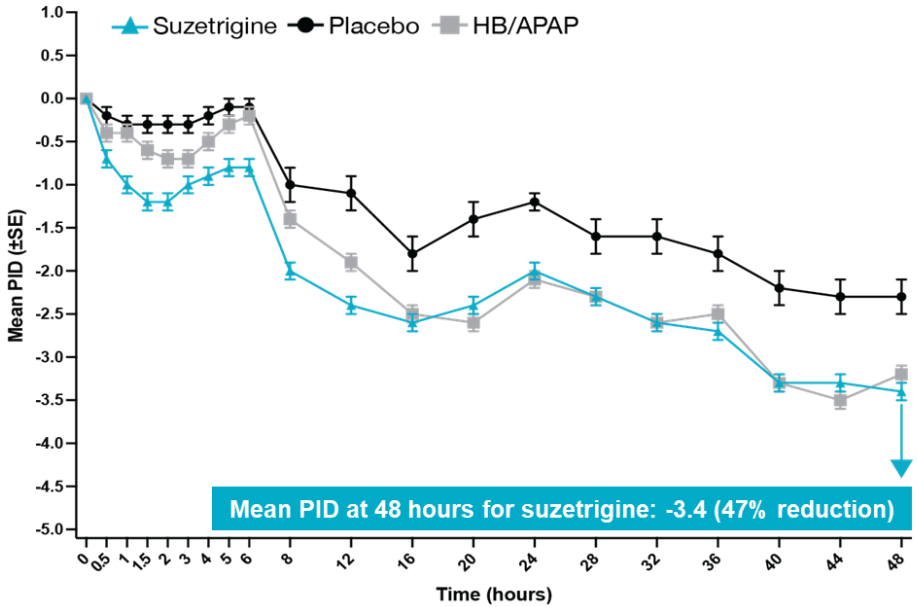
The magnitude of the treatment effect over 48 hours demonstrates that suzetrigine is effective as a monotherapy and as part of a multimodal therapy

CI: confidence interval; **LS mean:** least squares mean; **N**: number of participants in the analysis set; **NPRS:** numeric pain rating scale; **SE:** standard error; **SPID48:** time-weighted sum of the pain intensity difference as recorded on the NPRS from 0 to 48 hours

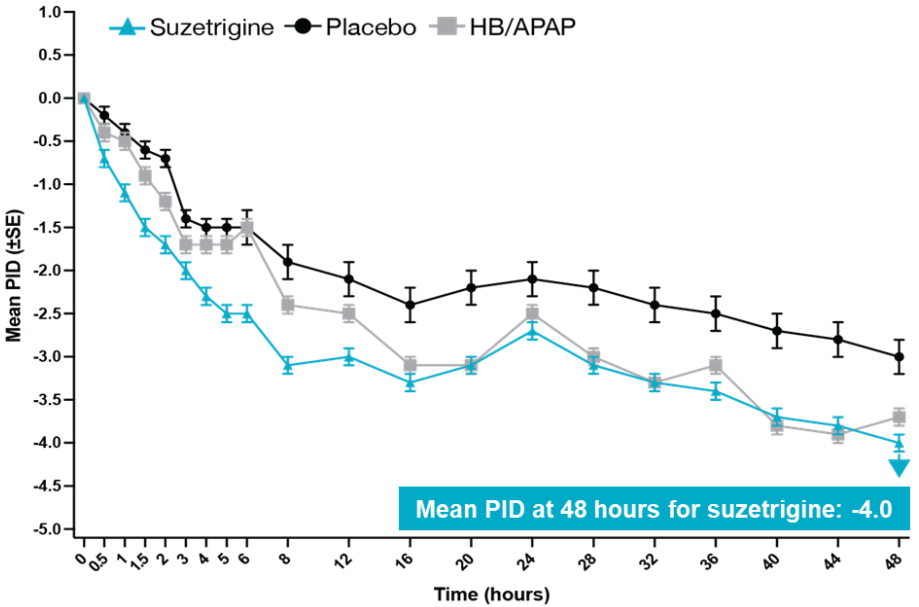
Rapid, Sustained, and Clinically Meaningful Pain Relief at 48 Hours was Observed With Suzetrigine After Abdominoplasty

Abdominoplasty

Analysis with rescue imputation: effect of study drug only (monotherapy)



Analysis without rescue imputation: effect of study drug *plus* ibuprofen (representative of multimodal therapy in real-world setting)

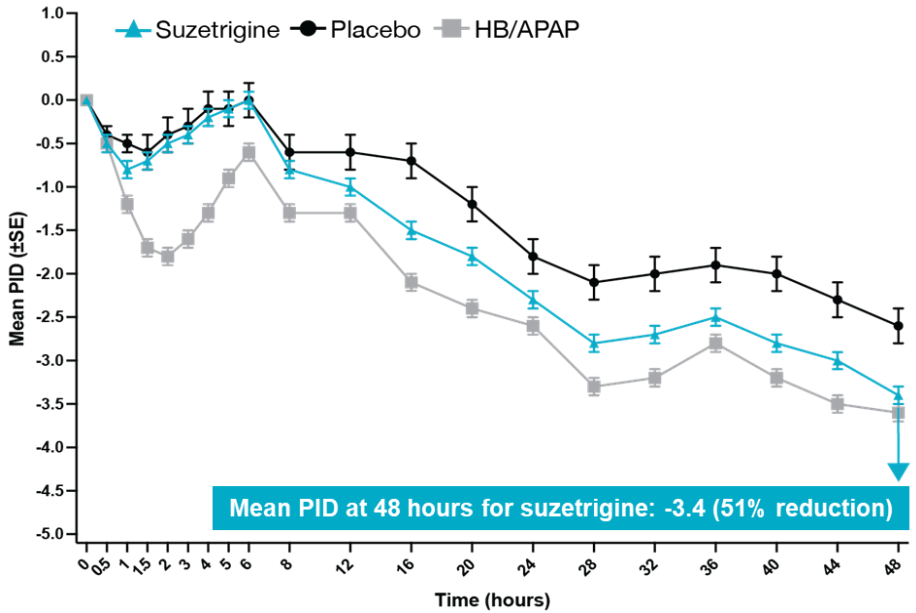


Includes participants who were randomized and received at least one dose of study drug. Participants were analyzed according to their randomized treatment.
HB/APAP: hydrocodone bitartrate/acetaminophen; **PID**; pain intensity difference; **SE:** standard error

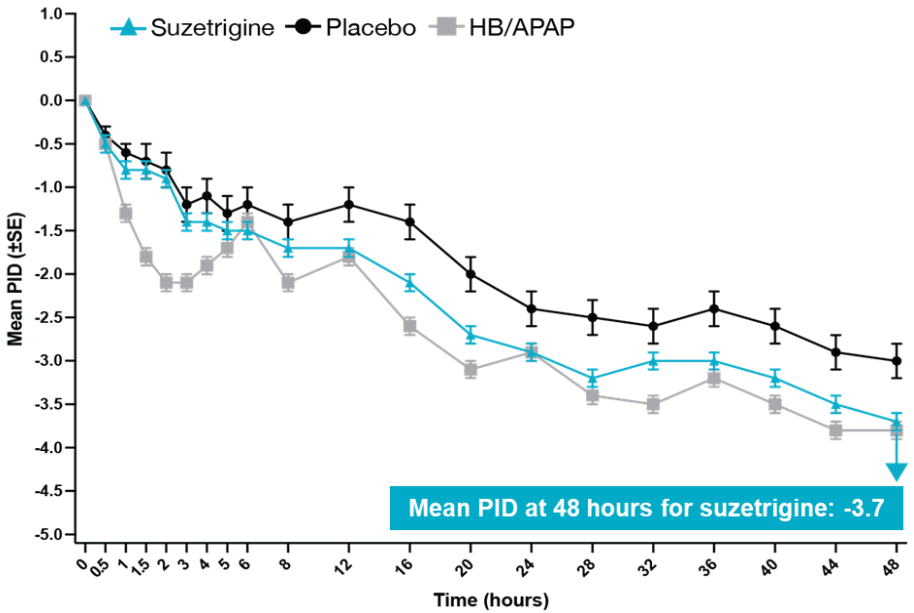
Rapid, Sustained, and Clinically Meaningful Pain Relief at 48 Hours was Observed With Suzetrigine After Bunionectomy

Bunionectomy

Analysis with rescue imputation: effect of study drug only (monotherapy)



Analysis without rescue imputation: effect of study drug *plus* ibuprofen (representative of multimodal therapy in real-world setting)



Includes participants who were randomized and received at least one dose of study drug. Participants were analyzed according to their randomized treatment.
HB/APAP: hydrocodone bitartrate/acetaminophen; **PID**; pain intensity difference; **SE:** standard error

Suzetrigine Monotherapy Did Not Meet the First Key Secondary Endpoint of Superiority to HB/APAP Combination Product

First Key Secondary Endpoint: SPID48 Compared to HB/APAP

	Abdominoplasty		Bunionectomy	
	Suzetrigine N=447	HB/APAP N=448	Suzetrigine N=426	HB/APAP N=431
With Rescue Imputation (monotherapy)				
LS mean (SE)	118.4 (4.3)	111.8 (4.3)	99.9 (4.5)	120.1 (4.5)
LS mean difference from HB/APAP	6.6	--	-20.2	--
95% CI	(-5.4, 18.7)	--	(-32.7, -7.7)	--
P value vs. HB/APAP	0.2781	--	0.0016	--
Without Rescue Imputation (representative of multimodal therapy in real-world setting)				
LS mean (SE)	153.0 (4.5)	141.0 (4.5)	128.8 (4.7)	140.6 (4.7)
LS mean difference from HB/APAP	12.0	--	-11.8	--
95% CI	(-0.5, 24.4)	--	(-24.8, 1.2)	--
Nominal *P* value vs. HB/APAP*	0.0595	--	0.0752	--

Note: Table includes participants who were randomized and received at least one dose of study drug. Participants were analyzed according to their randomized treatment.
*Analyses for SPID48 compared to HB/APAP without rescue imputation are ad hoc; therefore, *P* values are nominal.

CI: confidence interval; **HB/APAP:** hydrocodone bitartrate/acetaminophen; **LS mean:** least squares mean; **N**: number of participants in the analysis set; **NPRS:** numeric pain rating scale; **SE:** standard error; **SPID48:** time-weighted sum of the pain intensity difference as recorded on the NPRS from 0 to 48 hours

Suzetrigine Treatment Led to Rapid Onset of Clinically Meaningful Pain Relief

Second Key Secondary Endpoint: Time to ≥2-Point Reduction in NPRS from Baseline Compared to Placebo

	Abdominoplasty		Bunionectomy	
	Suzetrigine N=447	Placebo N=223	Suzetrigine N=426	Placebo N=216
With Rescue Imputation (monotherapy)				
Median time (minutes)	119	480	240	480
95% CI	(90, 180)	(477, 705)	(117, 477)	(476, 716)
Nominal *P* value vs. placebo* (Log rank test)	<0.0001	--	0.0016	--
Without Rescue Imputation (representative of multimodal therapy in real-world setting)				
Median time (minutes)	91	180	122	180
95% CI	(89, 116)	(175, 235)	(115, 177)	(120, 245)
Nominal *P* value vs. placebo† (Log rank test)	<0.0001	--	0.0353	--

Note: Table includes participants who were randomized and received at least one dose of study drug. Participants were analyzed according to their randomized treatment.

* *P* values for the secondary endpoint of time to ≥2-point reduction in NPRS from baseline were nominal due to the break in hierarchical testing.
† Analyses for time to ≥2-point reduction in NPRS from baseline without rescue imputation are ad hoc; therefore, *P* values are nominal.

CI: confidence interval; **N**: number of participants in the analysis set; **NPRS:** numeric pain rating scale

Onset of Clinically Meaningful Pain Relief for Suzetrigine Was Similar Between All Participants in Abdominoplasty Trial and Subgroup of Participants in Bunionectomy Trial with Baseline NPRS ≥6

Abdominoplasty: All Participants Mean baseline NPRS: 7.4	Suzetrigine N=447	Placebo N=223
With Rescue Imputation (monotherapy)		
Median time (minutes)	119	480
95% CI	(90, 180)	(477, 705)
Nominal *P* value vs. placebo* (Log rank test)	<0.0001	--
Without Rescue Imputation (representative of multimodal therapy in real-world setting)		
Median time (minutes)	91	180
95% CI	(89, 116)	(175, 235)
Nominal *P* value vs. placebo† (Log rank test)	<0.0001	--

Bunionectomy: Participants With Baseline NPRS ≥6 Mean baseline NPRS: 7.7	Suzetrigine N=285	Placebo N=159
With Rescue Imputation (monotherapy)		
Median time (minutes)	115	480
95% CI	(87, 475)	(180, 716)
Nominal *P* value vs. placebo† (Log rank test)	0.0008	--
Without Rescue Imputation (representative of multimodal therapy in real-world setting)		
Median time (minutes)	95	175
95% CI	(86, 123)	(90, 235)
Nominal *P* value vs. placebo† (Log rank test)	0.0128	--

* *P* value for the secondary endpoint of time to ≥2-point reduction in NPRS from baseline was nominal due to the break in hierarchical testing.
† These are ad hoc analyses; therefore, *P* values are nominal.

CI: confidence interval; **N**: number of participants in the analysis set; **NPRS:** numeric pain rating scale

Suzetrigine Was Generally Safe and Well Tolerated; Lower Incidence of Adverse Events Was Observed With Suzetrigine Than HB/APAP or Placebo

	Abdominoplasty			Bunionectomy		
	Suzetrigine N = 448	HB/APAP N = 448	Placebo N = 222	Suzetrigine N = 426	HB/APAP N = 431	Placebo N = 216
Participants with any AEs, n (%)	224 (50.0)	272 (60.7)	125 (56.3)	132 (31.0)	180 (41.8)	76 (35.2)
Participants with AEs by maximum severity, n (%)						
Mild	131 (29.2)	149 (33.3)	72 (32.4)	104 (24.4)	134 (31.1)	61 (28.2)
Moderate	83 (18.5)	112 (25.0)	46 (20.7)	27 (6.3)	42 (9.7)	15 (6.9)
Severe	8 (1.8)	9 (2.0)	6 (2.7)	1 (0.2)	4 (0.9)	0
Life-threatening*	2 (0.4)	2 (0.4)	0	0	0	0
Death†	0	0	1 (0.5)	0	0	0
Participants with SAEs, n (%)	11 (2.5)	7 (1.6)	5 (2.3)	0	0	0
Participants with AEs leading to treatment discontinuation, n (%)‡	5 (1.1)	5 (1.1)	1 (0.5)	0	0	0
AEs (≥4% in any treatment group in either trial), n (%)						
Nausea	85 (19.0)	147 (32.8)	56 (25.2)	35 (8.2)	62 (14.4)	23 (10.6)
Constipation	47 (10.5)	39 (8.7)	24 (10.8)	15 (3.5)	22 (5.1)	9 (4.2)
Headache	19 (4.2)	32 (7.1)	11 (5.0)	21 (4.9)	45 (10.4)	20 (9.3)
Dizziness	18 (4.0)	24 (5.4)	17 (7.7)	15 (3.5)	23 (5.3)	11 (5.1)
Hypotension	11 (2.5)	16 (3.6)	15 (6.8)	0	0	1 (0.5)
Vomiting	10 (2.2)	18 (4.0)	3 (1.4)	7 (1.6)	19 (4.4)	6 (2.8)

Note: Table includes participants who received at least one dose of study drug. Participants were analyzed according to the treatment they received. In the abdominoplasty trial, one participant was randomized to receive placebo but received one dose of suzetrigine due to an error in dispensing study drug kits at one site.

* In the abdominoplasty trial, life-threatening SAEs were pulmonary embolism (suzetrigine), anemia (suzetrigine), pulmonary embolism (HB/APAP), and intra-abdominal hematoma (HB/APAP); all SAEs were considered unlikely related or not related to study drug.
† In the abdominoplasty trial, one participant who received placebo had an SAE of pulmonary embolism that led to death; the SAE was considered not related to study drug.
‡ In the bunionectomy trial, one participant who received HB/APAP discontinued due to a pre-treatment AE (hypotension).

AEs: adverse events; **HB/APAP:** hydrocodone bitartrate/acetaminophen; **N**: number of participants in the analysis set; **n:** number of participants; **SAEs:** serious adverse events

Conclusions

- Suzetrigine is an **oral,** non-opioid, non-addictive**, pain signal inhibitor** of $Na_V1.8$.
- Suzetrigine was evaluated in the **largest** phase 3 randomized, controlled trials in established models of acute pain (abdominoplasty and bunionectomy).
    - **Statistically significant, clinically meaningful,** and **rapid reduction in moderate-to-severe acute pain was observed with suzetrigine.**
    - The magnitude of the treatment effect over 48 hours demonstrates that **suzetrigine is effective as a monotherapy and as part of a multimodal therapy**.
- Suzetrigine was generally **safe** and **well tolerated with lower incidence of AEs than placebo and HB/APAP;** most AEs were **mild or moderate** in severity and **consistent with the post-surgical setting.**

Suzetrigine, a non-opioid, non-addictive, highly selective $Na_V1.8$ pain signal inhibitor, holds the promise to be the first new class of treatment for moderate-to-severe acute pain in over two decades.

AEs: adverse events

Acknowledgments

We thank the trial participants, their families, and the site investigators.

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Todd Bertoch, M.D., Dominick D'Aunno, M.D., Grant Garbo, M.D., George Konis M.D., Timothy Melson, M.D., Jessica McCoun, M.D., Daneshvari Solanki, M.D. , Louise Taber, M.D., Nick Brown, M.D., Brandon Broome, M.D., Shankar Lakshman, M.D., Arash Matian, M.D., Hernan Salazar, M.D., Joshua Terry, M.D., Babak Alavynejad, D.P.M., Fabien Anayati, D.P.M., Alina Beaton, M.D., Tanya Bogle, M.D., Joseph Caporusso, D.P.M., Brian Chalkin, D.O., J. Richard Lee Evanson, D.O., Alfredo Fernandez, M.D., Steven Folkerth, M.D., Seth Forman, M.D., Ray Grundmeyer, M.D., Fardin Hakakian, D.P.M., Chad Howze, M.D., Clark Larsen, D.P.M., David Vanderweide, M.D., Peter Winkle, M.D., John Zimmerman, D.P.M.

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Clinical trials NAVIGATE 1 and NAVIGATE 2 were sponsored by Vertex Pharmaceuticals.

Poster #74:
A Phase 3, Single-Arm Study of Suzetrigine, a Non-Opioid, Pain Signal Inhibitor For Treatment of Acute Pain From Surgical and Non-surgical Conditions

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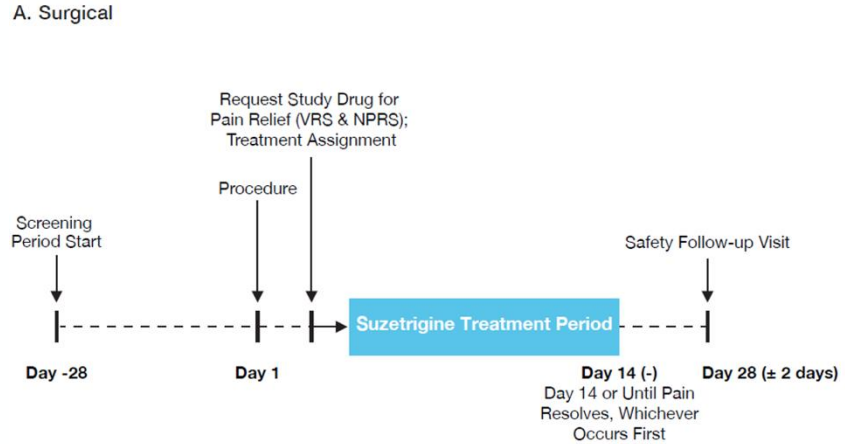
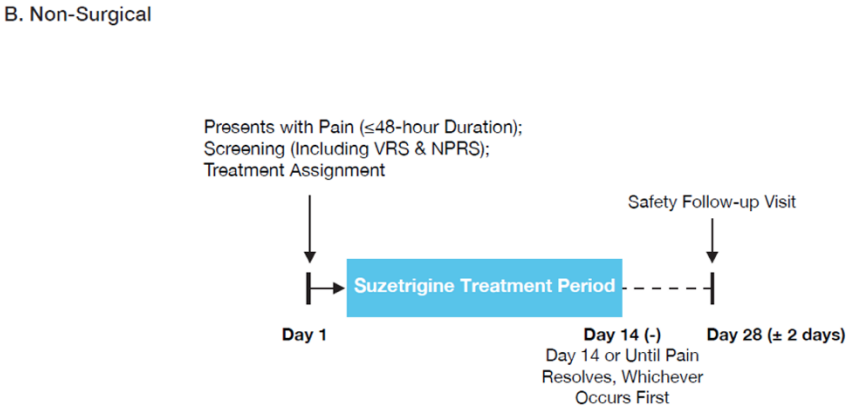
Single-arm Study Evaluated Safety and Effectiveness of Suzetrigine for Treatment of Diverse Acute Pain Conditions in a Real World Setting

Figure 2. Study Design





Key Eligibility Criteria

- **Age:** 18 to 80 years
- **Reported pain:** moderate or severe on the VRS and ≥4 on the NPRS following surgical procedures or after presenting to a medical facility with non-surgical pain of new origin (prior 48 hours; not related to a prior known condition)

Study Design

- **Suzetrigine tablets:** 100-mg first dose, then 50-mg every 12 hours administered orally for 14 days or until pain resolved
- **Rescue medication:** ibuprofen and acetaminophen were permitted, if needed, for pain relief, in line with standard multimodal therapy

Outcomes

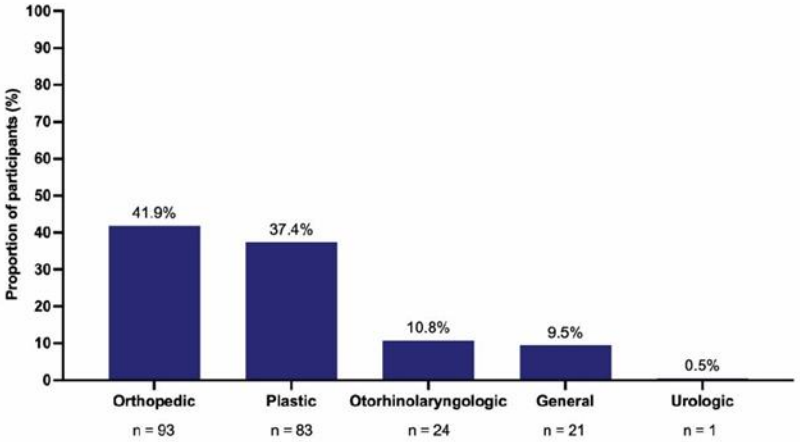
- **Primary Endpoint:** Safety
- **Secondary Endpoint:** Participant perception of the effectiveness of suzetrigine in managing pain at the end of treatment assessed by the proportion of participants reporting good, very good, or excellent on a patient global assessment (PGA)

NPRS: numeric pain rating scale; **VRS:** verbal categorical rating scale

Study Included Participants With Wide Variety of Acute Pain Conditions

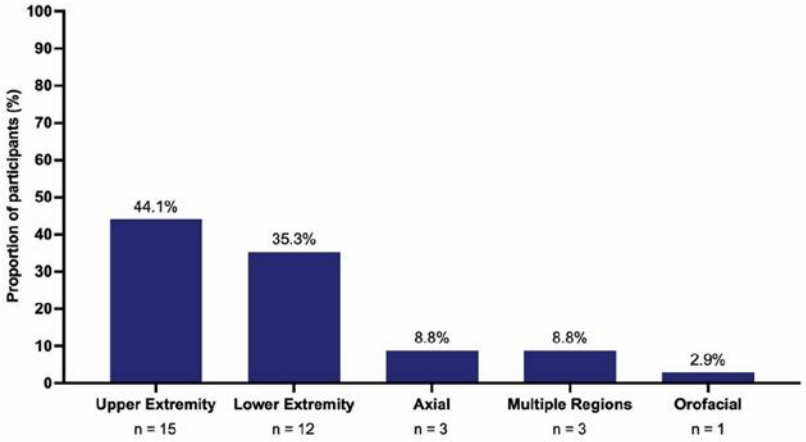
Figure 3. Study Participants

A. Surgical Type



Most Common				Included
Foot	Liposuction	Nasal septal	Inguinal hernia	Circumcision
Ankle	Mammoplasty	Turbinoplasty	Abdominal hernia	
Shoulder	Abdominoplasty	Nasal valve		
Knee	Rhinoplasty			
Hip				
Toe				

B. Non-surgical Region



Included				
Wrist	Ankle	Back	Ankle	Jaw pain
Elbow	Knee	Neck	Arm	
Arm	Leg		Neck	
Shoulder	Hip		Thorax	
Hand	Foot		Hip	
			Shoulder	

n: number of participants in specified category
Note: Figure includes participants who received at least one dose of suzetrigine.

Most Participants Completed Treatment With Suzetrigine

Table 2. Disposition

	Suzetrigine N = 256
Completed study drug, n (%)	242 (94.5)
Reason for completion of treatment, n (%)	
Pain resolution	137 (53.5)
Completed dosing until Day 14	105 (41.0)
Discontinued study drug, n (%)	14 (5.5)
Reason for discontinuation from study drug, n (%)	
Adverse event[a]	5 (2.0)
Lack of efficacy	4 (1.6)
Sponsor decision	1 (0.4)
Other	4 (1.6)

N: number of participants in the analysis set; **n:** number of participants

Note: Table includes participants who received at least one dose of suzetrigine.

[a] Adverse events that led to treatment discontinuation in 5 participants were accidental overdose, arrhythmia, nausea, rash, and somnolence. All adverse events that led to treatment discontinuation occurred in a single participant each, and all but 1 (arrhythmia) resolved by the end of the study.

Suzetrigine was Generally Safe and Well Tolerated With No Serious Adverse Events Related to Suzetrigine

Table 3. Summary of Adverse Events

	Suzetrigine N = 256
Participants with any AEs, n (%)	94 (36.7)
Participants with any AEs by maximum severity, n (%)	
Mild	71 (27.7)
Moderate	21 (8.2)
Severe	2 (0.8)
Participants with SAEs, n (%)[a]	2 (0.8)
Participants with AEs leading to treatment discontinuation, n (%)	5 (2.0)
AEs occurring in ≥2% of participants, n (%)	
Headache	18 (7.0)
Constipation	9 (3.5)
Nausea	8 (3.1)
Fall[b]	6 (2.3)
Rash	5 (2.0)

AE: adverse event; **N:** number of participants in the analysis set; **n:** number of participants; **SAE:** serious adverse event

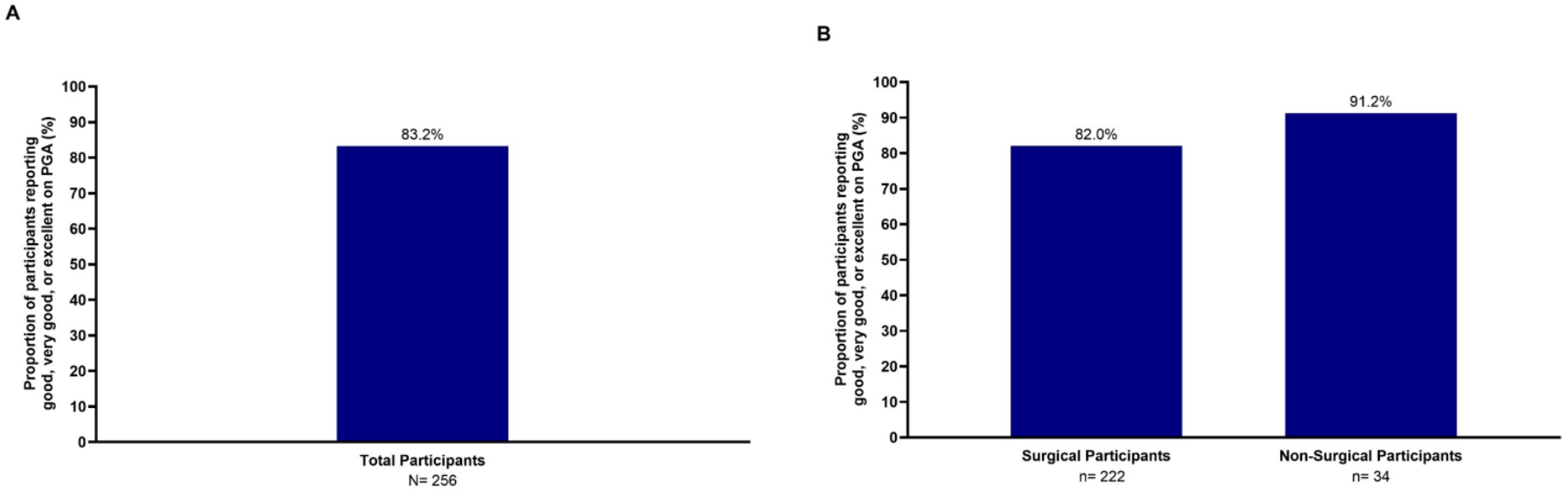
Note: Table includes participants who received at least one dose of suzetrigine.

[a] SAEs included cellulitis (1 participant) and suicidal ideation (1 participant); both SAEs were considered not related to suzetrigine.

[b] Six participants (2.3%) who had lower extremity, foot, and/or ankle surgeries had falls; these events were all mild and considered by investigators as not related or unlikely related to suzetrigine. None of the participants had dizziness or syncope and all recovered.

Most (83.2%) Participants Rated Suzetrigine Effectiveness for Treating Pain on a Patient Global Assessment as Good, Very Good, or Excellent

Figure 4. Patient Global Assessment



N; number of participants in the analysis set; **n:** number of participants; **PGA**: patient global assessment

Note: Figure includes participants who received at least one dose of suzetrigine. Participants complete the PGA at the end of suzetrigine treatment.

Most (83.2%) Participants Rated Suzetrigine Effectiveness for Treating Pain on a Patient Global Assessment as Good, Very Good, or Excellent

Table 4. Patient Global Assessment

	Suzetrigine N = 256
Participants reporting good, very good, or excellent on the PGA at end of treatment, n (%)	**213 (83.2)**
PGA at the end of treatment, n (%)	
Excellent	70 (27.3)
Very good	92 (35.9)
Good	51 (19.9)
Fair	26 (10.2)
Poor	11 (4.3)
Missing	6 (2.3)

N: number of participants in the analysis set; **n:** number of participants; **PGA:** patient global assessment

Note: Table includes participants who received at least one dose of suzetrigine.

Conclusions

For the first time in over two decades, suzetrigine, a novel small molecule and highly selective $Na_V1.8$ inhibitor, offers an effective and safe non-opioid, non-addictive treatment with broad applicability for the treatment of moderate-to-severe acute pain.

REAL-WORLD PERSPECTIVE ON ACUTE PAIN MANAGEMENT

Ashraf Habib, M.D.

Professor of Anesthesiology, Professor of Obstetrics and Gynecology, Chief of Division of Women's Anesthesiology, Duke University Hospital

Areas of Expertise: Acute Pain, Postoperative Nausea and Vomiting, Enhanced Recovery After Surgery, Obstetric Anesthesia

- Opening remarks
- Management of acute pain today
- Potential role of suzetrigine in acute pain management

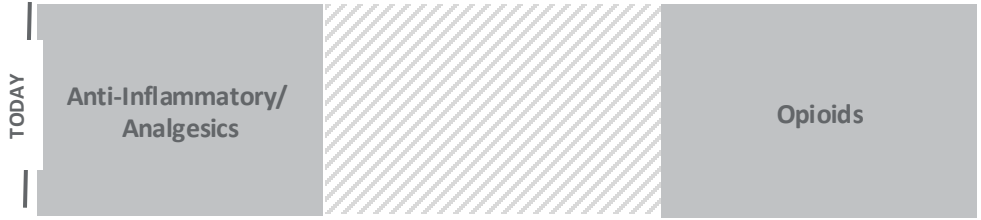
Disclosures: Dr. Habib has received research support from Pacira Biosciences and Haisco USA. He has also served on the Advisory Board for Heron Therapeutics and Merck & Co and is a consultant for Vertex Pharmaceuticals and Orion.

Duncan McKechnie
Senior Vice President,
Head of North America Commercial, Vertex

LIMITED TREATMENT OPTIONS IN ACUTE PAIN

Opioids are currently the **only** indicated oral option for moderate to severe acute pain

- Act on opioid receptors (μOR) in the brain to reduce the **perception of pain**
- Opioids are efficacious in mitigating pain, but with **significant side effects** including risk of addiction
- Approximately 50% of patients receiving prescription medications to manage acute pain are **prescribed opioids**
- **Significant unmet need** for medicines that are efficacious in reducing pain, well tolerated, with no risk of addiction



Sources: Vertex Pharmaceuticals research; CDC WONDER data, reported by the NIH; the Society of Actuaries Report 2019: Economic Impact of Non-Medical Opioid Use in the United States.

80M acute pain patients every year in the U.S.

40M acute pain patients receive an opioid every year

85K develop opioid use disorder (OUD) withing the first year

$180B estimated annual costs of OUD to the U.S. economy

$60B attributed to healthcare for the management of OUD

VERTEX U.S. PROVIDER AND PATIENT SURVEYS INDICATE SIGNIFICANT NEED FOR NEW OPTIONS TO TREAT ACUTE PAIN

THE STATE OF PAIN IN AMERICA

Healthcare Providers

88% reported that **risk of side effects** of current medications limits their ability to adequately treat their patients with acute pain

78% were concerned about the **risk of opioid addiction** among their patients with acute pain

88% reported that their patients prefer to manage pain without a prescribed opioid

Patients

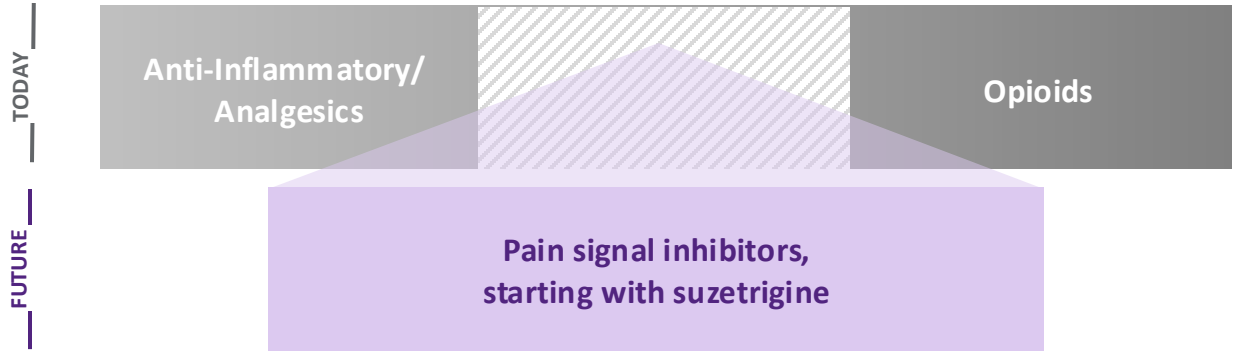
52% said they are seeking a new pain medication with fewer side effects than their last medication

67% reported that they will request a nonopioid medication for acute pain if they experience it again

Sources: Data on file. Vertex Pharmaceuticals Incorporated "State of Pain in America" survey of 547 U.S. healthcare providers who treated acute pain in the last month and 1,001 U.S. adults treated for acute pain in the last year. Boston, MA. REF-26477 (v1.0); 2024.

ACUTE PAIN IS A MULTI-BILLION DOLLAR OPPORTUNITY

Suzetrigine holds potential to fundamentally reshape the treatment of moderate to severe acute pain



>1B calendar days of treatment

- 2/3 of patients treated in the institutional setting
- 50% of prescriptions originate in the institutional setting

~2000 high volume hospitals/hospital systems

SUZETRIGINE IN ACUTE PAIN: LAUNCH PREPAREDNESS WELL UNDERWAY

PDUFA Target Action Date January 30, 2025

- Experienced team of strategic account leads and territory account managers fully trained and engaged
- Initiated contracting discussions with the goal of securing payer coverage and hospital formulary inclusion in 2025
- National disease education campaign underway, reached >40K healthcare providers
- Broad range of initiatives to support patient access in first year of launch
- Working to secure national retail distribution
- Continue to engage with federal and state policymakers

Launch focus

- Hospitals & hospital systems
- Select high volume procedures and conditions
- Key physician specialties: orthopedic, general & plastic surgeons, ED, anesthesiologists, pain management specialists
- Earliest uptake expected in the discharge segment

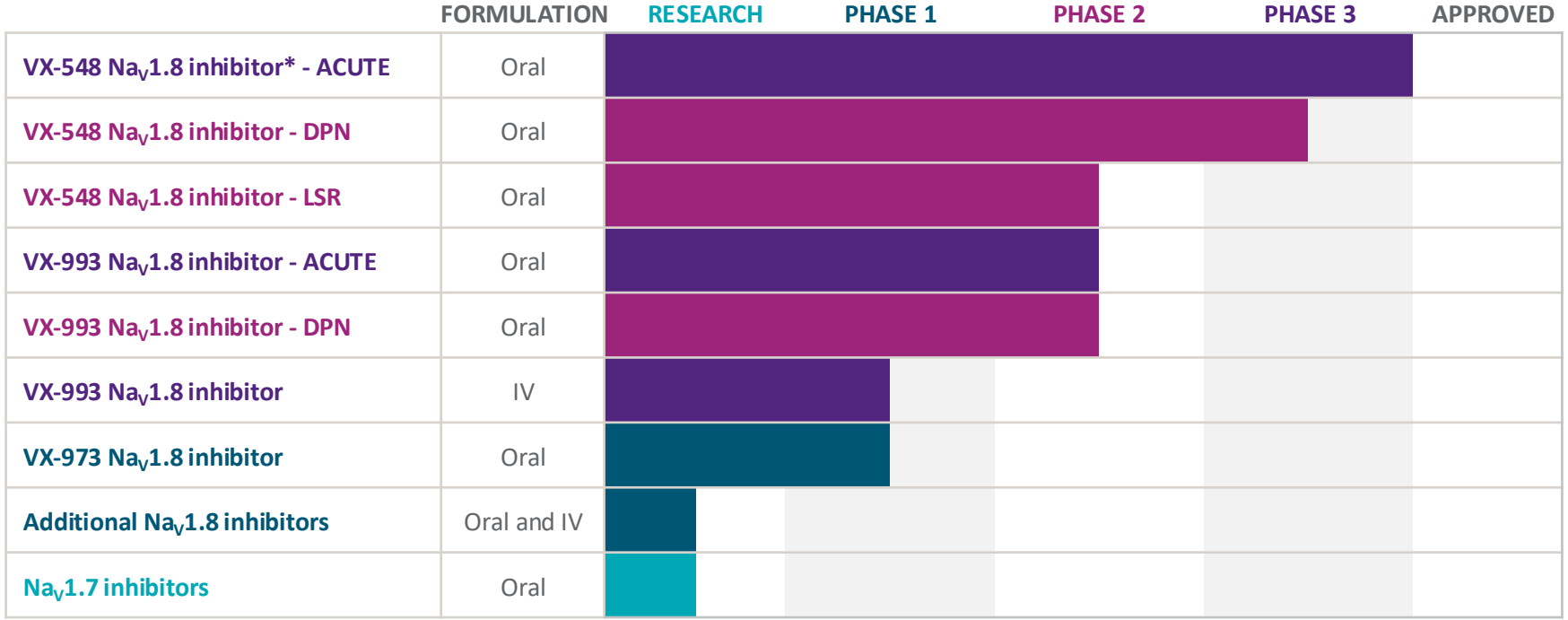
ED = Emergency Department

High levels of enthusiasm for a potential new class of pain medicine

Susie Lisa
Senior Vice President,
Investor Relations, Vertex

VERTEX IS COMMITTED TO TRANSFORMING THE TREATMENT OF PAIN

SERIAL INNOVATION, BROAD/DEEP PIPELINE FOR LEADERSHIP IN MULTIPLE PAIN STATES



DPN: diabetic peripheral neuropathy; LSR: lumbosacral radiculopathy; IV: intravenous

VERTEX

THE SCIENCE *of* POSSIBILITY

SUZETRIGINE (VX-548) ASA UPDATE

OCTOBER 20, 2024