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Suzetrigine, a Nonopioid $Na_v1.8$ Inhibitor for Treatment of Moderate-to-severe Acute Pain: Two Phase 3 Randomized Clinical Trials

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- The voltage-gated sodium channel 1.8 ($Na_v1.8$) plays a role in transmitting nociceptive signals and is selectively expressed in peripheral sensory nerves
- Suzetrigine is an oral nonopioid that selectively inhibits $Na_v1.8$
- In two previous phase 2 trials, suzetrigine demonstrated significant reduction in moderate-to-severe acute pain after abdominoplasty or bunionectomy compared to placebo and was safe and well tolerated

What This Article Tells Us That Is New

- In these two phase 3 studies, suzetrigine reduced moderate-to-severe acute pain over 48 h after abdominoplasty or bunionectomy as compared with placebo
- Pain reduction with suzetrigine was similar to that with hydrocodone/acetaminophen and was associated with mild to moderate adverse effects

ABSTRACT

Background: Opioids are effective for treating acute pain but have safety, tolerability, and addiction concerns while nonopioid analgesics have limited efficacy. Suzetrigine, an oral, nonopioid small molecule, selectively inhibits the voltage-gated sodium channel 1.8 ($Na_v1.8$) and has potential to provide efficacious and safe relief for acute pain without addiction concerns.

Methods: To evaluate suzetrigine for treatment of acute pain, two phase 3, randomized, double-blind, placebo- and active-controlled trials were conducted in adults with moderate-to-severe acute pain on the verbal categorical rating scale and 4 or greater on the numeric pain rating scale after abdominoplasty (n = 1,118) or bunionectomy (n = 1,073). After surgery, participants were randomized to suzetrigine (100 mg, then 50 mg every 12 h), hydrocodone bitartrate/acetaminophen (5/325 mg every 6 h), or placebo for 48 h. The primary endpoint was time-weighted sum of the pain intensity difference in numeric pain rating scale from 0 to 48 h (SPID48) *versus* placebo. Key secondary endpoints were SPID48 *versus* hydrocodone bitartrate/acetaminophen and time to 2-point or greater reduction in numeric pain rating scale from baseline *versus* placebo.

Results: The primary endpoint was achieved in both trials with suzetrigine demonstrating statistically significant and clinically meaningful reduction in pain *versus* placebo. The least squares mean difference in SPID48 between suzetrigine and placebo was 48.4 (95% CI, 33.6 to 63.1; $P < 0.0001$) after abdominoplasty and 29.3 (95% CI, 14.0 to 44.6; $P = 0.0002$) after bunionectomy. Neither trial achieved the first key secondary endpoint of superiority of suzetrigine *versus* hydrocodone bitartrate/acetaminophen on SPID48. For the second key secondary endpoint of time to 2-point or greater reduction in numeric pain rating scale, suzetrigine had a more rapid onset of clinically meaningful pain relief *versus* placebo after abdominoplasty (119 min *vs.* 480 min; nominal $P < 0.0001$) and bunionectomy (240 min *vs.* 480 min; nominal $P = 0.0016$). Adverse events were similar to those seen in postsurgical settings.

Conclusions: As compared with placebo, suzetrigine reduced moderate-to-severe acute pain over 48 h after abdominoplasty or bunionectomy. Pain reduction with suzetrigine was similar to that with hydrocodone bitartrate/acetaminophen. Suzetrigine was associated with adverse events that were mild to moderate in severity.

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There is a notable gap in the armamentarium of nonopioid analgesics that are effective for treating moderate-to-severe acute pain. As a result, opioids are still frequently prescribed because of their effectiveness but are associated with issues of tolerability (*e.g.*, nausea, vomiting, and constipation) and serious safety concerns including addiction and opioid use disorder. Consequently, there is a pressing need for alternative treatments to opioids that are effective, safe, and without concerns for addiction.

The voltage-gated sodium channel 1.8 ($Na_V1.8$) is a potential therapeutic target for pain management because it plays a critical role in transmitting nociceptive signals[1] as it is selectively expressed in nociceptors and transmits pain signals (action potentials) in peripheral sensory nerves.[2–5] Suzetrigine (VX-548) is an oral, nonopioid small molecule that is a potent, highly selective inhibitor of $Na_V1.8$.[6] $Na_V1.8$ is not expressed in the human brain or spinal cord[7–12]; therefore, suzetrigine should not have the central nervous system side effects associated with nonselective voltage-gated sodium channel blockers or have tolerability and addictive potential associated with centrally acting opioid therapies.[12] As such, we hypothesize that suzetrigine has the potential to provide an efficacious and safe treatment for moderate-to-severe acute pain, without addiction concerns.

Abdominoplasty and bunionectomy are accepted models of soft tissue and hard tissue (bone) pain, respectively, used to demonstrate the clinical potential of an investigational analgesic in treating a broad range of acute pain.[13–15] In two previous phase 2 trials, suzetrigine monotherapy demonstrated statistically significant and clinically meaningful reduction in moderate-to-severe acute pain after abdominoplasty or bunionectomy compared to placebo and was safe and well tolerated.[6] We describe herein the results from two phase 3 trials evaluating the efficacy and safety of suzetrigine in participants with moderate-to-severe acute pain after abdominoplasty or bunionectomy.

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Materials and Methods

We conducted two randomized, double-blind, placebo- and active-controlled phase 3 trials after abdominoplasty (Trial VX-548-105, NAVIGATE 2; ClinicalTrials.gov, NCT05558410; principal investigator, Dominick D'Aunno; registration date, October 10, 2022) or bunionectomy (Trial VX-548-104, NAVIGATE 1; ClinicalTrials.gov, NCT05553366; principal investigator, Todd Bertoch; registration date, October 3, 2022). The trial protocols were approved by an independent central institutional review board (ADVARRA, USA), and the trials were conducted according to the International Council for Harmonization (Geneva, Switzerland) Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All participants provided written informed consent before screening. The designs, objectives, endpoints, duration of treatment, and numeric pain rating scale analyses of our phase 3 trials are generally the same as the previously published phase 2 trials evaluating suzetrigine after abdominoplasty or bunionectomy.[6]

Participants

We enrolled men and women 18 through 80 yr of age. Eligible participants requested study drug for pain relief and had pain that was rated as moderate or severe on the verbal categorical rating scale (a four-level scale that ranges from no pain to severe pain) and 4 or greater on the numeric pain rating scale (a numeric version of a visual analog scale; scores range from 0 to 10, with higher scores indicating greater pain) after either a standard ("full") abdominoplasty procedure during general anesthesia or a primary unilateral bunionectomy with a ring-shaped field block at the first metatarsal or lesser metatarsal base proximal to the surgical site and internal fixation during regional anesthesia (Mayo and popliteal block with ropivacaine). In the bunionectomy trial, the dose of 0.5% or less ropivacaine and the exact manner of the perioperative regional anesthesia performed were at the discretion of the investigator. A continuous popliteal sciatic block infusion (0.2% ropivacaine) was started at an initial rate between 1 to 3 ml/h after surgery and remained in place until the morning of postoperative day 1.

Participants with a history of any sensory abnormality or who had painful physical conditions that, in the opinion of the investigator, might interfere with the participant's ability to assess postoperative pain were not eligible for either trial. In addition, participants with long-term use of opioids or nonsteroidal anti-inflammatory drugs were not eligible for participation. Details regarding eligibility criteria and perioperative anesthesia are provided in the Supplemental Digital Content (https://links.lww.com/ALN/D918).

Trial Design

Schematics of the trial designs are shown in the Supplemental Digital Content (eFigure 1, https://links.lww.com/ALN/D918). In both trials, participants who requested study drug for pain relief and met eligibility criteria were randomized in a 2:2:1 ratio to receive one of the following during a 48-h treatment period: suzetrigine, hydrocodone bitartrate/acetaminophen, or placebo. We evaluated suzetrigine with tablets administered orally as a 100-mg loading dose followed by 50 mg every 12 h. The combination product hydrocodone bitartrate/acetaminophen was orally administered as 5-mg/325-mg capsules every 6 h. We selected hydrocodone bitartrate/acetaminophen as an active control because it is the most frequently used opioid, with the 5-mg/325-mg dosage being the most commonly prescribed for acute pain in the United States.[16,17] To maintain the blind, a double-dummy design was used such that all participants received the same number of tablets and capsules at the dosing timepoints.

Randomization was stratified by site and baseline numeric pain rating scale (less than 8 *vs.* 8 or greater) using a block size of 5. A computer-generated randomization list was used to assign participants to treatment. The random allocation sequence was created by an independent randomization vendor using SAS version 9.4 (SAS Institute Inc., USA). Sites enrolled participants who were assigned to treatment using an interactive web response system. In both trials, enrollment and dosing were to pause if any of the following events occurred and were considered related or possibly related to suzetrigine by the investigator or the sponsor: three or more serious adverse events of QTc prolongation, one serious adverse event of Torsades de pointes, or death.

In the abdominoplasty trial, midazolam and fentanyl were permitted preoperatively, fentanyl and propofol were administered for general anesthesia, and fentanyl was permitted, as needed, as postoperative supplemental analgesia. Randomization did not occur until at least 15 min after the last administration of supplemental analgesic medication. In the bunionectomy trial, midazolam and fentanyl were permitted followed by propofol, with the Mayo (lidocaine) and popliteal sciatic nerve blocks (ropivacaine) perioperatively. Fentanyl, acetaminophen, and ropivacaine boluses/infusion rate changes were permitted, as needed, as postoperative supplemental analgesia; however, no pain treatments were allowed after removal of the popliteal block up to randomization, which was within 9 h after removal of the popliteal block. In both trials, these analgesics were administered intravenously.

Participants reported pain intensity on the numeric pain rating scale at scheduled timepoints at approximately 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 h after the first dose of study drug (19 measurements). Ibuprofen (400 mg orally every 6 h, as needed) was permitted as a rescue medication for pain relief upon the participant's request starting any time after the first dose of study drug. Participants were encouraged to wait 90 min after the first dose of study drug to request rescue medication. Pain intensity (as measured on the numeric pain rating scale) was also recorded immediately before each administration of ibuprofen rescue. No other analgesic medications (*e.g.*, nonsteroidal anti-inflammatory drugs other than ibuprofen, opioids) were allowed. Participants who did not have pain relief with protocol specified medications could discontinue study drug treatment and receive any alternative medication as directed by their treating physician.

Outcomes

All endpoints were the same in both trials. The primary efficacy endpoint was the time-weighted sum of the pain intensity difference for suzetrigine compared to placebo as recorded on the numeric pain rating scale from 0 to 48 h (SPID48) after the first dose of study drug. The sum of the pain intensity difference (SPID) is calculated by first determining the pain intensity difference between the numeric pain rating scale at 19 scheduled timepoints and the baseline, then multiplying each pain intensity difference by the time interval since the last measurement. Baseline is defined as the most recent assessment collected before the first dose of study drug. These time-weighted differences are summed over the 48-h treatment period, providing a cumulative measure of pain relief. A positive SPID48 value indicates a reduction in pain from baseline, with a higher value indicating a greater reduction in pain.

The first key secondary efficacy endpoint was SPID48 for suzetrigine compared to hydrocodone bitartrate/acetaminophen. The second key secondary efficacy endpoint was time to 2-point or greater reduction in numeric pain rating scale from baseline (*i.e.*, time to clinically meaningful pain relief)[18,19] for suzetrigine compared to placebo.

Safety was assessed as a secondary endpoint and based on the incidence of adverse events, changes from baseline in clinically significant laboratory test results, vital signs, and electrocardiograms. All other secondary efficacy endpoints are provided in the Supplemental Digital Content (https://links.lww.com/ALN/D918).

Sample Size Calculation

In both trials, approximately 1,000 participants were enrolled to provide greater than 90% power to detect a standardized effect size of 0.40 for the primary endpoint of suzetrigine compared to placebo on SPID48, based on two-sample *t* tests with significance level of 0.05. This accounted for approximately a 15% dropout rate. EAST 6.4.1 (Cytel Inc., USA) was used for the sample size calculation.

Statistical Analysis

The primary endpoint was SPID48 for suzetrigine compared to placebo. The primary estimand of the primary endpoint, which was prespecified, used the hypothetical strategy for handling the intercurrent events of use of rescue medication and treatment discontinuation, aiming to

answer the clinical question of "what is the treatment effect of suzetrigine compared to placebo, had subjects not used rescue medication and not discontinued treatment early." The primary analysis was based on an analysis of covariance model. The model included SPID48 as the dependent variable and treatment as a fixed effect, with site and baseline numeric pain rating scale as covariates.

The following imputation scheme for numeric pain rating scale scores was used: (1) scores in subsequent 6 h after rescue medication use were replaced by the prerescue score; (2) missing scores after treatment discontinuation were imputed using the baseline score when discontinuation was due to an adverse event and with the last score before discontinuation when discontinuation was due to other reasons; (3) missing scores for subjects who completed the treatment but with missing data from a certain timepoint to 48 h were imputed with the last numeric pain rating scale score; and (4) intermittently missing scores were imputed using linear interpolation. Note that the 6-h period in step 1 represents the analgesic duration of ibuprofen, and the imputed values using the prerescue score represent what the numeric pain rating scale scores would have been without ibuprofen, which allows estimation of the effect of suzetrigine. This analysis is referred to as analysis with imputation.

SPID48 was a cumulative measure of pain relief and was calculated as time-weighted sum of pain intensity differences (change from baseline in numeric pain rating scale scores) at each timepoint. To support the SPID48, mean pain intensity differences at each timepoint and standard errors were plotted to show the pain reduction over time. The mean pain intensity difference at 48 h was calculated to assess the pain reduction from baseline. The percentage of reduction in the mean numeric pain rating scale was also determined to assess the magnitude of reduction relative to baseline (calculated as mean pain intensity difference at 48 h/mean baseline numeric pain rating scale × 100%).

Analyses for secondary efficacy endpoints are described in the Supplemental Digital Content (https://links.lww.com/ALN/D918).

A hierarchical testing procedure was used to control the overall type 1 error at a significance level of 0.05 for the primary endpoint and the two key secondary endpoints.

To provide a real-world assessment of the efficacy of suzetrigine as part of a multimodal therapy, *post hoc* analyses for an alternative estimand were conducted to evaluate the primary endpoint of SPID48 compared to placebo without imputation for numeric pain rating scale scores after ibuprofen rescue. This alternative estimand uses the treatment policy strategy to handle use of rescue medication, aiming to answer the question "What is the treatment effect of suzetrigine compared to placebo, regardless of rescue medication use and had subjects not discontinued treatment early?" These analyses differ from the primary analysis in that numeric pain rating scale scores in the subsequent 6 h after rescue medication use were not imputed; observed scores were used instead. These analyses (referred to as analyses without imputation) allowed for estimation of the combined effect of suzetrigine and ibuprofen (if used) compared to the combined effect of placebo and ibuprofen (if used). *Post hoc* analyses without imputation for ibuprofen rescue were also performed for the key secondary endpoints.

To assess the potential impact of baseline pain on the time to meaningful pain relief and to understand the difference between the two studies in the time to 2-point or greater reduction in numeric pain rating scale from baseline, *post hoc* subgroup analysis for this endpoint was performed for subjects with a baseline numeric pain rating scale 6 or greater.

To aid the assessment of the clinically meaningfulness of the effect of suzetrigine, *post hoc* analyses of the cumulative response based on the percentage of reduction in numeric pain rating scale from baseline at 12, 24, and 48 h were presented in figures as well as in tables for the proportion of participants achieving at least 30%, 50%, or 70% response, for both with imputation and without imputation for ibuprofen rescue.

Results

Participants

We conduced both of our trials in the United States between 2022 and 2023. Participant demographics and baseline characteristics are shown in table 1. In the abdominoplasty trial, the mean ± SD age for participants was 42 ± 9 yr; most participants were women (98%) and White (70%). In the bunionectomy trial, the mean ± SD age was 48 ± 13 yr; most participants were women (85%) and White (71%). The mean age and race or ethnicity of participants in these trials is representative of the age of participants who have had abdominoplasty (74% White, 30 to 54 yr) and bunionectomy (64 to 82% White, 45 to 64 yr) in the United States.[20–23] Overall, demographics and baseline characteristics were generally balanced across treatments within each trial. However, baseline pain was greater in the abdominoplasty trial than the bunionectomy trial; mean ± SD numeric pain rating scale at baseline was 7.4 ± 1.7 and 6.8 ± 1.8, respectively. Additionally, more participants reported severe pain (numeric pain rating scale 8 or greater) after abdominoplasty (49%) than after bunionectomy (36%).

Disposition

In the abdominoplasty trial, 1,118 participants were randomized and received at least one dose of study drug (suzetrigine, n = 447; hydrocodone bitartrate/acetaminophen, n = 448; placebo, n = 223), and 84.6% completed treatment (fig. 1; Supplemental Digital Content, eTable 1, https://links.lww.com/ALN/D918). In the bunionectomy

Table 1. Demographics and Baseline Clinical Characteristics

	Abdominoplasty				Bunionectomy			
	Suzetrigine N = 447	HB/APAP N = 448	Placebo N = 223	Total N = 1,118	Suzetrigine N = 426	HB/APAP N = 431	Placebo N = 216	Total N = 1,073
Age, yr, mean ± SD	42 ± 9	42 ± 9	42 ± 8	42 ± 9	48 ± 13	48 ± 13	48 ± 13	48 ± 13
Male, n (%)	10 (2)	7 (2)	3 (1)	20 (2)	60 (14)	72 (17)	29 (13)	161 (15)
Age, yr, mean ± SD	38 ± 10	40 ± 8	33 ± 16	38 ± 10	46 ± 15	47 ± 13	46 ± 15	47 ± 14
Female, n (%)	437 (98)	441 (98)	220 (99)	1,098 (98)	366 (86)	359 (83)	187 (87)	912 (85)
Age, yr, mean ± SD	42 ± 9	42 ± 9	42 ± 8	42 ± 9	48 ± 13	48 ± 13	48 ± 13	48 ± 13
Race, n (%)								
White	307 (69)	316 (71)	155 (70)	778 (70)	285 (67)	314 (73)	160 (74)	759 (71)
Black or African American	123 (28)	114 (25)	62 (28)	299 (27)	116 (27)	96 (22)	48 (22)	260 (24)
Other*	17 (4)	18 (4)	6 (3)	41 (4)	25 (6)	21 (5)	8 (4)	54 (5)
BMI, kg/m^2, mean ± SD	29 ± 4	29 ± 4	30 ± 4	29 ± 4	28 ± 5	28 ± 5	28 ± 5	28 ± 5
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 (51)	229 (51)	111 (50)	567 (51)	274 (64)	274 (64)	143 (66)	691 (64)
≥ 8	220 (49)	219 (49)	112 (50)	551 (49)	152 (36)	157 (36)	73 (34)	382 (36)
VRS, n (%)								
Moderate	266 (60)	262 (58)	127 (57)	655 (59)	291 (68)	279 (65)	147 (68)	717 (67)
Severe	181 (40)	186 (42)	96 (43)	463 (41)	135 (32)	152 (35)	69 (32)	356 (33)

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; VRS, verbal categorical rating scale.

trial, 1,073 participants were randomized and received at least one dose of study drug (suzetrigine, n = 426; hydrocodone bitartrate/acetaminophen, n = 431; placebo, n = 216), and 87.4% completed treatment (fig. 1; Supplemental Digital Content, eTable 1, https://links.lww.com/ALN/D918). The most common reasons for discontinuation are provided in figure 1 and in the Supplemental Digital Content, eTable1, https://links.lww.com/ALN/D918.

Efficacy Outcomes

Primary Endpoint: SPID48 for Suzetrigine Compared to Placebo. The least squares mean difference in SPID48 between suzetrigine and placebo was 48.4 (95% CI, 33.6 to 63.1; $P < 0.0001$) after abdominoplasty and 29.3 (95% CI, 14.0 to 44.6; $P = 0.0002$) after bunionectomy (table 2). The treatment effect of suzetrigine was also evaluated in a *post hoc* analysis of SPID48 without imputation for ibuprofen rescue (suzetrigine plus ibuprofen *vs.* placebo plus ibuprofen).

The mean pain intensity difference and the mean numeric pain rating scale over time for all participants (*i.e.*, not individual-level analyses) are presented for both studies in figure 2 and figure 3, respectively. Those receiving suzetrigine had a greater reduction in mean numeric pain rating scale score compared to those taking placebo in both trials (no statistical testing was performed). For the pain intensity difference at 48 h, similar pain relief was demonstrated in participants receiving suzetrigine or hydrocodone bitartrate/acetaminophen at 48 h. Results were similar in a *post hoc* analysis without imputation for ibuprofen rescue (fig. 2, B and D; Supplemental Digital Content, eTable 2, https://links.lww.com/ALN/D918).

First Key Secondary Endpoint: SPID48 for Suzetrigine Compared to Hydrocodone Bitartrate/Acetaminophen. Neither trial achieved the first key secondary endpoint of superiority of suzetrigine compared to hydrocodone bitartrate/acetaminophen (a combination product) on SPID48. The least squares mean difference between suzetrigine and hydrocodone bitartrate/acetaminophen was 6.6 (95% CI, –5.4 to 18.7; $P = 0.2781$) after abdominoplasty and –20.2 (95% CI, –32.7 to –7.7; $P = 0.0016$) after bunionectomy (table 3). In the *post hoc* analysis of SPID48 without imputation for ibuprofen rescue, the least squares mean difference between suzetrigine and hydrocodone bitartrate/acetaminophen was 12.0 (95% CI, –0.5 to 24.4) after abdominoplasty and –11.8 (95% CI, –24.8 to 1.2) after bunionectomy (table 3).

Second Key Secondary Endpoint: Time to 2-Point or Greater Reduction in Numeric Pain Rating Scale from Baseline for Suzetrigine Compared to Placebo. Time to 2-point or greater reduction in numeric pain rating scale from baseline was evaluated as a key secondary endpoint to assess the time to clinically meaningful pain relief. In both trials, the time to onset of clinically meaningful pain relief was faster for suzetrigine compared to placebo (table 4). The median time to 2-point or greater reduction in numeric pain rating scale from baseline was 119 min with suzetrigine compared to 480 min with placebo (nominal $P < 0.0001$) after

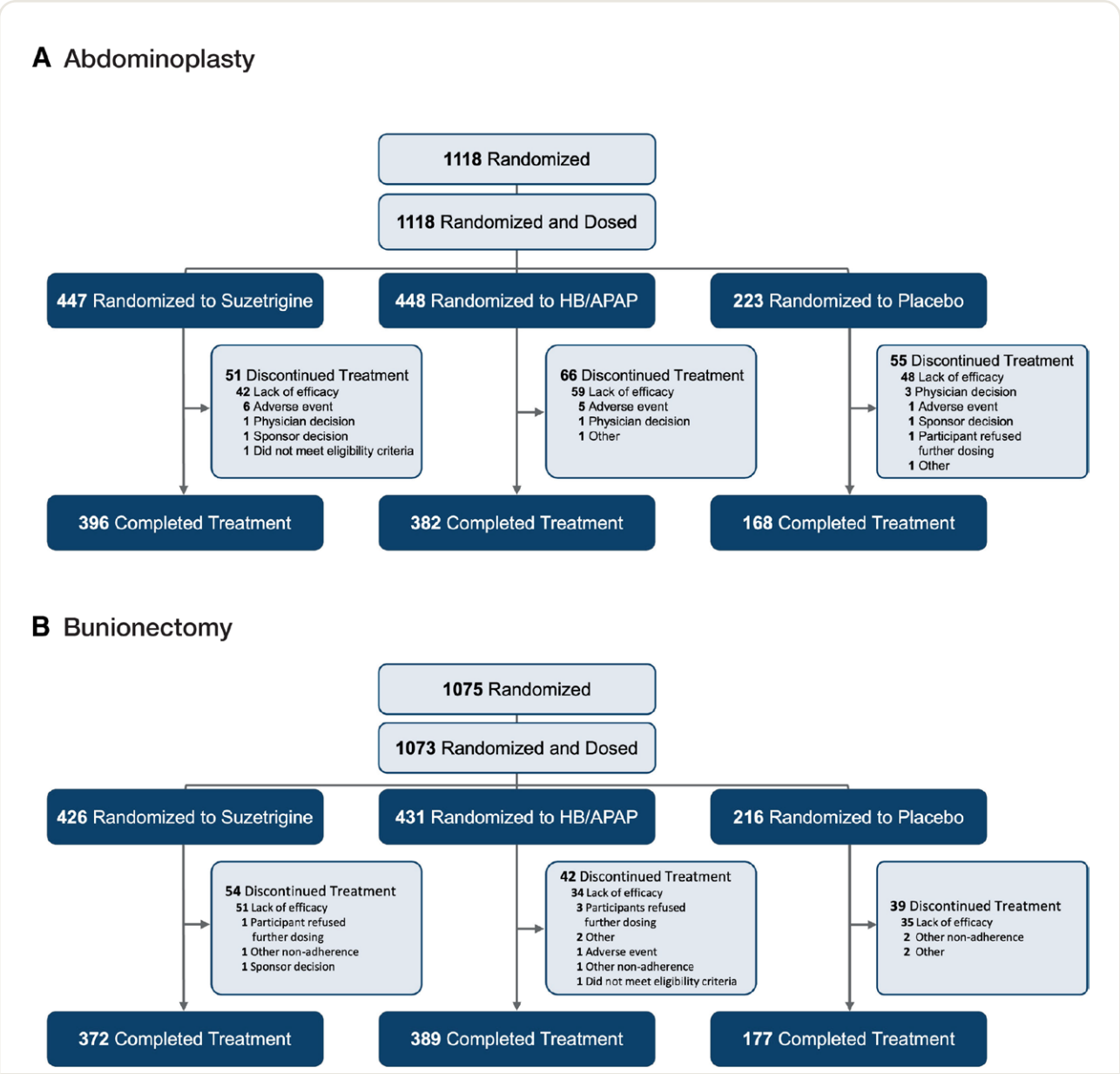

Fig. 1. Participants in the acute pain trials of suzetrigine. The figure includes participants in the acute pain randomized control trials of suzetrigine. (*A*) Participants in the abdominoplasty trial. (*B*) Participants in the bunionectomy trial. HB/APAP, hydrocodone bitartrate/acetaminophen.

abdominoplasty and 240 min with suzetrigine compared to 480 min with placebo (nominal $P = 0.0016$) after bunionectomy. In both trials, a *post hoc* analysis without rescue imputation showed that participants receiving suzetrigine achieved clinically meaningful pain relief more rapidly than participants receiving placebo, with both suzetrigine and placebo leading to a faster time to meaningful pain relief than in the prespecified analysis with imputation (table 4).

Given the difference in baseline numeric pain rating scale score between the two trials (*i.e.*, lower baseline pain after bunionectomy than abdominoplasty) and the potential that lower pain at baseline could lead to slower onset of clinically meaningful pain relief, we conducted a *post hoc* subgroup analysis in participants with baseline numeric pain rating scale score 6 or greater after bunionectomy (table 5). In this analysis, the subgroup of participants receiving suzetrigine after bunionectomy had similar pain at baseline as all participants receiving suzetrigine after abdominoplasty (7.7 [table 5] compared to 7.4 [table 1], respectively). The median time to 2-point or greater reduction in numeric pain rating scale was 115 min in this subgroup of

Table 2. Primary Endpoint: SPID48 Compared to Placebo

	Abdominoplasty		Bunionectomy	
	Suzetrigine N = 447	Placebo N = 223	Suzetrigine N = 426	Placebo N = 216
Prespecified analysis with rescue imputation (imputed)				
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 *vs.* placebo	<0.0001	—	0.0002	—
Post hoc analysis without rescue imputation (as treated)				
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 *vs.* 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 *post hoc*; therefore, *P* values are nominal.

LS mean, least squares mean; N, number of participants in the analysis set; SE, standard error; SPID48, time-weighted sum of the pain intensity difference as recorded on the numeric pain rating scale from 0 to 48 h.

participants with baseline numeric pain rating scale score 6 or greater receiving suzetrigine after bunionectomy compared to 119 min for all participants (regardless of baseline numeric pain rating scale score) receiving suzetrigine after abdominoplasty. The median time for placebo was consistent in both groups (480 min). The subgroup of participants with baseline numeric pain rating scale score 6 or greater receiving suzetrigine after bunionectomy also showed consistent results with all participants in abdominoplasty in the *post hoc* analysis without rescue imputation; the median time to 2-point or greater reduction in numeric pain rating scale was 95 min for suzetrigine participants with numeric pain rating scale 6 or greater after bunionectomy and 91 min for all participants receiving suzetrigine after abdominoplasty. The median time for placebo was approximately 180 min in both groups. Results from the subgroup of participants with baseline numeric pain rating scale score 6 or greater (table 5) after abdominoplasty were also included as a reference.

Other Secondary Efficacy Endpoints. The results for the other secondary endpoint of time to 1-point or greater reduction in numeric pain rating scale from baseline for suzetrigine compared to placebo are presented in Supplemental Digital Content eTable 3 (https://links.lww.com/ALN/D918). This endpoint measures time to onset of the minimum clinically important pain relief (or perceptible pain relief) from baseline.[24,25] The suzetrigine group had rapid time (median time within 1 h) to minimum clinically important pain relief in both abdominoplasty and bunionectomy studies.

We conducted *post hoc* descriptive analyses of the cumulative response based on the percentage of reduction in numeric pain rating scale from baseline at 12, 24, and 48 h. The proportions of participants who responded ("responders") to suzetrigine at 12, 24, and 48 h is provided in Supplemental Digital Content eFigure 2 and eFigure 3 (https://links.lww.com/ALN/D918).

In the abdominoplasty trial, a greater proportion of participants in the suzetrigine treatment group reported good or excellent on the patient global assessment (67.8%) compared to the placebo group (49.8%) at 48 h (nominal $P < 0.0001$; Supplemental Digital Content eTable 4, https://links.lww.com/ALN/D918). Similarly, in the bunionectomy trial, a greater proportion of participants in the suzetrigine treatment group reported good or excellent on the PGA (61.7%) compared to the placebo group (53.2%) at 48 h (nominal $P = 0.0343$).

In both trials, the incidence of nausea or vomiting was lower with suzetrigine compared to hydrocodone bitartrate/acetaminophen (Supplemental Digital Content eTable 5, https://links.lww.com/ALN/D918). In the abdominoplasty trial, the incidence of nausea or vomiting was 20.3% in the suzetrigine group and 33.5% in the hydrocodone bitartrate/acetaminophen group with a nominal $P < 0.0001$. In the bunionectomy trial, the incidence of nausea or vomiting was 9.2% in the suzetrigine group and 16.5% in the hydrocodone bitartrate/acetaminophen group with a nominal $P = 0.0014$. Results of the analysis of the sum of the pain intensity difference for suzetrigine compared to placebo as recorded on the numeric pain rating scale from 0 to 24 h (SPID24) for suzetrigine compared to placebo were consistent with and supportive of the primary endpoint results. The least squares mean difference in SPID24 between suzetrigine and placebo was 23.8 (95% CI, 17.1 to 30.5; nominal $P < 0.0001$) in the abdominoplasty trial and 10.7 (95% CI, 3.6 to 17.9; nominal $P = 0.0032$) in the bunionectomy trial (Supplemental Digital Content eTable 6, https://links.lww.com/ALN/D918).

Rescue medication use is summarized in Supplemental Digital Content eTable 7 (https://links.lww.com/ALN/

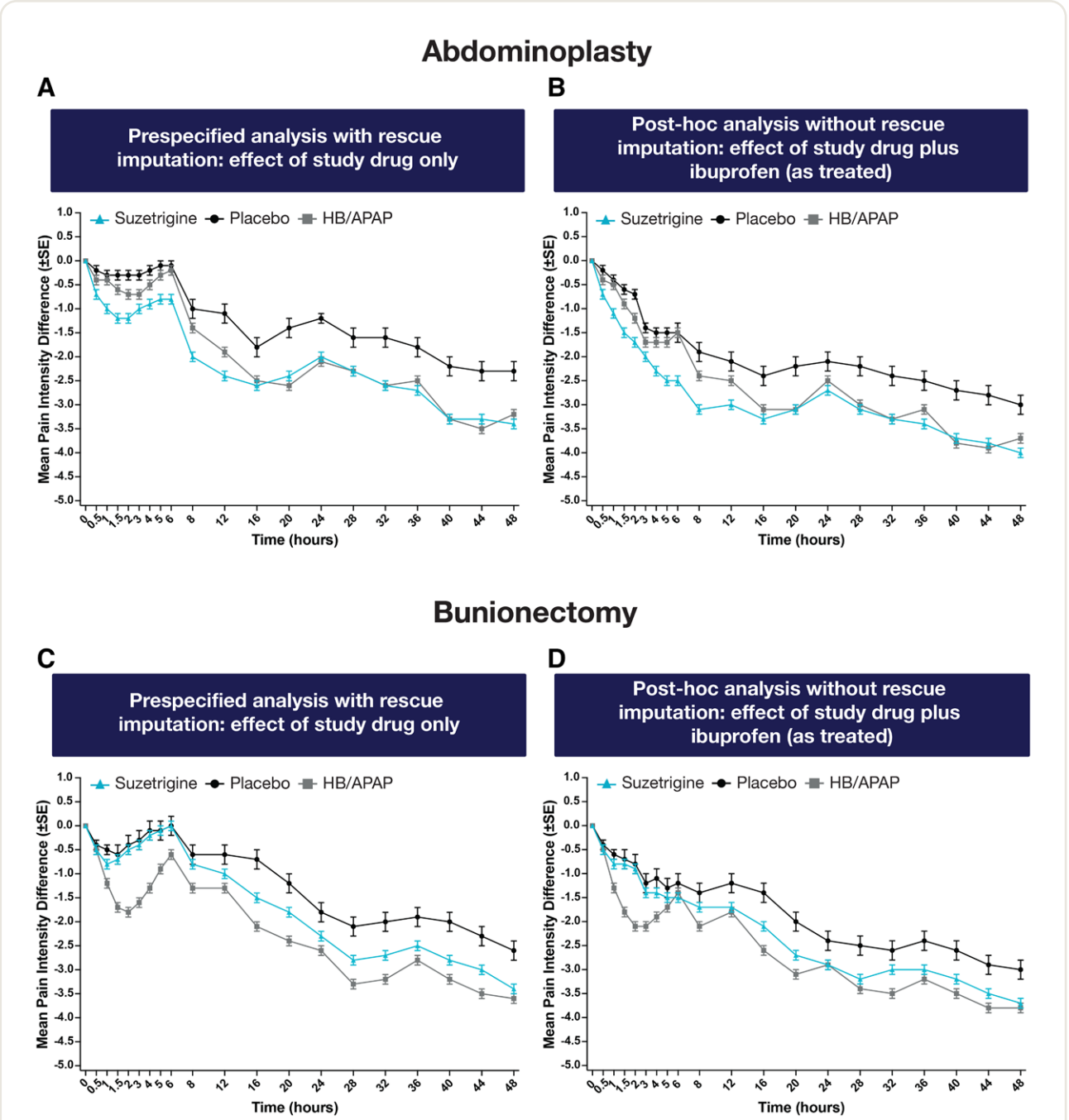

Fig. 2. Mean PID over time. The figure includes participants who were randomized and received at least one dose of study drug. Participants were analyzed according to their randomized treatment. (*A* and *B*) Participants included in the prespecified analysis with rescue imputation (effect of suzetrigine only) after abdominoplasty and bunionectomy, respectively. (*C* and *D*) Participants included in the *post hoc* analysis without rescue imputation (effect of suzetrigine and ibuprofen) after abdominoplasty and bunionectomy, respectively. HB/APAP, hydrocodone bitartrate/acetaminophen; PID, pain intensity difference; SE, standard error.

D918). In the abdominoplasty trial, the suzetrigine group had a lower proportion of participants using rescue medication (81.0%) than in the placebo group (87.9%) during the 48-h treatment period (nominal $P = 0.0237$), and a longer median time to first rescue medication use (186 min) than in the placebo group (115 min) with a nominal $P < 0.0001$. The median total rescue medication usage from 0 to 48 h was lower in the suzetrigine group (800 mg) than in the placebo group (1,200 mg) with a nominal $P = 0.0080$. In the bunionectomy trial, the suzetrigine group had a similar

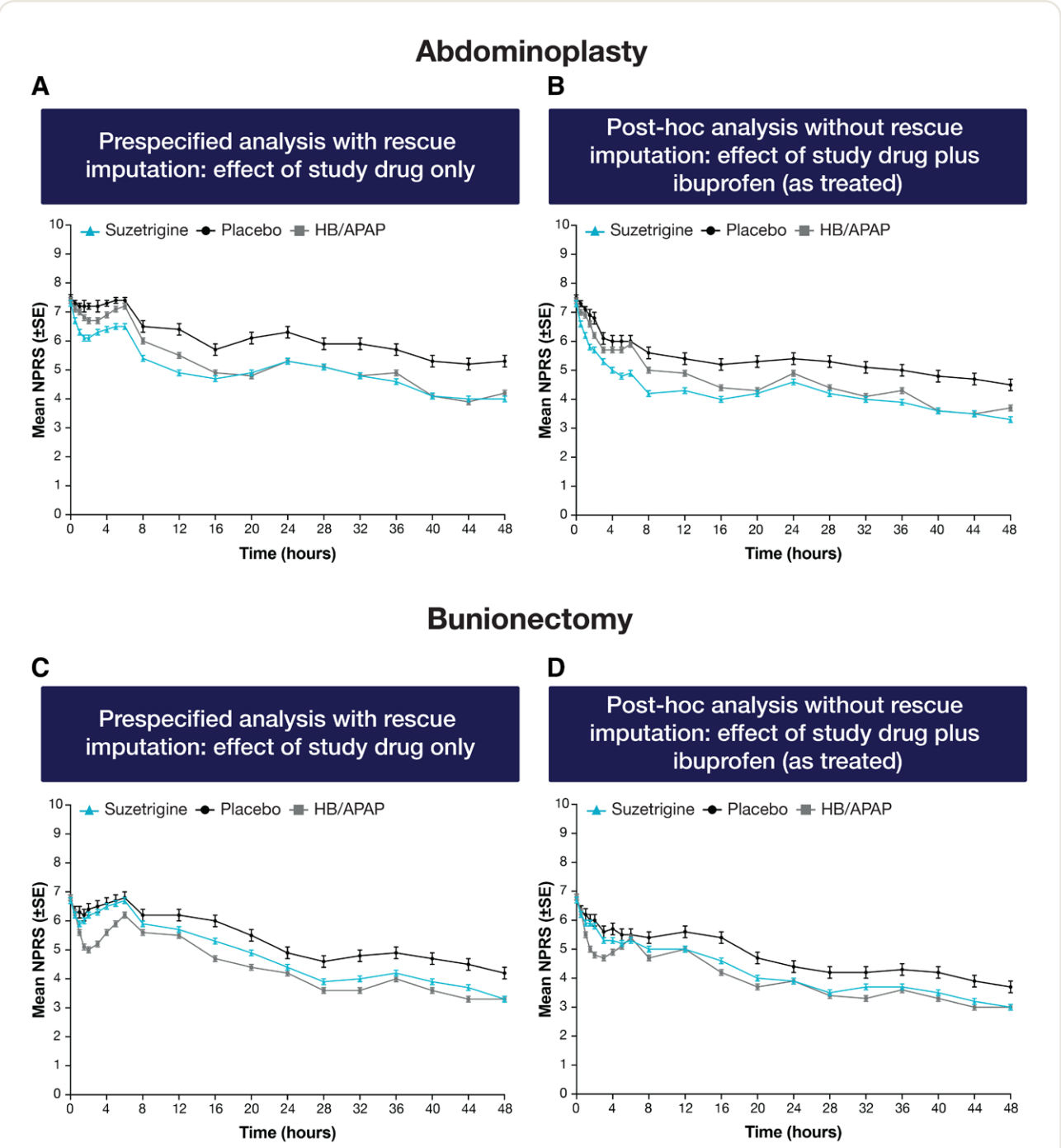

Fig. 3. Mean NPRS over time. The figure includes participants who were randomized and received at least one dose of study drug. Participants were analyzed according to their randomized treatment. (*A* and *B*) Participants included in the prespecified analysis with rescue imputation (effect of suzetrigine only) after abdominoplasty and bunionectomy, respectively. (*C* and *D*) Participants included in the *post hoc* analysis without rescue imputation (effect of suzetrigine and ibuprofen) after abdominoplasty and bunionectomy, respectively. HB/APAP, hydrocodone bitartrate/acetaminophen; NPRS, numeric pain rating scale; SE, standard error.

proportion of participants using rescue medication (85.4%) as the placebo group (85.6%) during the 48-h treatment period (nominal $P = 0.9143$), and a similar median time to first rescue medication use (157 min) as the placebo group (185 min) with a nominal $P = 0.8592$. The median total rescue medication usage from 0 to 48 h was 800 mg in both the suzetrigine and placebo groups with a nominal $P = 0.0205$.

Table 3. 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
Prespecified analysis with rescue imputation (imputed)				
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 to 18.7)	—	(–32.7 to –7.7)	—
P value *vs.* HB/APAP	0.2781	—	0.0016	—
Post hoc analysis without rescue imputation (as treated)				
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 to 24.4)	—	(–24.8 to 1.2)	—
Nominal *P* value *vs.* HB/APAP*	0.0595	—	0.0752	—

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 *post hoc*; therefore, *P* values are nominal.

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

Table 4. Second Key Secondary Endpoint: Time to 2-Point or Greater Reduction in NPRS from Baseline Compared to Placebo

	Abdominoplasty		Bunionectomy	
	Suzetrigine N = 447	Placebo N = 223	Suzetrigine N = 426	Placebo N = 216
Prespecified analysis with rescue imputation (imputed)				
Median time, min	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	—
Post hoc analysis without rescue imputation (as treated)				
Median time, min	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	—

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 *post hoc*; therefore, *P* values are nominal.

N, number of participants in the analysis set; NPRS, numeric pain rating scale.

Safety Outcomes

Suzetrigine was generally safe and well tolerated (table 6). The proportion of participants receiving suzetrigine, hydrocodone bitartrate/acetaminophen, or placebo with any adverse events was 50.0%, 60.7%, and 56.3%, respectively, after abdominoplasty and 31.0%, 41.8%, and 35.2%, respectively, after bunionectomy. Most adverse events in both trials were mild or moderate in severity. The most common adverse events occurring in 4% or more of participants in any treatment group (suzetrigine, hydrocodone bitartrate/acetaminophen, placebo) in either trial were nausea, constipation, headache, dizziness, hypotension, and vomiting (table 6).

In the abdominoplasty trial, the incidence of serious adverse events was low and balanced: 2.5% with suzetrigine, 1.6% with hydrocodone bitartrate/acetaminophen, and 2.3% with placebo. None of the serious adverse events were considered related or possibly related to suzetrigine, hydrocodone bitartrate/acetaminophen, or placebo. There was one death in the trial: one participant who received placebo had a serious adverse event of pulmonary embolism that led to death, preceded by life-threatening serious adverse events of cardiogenic shock and disseminated intravascular coagulation. The incidence of adverse events leading to treatment discontinuation was low and balanced across treatment groups (1.1% with suzetrigine, 1.1% with hydrocodone bitartrate/acetaminophen, and 0.5% with placebo).

In the bunionectomy trial, there were no serious adverse events, deaths, or adverse events leading to treatment discontinuation.

Table 5. *Post Hoc* Subgroup Analysis of Time to 2-Point or Greater Reduction in NPRS from Baseline Compared to Placebo in Participants with Baseline NPRS 6 or Greater

	Abdominoplasty		Bunionectomy	
	Suzetrigine N = 363	Placebo N = 198	Suzetrigine N = 285	Placebo N = 159
NPRS, mean ± SD	7.9 ± 1.3	7.9 ± 1.4	7.7 ± 1.3	7.6 ± 1.3
With rescue imputation (imputed)				
Median time, min	115	480	115	480
95% CI	(90–179)	(476–481)	(87–475)	(180–716)
Nominal *P* value *vs.* placebo* (log-rank test)	< 0.0001	—	0.0008	—
Without rescue imputation (as treated)				
Median time, min	90	180	95	175
95% CI	(86–115)	(124–182)	(86–123)	(90–235)
Nominal *P* value *vs.* placebo* (log-rank test)	< 0.0001	—	0.0128	—

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

*These are *post hoc* analyses; therefore, *P* values are nominal.

N, number of participants in the analysis set; NPRS, numeric pain rating scale.

Table 6. Summary of Adverse Events

	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)

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 intraabdominal 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 pretreatment AE (hypotension).

AE, adverse event; HB/APAP, hydrocodone bitartrate/acetaminophen; N, number of participants in the analysis set; n, number of participants; SAE, serious adverse event.

In both trials, the other secondary endpoint of incidence of vomiting or nausea, a common opioid-associated adverse event, was lower with suzetrigine compared to hydrocodone bitartrate/acetaminophen (Supplemental Digital Content, eTable 5, https://links.lww.com/ALN/D918). In the abdominoplasty trial, the incidence of vomiting or nausea was 20.3% with suzetrigine and 33.5% with hydrocodone bitartrate/acetaminophen (nominal $P < 0.0001$). In the bunionectomy trial, the incidence of vomiting or nausea was 9.2% with suzetrigine and 16.5% with hydrocodone bitartrate/acetaminophen (nominal $P = 0.0014$).

Discussion

For more than two decades, there has been a paucity of efficacious nonopioid analgesics for acute pain management. This has led clinicians to rely on opioid analgesics despite their side effects (*e.g.*, nausea and vomiting) and serious risks of addiction. This reliance has contributed to two interrelated public health issues in the United States: inadequate pain management and an opioid crisis. To address this gap, there is a need for novel analgesics. One promising approach involves inhibition of $Na_V1.8$, a sodium channel that plays a critical role in pain transmission based on genetic and pharmacologic evidence.[1] In addition, $Na_V1.8$ is selectively expressed in peripheral sensory nociceptors,[1] and there is no $Na_V1.8$ expression in the brain.[7–12] Therefore, inhibiting $Na_V1.8$ interrupts the transmission of peripheral pain signals to the brain and should not have the risk of addiction.[12]

Suzetrigine is a novel, oral, nonopioid analgesic that selectively inhibits peripheral $Na_V1.8$ channels.[6] To demonstrate the clinical potential of suzetrigine for treating a broad range of acute pain, we conducted two large, randomized, controlled phase 3 trials in established acute pain models. The primary endpoint was achieved in both trials. Suzetrigine demonstrated a statistically significant reduction in moderate-to-severe acute pain compared to placebo after abdominoplasty (least squares mean difference in SPID48 *vs.* placebo, 48.4; $P < 0.0001$) and bunionectomy (least squares mean difference in SPID48 *vs.* placebo, 29.3; $P = 0.0002$). In addition, in both trials, the time to onset of clinically meaningful pain relief (defined as the time to 2-point or greater reduction in numeric pain rating scale from baseline), the second key secondary endpoint, was faster for those treated with suzetrigine compared to placebo.

Although neither trial achieved the first key secondary endpoint of superiority of suzetrigine compared to hydrocodone bitartrate/acetaminophen (a combination product) on SPID48, the efficacy of orally administered suzetrigine is in the range seen with opioids (*e.g.*, morphine, tramadol, oliceridine) administered intravenously that have been studied in both abdominoplasty and bunionectomy (abdominoplasty: SPID48, 4.0 to 59.7; bunionectomy: SPID48, 13.1 to 107.6).[14,26–29] *Post hoc* analyses without imputation also provided evidence of efficacy in combination with ibuprofen, suggesting suzetrigine is efficacious both as a monotherapy and as the base for a multimodal regimen in the real-world setting.

Given the variability of efficacy seen across pain studies,[14,26–29] the consistency of suzetrigine results between these phase 3 trials and previously reported phase 2 abdominoplasty (SPID48, 37.8 *vs.* placebo) and bunionectomy (SPID48, 36.8 *vs.* placebo) trials is remarkable.[6]

Suzetrigine was generally safe and well tolerated in both trials, and adverse events were similar to those seen in the postsurgical setting. In addition, suzetrigine led to a lower incidence of vomiting or nausea than hydrocodone bitartrate/acetaminophen, addressing the common side effects of opioids.

Because the minimal clinically important difference for SPID48 compared to placebo has not been defined, we assessed the clinical meaningfulness of the effect of suzetrigine compared to placebo based on multiple factors as defined by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations for pain clinical trials.[30] These include the durability of treatment benefit, results of responder analyses, treatment effect compared to available treatments, rapidity of onset, safety and tolerability, patient adherence, and differences in mechanism of action compared to existing treatments. In addition to the statistically significant effect seen in the primary efficacy analysis of SPID48 compared to placebo, those receiving suzetrigine had a greater reduction in mean numeric pain rating scale score compared to those taking placebo in both trials. The cumulative response (percentage of subjects achieving various levels of pain reduction, including the proportion of patients achieving at least 30%, 50%, and 70% reduction in pain) at 12, 24, and 48 h suggests that the proportion of participants receiving suzetrigine might be greater at each timepoint, but further evaluation is needed. Pain reductions of at least 30% in the numeric pain rating scale score compared to baseline are considered clinically meaningful.[18,30] The time to 1-point or greater reduction in numeric pain rating scale from baseline (*i.e.*, minimum clinically important pain relief) for suzetrigine was rapid (within 1 h) in both abdominoplasty and bunionectomy studies. The clinical meaningfulness of suzetrigine was also supported by the key secondary endpoint of time to 2-point or greater reduction in numeric pain rating scale (which was the time to clinically meaningful reduction in pain), where suzetrigine had a more rapid onset of pain relief *versus* placebo after abdominoplasty (119 min *vs.* 480 min; nominal $P < 0.0001$) and bunionectomy (240 min *vs.* 480 min; nominal $P = 0.0016$). Adherence with suzetrigine was high in both trials (88.6% completed treatment in the abdominoplasty trial; 87.3% completed treatment in the bunionectomy trial). Last, suzetrigine represents a new pharmacologic class without the limitations of current analgesic therapies (*i.e.*, limited efficacy of nonopioid analgesics and safety, tolerability, and addiction concerns with opioids). These factors demonstrate that the effect of suzetrigine in reducing pain is clinically meaningful.

Limitations

Our trials had limitations. The participants in our trials were predominantly women; this is a limitation because acute pain also affects men. The patients enrolled in our studies were representative of the general population who undergo abdominoplasty (96% women) and bunionectomy (86% women) in United States[20,23] and were consistent with previous phase 3 trials of medications approved to treat acute

pain.[22,27,31–33] Although sex-specific differences in analgesic response have been suggested in studies of chronic pain, sex has not been shown to make a difference in the response to oral analgesics in persons with acute pain.[34–36] We permitted participants to receive rescue with ibuprofen, as is conventional in clinical trials in acute pain, and assessed the safety and efficacy of suzetrigine.[13,22,32,37]

While suzetrigine was statistically superior to placebo, multimodal regimens are often used for pain management in a real-world setting. Therefore, *post hoc* analyses without imputation for ibuprofen rescue (in which the efficacy was analyzed in combination with ibuprofen, as a multimodal regimen) were conducted and provided.

As part of this widely accepted bunionectomy acute pain model, a popliteal block with ropivacaine was used to extend analgesia into postoperative day 1, which differs from postoperative pain management in regular practice. As a result, ropivacaine (a nonselective sodium channel blocker) was active in the sciatic nerve after the removal of the popliteal catheter, exerting analgesia and thereby resulting in the lower baseline pain score we observed (31% of participants after bunionectomy had baseline numeric pain rating scale scores less than 6 compared to 16% after abdominoplasty). This resulted in a slower time to 2-point or greater reduction in numeric pain rating scale for participants after bunionectomy than after abdominoplasty, likely due to the difference in the baseline pain between the trials. A *post hoc* analysis showed that the subgroup of participants in the bunionectomy trial with comparable baseline pain to participants in the abdominoplasty trial had similar time to 2-point or greater reduction as in the overall population of participants in the abdominoplasty trial. This supports the hypothesis that baseline pain score and minimizing or eliminating the effect of the local anesthetic is important when considering time to onset of pain relief analyses in future analgesic trials.

The limitations, including the subjective nature of reported pain scores, use of perioperative medications, and imputation methodologies, are consistent with the known challenges of acute pain trials. Despite these challenges, suzetrigine demonstrated consistent efficacy and safety in five clinical trials,[6,38] including the two large phase 3 randomized trials reported here. *Post hoc* analysis without imputation demonstrated efficacy of suzetrigine and ibuprofen as a multimodal regimen compared to placebo and ibuprofen. Additional studies may be needed to further evaluate suzetrigine as a multimodal regimen in moderate-to-severe acute pain trials.

Conclusions

As compared with placebo, suzetrigine reduced moderate-to-severe acute pain over 48 h after abdominoplasty or bunionectomy. Pain reduction with suzetrigine was similar to that with hydrocodone bitartrate/acetaminophen. Suzetrigine was associated with adverse events that were mild to moderate in severity.

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Competing Interests

Drs. Bertoch, McCoun, Solanki, Taber, Urban, Oswald, Swisher, and Weiner have reported personal fees from Vertex Pharmaceuticals (Boston, Massachusetts) as members of the Acute Pain Steering Committee. Dr. Urban has reported personal fees and honoraria from Pacira Biosciences (Tampa, Florida). Dr. Swisher has reported fees or honoraria from Epimed International (Dallas, Texas), SPR Therapeutics (Cleveland, Ohio), InfuTronix (Natick, Massachusetts), Avanos Medical (Alpharetta, Georgia), Masimo (Irvine, California), and Varian Medical Systems (Palo Alto, California). Dr. Weiner has reported fees/honoraria from Cessation Therapeutics, Inc (Chapel Hill, North Carolina). Drs. Tian, Miao, Correll, Negulescu, and Bozic are employees of Vertex Pharmaceuticals and own stock and/or options in the company. Dr. D'Aunno reports no competing interests.

Reproducible Science

Vertex is committed to advancing medical science and improving participant health. This includes the responsible sharing of clinical trial data with qualified researchers. Proposals for the use of these data will be reviewed by a scientific board. Approvals are at the discretion of Vertex and will be dependent on the nature of the request, the merit of the research proposed, and the intended use of the data. Please contact CTDS@vrtx.com if you would like to submit a proposal or need more information.

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Supplemental Digital Content

Supplemental Materials, https://links.lww.com/ALN/D918

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