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Selective Inhibition of $Na_V1.8$ with VX-548 for Acute Pain

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ABSTRACT

BACKGROUND

The $Na_V1.8$ voltage-gated sodium channel, expressed in peripheral nociceptive neurons, plays a role in transmitting nociceptive signals. The effect of VX-548, an oral, highly selective inhibitor of $Na_V1.8$, on control of acute pain is being studied.

METHODS

After establishing the selectivity of VX-548 for $Na_V1.8$ inhibition in vitro, we conducted two phase 2 trials involving participants with acute pain after abdominoplasty or bunionectomy. In the abdominoplasty trial, participants were randomly assigned in a 1:1:1:1 ratio to receive one of the following over a 48-hour period: a 100-mg oral loading dose of VX-548, followed by a 50-mg maintenance dose every 12 hours (the high-dose group); a 60-mg loading dose of VX-548, followed by a 30-mg maintenance dose every 12 hours (the middle-dose group); hydrocodone bitartrate–acetaminophen (5 mg of hydrocodone bitartrate and 325 mg of acetaminophen every 6 hours); or oral placebo every 6 hours. In the bunionectomy trial, participants were randomly assigned in a 2:2:1:2:2 ratio to receive one of the following over a 48-hour treatment period: oral high-dose VX-548; middle-dose VX-548; low-dose VX-548 (a 20-mg loading dose, followed by a 10-mg maintenance dose every 12 hours); oral hydrocodone bitartrate–acetaminophen (5 mg of hydrocodone bitartrate and 325 mg of acetaminophen every 6 hours); or oral placebo every 6 hours. The primary end point was the time-weighted sum of the pain-intensity difference (SPID) over the 48-hour period (SPID48), a measure derived from the score on the Numeric Pain Rating Scale (range, 0 to 10; higher scores indicate greater pain) at 19 time points after the first dose of VX-548 or placebo. The main analysis compared each dose of VX-548 with placebo.

RESULTS

A total of 303 participants were enrolled in the abdominoplasty trial and 274 in the bunionectomy trial. The least-squares mean difference between the high-dose VX-548 and placebo groups in the time-weighted SPID48 was 37.8 (95% confidence interval [CI], 9.2 to 66.4) after abdominoplasty and 36.8 (95% CI, 4.6 to 69.0) after bunionectomy. In both trials, participants who received lower doses of VX-548 had results similar to those with placebo. Headache and constipation were common adverse events with VX-548.

CONCLUSIONS

As compared with placebo, VX-548 at the highest dose, but not at lower doses, reduced acute pain over a period of 48 hours after abdominoplasty or bunionectomy. VX-548 was associated with adverse events that were mild to moderate in severity. (Funded by Vertex Pharmaceuticals; VX21-548-101 and VX21-548-102 ClinicalTrials.gov numbers, NCT04977336 and NCT05034952.)

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*A complete list of the investigators in the VX21-548-101 and VX21-548-102 Trial Groups is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Acute pain, a pervasive cause of suffering, has major implications for patients and public health.[1,2] Opioids targeting central mechanisms involved in the perception of pain are often used for treatment of acute pain; however, their use is limited by safety concerns and the potential for misuse and addiction.[3-6] Nonopioid treatments for pain include nonselective sodium-channel inhibitors (e.g., lidocaine, mexiletine, and carbamazepine), nonsteroidal antiinflammatory drugs (NSAIDs), and acetaminophen. Most approved analgesic drugs either act on the opioid-receptor system or are NSAIDs.[7,8]

The voltage-gated sodium channel $Na_V1.8$ is a therapeutic target for pain because of its role in transmitting nociceptive signals and its selective expression in peripheral nociceptive neurons of the dorsal-root ganglia.[9-12] $Na_V1.8$ is a sodium ion channel subtype that in humans is encoded by *SCN10A*. Our understanding of the role of $Na_V1.8$ in pain transmission is supported by its function in normal sensory physiologic response,[10-14] pathologic states arising from mutations in *SCN10A*,[15,16] animal models,[17-20] and pharmacologic effects of $Na_V1.8$-modulating agents.[21,22] We hypothesized that selective inhibition of $Na_V1.8$ would provide effective pain relief without the risks associated with opioid treatments. We describe the preclinical characterization of VX-548, an oral, highly selective inhibitor of $Na_V1.8$, and we report the results of two phase 2 trials evaluating the efficacy and safety of VX-548 in persons who had acute pain after abdominoplasty or bunionectomy.

Methods

Preclinical Development

We performed a preclinical assessment of the selectivity and potency of VX-548 with respect to recombinant Na_V subtypes 1.1 through 1.9. These data are summarized in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Oversight of the Trials

The trials, which were sponsored by Vertex Pharmaceuticals and designed by the sponsor in collaboration with the steering committee, were conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All the participants provided written informed consent before screening. Data collection was performed by the sponsor and the VX21-548-101 and VX21-548-102 trial groups; data analysis was performed by the sponsor in collaboration with the steering committee.

The first draft of the manuscript was written by the second, third, and last authors with the assistance of medical writers; the second and third authors and the medical writers were employed by the sponsor, and medical illustrators who were paid by the sponsor assisted with earlier versions of the figures. All the authors had access to the data, critically reviewed the manuscript, and approved it for submission for publication. The investigators vouch for the accuracy and completeness of the data and for accurate reporting of adverse events at their respective sites, and the investigators and the sponsor vouch for the fidelity of the trials to the protocol, available at NEJM.org. There was no data safety and monitoring board. Confidentiality agreements were in place between the sponsor and the investigators. The sponsor could not interdict publication of the results of the trials.

Participants

We conducted two phase 2, randomized, double-blind, placebo-controlled clinical trials to evaluate VX-548 in participants who had acute pain after abdominoplasty or bunionectomy. Abdominoplasty, which is considered to be a model of soft-tissue pain, and bunionectomy, which is considered to be a model of bone pain, are common surgical procedures resulting in moderate-to-severe postoperative acute pain that is generally treated with analgesic medicines, including opioids, NSAIDs, and acetaminophen.[4,23-25]

Adult participants were enrolled in the abdominoplasty trial from August 2021 through November 2021 at seven sites in the United States, and adult participants were enrolled in the bunionectomy trial from July 2021 through January 2022 at nine sites in the United States; all the sites that participated in the abdominoplasty trial also participated in the bunionectomy trial. Eligible participants were 18 to 75 years of age and had rated their pain as a score of at least 4 on the Numeric Pain Rating Scale (NPRS, a numeric version of a visual-analogue scale; scores range from 0 to 10, with higher scores indicating greater pain) and had rated their pain as moderate or severe on the Verbal Categorical Rating Scale (VRS, a four-

level scale that ranges from no pain to severe pain) within 4 hours after completion of the surgery and general anesthesia in the abdominoplasty trial and within 9 hours after removal of the popliteal sciatic nerve block on postoperative day 1 in the bunionectomy trial.

Participants with a history of any sensory abnormality or who had a painful physical condition that, in the opinion of the investigator, may have confounded the ability of the participant to assess postoperative pain were not permitted in either trial, and those with long-term use of opioids or NSAIDs were not eligible to participate. Additional details regarding eligibility criteria are provided in the Supplementary Appendix.

DESIGN OF THE CLINICAL TRIALS

Screening, randomization, the trial regimens, and follow-up are shown in Figure 1. In both trials, randomization was stratified according to trial site and baseline NPRS score (<8 or ≥8), and VX-548 was administered orally with a loading dose followed by a maintenance dose every 12 hours. All the participants received the same number of pills in these trials, which had a double-dummy design.

In the abdominoplasty trial, participants who requested pain relief and met eligibility criteria were randomly assigned, in a 1:1:1:1 ratio, to receive one of the following during a 48-hour treatment period: oral VX-548 at a loading dose of 100 mg, followed by a maintenance dose of 50 mg every 12 hours (high-dose VX-548); oral VX-548 at a loading dose of 60 mg, followed by a maintenance dose of 30 mg every 12 hours (middle-dose VX-548); oral hydrocodone bitartrate–acetaminophen (5 mg of hydrocodone bitartrate and 325 mg of acetaminophen every 6 hours); or oral placebo every 6 hours. Midazolam and fentanyl were permitted preoperatively, and propofol and fentanyl were administered for general anesthesia. Fentanyl was permitted as postoperative supplemental analgesia, and randomization did not occur until at least 15 minutes after the last administration of fentanyl.

In the bunionectomy trial, participants underwent a primary unilateral bunionectomy with a distal first metatarsal osteotomy (Austin procedure)[26] and internal fixation while receiving regional anesthesia (Mayo block and popliteal sciatic nerve block).[27] Participants who requested pain relief and met eligibility criteria were randomly assigned in a 2:2:1:2:2 ratio to receive one of the following over a 48-hour treatment period: oral high-dose VX-548 every 12 hours; middle-dose VX-548 every 12 hours; low-dose VX-548 (oral VX-548 at a loading dose of 20 mg, followed by a maintenance dose of 10 mg every 12 hours); oral hydrocodone bitartrate–acetaminophen (5 mg of hydrocodone bitartrate and 325 mg of acetaminophen every 6 hours); or oral placebo every 6 hours. For perioperative use, midazolam, fentanyl, or both were permitted, followed by propofol, with the Mayo block (lidocaine) and popliteal sciatic nerve block (ropivacaine). Fentanyl, acetaminophen, and ropivacaine boluses and infusion rate changes were permitted for postoperative supplemental analgesia; however, no treatments for pain were allowed after removal of the popliteal block up to the time of randomization.

In both trials, pain intensity (as measured on the NPRS) was recorded at approximately 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours after the first dose of VX-548, hydrocodone bitartrate–acetaminophen, or placebo (19 measurements). After this first dose, ibuprofen (400 mg orally every 6 hours) was permitted as a rescue medication for pain relief; participants were encouraged to wait 90 minutes after the first dose of VX-548, hydrocodone bitartrate–acetaminophen, or placebo to request rescue medication. No other medications were permitted as rescue therapy for pain relief after the first dose of VX-548, hydrocodone bitartrate–acetaminophen, or placebo; specifically, opioids, acetaminophen, hydrocodone bitartrate–acetaminophen, and other NSAIDs (with the exception of ibuprofen) were not permitted as rescue medication. Pain intensity (as measured on the NPRS) was also recorded immediately before administration of rescue medication.

In an attempt to minimize bias, clinical site staff were trained to provide participants with neutral information about the active treatments (VX-548 and hydrocodone bitartrate–acetaminophen) or placebo and expected effects. To ensure consistent reporting of pain measures, participants were informed before randomization about how to use pain scales. Additional details regarding the trial designs and perioperative pain management are provided in the protocol.

END POINTS

In both trials, the primary efficacy end point was the time-weighted sum of the pain-intensity dif-

ference (SPID) over a period of 48 hours (SPID48) in a comparison of VX-548 with placebo. We calculated the difference in pain intensity as measured by NPRS scores at each time point as compared with baseline, and the SPID48 values were determined by multiplying a weight factor to each score before summing these values; the weight factor at each of 19 time points was the time elapsed since the previous observation. Because SPID48 is a time-weighted assessment, pain-intensity differences have a greater contribution if they are associated with a longer time interval; higher SPID48 values represent greater reduction in pain.

Secondary efficacy end points were the time-weighted SPID between VX-548 and placebo (as measured by NPRS scores) over a 24-hour period (SPID24) and the percentages of participants with a reduction in pain of at least 30%, at least 50%, and at least 70% from baseline on the NPRS at 48 hours after the first dose of VX-548, hydrocodone bitartrate–acetaminophen, or placebo. Safe-

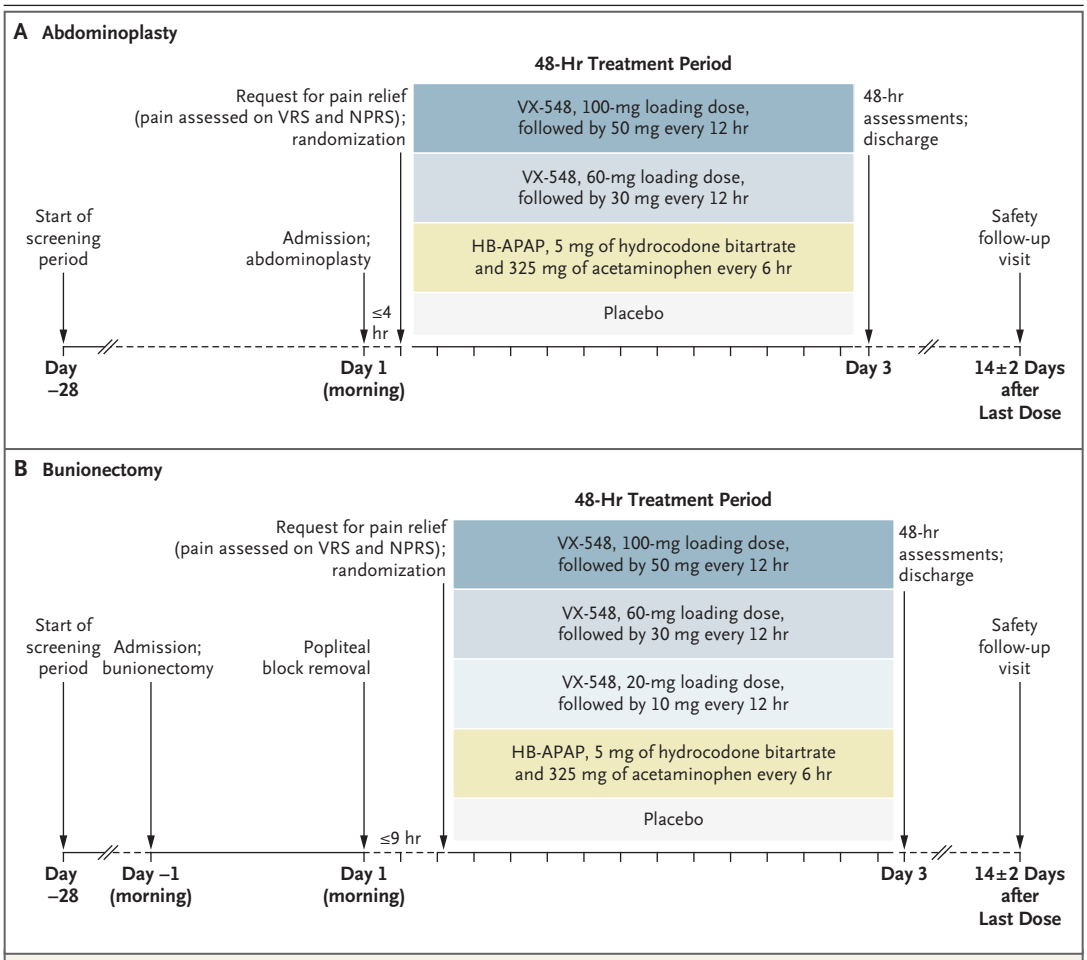

Figure 1. Designs of the Abdominoplasty and Bunionectomy Clinical Trials.

After completion of surgery (abdominoplasty, Panel A) or removal of the popliteal sciatic nerve block (bunionectomy, Panel B), participants were randomly assigned to a trial group if they requested pain relief, their pain was moderate or severe according to the Verbal Categorical Rating Scale (VRS, a four-level scale that ranges from no pain to severe pain) at rest, and the pain was rated at least 4 on the Numeric Pain Rating Scale (NPRS) (range, 0 to 10, with higher scores indicating a greater level of pain) at rest. Eligible participants met the NPRS and VRS criteria within 4 hours after surgery completion in the abdominoplasty trial and within 9 hours after removal of the popliteal sciatic nerve block in the bunionectomy trial. VX-548 was administered orally with a loading dose, followed by a maintenance dose every 12 hours. Hydrocodone bitartrate–acetaminophen (HB-APAP) and placebo were also administered orally.

ty was determined on the basis of adverse events, clinical laboratory values, 12-lead electrocardiograms (ECGs), and vital signs. All adverse events were assessed by the site investigators, who were unaware of the trial-group assignments, but these events were not adjudicated by an independent data monitoring committee.

STATISTICAL ANALYSIS

The sample-size calculation was based on the comparison between VX-548 and placebo with respect to the primary end point. The trials were powered on the basis of an assumed standardized effect size (the mean difference between the VX-548 group and placebo group, divided by the standard deviation) because of the expected variation in the placebo response observed in historical bunionectomy and abdominoplasty trials. Specifically, the trials were powered to detect a standardized effect size of 0.8 for VX-548, which was generally consistent with some abdominoplasty and bunionectomy trials.[28-30] These referenced trials did not provide standardized effect sizes; therefore, we calculated them on the basis of the reported mean differences and their confidence intervals.

We planned to enroll 256 and 243 participants in the abdominoplasty and bunionectomy trials, respectively, to allow for at least 90% power at a two-sided significance level of 0.05 to detect a standardized effect size of 0.8 for VX-548 as compared with placebo. The primary efficacy analysis was based on an analysis-of-covariance model. The model included SPID48 as the dependent variable and treatment as a fixed effect, with trial site and baseline score on the NPRS as covariates. The least-squares mean differences in the SPID48 between VX-548 and placebo and the corresponding 95% confidence intervals were calculated. There were no planned formal comparisons between VX-548 and hydrocodone bitartrate–acetominophen or between hydrocodone bitartrate–acetominophen and placebo.

As prespecified in the statistical analysis plan, for the primary analysis, NPRS scores that were recorded within 6 hours after a dose of rescue medication were replaced by the prerescue NPRS score, in conformance with the last observation carried forward.[30-33] The last observation carried forward was used to impute missing NPRS scores to compute the value for the primary end point for participants who discontinued active treatment or placebo, irrespective of reason, and for those who completed the 48-hour treatment period but had missing data. Missing values after discontinuation of active treatment or placebo were imputed with the use of the last nonmissing observation or the previously imputed NPRS score carried forward. Missing values for participants who completed the treatment period but had missing data from a certain time point to 48 hours were also imputed with the last nonmissing observation or the previously imputed NPRS score. Intermittently missing NPRS scores were imputed with the use of linear interpolation. In addition, a post hoc analysis of the primary end point was performed with the use of multiple imputation for missing data (see the Supplementary Appendix). There was no prespecified plan for adjustment of widths of confidence intervals for multiple comparisons of primary or secondary end points, and thus all values must be considered to be nominal.

For the secondary end points, the SPID24 was analyzed with the same method used to analyze the SPID48. The data for the percentages of participants with a reduction of at least 30%, at least 50%, and at least 70% in the NPRS score at 48 hours after the first dose of VX-548, hydrocodone bitartrate–acetaminophen, or placebo were summarized descriptively. Participants with missing NPRS scores at 48 hours were considered to have had no response (i.e., no reduction of ≥30%, ≥50%, or ≥70% in the NPRS score at 48 hours). Safety analyses involved participants who had received at least one dose of VX-548, hydrocodone bitartrate–acetaminophen, or placebo; safety data were summarized with the use of descriptive statistics.

RESULTS

SELECTIVITY OF VX-548 IN PRECLINICAL MODELS

In preclinical models, VX-548 had selectivity for $Na_v1.8$ that was at least 31,000 times as high as that with all other Na_v subtypes (i.e., $Na_v1.1$ to $Na_v1.7$, and $Na_v1.9$) in recombinant cells (Table S1 in the Supplementary Appendix). VX-548 also had subnanomolar potency in primary neurons isolated from human dorsal-root ganglia (Fig. S1).

TRIAL PARTICIPANTS

In the abdominoplasty trial, 303 participants were randomly assigned to a trial group and 81.5%

completed the treatment period. In the bunionectomy trial, 274 participants were randomly assigned to a trial group and 90.1% completed the treatment period. Baseline demographic and clinical characteristics were similar across the trial groups in each trial, including the baseline mean NPRS score (7.2 to 7.4 in the abdominoplasty trial and 6.6 to 6.9 in the bunionectomy trial) (Table 1 and Table S2). The representativeness of the population of patients undergoing abdominoplasty and bunionectomy is shown in Table S3. Approximately 22% of the participants in the abdominoplasty trial and 24% of those in the bunionectomy trial were Black.

In both trials, fewer participants discontinued high-dose VX-548 than placebo or hydrocodone bitartrate–acetaminophen (9.2% in the VX-548 group, 24.7% in the placebo group, and 27.6% in the hydrocodone bitartrate–acetaminophen group in the abdominoplasty trial and 3.3% in the VX-548 group, 13.6% in the placebo group, and 11.7% in the hydrocodone bitartrate–acetaminophen group in the bunionectomy trial) (Table S4). In both trials, fewer participants discontinued high-dose VX-548 owing to lack of efficacy than those who discontinued placebo or hydrocodone bitartrate–acetaminophen (7.9% of the participants in the VX-548 group, 23.4% in the placebo group, and 25.0% in the hydrocodone bitartrate–acetaminophen group in the abdominoplasty trial and 3.3% of the participants in the VX-548 group, 8.5% in the placebo group, and 10.0% in the hydrocodone bitartrate–acetaminophen group in the bunionectomy trial).

As prespecified in the statistical analysis plan, the last observation carried forward was used to impute missing NPRS scores to compute the time-weighted SPID48 in the NPRS score (the primary end point) for participants who discontinued VX-548, hydrocodone bitartrate–acetaminophen, or placebo, irrespective of reason, and for those who completed the 48-hour treatment period but had missing data from a certain time point to 48 hours. In the abdominoplasty trial, last observation carried forward was applied for 6.2% of the total number of NPRS scores used to compute the SPID48 for participants in the high-dose VX-548 group and 17.7% in the placebo group, and in the bunionectomy trial, last observation carried forward was applied for 2.8% of the total number of NPRS scores in the high-dose VX-548 group and 6.7% in the placebo group (Table S5). Windowed last observation carried forward (the last NPRS score carried forward 6 hours) was used to handle the use of rescue medication, as prespecified in the statistical analysis plan; in the abdominoplasty trial, 26.2% of the total number of NPRS scores in the high-dose VX-548 group were imputed in this manner, as compared with 34.1% in the placebo group, and in the bunionectomy trial, 28.0% of the total number of NPRS scores in the high-dose VX-548 group were imputed in this manner, as compared with 29.8% in the placebo group.

EFFICACY

The least-squares mean difference in the SPID48 between the high-dose VX-548 group and the placebo group was 37.8 (95% confidence interval [CI], 9.2 to 66.4) in the abdominoplasty trial and 36.8 (95% CI, 4.6 to 69.0) in the bunionectomy trial. The difference between VX-548 and placebo in the SPID24 was 19.6 (95% CI, 6.5 to 32.7) in the abdominoplasty trial and 13.7 (95% CI, –1.8 to 29.1) in the bunionectomy trial (Table 2). Post hoc multiple imputation for missing data in analysis of the primary end point with the use of methods described in the Supplementary Appendix showed results that were similar to those with the prespecified approach (Table S6).

Decreases in pain were indicated by decreases in NPRS scores shown on graphs of scores in the first hour of the treatment period in both the high-dose VX-548 and placebo groups; the magnitude of the treatment effect was similar throughout the 48-hour treatment period. Figure 2 shows these results with standard error bars, and Figure S2 shows similar data with 95% confidence intervals instead of standard errors. However, no formal analysis of the time course of effect was performed. Table 2 shows the percentages of participants with at least a 30%, at least a 50%, and at least a 70% reduction in the NPRS score 48 hours after the first dose of VX-548, hydrocodone bitartrate–acetaminophen, or placebo in both trials. The response with respect to acute pain was similar among participants who received VX-548 at the lower doses, those who received hydrocodone bitartrate–acetaminophen, and those who received placebo.

SAFETY

The site investigators, who were unaware of the trial group assignments, assessed most adverse

Table 1. Baseline Demographic and Clinical Characteristics of the Participants.*

Characteristic	Abdominoplasty Trial				Bunionectomy Trial				
	High-Dose VX-548 (N=76)	Middle-Dose VX-548 (N=74)	Hydrocodone Bitartrate–Acetaminophen (N=76)	Placebo (N=77)	High-Dose VX-548 (N=60)	Middle-Dose VX-548 (N=62)	Low-Dose VX-548 (N=33)	Hydrocodone Bitartrate–Acetaminophen (N=60)	Placebo (N=59)
Age — yr	43.1±9.7	41.5±9.2	45.4±10.7	42.6±9.5	47.6±13.7	48.3±13.1	47.8±15.5	50.0±12.5	47.8±13.6
Female sex — no. (%)	75 (99)	74 (100)	73 (96)	76 (99)	53 (88)	57 (92)	25 (76)	50 (83)	49 (83)
Race and ethnic group — no. (%)†									
White	57 (75)	57 (77)	53 (70)	57 (74)	42 (70)	44 (71)	22 (67)	44 (73)	41 (69)
Black	13 (17)	15 (20)	18 (24)	20 (26)	14 (23)	17 (27)	9 (27)	13 (22)	13 (22)
Other	6 (8)	2 (3)	5 (7)	0	4 (7)	1 (2)	2 (6)	3 (5)	5 (8)
BMI‡	28.83±4.35	29.42±3.68	28.74±3.87	28.93±3.91	28.19±4.54	28.24±4.70	27.11±4.58	27.81±4.28	28.41±4.61
NPRS score at rest§	7.2±1.7	7.4±1.8	7.3±1.8	7.4±1.6	6.7±1.7	6.6±1.8	6.9±1.8	6.9±1.9	6.9±1.7
VRS — no. (%)¶									
Moderate	44 (58)	45 (61)	45 (59)	42 (55)	44 (73)	45 (73)	21 (64)	37 (62)	39 (66)
Severe	32 (42)	29 (39)	31 (41)	35 (45)	16 (27)	17 (27)	12 (36)	23 (38)	20 (34)

* Plus–minus values are means ±SD. Data on participants in any trial group who had undergone randomization and received at least one dose of active treatment (VX-548 or hydrocodone bitartrate–acetaminophen) or placebo are shown. The high-dose VX-548 groups received a loading dose of 100 mg, followed by a maintenance dose of 50 mg every 12 hours; the middle-dose VX-548 groups received a loading dose of 60 mg, followed by a maintenance dose of 30 mg every 12 hours; the low-dose VX-548 group (in the bunionectomy trial only) received a loading dose of 20 mg, followed by a maintenance dose of 10 mg every 12 hours; and the hydrocodone bitartrate–acetaminophen groups received 5 mg of hydrocodone bitartrate and 325 mg of acetaminophen every 6 hours.

† Race and ethnic group were reported by the participants. The "other" category includes all other reported races and ethnic groups (see Table S2 in the Supplementary Appendix).

‡ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

§ Scores on the Numeric Pain Rating Scale (NPRS) range from 0 to 10, with higher scores indicating a greater level of pain.

¶ The Verbal Categorical Rating Scale (VRS) is a four-level scale that ranges from no pain to severe pain.

Table 2. Primary and Secondary Efficacy End Points.*

End Point	Abdominoplasty Trial				Bunionectomy Trial				
	High-Dose VX-548 (N=76)	Middle-Dose VX-548 (N=74)	Hydrocodone Bitartrate–Acetaminophen (N=76)	Placebo (N=77)	High-Dose VX-548 (N=60)	Middle-Dose VX-548 (N=62)	Low-Dose VX-548 (N=33)	Hydrocodone Bitartrate–Acetaminophen (N=60)	Placebo (N=59)
Primary efficacy end point: SPID48									
LSM	110.5±10.3	95.1±10.4	85.2±10.3	72.7±10.2	137.8±11.5	86.9±11.3	112.9±15.5	115.6±11.5	101.0±11.6
LSM difference vs. placebo	37.8±14.5	22.4±14.6	12.5±14.5	NA	36.8±16.3	−14.1±16.2	11.9±19.4	14.7±16.3	NA
95% CI of the LSM difference	9.2 to 66.4	−6.4 to 51.1	−16.1 to 41.1	NA	4.6 to 69.0	−46.1 to 17.9	−26.2 to 50.1	−17.5 to 46.8	NA
Secondary efficacy end point: SPID24									
LSM	45.5±4.7	37.6±4.8	30.0±4.7	26.0±4.7	45.2±5.5	24.8±5.4	34.4±7.4	41.0±5.5	31.5±5.6
LSM difference from placebo	19.6±6.7	11.7±6.7	4.0±6.7	NA	13.7±7.8	−6.8±7.8	2.8±9.3	9.4±7.8	NA
95% CI of the LSM difference	6.5 to 32.7	−1.5 to 24.9	−9.1 to 17.1	NA	−1.8 to 29.1	−22.1 to 8.6	−15.5 to 21.1	−6.1 to 24.9	NA
Secondary efficacy end point: reduction in NPRS score at rest at 48 hr — no. (%)									
Participants with ≥30% reduction	46 (61)	44 (59)	41 (54)	37 (48)	50 (83)	39 (63)	25 (76)	41 (68)	40 (68)
Participants with ≥50% reduction	34 (45)	32 (43)	32 (42)	26 (34)	40 (67)	35 (56)	24 (73)	37 (62)	36 (61)
Participants with ≥70% reduction	19 (25)	14 (19)	18 (24)	11 (14)	31 (52)	24 (39)	17 (52)	30 (50)	24 (41)

* Plus–minus values are least-squares means (LSM) ±SE. Data on participants in any trial group who had undergone randomization and received at least one dose of active treatment (VX-548 or hydrocodone bitartrate–acetaminophen) or placebo are shown. As prespecified in the statistical analysis plan, the last observation carried forward was used to impute missing NPRS scores to compute the time-weighted sum of the pain-intensity difference (SPID) over a period of 48 hours (SPID48) in the NPRS score (the primary end point) for participants who discontinued VX-548, hydrocodone bitartrate–acetaminophen, or placebo, irrespective of reason, and for those who completed the 48-hour treatment period but had missing data from a certain time point to 48 hours. In the abdominoplasty trial, last observation carried forward was applied for 6.2% of the total number of NPRS scores used to compute the SPID for participants in the high-dose VX-548 group and 17.7% in the placebo group, and in the bunionectomy trial, last observation carried forward was applied for 2.8% of the total number of NPRS scores in the high-dose VX-548 group and 6.7% in the placebo group. Windowed last observation carried forward (the last NPRS score carried forward 6 hours) was used to handle the use of rescue medication, as prespecified in the statistical analysis plan; in the abdominoplasty trial, 26.2% of the total number of NPRS scores in the high-dose VX-548 group were imputed, as compared with 34.1% in the placebo group, and in the bunionectomy trial, 28.0% of the total number of NPRS scores in the high-dose VX-548 group were imputed, as compared with 29.8% in the placebo group. NA denotes not applicable, SPID48 the SPID over a period of 48 hours after the first dose of active treatment or placebo, and SPID24 the SPID over a period of 24 hours after the first dose of active treatment or placebo.

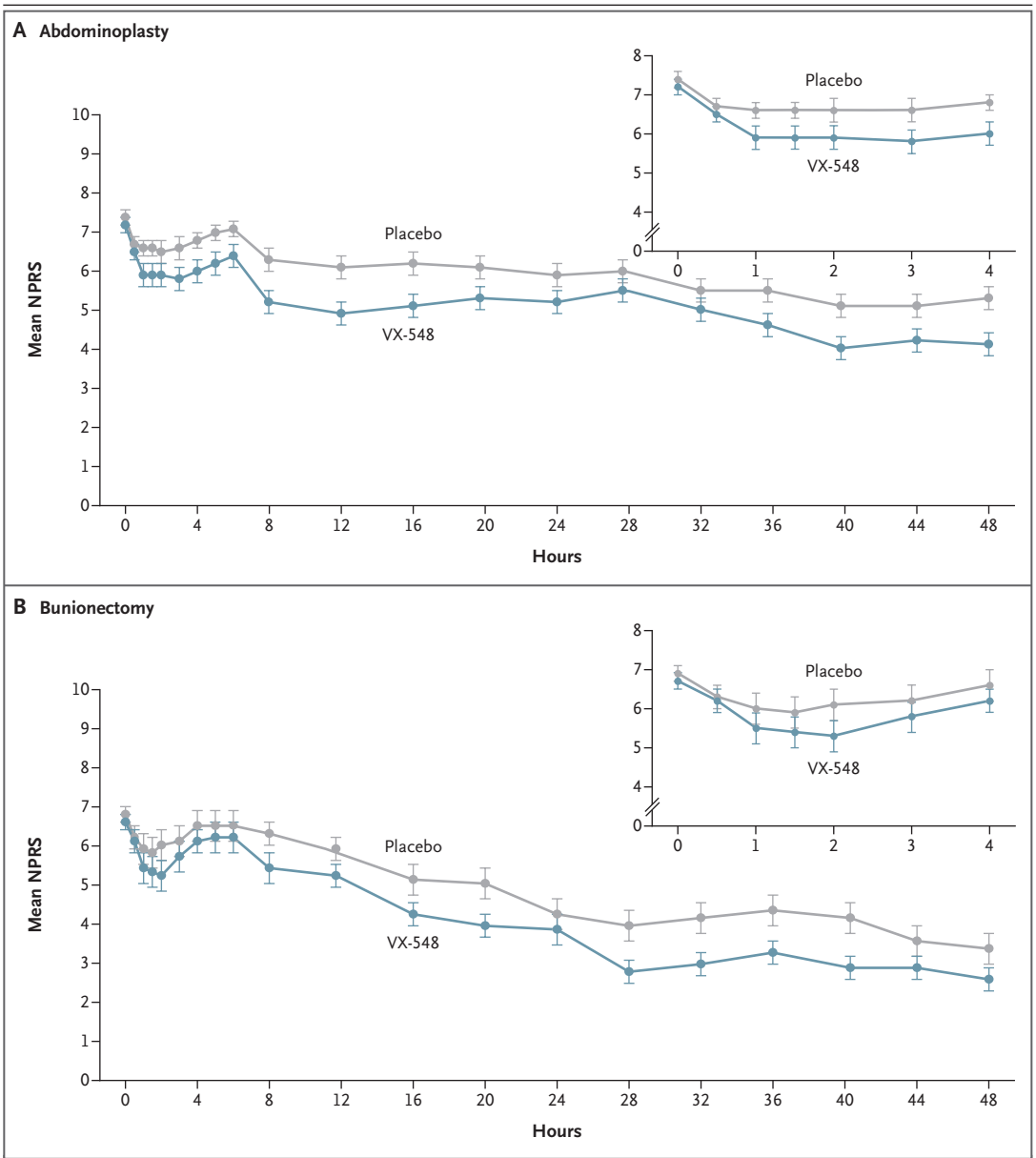

Figure 2. Mean NPRS Scores over Time.

Shown are data for participants who had undergone randomization and received at least one dose of VX-548 or placebo. Data only for the highest dose used in the trials are shown. The I bars indicate the standard error (SE). Panel A shows the mean NPRS scores over time for participants in the abdominoplasty trial who received VX-548 (a 100-mg loading dose, followed by 50 mg every 12 hours) or placebo throughout the entire treatment period and during the first 4 hours of the treatment period (inset). Panel B shows the mean NPRS scores over time for participants in the bunionectomy trial who received VX-548 (a 100-mg loading dose, followed by 50 mg every 12 hours) or placebo throughout the entire treatment period and during the first 4 hours of the treatment period (inset).

events as being mild or moderate in severity. The most common adverse events that occurred in at least 10% of the participants in any trial group were nausea, headache, constipation, dizziness, and vomiting in the abdominoplasty trial and nausea and headache in the bunionectomy trial (Table 3). In the abdominoplasty trial, the incidence of most of these adverse events was similar or there was a lower incidence in the VX-548 groups than in the placebo groups, except for

headache (14% in the high-dose VX-548 group vs. 6% in the placebo group) and constipation (9% in the high-dose VX-548 group vs. 5% in the placebo group). According to the site investigators in both trials, most headaches were mild and resolved within 1 day without treatment, and most cases of constipation were mild and resolved within 5 days, but most required treatment that may have included stool softeners or laxatives. Neither headache nor constipation resulted in discontinuation of active treatment or placebo.

In the abdominoplasty trial, three participants had serious adverse events: incision-site cellulitis and sepsis (in one participant in the placebo group), laryngeal stenosis (in one participant in the hydrocodone bitartrate–acetaminophen group), and pulmonary embolism (in one participant in the middle-dose VX-548 group). None of the serious adverse events were related to VX-548, hydrocodone bitartrate–acetaminophen, or placebo, according to the site investigator; all serious adverse events resolved. In the abdominoplasty trial, two participants in the middle-dose VX-548 group discontinued VX-548 owing to adverse events (anemia and chest discomfort in one participant each); both events were nonserious and were not related to VX-548, according to the site investigator. In the bunionectomy trial, no serious adverse events and no discontinuations of VX-548 or placebo owing to adverse events were observed. No clinically significant safety findings in laboratory assessments, assessments of vital signs, standard 12-lead ECGs, and physical examinations were reported in either trial.

DISCUSSION

The sodium channel $Na_V1.8$ is selectively expressed in peripheral neurons, including neurons of the dorsal-root ganglia that transmit nociceptive signals.[10-12] VX-548 is an oral, small molecule that potently inhibits $Na_V1.8$ currents and is more highly selective for $Na_V1.8$ than other Na_V channels in vitro. *SCN10A* expression is minimal to undetectable in the human brain, and functional protein expression has not been reported. On this basis, we consider selective $Na_V1.8$ inhibitors to be unlikely to be associated with central nervous system effects, including potential for abuse and dependence; however, these risks were not tested in these trials.[34-37]

In these two phase 2 trials, participants who received high-dose VX-548 had reduced acute pain over the 48-hour treatment period after abdominoplasty and bunionectomy; lower doses of VX-548, as compared with placebo, did not show an effect in decreasing acute pain. Among the participants who received high-dose VX-548, results with respect to secondary efficacy end points were generally in the same direction as those in the primary analysis; however, there was no prespecified plan for adjustment of the widths of the confidence intervals for multiple comparisons, and no conclusions can be drawn from these data. The percentage of participants who discontinued high-dose VX-548 owing to lack of efficacy was lower than the percentages of those who discontinued hydrocodone bitartrate–acetaminophen or placebo for that reason. The use of VX-548 was not associated with respiratory depression or sedation. However, in the abdominoplasty trial, headache and constipation were more common with VX-548 than with placebo.

These trials have limitations. Abdominoplasty and bunionectomy are typically performed in outpatient settings where pain is usually treated with multiple different therapies in combination, whereas the current trials evaluated VX-548 as a monotherapy; however, attempted standardization of the surgical and anesthetic procedures in these trials enabled observation of treatment effects while minimizing potential confounding factors (e.g., the use of ice packs, timing of perioperative analgesia, and physical activities). Most participants in these trials were women; this is a limitation because acute pain also affects men. Currently, no well-accepted effect size based on SPID is considered to be minimally clinically meaningful; however, in both of our trials, the results showed reduced pain with high-dose VX-548 as compared with placebo. In both trials, there was an apparent treatment effect with VX-548 as compared with hydrocodone bitartrate–acetaminophen. However, because we did not design the trials to provide a direct comparison between these agents, it was difficult to ascertain the magnitude of pain relief as compared with that associated with a standard-of-care analgesic; thus, conclusions cannot be drawn. The treatment effect of VX-548 as compared with hydrocodone bitartrate–acetaminophen is being tested in ongoing, phase 3, controlled trials

Table 3. Summary of Adverse Events.*

Event	Abdominoplasty Trial				Bunionectomy Trial				
	High-Dose VX-548 (N = 76)	Middle-Dose VX-548 (N = 74)	Hydrocodone Bitartrate–Acetaminophen (N = 76)	Placebo (N = 77)	High-Dose VX-548 (N = 60)	Middle-Dose VX-548 (N = 62)	Low-Dose VX-548 (N = 33)	Hydrocodone Bitartrate–Acetaminophen (N = 60)	Placebo (N = 59)
	number of participants (percent)								
Any adverse event	42 (55)	45 (61)	46 (61)	54 (70)	18 (30)	17 (27)	7 (21)	25 (42)	23 (39)
Mild	24 (32)	27 (36)	19 (25)	35 (45)	15 (25)	16 (26)	5 (15)	18 (30)	17 (29)
Moderate	18 (24)	15 (20)	26 (34)	19 (25)	3 (5)	1 (2)	2 (6)	7 (12)	6 (10)
Severe	0	2 (3)	1 (1)	0	0	0	0	0	0
Life-threatening†	0	1 (1)	0	0	0	0	0	0	0
Serious adverse events‡	0	1 (1)	1 (1)	1 (1)	0	0	0	0	0
Adverse events leading to discontinuation of VX-548, hydrocodone bitartrate–acetaminophen, or placebo§	0	2 (3)	1 (1)	0	0	0	0	0	0
Adverse events in ≥10% of participants in any trial group									
Nausea	14 (18)	22 (30)	23 (30)	28 (36)	5 (8)	3 (5)	2 (6)	11 (18)	5 (8)
Headache	11 (14)	6 (8)	5 (7)	5 (6)	5 (8)	4 (6)	0	4 (7)	7 (12)
Constipation	7 (9)	7 (9)	9 (12)	4 (5)	0	1 (2)	0	1 (2)	1 (2)
Dizziness	6 (8)	11 (15)	8 (11)	14 (18)	2 (3)	2 (3)	0	1 (2)	1 (2)
Vomiting	2 (3)	1 (1)	8 (11)	5 (6)	0	0	0	3 (5)	1 (2)

* Data on participants in any trial group who had undergone randomization and received at least one dose of active treatment (VX-548 or hydrocodone bitartrate–acetaminophen) or placebo are shown.

† In the abdominoplasty trial, one participant had a life-threatening pulmonary embolism. This serious adverse event was not considered by the investigators to be related to VX-548, and it resolved.

‡ In the abdominoplasty trial, serious adverse events were pulmonary embolism (in one participant in the middle-dose VX-548 group), laryngeal stenosis (in one participant in the hydrocodone bitartrate–acetaminophen group), and incision-site cellulitis and sepsis (in one participant in the placebo group); none of the serious adverse events were considered by the investigators to be related or possibly related to active treatment or placebo. All the serious adverse events resolved.

§ In the abdominoplasty trial, one participant discontinued VX-548 owing to anemia and another discontinued VX-548 owing to chest discomfort; neither event was considered by the investigators to be related to VX-548. One participant discontinued hydrocodone bitartrate–acetaminophen owing to laryngeal stenosis.

(ClinicalTrials.gov numbers, NCT05558410 and NCT05553366).

To limit the potential consequences of the placebo effect, we implemented mitigation measures, including educating staff to provide participants with neutral information about active treatment or placebo and expected effects and training participants on how to use pain scales consistently, including how to use previous experience to rate current pain. We also used a double-dummy design to maintain blinding among the participants and investigators with respect to the administration of VX-548, hydrocodone bitartrate–acetaminophen, and placebo (i.e., all participants received the same number of pills in these trials). However, the participants were not queried at the end of the trials to assess their awareness of the trial-group assignments. Adverse events were judged by investigators, and there was no independent adjudication by a data monitoring committee.

VX-548 is a potent and selective inhibitor of $Na_V1.8$ currents relative to other Na_V channels in human dorsal-root ganglion neurons in vitro. In two phase 2 clinical trials of postoperative pain, as compared with placebo, the highest dose, but not lower doses, of VX-548 reduced pain over a 48-hour period. Headache and constipation were adverse events.

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APPENDIX

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