# A novel NaV1.8 inhibitor approved as a proof-of-concept for postoperative acute pain

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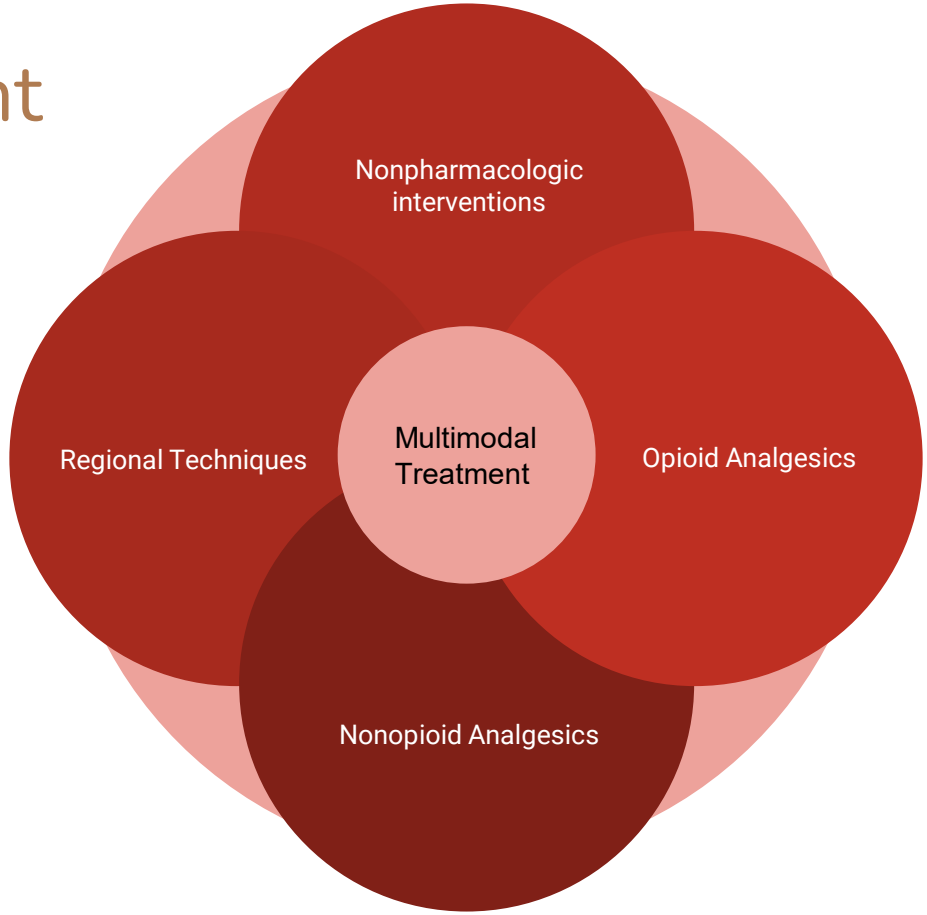
# Disclosures

***EPA management to edit this slide for CME purposes.

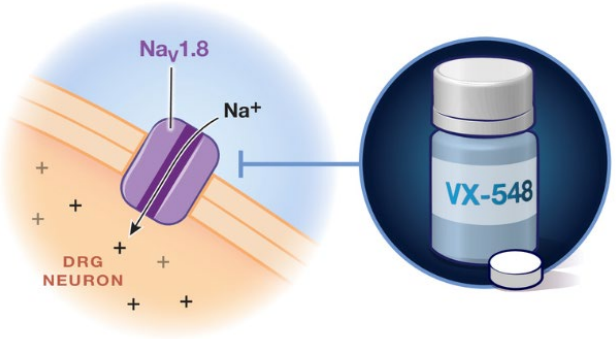
# Acute Pain Management

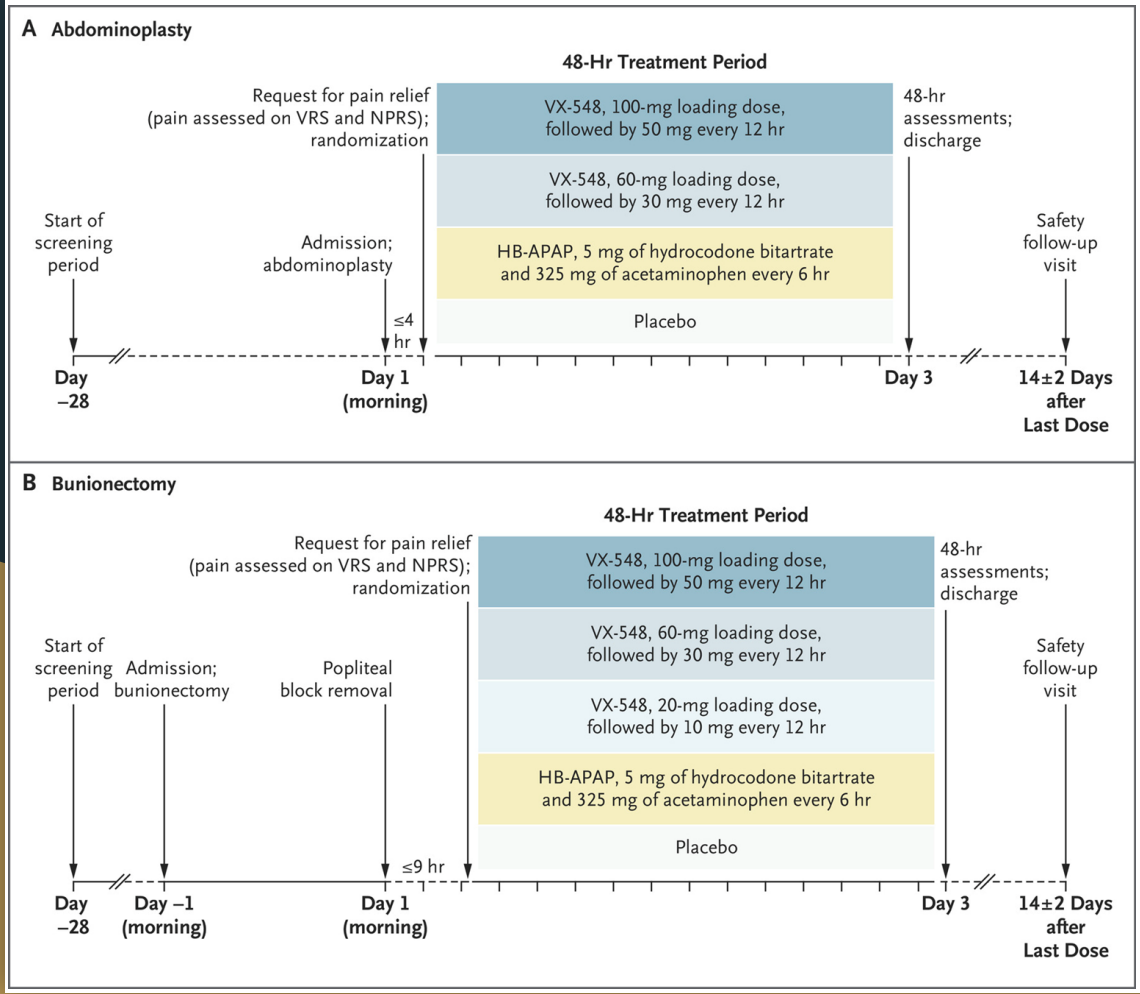
- Goal: enhance outcomes and patient experience
- Balance analgesia with functional goals
- Individualize based on pain etiology
- Reduce opioid consumption
- Focus today is on peripheral nociception and voltage gated sodium channels expressed on DRG



# VX-548: an oral, highly-selective small-molecule inhibitor of NaV1.8

- Preclinical Development
  - In-Vitro pharmacologic studies
  - Potency and Selectivity metrics (peak current change)
- Clinical Development
  - Pharmacodynamics
  - Pharmacokinetics



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Selective Inhibition of $Na_v1.8$ with VX-548 for Acute Pain

J. Jones, D.J. Correll, S.M. Lechner, I. Jazic, X. Miao, D. Shaw, C. Simard, J.D. Osteen, B. Hare, A. Beaton, T. Bertoch, A. Buvanendran, A.S. Habib, L.J. Pizzi, R.A. Pollak, S.G. Weiner, C. Bozic, P. Negulescu, and P.F. White, for the VX21-548-101 and VX21-548-102 Trial Groups*

## End Points

- Efficacy Endpoint:
  - Time-Weighted sum of the pain-intensity difference (SPID48)
  - Pain Scores obtained at 19 time points within 48 hours
- SPID at 24 hrs
- Pain Percentage reduction after Loading dose
- Comparisons between VX-548, Hydrocodone, and Placebo

## Statistical Analysis

- analysis of covariance was used for SPID48 values
- Missing data imputations

# Enrollment Characteristics

**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.

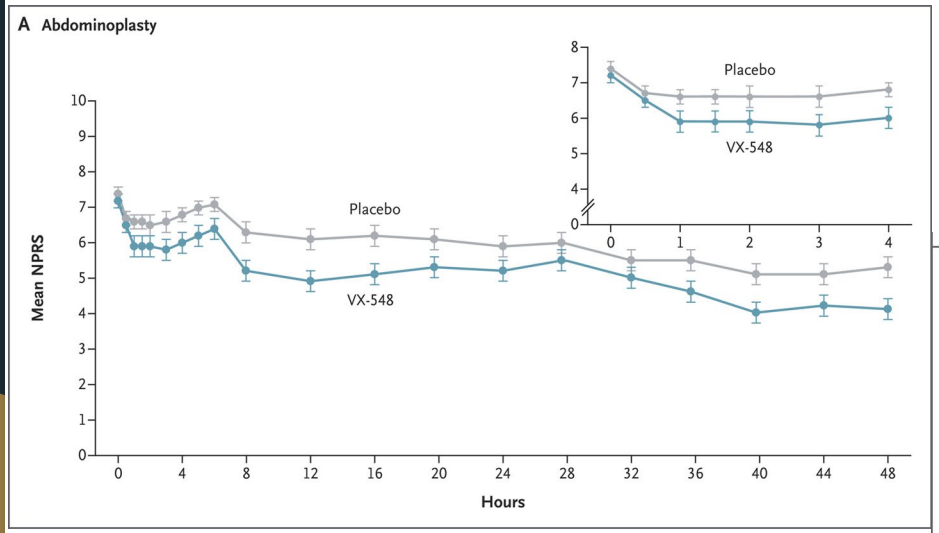
† Race and ethnic group were reported by the participants. The "other" category includes all other reported races and ethnic groups (see Table S2 in the Supplementary Appendix).

‡ 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.

# Efficacy


A Abdominoplasty
Mean NPRS
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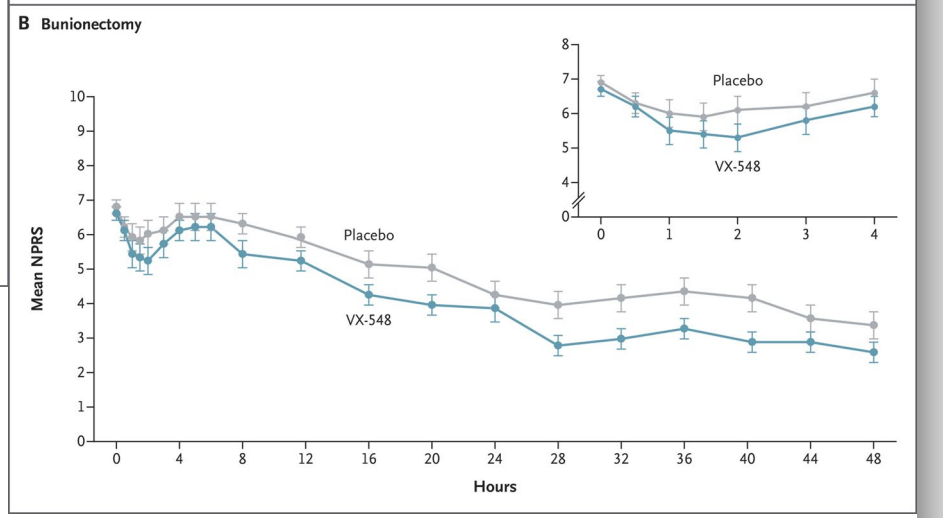
B Bunionectomy
Mean NPRS
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0
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**Table 2. Primary and Secondary Efficacy End Points.***

| 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.

# Safety and Adverse Events

- Mild to moderate events reported:
  - Abdominoplasty trial: nausea, headache, constipation, dizziness, and vomiting
  - Bunionectomy trial: nausea, headache
- Incidence of most adverse events was similar or lower in the VX-548 groups compared to the placebo groups in the abdominoplasty trial, except for headache and constipation.
- Three serious adverse events reported (incisional cellulitis, sepsis, etc.) though site investigators determined it unrelated to VX-548
- No significant safety findings were reported in laboratory assessments, vital signs, ECGs, or physical examinations in either trial

# Conclusions and Future

- VX-548, as a potent and selective inhibitor of NaV1.8 in peripheral nociceptive neurons
  - Demonstrated effectiveness in reducing acute postoperative pain over a 48-hour period in high-dose treatment, as observed in the abdominoplasty and bunionectomy trials
  - Low doses of VX-548 were not significant compared to placebo
- Favorable Safety Profile
  - Adverse events such as headache and constipation were more commonly associated with VX-548 treatment than with placebo
  - No direct comparison between Hydrocodone (foreshadowing to Phase 3!)
- Trial is limited by female predominance and the lack of a consensus on a minimally clinically meaningful effect size
- Phase 3 trial underway

# References:


1. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology. 2012 Feb;116(2):248-73. doi: 10.1097/ALN.0b013e31823c1030. PMID: 22227789.

2. Jones J, Correll DJ, Lechner SM, Jazic I, Miao X, Shaw D, Simard C, Osteen JD, Hare B, Beaton A, Bertoch T, Buvanendran A, Habib AS, Pizzi LJ, Pollak RA, Weiner SG, Bozic C, Negulescu P, White PF; VX21-548-101 and VX21-548-102 Trial Groups. Selective Inhibition of $Na_V1.8$ with VX-548 for Acute Pain. N Engl J Med. 2023 Aug 3;389(5):393-405. doi: 10.1056/NEJMoa2209870. PMID: 37530822.

3. Supplementary Index: : Jones J, Correll DJ, Lechner SM, et al. Selective inhibition of NaV 1.8 with VX-548 for acute pain. N Engl J Med 2023;389:393-405. DOI: 10.1056/NEJMoa2209870