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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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