

PHASE 3 CLINICAL
DEVELOPMENT OF VERTEX
VX-548 (NA_v1.8 INHIBITOR)

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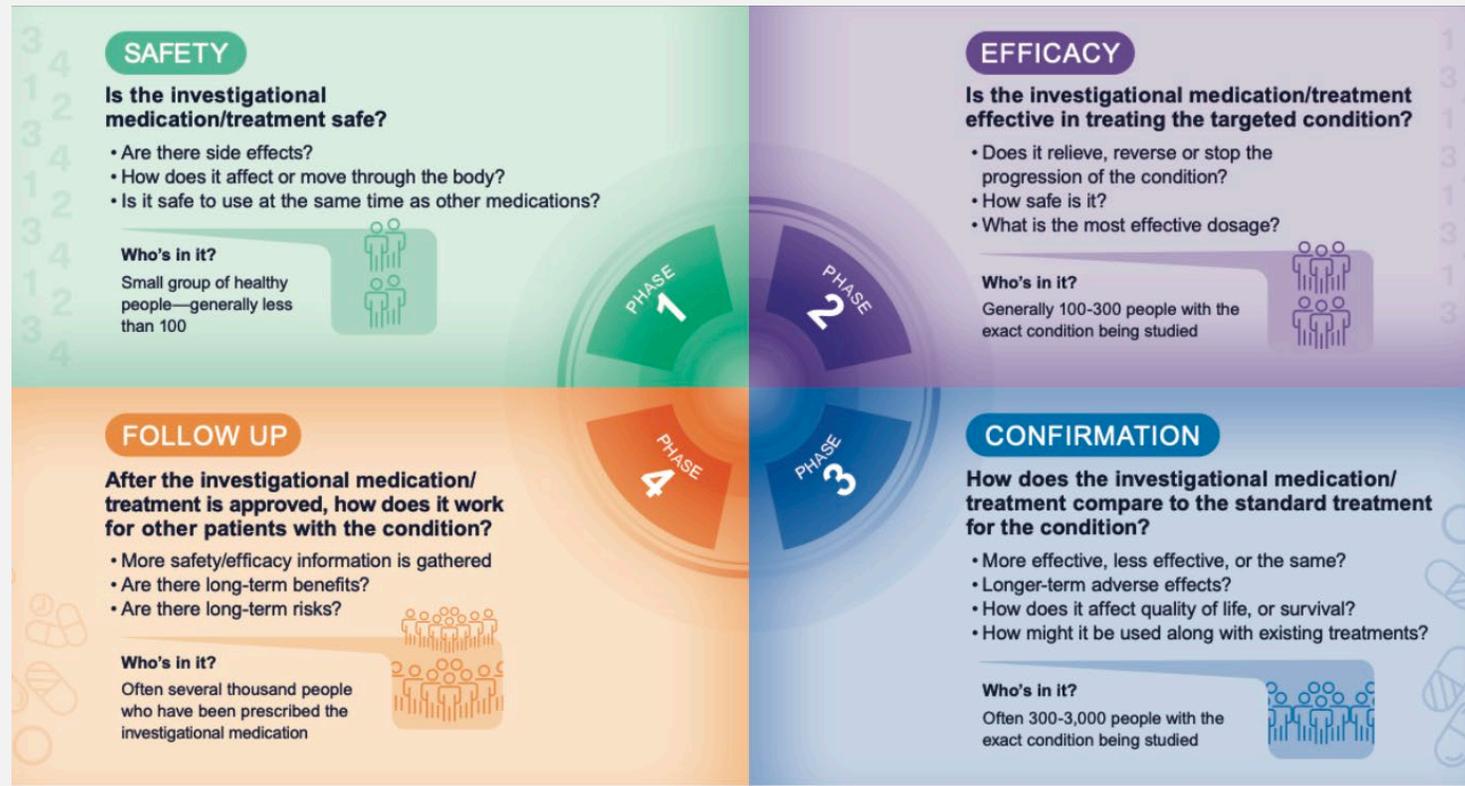
BACKGROUND

- $\text{Na}_v1.7$ and $\text{Na}_v1.8$ are sodium ion channel isoforms with known involvement in the development of pathologic inflammatory and neuropathic pain signals in the peripheral nervous system
- $\text{Na}_v1.8$ has a role in the pathophysiology of acute neuropathic pain and the development of hyperalgesia and allodynia - manifestations of chronic neuropathic pain
- Therapeutic efficacy of $\text{Na}_v1.8$ inhibitors in mice models have been shown
- VX-548 is an oral pain medication being developed by Vertex that is a **highly selective inhibitor for the $\text{Na}_v1.8$ channel**

OVERVIEW OF CLINICAL TRIALS

- 2022: Phase 2 study evaluating VX-548 in subjects with acute pain after bunionectomy completed
- 2022: Phase 2 study evaluating VX-548 in subjects with acute pain after abdominoplasty completed
- 2022: Phase 3 study evaluating VX-548 in subjects with acute pain after bunionectomy initiated
- 2022: Phase 2 study evaluating VX-548 in subjects with acute pain after abdominoplasty initiated

OVERVIEW OF CLINICAL TRIALS



CLINICAL TRIALS

- The Phase 2 Trials
 - Randomized, double-blind, placebo-controlled
 - Evaluating the efficacy and safety of this medication
 - Experimental Arms
 - *Experimental arm – randomized to receive different VX-548 dosing levels*
 - *Active Comparison arm – hydrocodone bitartrate/acetaminophen given*
 - *Placebo arm – matched to both the above arms respectively*

CLINICAL TRIALS

VX-548 – acute pain after bunionectomy – phase 2 trial (N= 274)

- Inclusion Criteria
 - Scheduled to undergo a primary unilateral bunionectomy with distal metatarsal osteotomy [*prior to surgery*]
 - Participant is lucid/can follow commands; all analgesic guidelines followed during and after surgery [*after surgery*]
- Exclusion Criteria
 - Prior history of bunionectomy/foot surgery on same foot; any prior surgery within 1 month of study [*prior to surgery*]
 - Hx of cardiac dysrhythmia(s) requiring anti-arrhythmia treatment [*prior to surgery*]
 - Had type 3 deformity requiring a base wedge osteotomy or concomitant surgery such as hammertoe repair, or had medical complication during surgery [*after surgery*]



CLINICAL TRIALS

VX-548 – acute pain after bunionectomy – phase 2 trial (N= 274)

- Primary Outcome
 - Time-weighted Sum of Pain Intensity Difference (SPID) as recorded on a Numeric Pain Rating Scale (NPRS) – 0-48 hours after first dose of study drug
- Secondary Outcomes
 - Time-weighted SPID as recorded on an NPRS – 0-24 hours after first dose of study drug
 - Proportions of participants with $\geq 30\%$, $\geq 50\%$, and $\geq 70\%$ reduction in NPRS at 48 Hours after the first dose
 - Maximum observed plasma concentration of VX-548
 - Time to reach maximum observed plasma concentration (T_{max}) of VX-548
 - AUC as a function of time
 - Safety and tolerability – number of participants with adverse events and serious adverse events

CLINICAL TRIALS

VX-548 – acute pain after abdominoplasty – phase 2 trial (N= 303)

- Inclusion Criteria

- Scheduled to undergo a abdominoplasty without collateral procedures [*prior to surgery*]
- Participant is lucid/can follow commands; all analgesic guidelines followed during and after surgery [*after surgery*]
- Abdominoplasty duration ≤ 3 hours without collateral procedures [*after surgery*]

- Exclusion Criteria

- Prior history of abdominoplasty/intra-abdominal/pelvic surgery; any prior surgery within 1 month of study [*prior to surgery*]
- Hx of cardiac dysrhythmia(s) requiring anti-arrythmia treatment [*prior to surgery*]
- Collateral procedure during abdominoplasty or had medical complication during surgery [*after surgery*]



CLINICAL TRIALS

VX-548 – acute pain after abdominoplasty – phase 2 trial (N= 303)

- Primary Outcome
 - Time-weighted SPID as recorded on an NPRS – 0-48 hours after first dose of study drug
- Secondary Outcomes
 - Time-weighted SPID as recorded on an NPRS – 0-24 hours after first dose of study drug
 - Proportions of participants with $\geq 30\%$, $\geq 50\%$, and $\geq 70\%$ reduction in NPRS at 48 Hours after the first dose
 - Safety and tolerability – number of participants with adverse events and serious adverse events

CLINICAL TRIALS

- The Phase 3 Trials
 - Estimated enrollment of 1000 participants in each; projected end date of March 2024
 - Randomized, double-blind, placebo-controlled
 - Experimental Arms
 - *Experimental arm – randomized to receive different VX-548 dosing levels*
 - *Active Comparison arm – hydrocodone bitartrate/acetaminophen given*
 - *Placebo arm – matched to both the above arms respectively*
 - The Phase 3 Trials – Both have same outcome measures
 - The Phase 3 Trials – the inclusion/exclusion criteria are the same as in the phase 2 trials

CLINICAL TRIALS

- Primary Outcomes
 - Time-weighted SPID as recorded on an NPRS – 0-48 hours compared to placebo
- Secondary Outcomes
 - Time-weighted SPID as recorded on an NPRS – 0-48 hours compared to hydrocodone bitartrate/acetaminophen
 - Time to greater than or equal to 2-point reduction on NPRS from baseline compared to placebo [0-48 h]
 - Time to greater than or equal to 1-point reduction on NPRS from baseline compared to placebo [0-48 h]
 - Proportion of participants reporting good or excellent on the Patient Global Assessment (PGA) compared to placebo [at 48h]
 - Incidence of Vomiting or Nausea Compared to hydrocodone bitartrate/acetaminophen [0 to day 17]
 - Time-weighted SPID as recorded on an NPRS – 0-24 hours compared to placebo
 - Time to first use of rescue medication compared to placebo [0-48 h]
 - Proportion of participants using rescue medication compared to placebo [0-48 h]
 - Total rescue medication usage compared to placebo [0-48 h]
 - Safety and tolerability – number of participants with adverse events and serious adverse events [0 to day 17]

REFERENCES

- Hameed S. Na_v1.7 and Na_v1.8: Role in the pathophysiology of pain. *Mol Pain*. 2019;15:1744806919858801. doi:10.1177/1744806919858801
- NIH: U.S. National Library of Medicine: ClinicalTrials.gov
 - NCT04977336, NCT05034952, NCT05553366, NCT05558410