Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Suzetrigine (Nav1.8 Inhibitors)

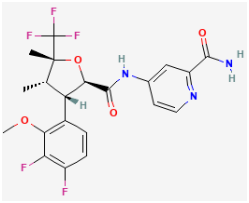
Evidence Summary

Inhibition of Nav1.8 can attenuate peripheral nerve pain. Suzetrigine has good short-term safety and efficacy, but the long-term durability of analgesic responses remains to be determined.

Neuroprotective Benefit: Nav1.8 is not meaningfully expressed in the human brain under physiological conditions, thus Nav1.8 inhibitors are not expected to have any direct effects on cognition or neuropathology in the CNS.

Aging and related health concerns: Suzetrigine attenuates acute pain. Nav1.8 inhibitors may also modestly mitigate some types of chronic pain, such as neuropathy, but large validation clinical trials are needed.

Safety: Suzetrigine is safe and well-tolerated with short term use, with headache and gastrointestinal events as the primary adverse events. It shows a superior safety profile to opioids, but long-term safety profile has not yet been established.

Availability: Rx (other Nav1.8 inhibitors are in development)	**Dose**: The recommended starting dose is 100 mg orally on an empty stomach (at least 1 hour before or 2 hours after food). Then, 50 mg every 12 hours, as needed.	**Chemical formula:** $C_{21}H_{20}F_5N_3O_4$ **MW**: 473.4 g/mol  Source: PubChem
Half-life: 23.6 hours	**BBB**: Nav1.8 is not appreciably expressed in the CNS	
Clinical trials: Suzetrigine has been tested in two Phase 3 RCTs for acute pain (n=1,118; n= 1,073), as well as Phase 2 trials for more chronic pain, including diabetic neuropathy (n=192) and sciatica (n=218). A Phase 3 trial for diabetic neuropathy is ongoing (~n=1,100).	**Observational studies**: Gain of function mutations in *SCN10A* are associated with small fiber neuropathy.	

What is it?

Suzetrigine (VX-548) is the first FDA-approved selective Nav1.8 inhibitor for the treatment of moderate to severe acute pain in adults. This first-in-class drug is a non-opioid analgesic. It was approved by the FDA on January 30, 2025, and is marketed under the tradename Journavx™ by Vertex Pharmaceuticals.

Nav1.8, encoded by the gene *SCN10A*, belongs to the class of tetrodotoxin (TTX)-sensitive voltage-gated sodium channels, and is involved in rapid neuronal transmission, including the propagation of action potentials [1]. This class of channels is blocked by traditional anesthetics, however, these agents are not selective, and their affinity is voltage dependent, such that they bind best to the active/open channel state following neuronal activity (depolarization) [2]. Nav1.7, Nav1.8, and Nav1.9 have been found to be primarily expressed in peripheral sensory neurons, the dorsal root ganglia (DRG), and play a role in the transmission of peripheral pain signals [3]. These channels preferentially contribute to different phases of the sodium current, and Nav1.8 appears to contribute predominantly to the action potential upstroke in the context of repetitive firing, and thus may play an outsized role in transmitting pain signals. Due to their peripheral expression pattern, selectively targeting these channels is expected to avoid central effects or adverse effects in other organ systems, such as the key role of Nav1.5 channels in the heart [2]. Consequently, the safety of Nav inhibitors is likely an extension of their selectivity and specificity profiles. The role of these channels in pain transmission was first discovered through the identification

of individuals with mutations in Nav1.7 showing either heightened or lowered sensitivity to pain signals [4], thus the first selective inhibitors were developed targeting Nav1.7. The early clinical failures of these drugs and increasing evidence for the role of Nav1.8 in pain led to the development of drugs targeting this subtype [5]. Early clinical programs highlight the difficulty in developing drugs that selectively target a particular Nav subtype with high affinity, resulting in the discontinuation of numerous clinical candidates due to narrow therapeutic windows and suboptimal efficacy.

Suzetrigine is the first selective Nav1.8 inhibitor to show benefit relative to placebo in Phase 3 trials, leading to its approval for acute pain. There are trials ongoing to determine whether it is also a viable analgesic for the treatment of chronic pain conditions, particularly neuropathic pain. Stemming from the approval of suzetrigine, Vertex and many other companies are developing next generation Nav1.8 inhibitors.

Neuroprotective Benefit: Nav1.8 is not meaningfully expressed in the human brain under physiological conditions, thus Nav1.8 inhibitors are not expected to have any direct effects on cognition or neuropathology in the CNS.

Types of evidence:

- No clinical or preclinical studies related to cognition

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

Suzetrigine is not expected to have any direct effects on cognition. The theoretical benefit of suzetrigine stems from the avoidance of cases of opioid-related cognitive impairment, as some studies have found an association between long-term opioid use and increased dementia risk [6].

Human research to suggest benefits to patients with dementia:

Suzetrigine has not yet been tested in dementia patients. It is not expected to impact disease course. It may, however, be useful as a non-opioid analgesic alternative in this population. Some studies have found opioid use to be associated with an increased risk for death in dementia patients [7; 8].

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Evidence to date suggests that Nav1.8 channels are not meaningfully expressed in the human brain [2], thus Nav1.8 inhibitors are not expected to modulate sodium currents in the brain or have any direct neuroprotective effects in the CNS.

APOE4 interactions: Not established

Aging and related health concerns: Suzetrigine attenuates acute pain. Nav1.8 inhibitors may also modestly mitigate some types of chronic pain, such as neuropathy, but large validation clinical trials are needed.

Types of evidence:

- 2 Phase 2 RCTs of suzetrigine in post-surgical acute pain
- 2 Phase 3 RCTs of suzetrigine in post-surgical acute pain
- 1 Phase 3 open-label trial of suzetrigine for acute pain
- 1 Phase 2 trial of suzetrigine for painful diabetic neuropathy
- 1 Phase 2 trial of suzetrigine for painful lumbosacral radiculopathy
- Several case reports linking mutations in Nav1.8 with altered pain
- Numerous laboratory studies

Acute pain: MODEST BENEFIT

Suzetrigine was approved for the treatment of moderate to severe acute pain based on its performance in attenuating acute post-surgical pain in two Phase 3 randomized, double-blind, placebo- and active-controlled trials [3].

The trials included participants with moderate to severe acute pain on the verbal categorical rating scale and ≥4 on the numeric pain rating scale (NPRS) following abdominoplasty (n=1,118) (NCT05558410) or bunionectomy (n=1,073) (NCT05553366) [9]. NPRS is an 11-point scale from 0 (no pain) to 10 (worst pain). Due to the sex bias in those who choose to undergo these elective surgeries, the participants were overwhelming female (98% in the abdominoplasty trial and 85% in the bunionectomy trial). Participants were randomized to receive suzetrigine (at a starting dose of 100 mg, followed by 50 mg every 12 hours), an active comparator of hydrocodone bitartrate/acetaminophen (HB/APAP; 5 mg /325 mg every 6 hours), or placebo for 48 hours. Participants were also able to receive ibuprofen (400 mg orally every 6

hours, as needed) as a rescue medication for pain relief upon request starting any time after the first dose of study drug. The majority of participants in the suzetrigine (81% and 85.4%) and placebo (87.9% and 85.6%) arms utilized rescue medication in the abdominoplasty and bunionectomy trials, respectively, while the use of rescue medication in the active comparator HB/APAP arm was not reported.

The primary endpoint was the time-weighted sum of the pain intensity difference in NPRS from 0 to 48 hours (SPID48) compared to placebo, in participants using rescue medication (higher scores indicate better relative pain relief). Both trials achieved this primary endpoint with suzetrigine exhibiting a least squares mean difference in SPID48 of 48.4 (95% Confidence Interval [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, relative to placebo. These results were consistent with those of the Phase 2 trials testing suzetrigine with the same dosing scheme, such that the time-weighted SPID48 was 37.8 (95% CI 9.2 to 66.4) after abdominoplasty and 36.8 (95% CI 4.6 to 69.0) after bunionectomy, while lower doses of suzetrigine did not exhibit significant pain relief relative to placebo [10].

The Phase 3 trials also achieved a secondary endpoint of time to ≥2-point reduction in NPRS from baseline for suzetrigine compared to placebo, indicative of faster pain relief [9]. The median times were 119 minutes and 240 minutes with suzetrigine in the abdominoplasty and bunionectomy trials, respectively, compared to 480 minutes with placebo.

However, suzetrigine did not achieve a key secondary endpoint of SPID48 compared to HB/APAP. In the abdominoplasty trial, there were no significant differences in SPID48 between the active treatment arms, but in the bunionectomy trial, HB/APAP outperformed suzetrigine (least squares mean difference -20.2, 95% CI -32.7 to -7.7; P= 0.0016). Differences in the time to NPRS reduction between the active comparators were not reported.

The degree of difference on SPID48 that would be considered clinically important has not yet been established, thus the clinical relevance of suzetrigine's performance on this measure is unclear [11]. A reduction in pain of 30% is generally considered clinically meaningful. At all measured timepoints (12, 24, and 48 hours), a greater percentage of patients achieved this threshold with suzetrigine (with or without rescue medication) relative to placebo, in both trials. At 48 hours, the percentage of patients achieving this threshold was 65.3% for suzetrigine vs 45.7% for placebo and 70.9% vs 58.8% for the abdominoplasty and bunionectomy trials, respectively. The levels achieved with suzetrigine were comparable to those of HB/APAP in the two trials (61.8% and 70.9%, respectively).

A single-arm Phase 3 trial (NCT05661734) in adults with moderate to severe acute surgical or non-surgical pain (n=256; 67.6% female) assessed the safety and efficacy of suzetrigine, based on the 5-point Likert scale, in an outpatient setting [12]. Participants were treated with an initial dose of 100 mg,

followed by 50 mg every 12 hours as needed for up to 14 days, along with rescue medication (acetaminophen 650 mg and ibuprofen 400 mg, every 6 hours, as needed). The majority of participants used rescue medication (73%), and had a favorable rating of suzetrigine for pain management of Excellent (27.3%), Very good (35.9%,) or Good (19.9%).

Caveats and considerations: It is notoriously difficult to conduct trials for pain treatments due to the well-established placebo effect for this indication. Other trials testing Nav1.8 inhibitors, including a related, but lower potency drug, VX-150, have failed to demonstrate meaningful efficacy within the desired therapeutic range [5]. Suzetrigine is the best tested Nav1.8 inhibitor to date in terms of safety and efficacy, however, next generation Nav1.8 (and multi Nav channel inhibitors) currently in development may be more efficacious. The general clinical utility of suzetrigine for acute surgical and non-surgical pain remains to be established [13]. The trials analyzed pain up to 48 hours, which may be too short for meaningful pain resolution for other pain-inducing events. The chosen surgical interventions, abdominoplasty and bunionectomy, may not be generalizable to more invasive surgical inventions with longer recovery periods, such as joint or back surgery [13]. The high use of rescue medication also complicates the interpretation of the degree of pain relief afforded by suzetrigine [11; 13]. The assertion that suzetrigine offers similar pain relief to an opioid, in this case hydrocodone, as part of the HB/APAP combination needs to be understood in context and taken with caution. The dose of HB/APAP used for comparison was on the lower side for what is typically used in post-operative pain [13]. A comparison with higher potency opioids is also lacking. Cost effectiveness analyses regarding the potential utility of suzetrigine center around the assumption that use of suzetrigine will avoid the need for opioid-based pain medications, and thus eliminate future prospective cases of opioid abuse [11]. The validity of this assumption remains unclear until further real-world testing is conducted. It is unclear how many types of pain patients would achieve meaningful pain relief from the use of suzetrigine (and non-opioid rescue medication) alone, and its impact on clinical practice.
Several preclinical studies provide evidence regarding factors that may limit the overall clinical utility of suzetrigine, and potentially other Nav1.8 inhibitors.

Issue of reverse use dependence: Many Nav1.8 inhibitors demonstrate a property *in vitro* referred to as 'reverse use dependence', which means that the drug becomes less effective at higher channel activity [14]. This class of Nav channels experience a closed state, an open active state, as well as an inactivated state following recent activity, associated with the 'refractory period' in action potential firing. The binding of most tested Nav1.8 inhibitors, including suzetrigine, is state dependent. Suzetrigine binds to and stabilizes the closed state of the channel, however, this interaction is disrupted in the inactivated

state of the channel [2]. Therefore, suzetrigine works well to inhibit low-level tonic activity, but with repeated bouts of depolarization, its ability to inhibit the channel wanes. Some studies suggest that this could occur under physiologically relevant conditions, and may limit the ability of these inhibitors to dampen pain signals [15], though this is also impacted by the re-inhibition kinetics [16]. Some groups are working on developing Nav inhibitors that do not exhibit reverse use dependence.

Channel degeneracy: There are several Nav channels implicated in peripheral pain signaling, particularly Nav1.3, Nav1.7, Nav1.8, and Nav1.9 [17]. The contribution of each of the channels to a given pain signal may depend on the overall channel expression profile. As a result, selectively blocking one channel will reduce nociceptor excitability only if there is weak/minimal expression of the other Nav subtypes [17]. The different subtypes contribute preferentially, but not exclusively, to different phases of the action potential. Additionally, context may differentially tune the Nav subtypes. For example, inflammation appears to shift towards Nav1.7 dominance, suggesting that Nav1.7 inhibitors may be best suited for inflammatory pain [17]. In mice, a double knockout of both Nav1.8 and Nav1.9 affected the shape, but not the firing frequency of nociceptors [18]. The loss of these channels increased the threshold for noxious mechanical stimuli, but did not impact the thresholds for heat, cold, or formalin-induced responses. These studies highlight how compensatory responses may play a role in limiting the efficacy of subtype specific Nav inhibitors.

Neuropathic pain: POTENTIAL/UNCLEAR BENEFIT
Gain of function mutations in Nav1.7 and Nav1.8 have been associated with painful neuropathy, primarily small-fiber neuropathy [19]. The relevant variants increase the excitability of peripheral DRG neurons.
Early studies targeted Nav1.7, however, these compounds failed to show clinical efficacy, such as the PF-05089771, which failed in a trial for diabetic peripheral neuropathy [20]. The early attempts at Nav1.8 inhibitors also failed at early clinical stages. The key question is whether these inhibitors can maintain efficacy with long-term use to manage chronic pain. Potent recent inhibitors should allow for this question to be addressed. There is some evidence to suggest that pain reduction can be maintained for several weeks, though there may be a plateauing effect.
To date, the clinical evidence supporting a potential benefit for suzetrigine and other Nav1.8 inhibitors in neuropathic pain is less robust than for acute pain. Due to channel degeneracy and compensatory effects, it may be necessary to target multiple Nav channels to achieve meaningful pain reduction for more chronic pain.

In a Phase 2 dose ranging trial in 192 patients with bilateral lower limb diabetic peripheral neuropathy occurring for at least one year, suzetrigine was tested at 69 mg, 46 mg, or 23 mg per day for 12 weeks (NCT05660538). The study included an active comparator reference arm testing pregabalin at a dose of 100 mg three times daily (t.i.d.), which is currently used as a first line treatment for painful diabetic neuropathy, but did not have a placebo control arm. Based on topline results, the trial met its primary endpoint of change from baseline in the weekly average of daily pain intensity on NPRS at week 12, with changes of -2.26 (95% CI -2.94 to -1.41), -2.11 (95% CI -2.67 to -1.55) and -2.18 (95% CI -2.82 to -1.70) for the high, mid, and low doses, respectively (Press release). The degree of reduction was comparable to gabapentin (-2.09, 95% CI -2.65 to -1.52).

Based on the results of this study, Vertex announced that it will test suzetrigine (70 mg/day) in two 12-week Phase 3 randomized, double-blind, placebo-controlled trials in approximately 1,100 patients per trial with diabetic peripheral neuropathy (Press release). The primary outcome will be change from baseline in weekly average of daily pain intensity on the NPRS at week 12 compared to placebo, with a key secondary endpoint of change from baseline in the weekly average of daily pain intensity on the NPRS at week 12 compared to pregabalin. One of these Phase 3 trials is currently in the recruiting stage (NCT06628908).

A Phase 2 trial in 218 patients with painful lumbosacral radiculopathy (i.e. sciatica) (NCT06176196) met its primary endpoint of within-group change from baseline in the weekly average of daily leg pain intensity on the NPRS at week 12, however, the degree of pain reduction was similar for suzetrigine (-2.02, 95% CI -2.40 to -1.64) and placebo (-1.98, 95% CI -2.36 to -1.60) (Press release). Efficacy data was based on 102 participants treated with 69 mg suzetrigine and 100 participants treated with placebo for 12 weeks.

Safety: Suzetrigine is safe and well-tolerated with short term use, with headache and gastrointestinal events as the primary adverse events. It shows a superior safety profile to opioids, but long-term safety profile has not yet been established.

Types of evidence:

- 2 reviews of history of trials for Nav1.8 (and Nav1.7) inhibitors
- 2 Phase 2 RCTs of suzetrigine in post-surgical acute pain
- 2 Phase 3 RCTs of suzetrigine in post-surgical acute pain
- 1 Phase 3 open-label trial of suzetrigine for acute pain
- 1 Phase 2 trial of suzetrigine for painful diabetic neuropathy

- 1 Phase 2 trial of suzetrigine for painful lumbosacral radiculopathy
- Numerous laboratory studies

Suzetrigine has been generally well-tolerated in clinical trials, though to date, the trials have been relatively short in duration [2]. In the Phase 3 trials testing suzetrigine for acute pain (48 hours), adverse event rates were generally balanced between suzetrigine and placebo arms, and lower in suzetrigine arms, relative to HB/APAP [9]. Adverse events were generally mild to moderate severity, and there were no study drug-related serious adverse events. The most common adverse events were nausea, constipation, headache, and dizziness, with event rates similar between suzetrigine and placebo groups. Suzetrigine was associated with a lower incidence of nausea and vomiting relative to HB/APAP (20.3% vs 33.5% and 9.2% vs 16.5%) for the abdominoplasty and bunionectomy trials, respectively. Headache and constipation were the most common adverse events associated with suzetrigine in the Phase 2 trials for post-surgical acute pain [10]. In an open-label Phase 3 trial assessing suzetrigine for pain in an outpatient setting for up to 14 days (n=256), suzetrigine was associated with a similar set of adverse events, with headache (7%) as the most common [12].

In a dose ranging Phase 2 trial in diabetic neuropathy (n=192), treatment with suzetrigine (23, 46, or 68 mg/day) for 12 weeks, there were no serious adverse events related to suzetrigine (Press release). The most common adverse event with suzetrigine was a decrease in creatinine clearance (5.1%), while other adverse events were more common with the comparator pregabalin, including dizziness (0.7% vs 9.3%), peripheral edema (0.7% vs 5.6%) and weight increase (0% vs 7.4%).

In a Phase 2 trial in patients with painful lumbosacral radiculopathy (n=218), adverse events were primarily mild or moderate severity, with a lower overall adverse event rate with suzetrigine (22.9%), relative to placebo (32.4%) (Press release).

The trials to date have all been relatively short in duration, thus long-term safety has not been established. It is unclear whether patients will develop a tolerance to the drug over time which may necessitate higher doses and the potential emergence of new safety signals.

The FDA prescribing label for suzetrigine indicates that the most common adverse events associated with suzetrigine in clinical trials were pruritis, muscle spasms, increased creatine phosphokinase, and rash.

There is a warning for patients with moderate to severe hepatic impairment. Its use is not recommended in patients with severe hepatic impairment (Child-Pugh Class C), while a dose reduction is advised for those with moderate hepatic impairment due to an increased risk of adverse events.

One of the main drivers of suzetrigine's approval relates to its anticipated non-addictive nature. Since Nav1.8 is not expressed in the CNS at appreciable levels, targeting this channel is not expected to have any direct effects on pain tolerance in the CNS that could lead to addiction or dependence. The ability to prescribe suzetrigine instead of opioids for acute pain is projected to decrease the percentage of patients who experience opioid addiction by preventing exposure to prescription opioids in the first place [11]. It remains to be seen the degree to which suzetrigine can substitute for opioids for pain management in clinical care.
Nav1.7 has also been a key target of interest for peripheral pain, though no selective Nav1.7 inhibitors have yet succeeded in later stage clinical testing. Unlike Nav1.8, one of the mechanisms by which Nav1.7 exerts pain relief is through the modulation of the expression of endogenous opioids [17; 20], thus the potential for dependence or interactions with opioids may be a concern, or should at least be monitored, with prospective Nav1.7 inhibitors in the pipeline.

Prior studies testing Nav1.8 inhibitors were hampered by issues with efficacy and/or safety, which may have been related to low potency and selectivity of the compounds, such that high doses needed to achieve target engagement also resulted in off-target effects, while others may have had compound specific issues with pharmacokinetics or tolerability [5]. For example, VX-128 was discontinued due to the emergence of a skin rash with multiple dosing, which is thought to be a compound related, rather than a class related effect [21]. The clinical experience in this class of drugs underscores the challenges associated with developing safe and effective therapeutics for this target. As next generation Nav1.8 inhibitors are developed, it will be important to compare safety profiles and look for the emergence of class/target-related side effects.

Drug interactions: According to Drugs.com, there are 436 drug interactions with suzetrigine, including 84 major interactions. Suzetrigine is an inducer of CYP3A, and consequently has interactions with other CYP3A modulators. The use of suzetrigine with strong CYP3A inhibitors is contraindicated, while a dose reduction is needed for use with moderate CYP3A inhibitors. Use with strong or moderate CYP3A inducers should also be avoided. Dosage modifications may be needed when used with CYP3A substrates. Grapefruit should also be avoided. It is advised that individuals using hormonal contraceptives containing progestins other than levonorgestrel and norethindrone use an additional nonhormonal contraceptive method or an alternative hormonal contraceptive during concomitant use and for 28 days after discontinuation of suzetrigine. (FDA label)

Sources and dosing:

Suzetrigine is FDA approved for the treatment of moderate to severe acute pain in adults. It is marketed under the brand name Journavx™ by Vertex Pharmaceuticals. Suzetrigine is administered orally in the form of 50 mg tablets. To date it is only approved for acute pain, with Phase 3 studies testing up to 14 days of treatment. The recommended starting dose is 100 mg orally on an empty stomach (at least 1 hour before or 2 hours after food), followed by 50 mg every 12 hours, as needed.

Research underway:
There are currently several active clinical trials testing suzetrigine for pain-related conditions.

Acute Postoperative Pain:
A Phase 4 single-arm study evaluating the effectiveness and safety of suzetrigine for acute pain after aesthetic or reconstructive surgeries. Participants will be treated with suzetrigine for up to 14 days. The study has an expected completion date in early 2026 (NCT06887972).

A Phase 4, open-label, single-arm study evaluating the effectiveness and safety of suzetrigine as part of multimodal therapy for acute pain after laparoscopic procedures of the intraperitoneal or retroperitoneal cavities or arthroscopic orthopedic procedures. Participants will be treated with suzetrigine for up to 14 days. The study has an expected completion date in early 2026 (NCT06887959).

Peripheral neuropathy:
A Phase 3, randomized, double-blind, placebo- and active-controlled study of the efficacy and safety of suzetrigine in subjects with pain associated with diabetic peripheral neuropathy (NCT06628908). This 12-week study uses pregabalin as an active comparator and has an expected completion date in mid-2027.

Formulation study:
A Phase 1, open-label, taste assessment study of suzetrigine spray-dried dispersion in healthy adult panelists has an expected completion date in mid-2025 (NCT06834009).

Other Nav1.8 inhibitors in development for pain/neuropathy:

Phase 2:

VX-993 is a Nav1.8 inhibitor in clinical development by Vertex Pharmaceuticals. It has been tested in Phase 1 trials in i.v. and oral formulations. It is currently being tested in an oral formulation in a Phase 2 double-blind, placebo-controlled trial for acute pain after a bunionectomy (NCT06619847), which has an expected completion date in late 2025. HB/APAP (hydrocodone bitartrate/acetaminophen) is used as an active comparator. VX-993 is also being tested as an oral formulation in a Phase 2 randomized, double-blind, active-controlled, and placebo-controlled clinal trial in diabetic peripheral neuropathy (NCT06619860), which has an expected completion date in mid-2026. Pregabalin is used as an active control in this study.

LTG-001 is a Nav1.8 inhibitor in clinical development for acute pain from Latigo Biotherapeutics. It has been tested in a Phase 1 trial in healthy adults (n=72). Topline data from the company indicates that it was rapidly absorbed with dose proportional exposure, with no food effect, and was well tolerated (Press release). In March 2025, LTG-001 was granted Fast Track Designation for the treatment of acute pain (Press release). It is currently being tested in a dose-ranging, placebo-controlled Phase 2 trial for acute pain after surgical removal of impacted third molars (i.e. wisdom teeth) (NCT06774625). Suzetrigine will be used as an active comparator. The study has an expected completion date in late 2025.

Phase 1:

VX-973 is a Nav1.8 inhibitor in clinical development by Vertex Pharmaceuticals. It was recently tested in a Phase 1 dose escalation trial as an oral formulation in healthy volunteers in the UK (NCT05866055), and is currently being tested as an oral formulation in a dose escalation Phase 1 trial in healthy participants in the US (NCT06615570), which has an expected completion date in late 2025.

ANP-230 is a novel sodium channel inhibitor which shows inhibitory activity towards Nav1.7, Nav1.8, and Nav1.9. It was originally called DSP-2230 and developed by Sumitomo Dainippon Pharma, who sponsored Phase 1 trials for this compound in the 2010s. In 2019, AlphaNavi Pharma spun out from Sumitomo Dainippon as a separate business venture, and has licensed DSP-2230 for development in neuropathic pain (Press Release). Preclinical studies indicate that ANP-230 can shift the voltage dependence of activation and decelerate channel gating, leading to a decrease in the sodium current and reduction of hyperexcitability in DRG neurons [22]. These studies also suggest that, in contrast to many other tested inhibitors, this compound may not show state and use dependency. In 2021, an

exploratory Phase 1/2 trial testing the safety, efficacy, and pharmacokinetics of ANP-230 in patients with infantile episodic limb pain (JPRN-jRCT2061200046) was initiated.

LTG-305 is a Nav1.8 inhibitor in clinical development for chronic pain from Latigo Biotherapeutics. It is currently being tested in a Phase 1 trial in healthy volunteers (NCT06554574). Topline results are expected in mid-2025 (Press release).
STC-004 is a Nav1.8 inhibitor in clinical development by SiteOne Therapeutics. It was recently tested in a Phase 1 single and multiple ascending dose trial in healthy volunteers (ACTRN12624000642583). Details have not been disclosed, but according to the trial protocol, STC-004 was administered orally in a fasted state with single doses starting at 5 mg, with a maximum dose of 100 mg. Topline results indicate that STC-004 showed pharmacokinetic data consistent with once-daily oral dosing, with dose proportional exposure and low variability. Pharmacodynamic target engagement on pain was assessed in the multiple dosing cohort using the cold pressor test. STC-004 was associated with statistically significant increases in the pain tolerance threshold on this test. Based on the results from this study, the company is planning for a Phase 2 study later this year (Press release).

HBW-004285 is a Nav1.8 inhibitor in clinical development from Hyperway Pharma (China). It showed analgesic properties in acute and chronic pain models in rats. In a Phase 1 trial in healthy volunteers, capsules of HBW-004285 showed rapid absorption, dose-proportional drug exposure, and were well tolerated. There was also a trend toward analgesia on the pressure pain test. To improve drug bioavailability, the formulation has been switched to tablets, which, pending IND approval, will be used in future Phase 2 trials (Press release).

HRS-2129 is a Nav1.8 inhibitor in clinical development from Shangdong Suncadia Medicine (subsidiary of Jiangsu Hengrui Pharmaceuticals, China). A Phase 1 single ascending dose trial in healthy volunteers was recently completed in early 2025 (NCT06619392). A Phase 1 multiple ascending trial in healthy volunteers is currently ongoing (NCT06742840), which has an expected completion date in 2026. HRS-2129 is also being tested in a Phase 1 trial at low and high doses for postoperative analgesia in orthopedics, which has an expected completion date in mid-2025 (NCT06780267).

Preclinical:
MSD199 is a Nav1.8 inhibitor in development by Merck. It has nanomolar potency towards Nav1.8 (IC_{50} of 4.7 ± 0.8 nM for human recombinant Nav1.8), shows ~2000 fold selectivity over Nav1.4 and no activity toward other Nav subtypes at millimolar concentrations [23]. It has not yet undergone clinical

testing, but has been tested in non-human primates (rhesus monkeys), in which it was found to show dose-dependent reductions in capsaicin-sensitized thermode response count and prevent capsaicin flare propagation.

LTGO-33 is a novel Nav1.8 inhibitor in development from Latigo Biotherapeutics. Preclinical studies indicate that it has nanomolar potency, with 600-fold selectivity for Nav1.8 over other human Nav subtypes [24]. These studies suggest that it shows state independent inhibition, has a novel binding site and stabilizes the deactivated state to prevent channel opening. Inhibition is relieved by membrane depolarization, but rapid re-inhibition prevents use-dependent relief of inhibition under physiological-like conditions *in vitro* [16].

Nav1.7 inhibitor in clinical development for neuropathy:

Halneuron® is a Nav1.7 inhibitor in clinical development for chemotherapy-induced neuropathic pain (CINP) and cancer pain by Dogwood Therapeutics. It has been tested in over 700 patients to date, including a Phase 2a study in CINP (n=125) and a Phase 2 study in cancer pain (n=165) and shown to have an acceptable safety profile (Corporate Presentation). Halneuron is administered via subcutaneous injection. In the Phase 2 cancer pain trial, 51% of participants treated with Halneuron experienced a ≥30% reduction in pain compared with 35% in the placebo group, with responders showing a reduction in pain for an average of 57.7 days, relative to 10.5 days for placebo. Halneuron is currently being tested in a Phase 2b trial for CINP (NCT06848348). The trial has a target enrollment of 200 patients, and an expected completion date in 2026.

Search terms:
Pubmed, Google: Suzetrigine, VX-548, Nav1.8 inhibitors

- Pain, neuropathy, clinical trial, safety

Websites visited for Suzetrigine:

- Clinicaltrials.gov
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma

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