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Suzetrigine: A First-in-Class NaV1.8 Inhibitor – Mechanism and Clinical Trial Evidence for Acute Pain

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Abstract

Pain management remains challenging due to opioid limitations and adverse effects. Suzetrigine is a novel, selective NaV1.8 sodium channel inhibitor developed as a non-opioid alternative for moderate-to-severe acute pain. This narrative review summarizes evidence on its mechanism of action, pharmacokinetics, clinical efficacy, safety profile, and regulatory status. Literature through March 2026 was reviewed from PubMed, Scopus, Google Scholar, and ClinicalTrials.gov. Clinical studies demonstrate Suzetrigine provides significant analgesic efficacy in acute post-operative pain with favorable tolerability. Common adverse effects – nausea, headache, constipation, and pruritus – were generally mild-to-moderate. However, benefit in chronic neuropathic pain appears limited. Suzetrigine received U.S. Food and Drug Administration approval in 2025 as the first oral selective NaV1.8 inhibitor for acute pain management, representing an important advancement in non-opioid analgesic therapy and a potential strategy to reduce opioid dependence.

Keywords: Acute pain, Analgesics, Voltage-gated sodium channels

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Introduction

Pain continues to be one of the most common and difficult clinical issues in the world, severely reducing quality of life and placing a heavy financial burden on society. Pain is estimated to afflict more than 20% of the global population, incurring enormous health and economic consequences.[1] The International Association for the Study of Pain defines pain as:

"An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."

It is regarded as the most fundamental and pervasive human experience. Due to its subjective nature, the interaction of nociceptive, cognitive, emotional, and social components collectively shape the pain sensation.[2]

The earliest known records go all the way back to 3000–8000 B.C., when the Sumerians extracted opium for medicinal purposes from poppy seeds.[3] In the early 1800s, Germany started producing morphine industrially, which led to its widespread availability over-the-counter.

Opioids are still a mainstay for treating moderate-to-severe pain, but their usage is restricted by well-known side effects, such as tolerance, dependency, respiratory depression, and misuse risk, all of which have contributed to the global opioid crisis.[4]

Voltage-gated sodium (NaV) channels play a pivotal role in the initiation and propagation of action potentials in nociceptive neurons. Among the nine known NaV subtypes, NaV1.7, NaV1.8, and NaV1.9 are preferentially expressed in peripheral sensory neurons, with NaV1.8 being critically involved in the transmission of nociceptive signals, particularly under conditions of inflammation and nerve injury Unlike other sodium channel isoforms, NaV1.8 is largely restricted to dorsal root ganglion (DRG) neurons, making it an attractive therapeutic target for selectively modulating pain without affecting cardiac or central nervous system function.[5]

Suzetrigine is a novel, orally active, highly selective NaV1.8 inhibitor also known as VX-548 and commercialized under the brand name JOURNAVX by Vertex Pharmaceuticals in January 2025. It is the first and only U.S. Food and Drug Administration (FDA)-approved non-opioid oral medication designed to be used for the treatment of moderate-to-severe acute pain.[6]

The purpose of this review is to outline Suzetrigine's regulatory status, mechanism of action, clinical pharmacology, and relevant studies.

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Methodology

This structured narrative review synthesizes current evidence on Suzetrigine (VX-548), a selective NaV1.8 inhibitor, focusing on its pharmacology, mechanism, clinical efficacy, safety, and regulatory status. A comprehensive literature search was conducted using PubMed, Scopus, Google Scholar, and ClinicalTrials.gov for studies published up to March 2026. Search terms included "*Suzetrigine,*" "*VX-548,*" "*NaV1.8 inhibitor,*" "*acute pain,*" and "*non-opioid analgesic,*" combined using Boolean operators.

Eligible sources comprised peer-reviewed articles and clinical trials (Phase 1–3) published in English. Editorials, duplicates, and studies lacking methodological clarity were excluded. Data extracted included study design, sample size, patient population, dosing regimens, efficacy endpoints (e.g., Summed Pain Intensity

Difference Over 48 h (SPID48), Numeric Pain Rating Scale (NPRS), Patient Global Assessment [PGA]), and safety outcomes.

Key clinical trial data were obtained from registered studies (NCT05661734, NCT04977336, NCT05034952, NCT06176196). Findings were qualitatively synthesized into thematic domains, with quantitative outcomes summarized descriptively. Emphasis was placed on high-quality evidence, including randomized controlled trials and regulatory reports, with cross-verification where applicable. As this review utilized published data, ethical approval was not required.

Structure

Its molecular formula is $C_{21}H_{20}F_5N_3O_4$, with a molecular weight of 473.4 g/mol. The full International Union of Pure and Applied Chemistry name is 4-[[(2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)oxolane-2-carbonyl]amino]pyridine-2-carboxamide [Figure 1].[7] Key structural features are Central oxolane (tetrahydrofuran) ring with stereochemistry at positions 2R,3S,4S,5R, bearing a trifluoromethyl group at C5 and methyl groups at C4 and C5.3,4-difluoro-2-methoxyphenyl substituent at C3. Pyridine-2-carboxamide linked through an amide to C2 of the oxolane. Fluorine-rich design enhances metabolic stability and binding affinity.

Pharmacokinetics

The selective NaV1.8 inhibitor Suzetrigine, which is authorized for moderate-to-severe acute pain, has good pharmacokinetics that support twice-daily oral dosage.[8] After oral administration, Suzetrigine is quickly absorbed; Its median Tmax is 3 h under fasting conditions and 5 h after food. According to preclinical research, oral bioavailability is approximately 71% at dosages of 2 mg/kg, with peak plasma concentrations being reached in less than an hour. It takes three to five days for suzetrigine and its active metabolite M6-SUZ to achieve steady-state concentrations.[9] The drug's enormous volume of distribution (~495 L) indicates significant tissue penetration, which aligns with its peripheral nociceptor targets. Plasma protein binding is strong (99%), predominantly to albumin.[10] Suzetrigine is largely metabolized in the liver by CYP3A4/5 (and CYP2C11 in preclinical animals), with glucuronidation contributing to the production of M6-SUZ. At therapeutic levels, the effective half-life is around 23.6 h, allowing for BID regimens, while the preclinical half-life is approximately 5.9 h.[8] Oral clearance is around 13.9 L/h, with negligible renal excretion (~1–2% unaltered). In steady state, suzetrigine has an AUC0-24 h of 11.5 µg·h/mL and a Cmax of 0.62 µg/mL, but M6-SUZ has a greater exposure (AUC0-24 h 34.7 µg·h/mL; Cmax 1.5 µg/mL).[11]

Suzetrigine's metabolism poses a danger of drug-drug interactions in clinical settings [Table1]. In particular, Suzetrigine's plasma exposure rises in the presence of potent CYP3A inhibitors and falls in the presence of CYP3A inducers, requiring dose modifications or contraindications.

Furthermore, hepatic impairment alters medication exposure, with AUC increasing by 1.5-fold and Cmax increasing by 1.3-fold in patients with Child-Pugh Class B. This emphasizes the importance of dose changes in patients with Child-Pugh Class B, although Suzetrigine is still contraindicated in individuals with Child-Pugh Class C.[12] There were no significant pharmacokinetic changes based on age, sex, body weight, race, or moderate renal or hepatic impairment.

Mechanism of Action

Pain is thought to be caused by the increased excitability of sensory neurons in the DRG.[13] DRG neurons' excitability is linked to numerous voltage-gated sodium channels (VGSCs).[14]

NaV, NaV 1.1-1.9, NaV 1.7, NaV 1.8, NaV 1.3, which is upregulated in nociceptive neurons after injury. It is hoped that these channel isoforms will make promising targets for the pharmacological treatment of pathological pain states.[16]

NaV1.8, expressed by the *SCN10A* gene, is a subtype of Tetrodotoxin-resistant VGSCs, first found in DRG and hence initially referred to as a sensory neuron-specific channel.[17] In pain pathways, NaV1.8 is essential for the production and transmission of action potentials, especially when there is inflammation or nerve damage.[18]

Suzetrigine is an extremely selective inhibitor of the NaV1.8 channel, with a half-maximal inhibitory concentration of 0.27 nanomoles (nM) and over 30,000-fold preference over other sodium channel subtypes.[19] There was no substantial off-target action across the 180 molecular targets evaluated.[7]

In animal electrophysiological and behavioral experiments, Suzetrigine decreased tetrodotoxin-resistant sodium currents in mouse DRG neurons in a concentration-dependent way while also reducing pain responses in multiple *in vivo* pain models.[20]

Suzetrigine works by binding to a specific motif on the second voltage-sensing domain-2 of NaV1.8, namely the KKGS (Lys-Lys-Gly-Ser) amino acid sequence, which is not conserved in other sodium channels.[8] By keeping the channel tight and blocking sodium inflow, this selective interaction lowers neuronal excitability and lessens the transmission of pain from peripheral tissues to the central nervous system [Figure 2].[17]

Clinical Trial Results

The following Table 2 summarizes the four specified trials based on available data from ClinicalTrials.gov entries. All studies were multi-center in the USA, focusing on Suzetrigine for pain management.

Clinical Efficacy and Safety

Across four clinical trials (Phase 2 and Phase 3), Suzetrigine (VX-548) demonstrated consistent efficacy and an acceptable safety

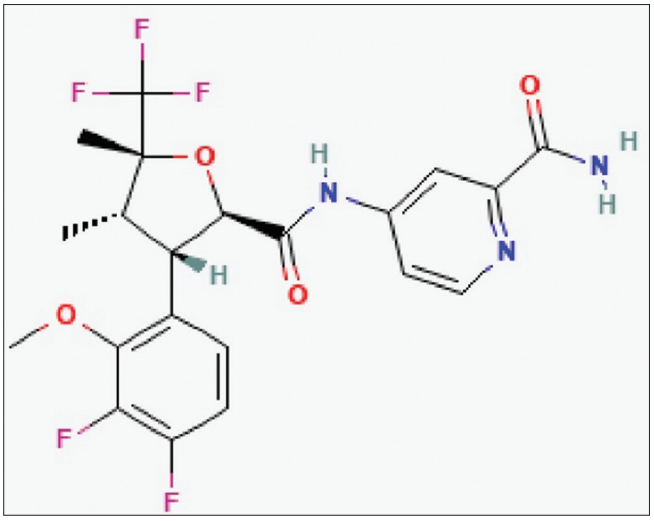

Figure 1: Chemical structure of suzetrigine

profile in the management of acute pain, with comparatively limited benefit in chronic neuropathic pain conditions.

In a Phase 3, single-arm, open-label study (NCT05661734) involving 256 participants, suzetrigine monotherapy (100 mg loading dose followed by 50 mg twice daily for 14 days) achieved a high treatment completion rate of 94.5%. Based on Patient Global Assessment, 83% of participants reported good, very good, or excellent pain relief, with higher efficacy observed in non-surgical pain (91%) compared to surgical pain (82%). Adverse drug reactions (ADRs) were predominantly mild-to-moderate, including gastrointestinal disturbances and headache.[21]

Two Phase 2 randomized, double-blind, placebo-controlled trials (NCT04977336 and NCT05034952), with sample sizes of 274 and 303, respectively, evaluated suzetrigine using the SPID48 endpoint. Both studies demonstrated statistically significant improvements in pain intensity compared to placebo. In NCT04977336, the SPID48 improvement was 36.8 points over placebo ($P < 0.001$), while NCT05034952 reported an improvement of 37.8 points ($P < 0.001$). The safety profile remained favorable, with commonly reported ADRs including nausea, pruritus, constipation, and headache, all of mild-to-moderate severity.[22,23]

In contrast, a Phase 2 randomized, double-blind, placebo-controlled study (NCT06176196) assessing Suzetrigine in 218 patients with lumbosacral radiculopathy over 12 weeks showed minimal clinical benefit. The reduction in NPRS scores was comparable between the treatment and placebo groups (−2.02 vs. −1.98), indicating limited efficacy in chronic neuropathic pain.

Table 1: An overview of the clinically significant interactions between concurrent medicines and suzetrigine

Interacting drug/Class	*Mechanism of interaction*	*Clinical effect*	*Recommendation*
Strong CYP3A inhibitors (Ketoconazole, Itraconazole, Posaconazole, Voriconazole, Clarithromycin, Telithromycin, Ritonavir, Cobicistat, Indinavir, Saquinavir, etc.)	Inhibition of CYP3A-mediated metabolism	Increased suzetrigine plasma concentration → risk of toxicity	Contraindicated
Moderate CYP3A inhibitors (Fluconazole, Erythromycin, Diltiazem, Verapamil, Ciprofloxacin, Aprepitant, etc.)	Reduced metabolism via CYP3A	Increased drug exposure	Dose reduction of suzetrigine required
Grapefruit-containing food/drink	CYP3A inhibition (intestinal)	Increased bioavailability of suzetrigine	Avoid concomitant use
Strong CYP3A inducers (Rifampin/Rifampicin, Carbamazepine, Phenytoin, Phenobarbital, St. John's Wort, etc.)	Increased CYP3A activity	Reduced plasma concentration → decreased efficacy	Avoid concomitant use
Moderate CYP3A inducers (Bosentan, Efavirenz, Modafinil, etc.)	Enhanced metabolism	Reduced therapeutic effect	Avoid concomitant use
CYP3A substrates (sensitive) (Midazolam, Alfentanil, Quinidine, Pimozide, Eplerenone, Tacrolimus, Sirolimus etc)	Competitive metabolism via CYP3A	Altered substrate drug levels → loss of efficacy or toxicity	Adjust dose of substrate; refer to prescribing information
Hormonal contraceptives (non-levonorgestrel/ norethindrone)	Possible enzyme modulation affecting hormone levels	Reduced contraceptive efficacy	Use additional non-hormonal method during and 28 days after therapy

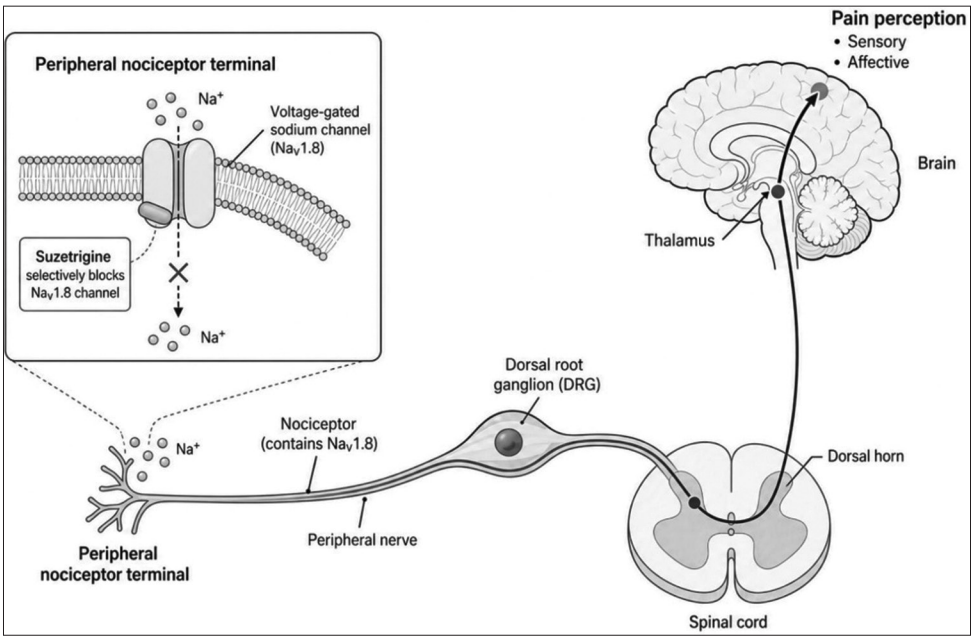

Figure 2: Mechanism of action of suzetrigine

Table 2: Clinical trials of suzetrigine: Efficacy and safety outcomes

Trial name (NCT)	*Study center*	*Study design*	*Sample size*	*Groups*	*Dose*	*Primary outcome*	*ADRs*	*Key findings*
NCT05661734: A single-arm study to evaluate safety and effectiveness of VX-548 for acute pain[21]	Multi-center, USA	Phase 3, single-arm, open-label	256	Suzetrigine monotherapy	100 mg load, 50 mg BID×14 days	Patient global assessment effectiveness	Gastro intestinal upset, headache (mild-moderate); 94.5% completion	83% reported good/very good/excellent relief (82% surgical, 91% non-surgical)
NCT04977336: A study evaluating efficacy and safety of VX-548 for acute pain[22]	Multi-center, USA	Phase 2, randomized, double-blind, placebo-controlled	274	Suzetrigine, placebo	100 mg load, 50 mg BID	SPID48	Nausea, pruritus, constipation (mild- moderate)	SPID48 improvement: 36.8 points versus placebo (P<0.001)
NCT05034952: A study evaluating efficacy and safety of VX-548 for acute pain[23]	Multi-center, USA	Phase 2, randomized, double-blind, placebo-controlled	303	Suzetrigine, placebo	100 mg load, 50 mg BID	SPID48	Nausea, headache (mild- moderate)	SPID48 improvement: 37.8 points versus placebo (P<0.001)
NCT06176196: Evaluation of efficacy and safety of VX-548 for lumbosacral radiculopathy[34]	Multi-center, USA	Phase 2, randomized, double-blind, placebo-controlled	218	Suzetrigine, placebo	50 mg BID×12 weeks	Change in NPRS at week 12	Mild-moderate; similar to placebo	Minimal benefit (−2.02 versus−1.98 placebo); limited for chronic neuropathy

BID: Twice daily, SPID48: Summed pain intensity difference over 48 h, NPRS: Numeric Pain Rating Scale

Adverse events were similar to placebo and primarily mild-to-moderate.[34]

Overall, Suzetrigine demonstrates robust efficacy in acute pain settings with a favorable tolerability profile, but its effectiveness appears limited in chronic neuropathic pain conditions.

Approval of Suzetrigine

Suzetrigine received regulatory approval from the U.S. FDA on January 30, 2025, for the treatment of moderate-to-severe acute pain in adults. This approval represents a significant milestone, as Suzetrigine is the first non-opioid analgesic belonging to a novel therapeutic class to be introduced in more than two decades.[24]

The drug underwent an accelerated regulatory pathway facilitated by multiple special designations granted by the FDA, including breakthrough therapy, fast track, and priority review status. These designations are typically reserved for drugs that demonstrate substantial improvement over existing therapies or address unmet medical needs. In the case of Suzetrigine, these pathways enabled expedited development and review, reflecting its potential to provide effective analgesia while reducing reliance on opioid medications and their associated risks.[24]

The FDA's approval decision was primarily based on robust evidence from two pivotal Phase 2 randomized, double-blind, placebo- and active-controlled clinical trials (NCT04977336 and NCT05034952). These studies evaluated the efficacy and safety of Suzetrigine in patients experiencing acute post-operative pain following surgical procedures such as abdominoplasty and bunionectomy. Both trials demonstrated statistically significant improvements in pain reduction, as measured by the SPID48, compared to placebo, along with a favorable safety and tolerability profile.[25]

Collectively, the streamlined regulatory designations, strong clinical efficacy data, and acceptable safety outcomes supported the FDA's decision to approve suzetrigine as a novel, non-opioid alternative for acute pain management, marking an important advancement in analgesic pharmacotherapy.

Approved Dosage and Recommendation

Suzetrigine is administered as an oral tablet with a fixed dose schedule for the treatment of moderate to severe acute pain in adults.[24] The recommended regimen consists of an initial loading dose of 100 mg taken orally on an empty stomach, at least 1 h before or 2 h after food.[26] This is followed by maintenance doses of 50 mg every 12 h (twice daily) for the 1st several days of treatment. Depending on the clinical situation and the prescribing information, the dose may then be reduced to 50 mg once daily toward the end of the course.[12] The total duration of treatment is generally limited to a maximum of 14 days for acute pain conditions such as post-surgical or injury-related pain.[27] Dose adjustments should be considered in patients with hepatic impairment or those receiving interacting medications, in accordance with the product label and local prescribing guidelines.

Cost

Suzetrigine (brand name Journavx) costs much more than standard opioid analgesics, indicating its status as a first-in-class non-opioid drug. The reported cost is $15.50/50 mg pill, which equates to about $420 for a regular 1-week course of treatment (usually 100 mg once, then 50 mg twice daily for up to 14 days).[28]

The higher initial cost poses a hurdle to wider adoption, especially in settings where opioids remain the norm due to their low cost. Compared to opioids, suzetrigine has a better safety profile, with lower risks of respiratory depression, sedation, constipation, and dependency. From a health economics standpoint, the medicine may be cost-effective by reducing the incidence of opioid use disorder and its related long-term healthcare expenditures.

Current Ongoing Clinical Trial

Following its approval for acute pain, Suzetrigine is being actively investigated to expand its use in chronic and neuropathic pain, particularly painful diabetic peripheral neuropathy (DPN), an area of unmet need in non-opioid analgesia.[9]

A key ongoing Phase 3 randomized, double-blind, placebo- and active-controlled trial (NCT06628908) is evaluating its efficacy and safety in DPN using endpoints such as the NPRS. The drug's selective inhibition of NaV1.8 channels supports its potential to reduce peripheral pain signaling without central adverse effects.[29]

In addition, a Phase 3 open-label extension study (NCT06696443) is assessing long-term safety, tolerability, and sustained efficacy over extended treatment durations, providing important data for chronic use.[30]

These studies are critical given earlier mixed results in chronic pain, such as limited efficacy observed in lumbosacral radiculopathy.[31] Ongoing trials aim to identify responsive patient populations and define Suzetrigine's role in long-term and multimodal pain management.

Overall, current research reflects a shift toward chronic pain indications and long-term evaluation, with the potential to establish Suzetrigine as a novel non-opioid alternative in pain therapy.

Future Perspectives of Suzetrigine

Suzetrigine represents a major advancement in non-opioid analgesia following its approval by the U.S. FDA in January 2025 for moderate-to-severe acute pain. This milestone highlights a critical shift toward reducing opioid dependence while expanding safer therapeutic alternatives in pain management.[24]

Although approval was supported by strong Phase III evidence in acute post-operative and injury-related pain, the long-term clinical trajectory of suzetrigine will depend on its performance in chronic and neuropathic pain conditions, which are more complex and heterogeneous.[30] Ongoing studies in conditions such as lumbosacral radiculopathy and Diabetic peripheral neuropathy are expected to clarify its broader therapeutic utility.

A major challenge in future development is the high placebo response and variability in chronic pain phenotypes, which complicate clinical trial design and outcome interpretation.[32] This underscores the urgent need for improved translational models, objective biomarkers, and refined patient phenotyping to better identify responders and optimize therapeutic outcomes. Furthermore, the limited efficacy of targeting a single sodium channel highlights the importance of diversifying analgesic targets, including other ion channels, neuroimmune interactions, and central pain modulation pathways.[33]

Ultimately, the clinical impact of Suzetrigine will depend on the outcomes of ongoing trials, the refinement of patient selection strategies based on pain phenotype or biomarkers, and its incorporation into comprehensive pain management frameworks across diverse clinical settings. Continued research into complementary mechanisms and personalized, data-driven approaches will be essential to fully realize its potential in transforming modern pain therapy.

Conclusion

Suzetrigine is a promising first-in-class non-opioid analgesic that specifically inhibits NaV1.8, introducing a new method for treating moderate-to-severe acute pain. Clinical trials show significant analgesic efficacy with mild-to-moderate side effects and acceptable tolerance. However, its efficacy in chronic neuropathic pain is limited, highlighting the need for additional clinical trials. Ongoing research will help to clarify its long-term safety, efficacy in chronic pain, and appropriate function in multimodal analgesia. Overall, suzetrigine represents a significant new strategy to acute pain management and may help to reduce reliance on opioid medications.

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Authors' Contribution

Planning of the Review Article – All of the authors; Literature search – S Shee, RK, PKM, S Singh; Tables – VM, SKS, AK, S Shee; Manuscript preparation - R K, PKM, SS, VM; Manuscript editing and manuscript review – All of the authors.

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