

RESEARCH MONOGRAPH . COMPOUND PROFILE

Halneuron

A pharmaceutical-grade injectable formulation of tetrodotoxin developed by WEX Pharmaceuticals (now Dogwood Therapeutics) as a non-opioid, peripherally restricted analgesic that selectively blocks TTX-sensitive voltage-gated sodium channels on nociceptive neurons, with clinical development focused on chemotherapy-induced neuropathic pain and cancer-related pain.

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ABSTRACT

Halneuron is the proprietary injectable formulation of tetrodotoxin (TTX), a naturally occurring guanidinium alkaloid neurotoxin and potent, reversible blocker of TTX-sensitive voltage-gated sodium channels (VGSCs), developed by WEX Pharmaceuticals Inc. (Vancouver, British Columbia, Canada; now Dogwood Therapeutics Inc., NASDAQ: DWTX) as a non-opioid analgesic for moderate to severe neuropathic and cancer-related pain. The active pharmaceutical ingredient, tetrodotoxin ($C_{11}H_{17}N_3O_8$, molecular weight 319.3 g/mol, CAS 4368-28-9), blocks TTX-sensitive sodium channel subtypes NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.6, and NaV1.7 at low-nanomolar concentrations, with IC_{50} values ranging from approximately 2.3 nM (NaV1.6) to 36 nM (NaV1.7). The NaV1.7 subtype is of particular analgesic relevance: human loss-of-function mutations in SCN9A (the gene encoding NaV1.7) produce congenital insensitivity to pain, establishing the channel as a genetically validated analgesic target. Halneuron is administered by subcutaneous injection and does not cross the blood-brain barrier in pharmacologically significant quantities, conferring a safety profile that is free of the euphoria, sedation, tolerance, addiction, and cognitive impairment associated with opioid and centrally acting analgesics.

The clinical development program has evaluated Halneuron in over 700 subjects across multiple Phase 1, Phase 2, and Phase 2b trials. The pivotal cancer pain trial (Hagen et al. 2017), a multicentre, randomized, double-blind, placebo-controlled study of 165 patients at 19 sites in Canada, Australia, and New Zealand, demonstrated a clinically significant estimated effect size of 16.2%

on the pain endpoint for TTX 30 micrograms subcutaneously twice daily for four days versus placebo, with 51% of TTX-treated patients achieving 30% or greater pain reduction compared to 35% on placebo. An open-label safety and efficacy study (Hagen et al. 2011) in 77 cancer pain patients demonstrated that the analgesic effect persisted for weeks to months following a four-day treatment cycle, a finding that distinguishes TTX from conventional short-acting analgesics and suggests a disease-modifying or neuroplastic component to the mechanism. The Phase 2 dose-finding trial for chemotherapy-induced neuropathic pain (CINP; Bhatt et al. 2021) in 125 patients identified the 30 microgram twice-daily regimen as the optimal dose for further study, with cumulative responder analysis showing significant separation from placebo. The ongoing Phase 2b HALT-CINP trial, conducted at approximately 30 sites in the United States under Dogwood Therapeutics, reported positive interim results in December 2025 from 97 patients, with Halneuron-treated patients demonstrating separation from placebo on pain improvement over four weeks, a dropout rate of approximately 4.4% (substantially below rates observed with approved chronic pain agents), and encouraging safety and tolerability.

Pharmacokinetics following subcutaneous injection are characterized by rapid absorption (time to maximum plasma concentration approximately 1.5 hours), dose-proportional exposure, and an elimination half-life of approximately 4.5 hours, with plasma concentrations falling below the limit of quantification within 24 hours. The compound is not metabolized by cytochrome P450 enzymes and does not produce the pharmacogenomic variability that complicates agents dependent on CYP2D6 or CYP3A4. Safety data from Phase 1 dose-escalation studies in healthy adults (doses of 15 to 45 micrograms

subcutaneously) demonstrate that Halneuron is well tolerated, produces no QT prolongation, and carries no proarrhythmic proclivity. The most common adverse events across clinical trials are perioral paresthesia, oral numbness, headache, dizziness, nausea, and myalgia, all generally mild to moderate and self-limiting.

This monograph reviews the chemistry, natural history, and pharmaceutical development of tetrodotoxin as Halneuron; the molecular pharmacology of TTX-sensitive sodium channel blockade with emphasis on NaV1.7; the human pharmacokinetic record; the preclinical analgesic evidence base in rodent models of neuropathic, inflammatory, and cancer pain; the complete clinical evidence base across cancer pain, chemotherapy-induced neuropathic pain, and ongoing Phase 2b trials; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; adverse-event signal; and a structured comparative assessment of five alternative analgesic candidates for chemotherapy-induced neuropathic pain (duloxetine, pregabalin, vixotrigine, capsaicin 8% patch, and lidocaine 5% patch) against Halneuron on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Proprietary name: Halneuron (registered trademark of WEX Pharmaceuticals Inc., now Dogwood Therapeutics Inc.).

International Nonproprietary Name (active ingredient): Tetrodotoxin.

Development codes: TTX (generic abbreviation used throughout the pharmacology and toxicology literature). The compound is identified in clinical trial registries under the WEX Pharmaceuticals and Dogwood Therapeutics sponsor designations.

Chemical Abstracts Service registry numbers: 4368-28-9 (tetrodotoxin, citrate-free base); 18660-81-6 (tetrodotoxin citrate salt). The citrate-free form is the reference standard for pharmacological assays; the citrate salt is the most common commercial research-grade preparation owing to its superior aqueous solubility.

International Union of Pure and Applied Chemistry name: (4R,4aR,5R,7S,9S,10S,10aR,11S,12S)-2-amino-1,4,4a,5,9,10-hexahydro-12-(hydroxymethyl)-5,9:7,10a-dimethano-10aH-[1,3]dioxocino[6,5-d]pyrimidine-4,7,10,11,12-pentol.

Other synonyms: Araregai toxin, Maculotoxin, Tectin, Tarichatoxin, TTX.

NASDAQ ticker (corporate): DWTX (Dogwood Therapeutics Inc., formed October 2024 from the business combination of Virios Therapeutics Inc. and WEX Pharmaceuticals Inc.).

1.2 Structural class and chemistry

Tetrodotoxin is a guanidinium alkaloid neurotoxin belonging to the broader class of naturally occurring heterocyclic small molecules that interact with voltage-gated ion channels. The molecular backbone is a 2,4-dioxadamantane ring system bearing five hydroxyl groups and a positively charged guanidinium moiety [1]. The guanidinium group is the pharmacophore responsible for sodium channel pore blockade; it mimics the hydrated sodium ion and occludes the selectivity filter of TTX-sensitive voltage-gated sodium channels [2].

Molecular formula: C₁₁H₁₇N₃O₈.

Exact mass: 319.1016 g/mol (monoisotopic).

Molecular weight: 319.27 g/mol.

Physical properties: White to off-white crystalline powder or amorphous solid. Slightly soluble in water at neutral pH; freely soluble in weakly acidic aqueous solutions (pH 3 to 7); insoluble in organic solvents including ethanol, diethyl ether, and benzene [3]. The compound is thermally stable and is not inactivated by conventional cooking temperatures, a property of toxicological significance in pufferfish poisoning but of no relevance to pharmaceutical formulation.

Stereochemistry: Tetrodotoxin contains nine stereocenters, producing a highly complex three-dimensional architecture. The naturally occurring (4R,4aR,5R,7S,9S,10S,10aR,11S,12S) stereoisomer is the biologically active and pharmaceutically relevant form. Multiple stereoisomeric analogs and derivatives (including 4,9-anhydrotetrodotoxin, 4-epi-TTX, 6-epi-TTX, 11-deoxyTTX, and others) have been identified in natural sources and by synthetic chemistry; these analogs vary substantially in sodium channel blocking potency and selectivity [4].

1.3 Natural sources and biosynthesis

Tetrodotoxin was first isolated from pufferfish (family Tetraodontidae, genus *Takifugu*) in 1909 by Tahara and structurally elucidated independently by three groups (Tsuda, Woodward, and Goto) in 1964 [5]. Despite its initial association with pufferfish, TTX has been identified in a phylogenetically diverse range of organisms including newts (genus *Taricha*), blue-ringed octopuses (genus *Hapalochlaena*), horseshoe crabs, xanthid crabs, starfish, flatworms, gobies, and several species of frogs and salamanders [6].

The current scientific consensus holds that TTX is produced by symbiotic bacteria (including species of *Vibrio*, *Pseudomonas*, *Alteromonas*, and other marine genera) and accumulated through the food chain by macroorganisms, although endogenous biosynthesis by the host organism has not been definitively excluded [7]. The biosynthetic pathway in bacteria has not been fully elucidated; isotope-labeling studies suggest that the carbon skeleton derives from arginine and a polyketide or terpenoid precursor, but the key biosynthetic genes have not been identified [7].

The difficulty of maintaining stable TTX-producing bacterial cultures under laboratory conditions and the rapid decay of toxin production in subculture have hindered pathway characterization.

1.4 Pharmaceutical synthesis and formulation

Total synthesis of tetrodotoxin was first achieved by Kishi et al. (2003) through an asymmetric route involving a Diels-Alder key step, producing the natural (4R,4aR,5R,7S,9S,10S,10aR,11S,12S) enantiomer in greater than 30 synthetic steps [8]. Several subsequent total syntheses have been reported by the Du Bois, Sato, Fukuyama, and other groups, with step counts ranging from 26 to 40 [9]. Total synthesis remains impractical for pharmaceutical-scale production owing to the low overall yields, the number of synthetic steps, and the multiple stereocenters.

The pharmaceutical supply of TTX for Halneuron and for research-grade material is derived predominantly from natural extraction from pufferfish ovaries, liver, and skin, followed by extensive chromatographic purification. The Halneuron formulation is a sterile, preservative-free aqueous solution of tetrodotoxin for subcutaneous injection, supplied in single-use vials. The exact excipient composition and concentration have not been disclosed in published literature but are consistent with standard subcutaneous injectable formulations (buffered saline, pH-adjusted to the weakly acidic range for TTX solubility).

2. Abstract

Halneuron (tetrodotoxin for injection) is a peripherally restricted, non-opioid analgesic under clinical development by Dogwood Therapeutics Inc. (formerly WEX Pharmaceuticals Inc.) for the treatment of moderate to severe chemotherapy-induced neuropathic pain (CINP) and cancer-related pain. The active pharmaceutical ingredient, tetrodotoxin, is a naturally occurring guanidinium alkaloid that reversibly blocks TTX-sensitive voltage-gated sodium channels at low-nanomolar concentrations, with the NaV1.7 subtype (encoded by SCN9A) representing the principal analgesic target based on human genetic validation [10].

The compound is distinguished from existing analgesic agents by three properties: peripheral restriction (TTX does not cross the blood-brain barrier and therefore produces no central sedation, euphoria, cognitive impairment, or addiction liability); prolonged post-treatment analgesia (clinical evidence demonstrates pain relief persisting for weeks to months after a four-day subcutaneous treatment cycle, a duration inconsistent with the 4.5-hour plasma half-life and suggestive of a disease-modifying or neuroplastic mechanism); and a favorable safety profile (no QT prolongation, no organ toxicity at clinical doses, and adverse events limited to transient perioral paresthesia, nausea, headache, and dizziness) [11, 12].

The clinical development program has generated evidence across three indications. In cancer-related pain, the Hagen et al. (2017) multicentre randomized controlled trial in 165 patients demonstrated a 16.2% effect size on pain reduction versus placebo, with a responder rate (30% or greater pain reduction) of 51% versus 35% [13]. In chemotherapy-induced neuropathic pain, the Bhatt et al. (2021) dose-finding trial in 125 patients identified the 30 microgram twice-daily subcutaneous regimen for further development [14]. The ongoing Phase 2b HALT-CINP trial reported positive interim results in December 2025, with separation from placebo and a 4.4% dropout rate, and is projected to report top-line results in the third quarter of 2026 [15, 16].

Halneuron addresses a substantial unmet medical need. Chemotherapy-induced peripheral neuropathy affects 30 to 70 percent of patients receiving neurotoxic chemotherapy regimens (platinum compounds, taxanes, vinca alkaloids), and the only pharmacological agent with moderate evidence of efficacy in CINP is duloxetine.

tine, which produces modest benefit and is limited by central nervous system side effects [17]. No approved treatment specifically targets CINP. Halneuron, if approved, would represent the first peripherally restricted sodium channel blocker developed for this indication and the first non-opioid analgesic with demonstrated prolonged post-treatment efficacy in cancer and chemotherapy-related pain populations.

3. Discovery and Development History

3.1 Historical context of tetrodotoxin

Tetrodotoxin has been recognized as a potent neurotoxin since at least the 18th century, when Captain James Cook documented pufferfish poisoning during his second Pacific voyage in 1774. The toxin was first isolated in crude form by Tahara in 1909 from the ovaries of the Japanese pufferfish *Takifugu rubripes*. The chemical structure was determined independently in 1964 by Tsuda (Kyoto), Woodward (Harvard), and Goto (Nagoya), representing a landmark in natural product chemistry [5]. The pharmacological mechanism (selective blockade of voltage-gated sodium channels at the external pore) was elucidated by Narahashi, Moore, and Scott in the 1960s and became the foundational tool for electrophysiology, enabling the distinction between TTX-sensitive and TTX-resistant sodium channel subtypes that underlies modern pain neuroscience [18].

3.2 Recognition of analgesic potential

The first systematic investigation of TTX as a potential analgesic agent was conducted by Marcil et al. (2004) and Gonzalez-Cano et al. (2021), building on earlier observations that systemic sublethal doses of TTX produced antinociception in rodent models without the sedation associated with opioid analgesics [19, 20]. The distinction between the lethal and the analgesic dose ranges proved operationally critical: the therapeutic index of TTX administered systemically is narrow (lethal dose in mice is approximately 10 micrograms per kilogram intravenously, while the analgesic ED₅₀ in neuropathic pain models is approximately 1 microgram per kilogram subcutaneously), but the subcutaneous route and the slow absorption kinetics it provides expanded the effective therapeutic window sufficiently to support clinical development [19].

3.3 WEX Pharmaceuticals and the Halneuron program

WEX Pharmaceuticals Inc. was founded in Vancouver, British Columbia, Canada, as a private biopharmaceutical company specifically to develop tetrodotoxin as a clinical analgesic. The company secured pharmaceutical-grade TTX supply, developed

the sterile injectable Halneuron formulation, and advanced the compound through a series of clinical studies beginning in the mid-2000s.

The first published clinical study was an open-label Phase 2a safety and efficacy trial (Hagen et al. 2007, published 2011) in 77 patients with moderate to severe cancer-related pain inadequately controlled by existing therapy [21]. This study established the feasibility of subcutaneous TTX administration at doses of 15 to 30 micrograms twice daily for four days and provided the initial clinical signal of prolonged post-treatment analgesia.

The pivotal Phase 2b/3 cancer pain trial (Hagen et al. 2017) enrolled 165 patients across 19 sites in Canada, Australia, and New Zealand and produced the primary efficacy signal that supported continued development [13].

The dose-finding Phase 2 trial for chemotherapy-induced neuropathic pain (Bhatt et al. 2021) enrolled 125 patients and characterized the dose-response relationship across four TTX dose cohorts [14].

3.4 Formation of Dogwood Therapeutics

On October 7, 2024, WEX Pharmaceuticals Inc. completed a business combination with Virios Therapeutics Inc. (NASDAQ: VIRI) to form Dogwood Therapeutics Inc. (NASDAQ: DWTX). The combined entity retained the Halneuron development program as its lead asset and commenced the Phase 2b HALT-CINP trial for chemotherapy-induced neuropathic pain. Positive interim results were announced on December 22, 2025 [15]. A long-term extension study was announced on May 18, 2026 [16]. Top-line Phase 2b results are anticipated in the third quarter of 2026, with a potential Phase 3 registration program to follow.

4. Mechanism of Action

4.1 Voltage-gated sodium channel blockade

Tetrodotoxin produces analgesia by blocking voltage-gated sodium channels (VGSCs) on peripheral nociceptive neurons, thereby inhibiting the initiation and propagation of action potentials that transmit pain signals from the periphery to the central nervous system [2].

VGSCs are heteromeric transmembrane protein complexes composed of a pore-forming alpha subunit and one or two auxiliary beta subunits. Nine alpha subunit isoforms (NaV1.1 through NaV1.9) have been identified in mammals, encoded by the genes SCN1A through SCN11A. These isoforms are classified pharmacologically as TTX-sensitive (NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.6, NaV1.7; blocked at nanomolar TTX concentrations) or TTX-resistant (NaV1.5, NaV1.8, NaV1.9; blocked only at micromolar concentrations, approximately 1000-fold higher) [22].

Tetrodotoxin binds to the external vestibule of the sodium channel pore, specifically at a site formed by residues in the S5-S6 linker (P-loop) regions of domains I through IV. The positively charged guanidinium group of TTX occupies the ion selectivity filter and physically occludes sodium ion flux. Binding is reversible, voltage-independent, and does not require the channel to be in the open or inactivated state, distinguishing TTX from use-dependent (state-dependent) sodium channel blockers such as lidocaine and carbamazepine [2, 22].

4.2 Sodium channel subtype selectivity and analgesic relevance

The IC₅₀ values of tetrodotoxin for the TTX-sensitive sodium channel subtypes, measured in heterologous expression systems, are approximately: NaV1.6, 2.3 nM; NaV1.1, 4.1 nM; NaV1.3, 5.3 nM; NaV1.4, 7.6 nM; NaV1.2, 14 nM; NaV1.7, 36 nM [23]. The approximately 15-fold range across the TTX-sensitive subtypes reflects differences in the amino acid composition of the P-loop binding site, particularly the presence or absence of aromatic residues that support cation-pi interactions with the guanidinium pharmacophore [4].

The NaV1.7 subtype is the most pharmacologically and genetically validated analgesic target among the VGSCs. Human loss-of-function mutations in SCN9A (the gene encoding NaV1.7) produce congenital insensitivity to pain (channelopathy-associated insensitivity to pain, CIP), while gain-of-function mutations produce inherited erythromelalgia and paroxysmal extreme pain disorder [10]. NaV1.7 is expressed predominantly on small-diameter dorsal root ganglion (DRG) neurons, trigeminal ganglion neurons, and sympathetic ganglion neurons, positioning it as a peripheral nociceptive channel whose blockade would produce analgesia without central nervous system effects.

NaV1.6 (the most potently blocked subtype) is expressed broadly in the central and peripheral nervous systems and contributes to action potential initiation at nodes of Ranvier. NaV1.1 is expressed on inhibitory interneurons in the central nervous system, and its blockade is associated with epilepsy phenotypes. NaV1.4 is the skeletal muscle sodium channel. NaV1.3 is normally expressed at low levels in adult sensory neurons but is re-expressed at high levels following peripheral nerve injury, contributing to ectopic discharges and neuropathic pain sensitization [22, 24].

The peripheral restriction of Halneuron (subcutaneous administration, no blood-brain barrier penetration) confines the pharmacological effect predominantly to peripheral NaV1.7 and NaV1.6 on sensory neurons, with minimal engagement of central NaV1.1, NaV1.2, and NaV1.6 populations. This peripheral selectivity is the mechanistic basis for the absence of central nervous system adverse effects (sedation, cognitive impairment, seizure risk) that limit centrally acting sodium channel blockers.

4.3 Mechanism of prolonged analgesia

A distinctive pharmacological property of Halneuron, observed across multiple clinical studies, is the prolonged duration of analgesic effect following a short (four-day) treatment course. In the Hagen et al. (2011) open-label study, pain relief persisted for weeks to months after the final dose in a substantial fraction of patients [21]. In the Hagen et al. (2017) controlled trial, the analgesic effect extended through the 28-day post-treatment observation period [13].

The 4.5-hour plasma half-life of TTX following subcutaneous injection is inconsistent with this prolonged effect, and the mechanism is not fully elucidated. Proposed explanations include: (a) reversal of peripheral sensitization through sustained blockade of ectopic discharges during the four-day treatment period, per-

mitting recovery of normal neuronal excitability; (b) reduction of neuroinflammatory signaling at sites of nerve injury through interruption of activity-dependent release of proinflammatory mediators; and (c) a neuroplastic resetting of pain processing circuits in the dorsal horn secondary to the period of reduced peripheral input [20, 25]. The prolonged effect is clinically significant because it suggests that intermittent short-course treatment may be sufficient for sustained pain control, reducing total drug exposure and adverse-event burden relative to chronic daily dosing with conventional analgesics.

4.4 Distinction from opioid and centrally acting analgesics

Halneuron operates through a mechanism entirely distinct from opioid receptor agonism. There is no interaction with mu, kappa, or delta opioid receptors; no modulation of descending inhibitory pathways; no engagement of reward circuitry; and no potential for tolerance, dependence, or addiction. The absence of blood-brain barrier penetration eliminates the central nervous system adverse effects (euphoria, sedation, respiratory depression, cognitive impairment) that define the opioid class and that limit the use of other centrally acting analgesics including gabapentinoids, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors in pain populations [11].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Halneuron is administered by subcutaneous injection. Following subcutaneous administration of 15 to 45 micrograms in healthy adults, tetrodotoxin is rapidly absorbed, reaching maximum plasma concentration (C_{max}) within approximately 1.5 hours [11]. Both C_{max} and the area under the concentration-time curve (AUC) increase proportionally with dose across the studied range, indicating linear pharmacokinetics. Time to peak concentration (T_{max}) is consistent across doses, suggesting that the absorption rate is not dose-dependent.

Oral bioavailability of tetrodotoxin has not been characterized in human clinical studies for the Halneuron program. TTX is a polar, hydrophilic molecule with poor membrane permeability, and oral absorption is expected to be low and erratic. The subcutaneous route was selected to ensure reliable systemic exposure while avoiding the rapid peak concentrations associated with intravenous administration (which would narrow the therapeutic index). Intramuscular administration has been studied in preclinical models but is not part of the current clinical program.

5.2 Distribution

Tetrodotoxin is a small, hydrophilic molecule (molecular weight 319.27 g/mol, multiple hydroxyl groups, charged guanidinium moiety at physiological pH) with low lipophilicity. The compound does not cross the blood-brain barrier in pharmacologically significant quantities, as demonstrated by the absence of central nervous system adverse effects at clinical doses and by preclinical distribution studies [11, 20]. Peripheral tissue distribution includes sensory nerve fibers, dorsal root ganglia, and subcutaneous and muscular tissue at the injection site. Protein binding data in humans have not been published; the highly polar structure predicts low protein binding.

5.3 Metabolism and elimination

The plasma elimination half-life of tetrodotoxin following subcutaneous injection is approximately 4.5 hours, consistent across the dose range of 15 to 45 micrograms [11]. Plasma TTX concentration decreases steadily following peak concentration and is undetectable (below the limit of quantification) in the majority of subjects at 24 hours post-dose.

Tetrodotoxin is not metabolized by cytochrome P450 enzymes. The compound does not undergo hepatic oxidative metabolism to a significant extent, distinguishing it from the large majority of small-molecule analgesics and eliminating the pharmacogenomic variability (CYP2D6, CYP3A4, CYP2C9 polymorphisms) that complicates dose-response prediction for agents such as codeine, tramadol, and tropisetron. The primary elimination pathway is renal excretion of unchanged compound. This metabolic profile simplifies drug-drug interaction assessment and reduces the risk of unexpected exposure variation in polypharmacy populations, which are common among cancer and chemotherapy patients.

5.4 Dose-response relationship

The Phase 1 dose-escalation study evaluated subcutaneous doses of 15, 30, and 45 micrograms in 25 healthy adults [11]. All three doses were safe and well tolerated. The dose-proportional pharmacokinetics support a predictable dose-exposure relationship.

In the clinical efficacy trials, the analgesic dose range has been 15 to 30 micrograms administered subcutaneously once or twice daily for four consecutive days. The Bhatt et al. (2021) dose-finding study evaluated four cohorts (7.5 micrograms twice daily, 15 micrograms twice daily, 30 micrograms once daily, and 30 micrograms twice daily) and identified the 30 microgram twice-daily regimen as producing the greatest separation from placebo on cumulative responder analysis [14].

5.5 Special populations

Published data on pharmacokinetics in renal impairment, hepatic impairment, pediatric populations, and geriatric populations are limited. The absence of hepatic CYP-mediated metabolism suggests that hepatic impairment should have minimal effect on TTX pharmacokinetics. The renal excretion pathway predicts that severe renal impairment could prolong exposure, though this has not been formally stud-

ied. No pregnancy or lactation data are available; the compound has not been studied in these populations and is not recommended for use during pregnancy or lactation.

6. Preclinical Pharmacology

6.1 Neuropathic pain models

Tetrodotoxin has demonstrated potent antinociceptive activity across multiple rodent models of neuropathic pain. In the chronic constriction injury (CCI) model of peripheral nerve injury, systemic TTX (0.5 to 3 micrograms per kilogram subcutaneously) diminished mechanical allodynia and thermal hyperalgesia in a dose-dependent manner, with an ED50 of approximately 1.08 micrograms per kilogram for mechanical allodynia and 0.62 micrograms per kilogram for thermal hyperalgesia [19]. The analgesic effect was achieved at doses that produced no observable sedation, motor impairment, or behavioral toxicity, in contrast to morphine, which produced comparable analgesia only at doses associated with marked sedation.

In the spinal nerve ligation (SNL) model, TTX reduced tactile allodynia and thermal hyperalgesia at comparable doses. In the vincristine-induced peripheral neuropathy model (a preclinical surrogate for chemotherapy-induced neuropathic pain), TTX reduced mechanical hypersensitivity, supporting the translational rationale for the CINP clinical program [20].

6.2 Inflammatory pain models

In the formalin test (a biphasic model of acute and persistent inflammatory pain), systemic TTX reduced both Phase 1 (acute nociceptive) and Phase 2 (inflammatory) behavioral responses. In the complete Freund's adjuvant (CFA) model of chronic inflammatory pain, TTX reduced mechanical and thermal hypersensitivity. TTX was more effective against the neuropathic and inflammatory components of pain than against acute nociception, consistent with the hypothesis that its primary analgesic mechanism is suppression of ectopic and injury-driven neuronal discharges rather than blockade of normal sensory transmission [19, 20].

6.3 Cancer pain models

In rodent models of bone cancer pain (tumor cell implantation into the tibia or femur), TTX reduced spontaneous and evoked pain behaviors at subcutaneous doses consistent with the neuropathic pain models. The preclinical cancer pain data provided the rationale for the clinical cancer pain trials conducted by WEX Pharmaceuticals [20].

6.4 Comparative preclinical potency

TTX has been reported to be approximately 3000 times more potent than aspirin and 150 times more potent than carbamazepine in standard rodent antinociceptive assays [20]. The comparison to morphine is more nuanced: TTX and morphine produce comparable analgesia in neuropathic pain models, but TTX does so without sedation, without tolerance development on repeated dosing, and without withdrawal phenomena on cessation.

6.5 Local anesthetic applications

TTX has been studied as a long-duration local anesthetic in combination with epinephrine and bupivacaine. Sciatic nerve block with TTX-bupivacaine combinations in rats produced nerve block durations exceeding those of either agent alone, with reduced systemic toxicity relative to high-dose bupivacaine [26]. These applications are outside the current Halneuron development program but represent a potential extension of the TTX pharmacology platform.

7. Clinical Evidence Base

7.1 Phase 2a open-label cancer pain study (Hagen et al. 2011)

The first published clinical study of Halneuron was a multicentre, open-label, Phase 2a safety and efficacy trial in 77 patients with moderate to severe cancer-related pain inadequately controlled by existing analgesic regimens [21]. Patients received subcutaneous TTX at doses of 15 to 30 micrograms twice daily for four consecutive days. The primary objective was safety assessment; secondary objectives included analgesic efficacy measured by numerical pain rating scale (NPRS) change from baseline.

The study demonstrated that subcutaneous TTX was safe and well tolerated at the studied doses. The most common adverse events were nausea (mild, transient), perioral paresthesia, and injection site discomfort. Analgesic efficacy was observed in a substantial fraction of patients, with pain reduction persisting for weeks to months after the four-day treatment course in responsive subjects. The prolonged post-treatment analgesic duration was an unexpected finding that distinguished TTX from conventional short-acting analgesics and motivated further clinical investigation.

7.2 Phase 2b/3 randomized controlled cancer pain trial (Hagen et al. 2017)

The pivotal cancer pain study was a multicentre, randomized, double-blind, placebo-controlled, parallel-design trial enrolling 165 patients at 19 sites in Canada, Australia, and New Zealand [13]. Eligible patients had moderate to severe cancer-related pain (NPRS 4 or greater on a 0 to 10 scale) inadequately controlled by existing therapy, including opioids in the majority. Patients were randomized to receive TTX 30 micrograms or placebo subcutaneously twice daily for four consecutive days, with efficacy assessment over a 28-day post-treatment observation period.

The primary analysis population comprised 149 patients. The primary endpoint was pain reduction assessed by the mean NPRS score during the observation period. The primary analysis demonstrated a clinically significant estimated effect size of 16.2% on the pain endpoint for TTX versus placebo. The responder analysis (proportion of patients achieving 30% or greater pain reduction from baseline) showed 51% of TTX-treated patients versus 35% of placebo-treated patients meeting this threshold.

The results were nominally statistically significant after prespecified Bonferroni-Holm adjustment for two co-primary endpoints but did not achieve significance at the prespecified two-sided 5% level for the composite endpoint. The investigators concluded that TTX demonstrates a favorable benefit-risk profile in uncontrolled moderate to severe cancer-related pain and recommended a sufficiently powered Phase 3 trial to confirm the prolonged analgesic signal.

7.3 Phase 2 dose-finding CINP trial (Bhatt et al. 2021)

A randomized, double-blind, placebo-controlled, parallel-dose-finding trial enrolled 125 patients with taxane- or platinum-related chemotherapy-induced neuropathic pain at multiple centers [14]. Patients were randomized to placebo or one of four TTX dose cohorts: 7.5 micrograms twice daily, 15 micrograms twice daily, 30 micrograms once daily, or 30 micrograms twice daily, administered subcutaneously for four consecutive days.

The primary outcome measure was the mean change from baseline in average NPRS score during Days 22 to 28 post-treatment. Mean NPRS change was greatest in the TTX 30 microgram once-daily cohort (change of negative 1.7, standard deviation 2.3), followed by the 30 microgram twice-daily cohort (change of negative 1.5, standard deviation 1.8). Changes were not statistically different between cohorts on the primary analysis owing to small cohort sizes and the influence of a few robust placebo responders.

Cumulative responder analysis, however, showed significant separation from placebo with the 30 microgram twice-daily cohort using the maximum response at any timepoint as the metric. This dose and regimen (30 micrograms subcutaneously twice daily for four days, repeated at three-week intervals) was selected for further evaluation in the Phase 2b HALT-CINP trial.

7.4 Phase 2b HALT-CINP trial (ongoing)

The HALT-CINP trial is a randomized, double-blind, placebo-controlled Phase 2b study evaluating the efficacy and safety of Halneuron in patients with established neuropathic pain secondary to prior platinum- or taxane-based chemotherapy [15, 16]. The study is being conducted at approximately 30 sites in the United States under the Dogwood Therapeutics corporate structure. Participants receive 8 subcutaneous doses of Halneuron or placebo over a 14-day treatment period, followed by 28 days of monitoring.

An independent statistical review committee conducted an interim analysis of unblinded data from 97 patients in December 2025 [15]. The committee concluded that Halneuron-treated patients are demonstrating separation from placebo on pain improvement over the four-week observation period. The interim analysis population had an average CINP duration of 5 years, and 67% were on stable background pain medications. The overall study dropout rate was approximately 4.4%, substantially below rates observed with approved chronic pain medications.

Dogwood Therapeutics announced in February 2026 that the trial had reached 50% enrollment, with top-line results anticipated in the third quarter of 2026 [16]. The enrollment trends provide approximately 80 to 85 percent statistical power for the primary endpoint. A 12-week open-label extension study was announced in May 2026 for patients who complete the Phase 2b trial, based on the positive interim assessment.

7.5 Phase 1 pharmacokinetic and safety studies

A randomized, double-blind, placebo-controlled dose-escalation Phase 1 study evaluated the safety, tolerability, pharmacokinetics, and concentration-QTc relationship of subcutaneous TTX in 25 healthy adults at doses of 15, 30, and 45 micrograms [11]. All doses were safe and well tolerated. There were no serious or severe adverse events and no withdrawals due to adverse events. The study met the criteria of a negative thorough QT study, demonstrating no proarrhythmic proclivity. A bioequivalence study comparing liquid and lyophilized formulations of subcutaneous TTX in healthy volunteers confirmed comparable pharmacokinetic profiles between formulations.

8. Sourcing and Quality Verification

Pharmaceutical-grade tetrodotoxin for the Halneuron clinical program is sourced and manufactured under current Good Manufacturing Practice (cGMP) conditions by or on behalf of Dogwood Therapeutics Inc. The pharmaceutical-grade material is not commercially available for independent purchase; access is through clinical trial participation or through regulated supply agreements.

Research-grade tetrodotoxin is available from multiple established suppliers including Tocris Bioscience (Bio-Techne), Cayman Chemical, Alomone Labs, Sigma-Aldrich (MilliporeSigma), Abcam, and Creative Diagnostics. The compound is supplied as the citrate salt (CAS 18660-81-6) or the citrate-free base (CAS 4368-28-9), typically at greater than 98 percent purity by HPLC, in quantities ranging from 100 micrograms to 10 milligrams. Pricing is high relative to conventional small-molecule research compounds, reflecting the complexity of natural extraction and purification; typical costs are in the range of \$100 to \$500 per milligram depending on supplier, purity grade, and quantity.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity (greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (320.1 for the protonated species $[M+H]^+$, or 319.1 for the monoisotopic exact mass)
- Mouse bioassay or electrophysiological functional assay to confirm biological activity (sodium channel blockade at the expected IC_{50})
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis if the preparation is derived from organic solvent extraction

Tetrodotoxin is classified as a potent neurotoxin and is subject to institutional biosafety and chemical safety regulations. Investigators should handle TTX in accordance with institutional policies for highly toxic compounds, including use of appropriate personal protective equipment, designated work areas, and spill con-

tainment procedures. TTX is not a controlled substance under United States Drug Enforcement Administration schedules but is regulated by institutional biosafety committees at many research institutions.

9. Reconstitution and Handling

Tetrodotoxin citrate is freely soluble in water (greater than 10 mM at room temperature as the citrate salt). The citrate-free base is slightly soluble in water at neutral pH but readily soluble in weakly acidic aqueous solutions (pH 3 to 7). Stock solutions for research applications are typically prepared in one of the following vehicles:

- Deionized water or ultrapure water at slightly acidic pH (pH 4 to 6) for the citrate-free base
- Deionized water for the citrate salt (no pH adjustment required; the citrate buffer provides the necessary acidity)
- Citrate buffer (10 to 50 mM, pH 4.8) for applications requiring defined pH

TTX is insoluble in organic solvents including ethanol, methanol, dimethyl sulfoxide, and dimethylformamide. Investigators accustomed to dissolving small-molecule research compounds in DMSO should note that this standard practice does not apply to TTX.

For reconstitution of lyophilized TTX citrate: add the appropriate volume of deionized water to achieve the desired stock concentration (for example, 313 microliters of water to 1 milligram of TTX citrate for a 10 mM stock solution). Tap the vial gently until fully dissolved. Centrifuge product vials before handling (10,000 g for 5 minutes) to collect lyophilized material at the bottom.

Storage of the dry compound is appropriate at room temperature for short periods (up to several weeks) and at negative 20 degrees Celsius for long-term storage. Aqueous stock solutions should be stored at 2 to 8 degrees Celsius for short-term use (up to 2 weeks) or aliquoted and frozen at negative 20 degrees Celsius for longer storage. TTX is thermally stable in weakly acidic aqueous solutions but decomposes in alkaline conditions (pH greater than 8). Light protection is not required but is reasonable practice.

For the Halneuron clinical formulation, the compound is supplied as a sterile, preservative-free solution in single-use vials for subcutaneous injection. The clinical formulation does not require reconstitution by the end user.

10. Stack Interactions and Combinations

Tetrodotoxin, as a peripherally restricted sodium channel blocker that is not metabolized by cytochrome P450 enzymes, has a relatively simple drug-drug interaction profile compared to centrally acting analgesics. Investigators conducting research with Halneuron should consider the following interaction categories:

Other sodium channel blockers: Concurrent use with local anesthetics (lidocaine, bupivacaine), antiepileptic sodium channel blockers (carbamazepine, oxcarbazepine, phenytoin, lamotrigine), or investigational NaV1.7 inhibitors (vixotrigine) could produce additive sodium channel blockade, increasing the risk of sensory or motor nerve conduction impairment and potentially cardiac conduction effects. The combination of TTX and lidocaine has demonstrated synergistic sodium channel blockade in electrophysiological studies and synergistic antiarrhythmic effects in rodent models [27]; this synergy should be considered a potentiation risk in the clinical context. Concurrent administration of Halneuron with systemic sodium channel blocking agents is not recommended without careful dose adjustment and monitoring.

Opioid analgesics: TTX does not interact with opioid receptors, and no pharmacokinetic interaction is expected. Concurrent opioid use is common in the cancer pain population studied in Halneuron trials; the Hagen et al. (2017) trial permitted stable background opioid therapy [13]. The principal interaction consideration is additive analgesia, which may permit opioid dose reduction (an intended therapeutic outcome of the Halneuron development program) but requires monitoring for opioid withdrawal if opioid doses are reduced precipitously.

Serotonin-norepinephrine reuptake inhibitors (duloxetine, venlafaxine): No pharmacokinetic interaction is expected. Duloxetine is the only agent with moderate evidence of efficacy in CINP and may be used concurrently with Halneuron in clinical trials or in off-label research. No pharmacodynamic interaction is expected; the mechanisms are complementary (peripheral sodium channel blockade and central monoamine reuptake inhibition).

Gabapentinoids (gabapentin, pregabalin): No pharmacokinetic or pharmacodynamic interaction is expected. These agents act on the alpha-2-delta subunit of voltage-gated calcium channels, a target mechanistically distinct from sodium channel blockade. Concurrent use is common in neuropathic pain populations and is not contraindicated.

Antiarrhythmic agents: Class I antiarrhythmic agents (procainamide, flecainide, propafenone) act on cardiac sodium channels (NaV1.5). Although NaV1.5 is classified as TTX-resistant (IC₅₀ for TTX approximately 1 to 2 micromolar, approximately 100-fold above clinical plasma concentrations), the combination of TTX with Class I antiarrhythmics warrants caution owing to the theoretical possibility of additive cardiac sodium channel effects at the extremes of dose and exposure.

QT-prolonging agents: The Phase 1 study demonstrated that TTX does not prolong the QT interval at doses up to 45 micrograms subcutaneously [11]. No specific interaction with QT-prolonging agents is expected, but standard clinical caution applies.

Neuromuscular blocking agents: TTX blocks NaV1.4 (the skeletal muscle sodium channel) at nanomolar concentrations. Concurrent use with neuromuscular blocking agents (succinylcholine, rocuronium, vecuronium) could theoretically produce additive neuromuscular blockade, though this has not been reported at clinical TTX doses. The interaction is relevant principally for perioperative and anesthesiology contexts.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events reported across the Halneuron clinical program are [11, 13, 14]:

- Perioral paresthesia and oral numbness or tingling (the most characteristic adverse event; dose-dependent; reflects local sodium channel blockade in oral mucosa, possibly from systemic distribution to highly innervated oral tissue; generally mild and self-limiting within hours of dosing)
- Nausea (mild to moderate; reported in 10 to 20 percent of TTX-treated patients across trials)
- Headache (5 to 15 percent)
- Dizziness (5 to 10 percent)
- Myalgia (approximately 5 percent)
- Injection site reactions (mild erythema, pain, or swelling at the subcutaneous injection site; generally mild and self-limiting)

These adverse events are consistent with the known pharmacology of peripheral sodium channel blockade and with the subcutaneous route of administration. They are generally mild to moderate in severity, self-limiting, and do not require treatment discontinuation in the majority of cases.

11.2 Absence of central nervous system adverse events

Critically, the clinical program has demonstrated the absence of the central nervous system adverse events that characterize opioid and centrally acting analgesics: no euphoria, no sedation, no cognitive impairment, no respiratory depression, no tolerance development, no dependence, and no withdrawal phenomena [11, 13]. This profile is consistent with the peripheral restriction of TTX and is the principal safety differentiator relative to existing analgesic classes.

11.3 Cardiac safety

The Phase 1 concentration-QTc analysis demonstrated no QT prolongation at doses up to 45 micrograms subcutaneously and no proarrhythmic proclivity [11]. This finding is reassuring given the theoretical concern about sodium channel blockade and cardiac conduction; the TTX resistance of the cardiac sodium channel (Nav1.5, IC50 approximately 1 to 2 micromolar) provides a large safety margin at clinical plasma concentrations (low-nanomolar range).

11.4 Serious adverse events

No serious adverse events attributable to TTX have been reported in the Halneuron clinical program at clinical doses [11, 13, 14]. The systematic review and meta-analysis by Campos-Rios et al. (2023) concluded that TTX increased the risk of non-severe adverse events but did not increase the risk of severe adverse events in pooled clinical trial data [28].

11.5 Toxicological considerations

Tetrodotoxin is a potent neurotoxin with a well-characterized acute toxicity profile from poisoning cases (predominantly pufferfish ingestion). The lethal dose in humans by oral ingestion is estimated at 1 to 2 milligrams (approximately 10 to 25 micrograms per kilogram) [3]. The clinical doses used in the Halneuron program (15 to 60 micrograms per day by subcutaneous injection) are approximately 30- to 100-fold below the estimated lethal oral dose, and the slow subcutaneous absorption kinetics further widen the therapeutic index by avoiding the rapid peak plasma concentrations that produce acute toxicity.

Symptoms of tetrodotoxin poisoning (from accidental oral ingestion at supratherapeutic exposures) include perioral and extremity paresthesia, progressive ascending paralysis, respiratory failure, and cardiovascular collapse. These symptoms are not observed at the clinical doses used in the Halneuron program; the relationship between the pharmaceutical application and the toxicological profile is analogous to that of botulinum toxin, where clinical doses are orders of magnitude below the lethal dose and produce therapeutically useful focal effects without systemic toxicity.

11.6 Pregnancy and lactation

No human data are available for TTX exposure during pregnancy or lactation. Animal reproductive toxicity studies have not been published in the context of the Halneuron development program. Use during pregnancy and lactation is not recommended.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative analgesic candidates for chemotherapy-induced neuropathic pain (CINP) against Halneuron, evaluated on five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five candidates were selected as the principal pharmacological agents that have been evaluated or are under investigation for CINP analgesia, with priority on those with published clinical data and those that share the non-opioid positioning of Halneuron.

12.1 Duloxetine

Mechanism: Serotonin-norepinephrine reuptake inhibitor (SNRI). Duloxetine modulates descending inhibitory pain pathways through central monoamine reuptake inhibition in the spinal dorsal horn and brainstem.

Clinical evidence in CINP: Duloxetine is the only pharmacological agent recommended by the American Society of Clinical Oncology (ASCO) clinical practice guideline for the treatment of established CINP, based on the Smith et al. (2013) randomized, double-blind, placebo-controlled trial of duloxetine 60 mg daily in 231 patients with painful CIPN secondary to oxaliplatin or paclitaxel [17]. The trial demonstrated a statistically significant 1.06-point greater decrease in average pain severity on the Brief Pain Inventory-Short Form for duloxetine versus placebo ($p = 0.003$), with 59% of duloxetine patients reporting at least some pain reduction compared to 38% on placebo.

Novelty: Low. Duloxetine is a well-established agent with multiple approved indications (major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathy, fibromyalgia, chronic musculoskeletal pain). Its use in CINP is an off-label extension of the diabetic neuropathy and fibromyalgia indications.

Effect size: Modest. The 1.06-point BPI difference, while statistically significant, is at the lower bound of clinical meaningfulness. The number needed to treat for 30% pain reduction is approximately 6 [17].

Promising potential: Moderate. Duloxetine is the current standard of care by default (no approved alternative), but its effect size in CINP is modest and a substantial proportion of patients do not respond.

Side-effect profile: Central nervous system adverse events are common: nausea (approximately 25%), fatigue (approximately 15%), somnolence (approximately 10%), dizziness (approximately 10%), dry mouth, constipation, and decreased appetite. These central effects limit tolerability in cancer patients already experiencing treatment-related fatigue and nausea. Discontinuation syndrome on abrupt cessation is well described.

Overall validation: Moderate. The single positive randomized controlled trial and the ASCO guideline recommendation provide the strongest current evidence base for any pharmacological CINP treatment, but the evidence is limited to one trial, the effect size is modest, and the side-effect profile is a practical barrier.

Comparison to Halneuron: Duloxetine acts centrally and produces central nervous system adverse effects; Halneuron acts peripherally and is free of central effects. Duloxetine has a stronger current evidence base (one positive Phase 3 trial, guideline recommendation) but a modest effect size. Halneuron has a smaller evidence base (Phase 2 and Phase 2b data) but the mechanism is more directly targeted to the peripheral neuropathic pathology and the prolonged post-treatment analgesia is a potential differentiator. The two agents are mechanistically complementary and could potentially be combined.

12.2 Pregabalin

Mechanism: Alpha-2-delta subunit ligand of voltage-gated calcium channels. Pregabalin reduces excitatory neurotransmitter release from presynaptic terminals in the dorsal horn by binding to the alpha-2-delta-1 auxiliary subunit of VGCCs.

Clinical evidence in CINP: Clinical trial evidence for pregabalin specifically in CINP is limited and mixed. Small trials have shown varying results, with some suggesting superiority to duloxetine in pain reduction but with more adverse events including insomnia [29]. Gabapentin (a related alpha-2-delta ligand) has produced directly conflicting results in two CINP trials. Neither pregabalin nor gabapentin is recommended by ASCO guidelines for CINP treatment, reflecting the insufficient and inconsistent evidence base.

Novelty: Low. Pregabalin is approved for multiple neuropathic pain indications (diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia, spinal cord injury pain) and its use in CINP is an off-label extension.

Effect size: Inconsistent. Some trials report greater pain reduction than duloxetine; others show no significant benefit versus placebo. The heterogeneity likely reflects differences in CINP subtypes (platinum-induced versus taxane-induced neuropathy have different pathophysiological mechanisms).

Promising potential: Low to moderate. The inconsistent evidence base and the lack of guideline recommendation limit clinical adoption for CINP specifically.

Side-effect profile: Somnolence (approximately 15 to 25%), dizziness (approximately 15 to 30%), weight gain, peripheral edema, cognitive impairment ("brain fog"), and ataxia. These central effects are clinically significant and limit tolerability, particularly in cancer patients.

Overall validation: Low to moderate. Established mechanism, approved for related neuropathic pain indications, but insufficient CINP-specific evidence.

Comparison to Halneuron: Pregabalin acts centrally on calcium channels; Halneuron acts peripherally on sodium channels. The mechanisms are non-overlapping. Pregabalin's central side-effect profile is a disadvantage relative to Halneuron's peripheral restriction. Halneuron's prolonged post-treatment effect is a further differentiator; pregabalin requires continuous daily dosing.

12.3 Vixotrigine (BIIB074/CNV1014802)

Mechanism: Broad-spectrum, state-dependent (use-dependent) voltage-gated sodium channel blocker with additional monoamine oxidase B (MAO-B) inhibitory activity [30]. Unlike TTX, which blocks sodium channels at the external pore in a voltage-independent manner, vixotrigine preferentially blocks channels in the inactivated state, conferring selectivity for neurons with high firing rates (as in neuropathic pain) over resting neurons.

Clinical evidence: Vixotrigine was developed by Biogen Inc. for trigeminal neuralgia, small fiber neuropathy, and other neuropathic pain conditions. A Phase 2a randomized, double-blind, placebo-controlled withdrawal trial in trigeminal neuralgia demonstrated safety and tolerability with signals of efficacy [31]. The com-

pound has not been evaluated in CINP-specific clinical trials. The development trajectory has been slow, and the compound has not advanced to Phase 3 registration trials in any indication as of the most recent monograph revision.

Novelty: Moderate. The state-dependent mechanism is pharmacologically differentiated from TTX's pore-blocking mechanism and from conventional sodium channel blockers. The dual sodium channel and MAO-B activity is unusual.

Effect size: Phase 2a signals are preliminary. No CINP-specific data are available.

Promising potential: Low to moderate. The compound is in early clinical development with no clear path to registration in CINP. It remains a research-stage candidate.

Side-effect profile: Phase 2a studies reported tolerability similar to placebo, with headache and dizziness as the most common adverse events [31]. The state-dependent mechanism theoretically provides a more favorable therapeutic index than non-selective sodium channel blockade.

Overall validation: Low. Early-phase clinical data in trigeminal neuralgia only; no CINP data; uncertain development trajectory.

Comparison to Halneuron: Vixotrigine and Halneuron both target sodium channels but through fundamentally different mechanisms (state-dependent intracellular block versus voltage-independent external pore occlusion). Halneuron has the advantage of substantially more clinical data, including CINP-specific trials. Vixotrigine has the theoretical advantage of state-dependent selectivity, which could reduce effects on normally functioning neurons. Neither compound has completed Phase 3 registration.

12.4 Capsaicin 8% patch (Qutenza)

Mechanism: TRPV1 agonist. The capsaicin 8% patch produces defunctionalization of TRPV1-expressing epidermal nerve fibers through initial excitation followed by prolonged desensitization and retraction of terminal nerve endings [32]. The mechanism targets C-fiber nociceptors directly and produces localized analgesia lasting 3 to 12 weeks per application.

Clinical evidence in CINP: The capsaicin 8% patch is FDA-approved for postherpetic neuralgia and has been evaluated in an open-label Phase 2 study in CINP with pain reduction signals [33]. Published case series and small trials report modest benefit in CINP patients, particularly those with predominantly small-fiber neuropathy. The compound is not approved for CINP, and the evidence base for this indication is limited.

Novelty: Low. Capsaicin-based pain treatments have a long history; the 8% patch formulation and the concept of epidermal nerve fiber defunctionalization are established.

Effect size: Modest to moderate in postherpetic neuralgia (the approved indication); the CINP-specific evidence is insufficient for effect size characterization.

Promising potential: Moderate. The prolonged per-application effect (3 to 12 weeks, similar in concept to Halneuron's prolonged post-treatment analgesia) is attractive. The localized mechanism limits utility for widespread or bilateral CINP patterns (glove-and-stocking distribution).

Side-effect profile: Application site pain (the most common adverse event, often severe), erythema, and localized burning. Systemic adverse events are minimal. The application procedure requires a clinical setting and 60 to 90 minutes of monitoring.

Overall validation: Moderate for postherpetic neuralgia; low for CINP specifically.

Comparison to Halneuron: Capsaicin 8% patch and Halneuron both produce prolonged analgesia from short treatment exposures and both act peripherally. Capsaicin targets TRPV1 on C-fibers; Halneuron targets NaV channels on all nociceptive fibers. Capsaicin requires topical application and is limited to accessible body surface areas; Halneuron is systemically administered and reaches all peripheral nerve sites. Halneuron has more extensive CINP-specific clinical data.

12.5 Lidocaine 5% patch (Lidoderm)

Mechanism: Use-dependent sodium channel blocker applied topically. The lidocaine 5% patch delivers lidocaine to the skin and underlying tissue, producing local sodium channel blockade without systemic exposure [34].

Clinical evidence in CINI: The lidocaine 5% patch is FDA-approved for postherpetic neuralgia. Off-label use in CINI has been reported in case series and small open-label studies, with variable results. No randomized controlled trial data specifically in CINI are available. The topical application limits the distribution of analgesia to the application site, which may be adequate for focal CINI but insufficient for the diffuse glove-and-stocking neuropathy patterns typical of platinum and taxane chemotherapy.

Novelty: Low. Topical lidocaine for neuropathic pain is well established.

Effect size: Not characterized for CINI in controlled trials.

Promising potential: Low. No active development program for CINI. The compound serves as a supportive or adjunctive treatment rather than a primary analgesic for CINI.

Side-effect profile: Minimal systemic adverse events. Local adverse events include application site erythema, pruritus, and irritation. The topical route limits systemic exposure and eliminates central nervous system adverse effects.

Overall validation: Low for CINI specifically; moderate for the broader postherpetic neuralgia indication.

Comparison to Halneuron: Both agents block sodium channels, but through different mechanisms (use-dependent intracellular block for lidocaine versus external pore occlusion for TTX) and different routes (topical versus systemic subcutaneous). Halneuron provides systemic distribution to all peripheral nerve sites; the lidocaine patch provides only local coverage. Halneuron has CINI-specific clinical trial data; the lidocaine patch does not. Halneuron produces prolonged post-treatment analgesia; lidocaine patch analgesia is limited to the duration of patch application.

12.6 Comparator summary

The five comparator agents occupy distinct positions in the CINI analgesic landscape. **Duloxetine** is the current standard of care by guideline recommendation, with the strongest clinical evidence but a modest effect size and a central side-effect profile that limits tolerability. **Pregabalin** has inconsistent CINI-specific evidence and a prominent central side-effect profile. **Vixotrigine** is mechanistically differentiated but lacks CINI data and is in early-stage development. **Capsaicin 8%**

patch shares the concept of prolonged analgesia from brief treatment but is limited by topical application and lack of CINP-specific registration data. **Lidocaine 5% patch** is a supportive topical treatment without CINP-specific evidence or systemic coverage.

Halneuron occupies a unique position in this comparator landscape: it is the only candidate with a peripherally restricted systemic mechanism that targets the genetically validated NaV1.7 channel, the only candidate with demonstrated prolonged post-treatment analgesia from a short treatment course, and the only candidate with an active, advanced clinical development program specifically in CINP (Phase 2b with positive interim data). Its principal limitations relative to the comparators are the absence of completed Phase 3 data and the absence of regulatory approval. The clinical trajectory is the most advanced among the candidates without an approved CINP indication, and the mechanism addresses the principal limitations of the current standard of care (central adverse effects, modest effect size, requirement for continuous daily dosing).

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