Pain - Introduction

WEX Pharmaceuticals Inc.is developing Halneuron®, (Tetrodotoxin (TTX), a small molecule derived from puffer fish,) **for the treatment of neuropathic and nociceptive pain**.

TTX is a non-opioid, non-peptide, potent small molecule which targets $Na_v1.7$, one of the voltage-gated sodium channels that propagate signals along nerves throughout the peripheral nervous system. TTX is known to block the Na+ (sodium) channels found on nociceptive pain fibres in a highly selective manner. The mechanism of action via which TTX exerts its analgesic properties is thought to be related to the product's ability to stabilize neuronal membranes by inhibiting the Na+ ionic fluxes required for the initiation and conduction of impulses. Somatosensory primary afferent neurons are generally silent; they issue action potentials only when adequately stimulated. Following nerve injury, primary afferent neurons of diverse functions, including the pain-responsive nociceptors and the low-threshold mechanoreceptors that mediate the sense of touch, begin to discharge spontaneously. The spontaneous discharge is seen in those afferents whose axons have been damaged and in afferents whose axons are undamaged but travel within the same nerve. The spontaneous discharge is said to be "ectopic" because it does not originate via the normal process of signal transduction at the receptor.

The mechanisms underlying neuronal hyperexcitability are not completely understood. Evidence suggests that changes in voltage-gated sodium channel (VGSC) expression on injured and uninjured primary afferent sensory neurons or abnormal accumulation of VGSC in the tips of injured primary sensory neurons may, at least in part, be responsible for this abnormal neuronal activity. Several subtypes of VGSC, in both the peripheral and central nervous systems, are very sensitive to blockade by TTX. It is hypothesised that TTX treatment prevents sodium current through subtypes of VGSC that are sensitive to TTX, which attenuates abnormal neuronal activity in nociceptive pathways resulting in a reduction of pain.

These is evidence that DRG neurons produce at least two types of sodium currents, including a fast TTX-S current and a slow TTX-R current. The slow TTX-R current is predominant in normal physiological conditions and this explains the discrete analgesic activity exerted by TTX in acute nociceptive pain models. However, in chronic pain conditions involving nerve injury and/or tissue inflammation, DRG neurons become hyperexcitable due to the emergence of a high density of kinetically fast sodium channels, pharmacologically distinguishable by their sensitivity to TTX, and thus susceptible to be efficiently blocked by TTX at low therapeutic doses.

Classification of pain

There are two types of pain:

- nociceptive pain is transmitted by the peripheral nerves from pain receptors that report an injury to some part of the body, such as an organ or tissue and
- neuropathic pain results from mechanical or metabolic injury to the nervous system itself.

Nociceptive pain – When tissue is injured – cut, burned, infected, frozen or otherwise harmed, nociceptors, the special nerves responsible for detecting the offending external or internal

stimulus, , fire off and a whole series of chemical mediators are released by the injured tissue. This tissue injury is the origin of "nociceptive pain." Nociceptive pain typically has a character of being sharp, intense and constant, although it can also take the form of a throbbing, constant pain.

The stimulus is transmitted by peripheral nerves from the nociceptors, which in cancer patients is usually secondary to invasion of a tumor into bone, joints, or connective tissue. Nociceptive pain can be somatic (usually sharp or dull and localized with an aching or squeezing sensation), visceral (usually poorly localized, with a deep pressure-like sensation), and often associated with invasive procedures such as biopsies or surgical intervention.

In general, nociceptive pain responds relatively well to traditional analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids in about half the patients. However, it has been reported that less than 50% of cancer patients receive adequate pain treatment and that the current WHO titration ladder method consistently fails to provide sufficient relief to 10%–20% of advanced cancer patients with pain, particularly in cases of neuropathic pain and pain associated with bone involvement (Ahmedzai 1997). Furthermore, attending physicians are reluctant to prescribe opioids [i] because of their addictive nature and toxicities/AEs, and [ii] because patients with severe pain can eventually become opioid resistant (Miguel 2000).

Neuropathic pain – this is the pain that results from mechanical or metabolic injury to the nervous system itself, either centrally or peripherally. In patients with advanced cancer, this type of pain is usually the result of exposure to chemotherapeutic agents or radiation therapy.

Neuropathic pain in general arises from two main mechanisms – demyelinative or axonal (loss), or a combination of both. When the spinal cord receives firing from nerves stimulated by some sensory stimulus that is uncoordinated in either time or space, the nervous system has trouble making sense of the signal and experiences it as tingling, numbness or pain. If the demyelinated nerves become irritable and fire off on their own in response to no incoming sensory stimulus, the resultant "shooting pains" are quite painful. If neurons have died (for example due to toxicity from exposure to alcohol or another toxin), then the "holes" in the pattern of transmission produce both diminished sensation and numbness, tingling or burning.

Neuropathic pain remains more difficult to treat, and more commonly is better alleviated by antiepileptic drugs or tricyclic antidepressant agents which modulate action potential propagation and the availability of chemical neurotransmitters such as norepinephrine and serotonin. It is important to keep in mind that cancer patients will generally experience a combination of pain types and that the treatment of the disease (i.e., surgery, radiation, chemotherapy) may be an important source of the painful stimuli along with progression of the disease itself. Chronic cancer-related pain ("CRP") involves both (i) persistent pain and (ii) breakthrough pain. Persistent pain is continuous and may last all day. Breakthrough pain is a brief flare-up of severe pain that occurs even while the patient is regularly taking pain medication. It usually comes on quickly and may last from a few minutes to an hour. CRP is thought to be largely due to the destruction of tissue by the tumor or by pressure on sensitive tissues as a result of tumor growth, both of which act as nociceptive pain stimuli.

Chemotherapy Induced Neuropathic Pain (CINP)

CINP is a common adverse effect of many anticancer drugs, such as platinum analogs, anti tubulins (e.g., Taxanes and vinca alkaloids such as vincristine), bortezomib (*Velcade*), and thalidomide (*Thalomid*). CINP can present as sensory symptoms in the hands and/or feet, typically in a "stocking-glove" pattern: pain, numbness, or tingling and/or motor symptoms, manifested as weakness, cranial nerve deficits, or autonomic neuropathy. In a recent meta-analysis of 31 CINP studies involving 4179 patients, the aggregate prevalence of CINP was 48%. Within the first month of completing chemotherapy, the prevalence of CINP was 68.1%; after 6 or more months of finishing/completing chemotherapy, the prevalence of CINP decreased to 30.0%. The course of CINP can be unpredictable: although some symptoms may improve with time, others may persist or worsen as a result of permanent nerve damage. There are limited data on the natural history of CINP in long-term cancer survivors who are beyond one year of completing chemotherapy:

- Patients with breast cancer who received taxane-based adjuvant chemotherapy had neuropathy symptoms up to two years after completing treatment and
- Patients with colon cancer receiving oxaliplatin-based adjuvant chemotherapy had numbness or tingling of hands and feet up to six years from starting treatment.

One of the challenges in managing and preventing CINP is that the exact pathophysiology is not well understood. The hypothesized mechanisms of taxane-induced neuropathy include the disruption of the axonal microtubule structure and a deficit in axonal energy supply from the toxic effect of chemotherapy on mitochondria in primary afferent neurons. Vinca alkaloid therapy caused CNIP is thought to result from alterations in the neuronal cytoskeleton that cause axonal degeneration. Platinum agents are thought to cause CINP by exerting damage in the dorsal root ganglion through mitochondrial dysfunction and neuronal apoptosis, either by DNA crosslinking or oxidative stress.

Despite investigations leading to the hypotheses of several mechanisms for CINP, none of the hypotheses have resulted in clinically relevant therapeutic interventions. Several studies have attempted to identify risk factors for CINP development, which also vary with different chemotherapeutic agents. Some of the clinical factors implicated in the development of CINP include baseline neuropathy, the presence of diabetes, smoking history, and decreased creatinine clearance. In addition, researchers are interested in pharmacogenomics and the identification of genes that may play a role in the development of CINP. Although numerous genes have been investigated, such as *GSTP1, CYP2C8,* and *AGXT*, there have been no conclusive findings. As a result, there are no pain medications specifically approved to treat CINP.

One of the clinical implications of CINP is that the symptoms can often result in dose reduction or discontinuation of the therapeutic agent, which may ultimately affect overall survival. In a retrospective single-institution study of 123 patients with breast cancer receiving taxane-based adjuvant or neoadjuvant chemotherapy regimens, 17 percent received chemotherapy dose reductions specifically due to CINP that developed during treatment. In addition, for cancer survivors, CINP symptoms can significantly impact quality of life.

Current therapeutics used off-label for CINP include the anti-epileptic drugs *Pregabalin* and *Gabapentin*, antidepressant drugs like the tricyclics and duloxetine, both classes being lightly prescribed due to scant efficacy. Cannabinoids have some future possibility, but data indicate a weak effect and are likely to be marginal in effect.

Cancer Related Pain (CRP)

Despite advances in prevention, early detection, and newer, more effective treatment modalities, cancer remains one of the most debilitating and deadly diseases and is the second leading cause of mortality in the US. The diagnosis and treatment of cancer can be a difficult experience for anyone, but pain is one of the most difficult of all cancer symptoms. Statistics published by the American Cancer Society in 2002, indicate that "50%–70% of people with cancer experience some degree of pain", which usually only intensifies as the disease progresses. Further, less than half of all patients receive adequate treatment and relief of their pain, which negatively impacts their quality of life. The incidence of pain in advanced stages of invasive cancer approaches 80 percent and it is 90 percent in patients with metastases, particularly to the bone (Nersesyan and Levin, 2007).

CRP involves both persistent pain and breakthrough pain. Persistent pain is continuous and may last all day. Breakthrough pain is a brief flare-up of severe pain that occurs even while the patient is regularly taking pain medication. It usually comes on quickly and may last from a few minutes to an hour. *Chronic cancer pain is thought to be largely due to the destruction of tissue by the tumor or by pressure on sensitive tissues because of tumor growth*, both of which act as nociceptive pain stimuli. The potential primary target of *Halneuron* is this more common, persistent pain; although given evidence of the effect on the Worst Pain scale, it may also reduce breakthrough pain as part of diminishing overall pain and lowering central sensitization.

The most common cancer pain is from tumors that metastasize to the bone. As many as 60-80% of cancer patients with bone metastasis experience pain. The second most common cancer pain is caused by tumors infiltrating the nerve and hollow viscus. Tumors near neural structures typically cause the most severe pain.

Breakthrough cancer pain can result from the cancer or cancer treatment, or it may occur during a certain activity (e.g., walking, dressing, coughing). It also can occur unexpectedly, without a preceding incident or clear cause. *Breakthrough pain usually is treated with strong, short-acting pain medications that work faster than persistent pain medications*. *Halneuron* is unlikely to be used as a symptomatic therapy for breakthrough pain because it is longer acting, but the clinical data showing improvement in the "worst pain" of the day tends to indicate that it will reduce the incidence of episodes of breakthrough pain.

Sub-optimal pain control can be extremely debilitating for cancer patients. Although many cancer patients have a very poor prognosis, prompt and effective pain control may (i) prevent needless suffering, (ii) significantly improve the quality of their lives, and (iii) potentially spare patients a feeling of helplessness about their condition. Although cancer is often a terminal disease, there is no reason to deny a patient the opportunity to live productively and free of pain.

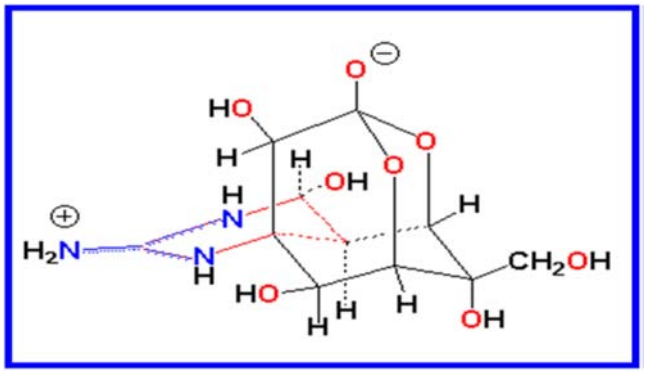
Severe pain can interfere with physical rehabilitation, mobility, and proper nutrition. Therefore, *the goals of pain control in any patient with cancer should be to optimize the patient's comfort and function, while avoiding unnecessary adverse effects from medications*.

Voltage Gated Sodium Channels are Fundamental to Neurotransmission

Voltage-gated sodium channels propagate signals along the nerves. When nerves are stimulated, there is a change in electrical potential which triggers sodium channels in the membrane of nerve cells to open and thereby allows positively charged sodium ions to enter the cell. The sodium ions change the electrical charge from negative to positive and initiate an action potential that travels along the length of the nerve. Human-validated analgesic targets, including the sodium channels $Na_v1.3$, $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$, are of great interest for the development of new pain therapies. Three sodium channels - $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ – are predominantly associated with peripheral neurons rather than central neurons, and they have all been linked to human monogenic pain disorders. Recently, gain-of-function mutations in *SCN9A*, the gene which encodes $Na_v1.7$, have been linked to two human-inherited pain syndromes, inherited erythromelalgia and paroxysmal extreme pain disorder, while loss-of-function mutations in *SCN9A* have been linked to complete insensitivity to pain.

The Structure of TTX restricts it to the Peripheral Nervous System (PNS)

Figure 1: Chemical structure of TTX



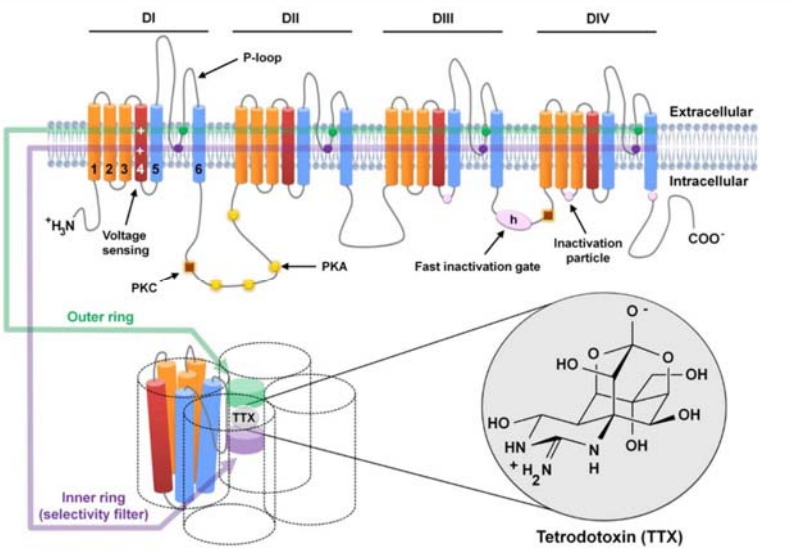
The important thing to note from the molecular structure of TTX (Figure 1) is the large number of oxygen atoms, reflecting the fact that this molecule is very polar. The highly polar nature of the molecule is thought to be important in understanding why TTX works. WEX believes that molecules which do penetrate to the brain to block $Na_v1.7$ end up producing substantial toxicities. In contrast, the highly-charged nature of TTX essentially precludes penetration to the brain and focuses all activity on the periphery. As a result, TTX is a drug that has demonstrated potential efficacy without the safety issues that have derailed the other $Na_v1.7$ blockers.

The Peripheral Action of TTX Inhibits the VGSC Nav1.7 and Blocks Pain

$Na_v1.7$ is preferentially expressed in peripheral somatic and visceral sensory neurons, olfactory sensory neurons and sympathetic ganglion neurons. $Na_v1.7$ accumulates at nerve fiber endings and amplifies small subthreshold depolarizations, positioning it to act as a threshold channel that

regulates excitability. Genetic and functional studies have added to the evidence that $Na_v1.7$ is a major contributor to pain signaling in humans. Homology modelling based on crystal structures of ion channels suggests an atomic-level structural basis for the altered gating of mutant $Na_v1.7$ that causes pain.

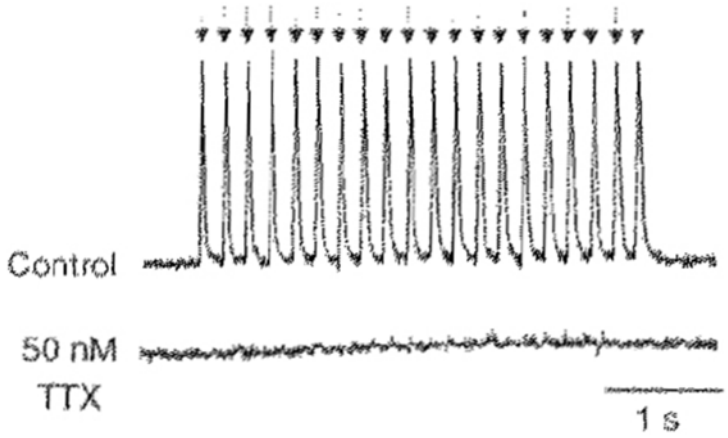
Figure 2: VGSCs are made up of a single polypeptide chain that contains four to six membrane-spanning domains that comprise the sodium pore. TTX blocks the pore of the $Na_v1.7$ channel in a highly selective manner.



TTX binds to neurotoxin receptor site 1 (Figure 2) on the α-subunit within the outer vestibule of the VGSC, and thus blocks the influx of sodium ions by occluding the outer pore of the channel. This binding inhibits electrical potentials, thereby paralyzing nerve and muscle function at high doses and blocking pain at lower doses.

Although TTX fits as a plug into several other sodium channels with varying levels of affinity, it is mainly pertinent to the peripheral $Na_v1.7$ channel. As depicted in Figure 3, when a train of impulses are delivered to a nerve with the $Na_v1.7$ channel, the nerve will fire. However, *with a sufficient quantity of TTX, the nerve firing shuts down. This resulting reduction of nerve firing is the key to the reduction of the pain signal.* In the Figure 3 example, a high concentration of TTX (50nM) was used to completely suppress firing. Clinically, a much lower concentration of TTX (3 nM) is sufficient to reduce firing enough to achieve a clinical effect while allowing the system to function. At this stage of development, WEX is targeting pain reduction, not complete pain elimination.

Figure 3- TTX stops nerve firing.



However, as shown in Table 1, because TTX does not penetrate the blood-brain barrier (BBB), it is unable to reach the $Na_v1.1$, 1.2, 1.3 and 1.6 channels in the brain. In the periphery, TTX has a relatively high affinity for the $Na_v1.7$ and $Na_v1.4$ channels (both at around 25nM EC50, but the affinity for other peripheral Na channels, such as $Na_v1.5$, 1.8, and 1.9, is so much lower (>200X, 2400X, 1600X) that TTX has no effect on them..

Beyond $Na_v1.7$, TTX at therapeutic concentrations has minimal impact on other sodium channels.

Table 1 - TTX's differentiated impact on the sodium channels.

Channel	Predominant distribution	TTX sensitivity
$Na_v1.7$	**PNS (DRG)**	**EC_{50} = 24.5 nM**
$Na_v1.8$	PNS (DRG)	EC_{50} = 60 µM
$Na_v1.9$	PNS (DRG)	EC_{50} = 40 µM
$Na_v1.4$	**Skeletal muscle**	**EC_{50} = 25 nM**
$Na_v1.5$	Heart	**EC_{50} = 5.7 µM**
$Na_v1.1$	CNS	**EC_{50} = 6 nM**
$Na_v1.2$	CNS	**EC_{50} = 18 nM**
$Na_v1.3$	CNS	**EC_{50} = 4 nM**
$Na_v1.6$	**CNS**/PNS	**EC_{50} = 6 nM**

The $Na_v1.4$ channel is encoded by the SCN4A gene and is responsible for the generation and propagation of action potentials in neurons and muscles. WEX has monitored for loss of muscle function outcomes in clinical trial subjects, but at the clinical potentially therapeutic doses

administered, evidence for muscle weakness has been mostly limited to uncommon episodes of some transient weakness of the legs around the time of injection. The relative rarity of this syndrome so far suggests that the low dosing of TTX used in the clinical trial setting is not producing sufficient blockage of the $Na_v1.4$. Because muscle weakness is a known effect of much higher doses of TTX occurring in human poisoning, WEX continues to monitor for skeletal muscle weakness and has studied the effects of *Halneuron* on respiration – with no significant effect currently evident in clinical trials conducted to date.

Mechanism of Action/Pharmacology

TTX mechanism of action assures safety by targeting only the peripheral nervous system (PNS). The $Na_v1.7$ mechanism is the best validated target in all of pain research. Because TTX does not penetrate the BBB, its action is restricted to the peripheral nervous system (PNS). In the PNS, TTX is very specific for the two voltage gated sodium channels, the $Na_v1.7$ system and the $Na_v1.4$ system, thus avoiding other receptors in the central nervous system. The $Na_v1.4$ system is a muscle channel. Blocking the $Na_v1.7$ system has a potent effect on pain, with human and animal data indicating a nearly complete ability to stop the major types of neuropathic and nociceptive pain through this mechanism involving both [i] modification of "generator potentials" which control sensitivity to stimuli and [ii] dorsal root ganglia neurons which appear to integrate with the spinal cord.

Clinical data generated to date in hundreds of patients demonstrates that TTX side effects are mostly mild to moderate and manageable – typically transient mild numbness around the lips or fingertips without the need for any intervention, an adverse event that resolves spontaneously and typically within hours. Moreover, as discussed above, the TTX target, the $Na_v1.7$ channel, is known to play a major role in the transmission of nociceptive and neuropathic pain.

Non-clinical Studies using TTX

Animal pharmacology studies showed that TTX has an analgesic effect. TTX is extremely potent, and much lower (~1000 times less) dosages are needed to produce an analgesic effect than with reference compounds such as aspirin, morphine, and meperidine. The analgesic activity and long-term effects of intramuscular – (i.m).or subcutaneous (s.c.) TTX have been demonstrated in the following animal models of acute and persistent pain: phenylquinone writhing test, visceral pain model, hot-plate and tail-flick tests, postoperative pain model, neuropathic pain model, and an allodynia model showing its activity after acute or 4-7 days of treatment. In rodent studies, TTX at reduced doses in combination with bupivacaine and epinephrine demonstrated long lived local anaesthesia.

WEX has completed a full series of animal toxicology studies as required by regulatory authorities prior to human clinical trials.

Clinical Development Program

Clinical Trials

Every drug in development is required to be tested in clinical trials for new treatments following several defined steps referred to as "Phases". Each phase of clinical trial is designed to answer

specific questions. In general, the most common phases for clinical trials for pain indications are as follows:

Phase 1 trials are often the first time a new therapy is tested in people. This phase is used to see how safe a treatment is and what the best dose is. These trials are usually offered to people who do not have a disease or significant medical condition. The maximum safe dose, schedule and pharmacokinetics are outcomes being tested. There are usually 15 to 50 people in the trial.

Phase 2 trials are used to show how well a treatment works for a certain type of pain condition. They continue to look at how safe the treatment is and what are the possible side effects but also start to determine the potential benefit. There are usually fewer than 100 to 175 people in these types of trials.

Phase 3 trials compare a promising new treatment to the standard available treatment or placebo, which is the accepted and commonly used treatment for a condition or a disease. In particular, researchers want to know if the new treatment is better than the standard one. Phase 3 trials may include people from one or more regions in the world. The usual number of people in the trial is several hundred.

WEX Experience with Clinical Trials of Halneuron

WEX has conducted fourteen clinical trials to date ranging from Phase I to Phase III in Canada, the US, Australia and New Zealand. Studies conducted have included:

Phase I studies – healthy volunteer studies designed to determine:

- maximum tolerated single dose
- dose scheduling
- pharmacokinetics

Phase II studies – in cancer pain patients comparing routes of administration, and preliminary efficacy:

- in cancer pain patients looking at preliminary efficacy
- comparison of subcutaneous versus intramuscular administration
- in chemotherapy induced neuropathic pain patients to determine optimal dose and schedule.

Phase III study – in late stage cancer patients with moderate to sever pain on optimized standard of care.

Key Clinical Trials

The following are summaries of some of the key clinical trials conducted by WEX Pharmaceuticals.

WEX-003: An Open, Multi-Dose Efficacy and Safety Study of Intramuscular Tetrodotoxin in Patients with Severe Cancer-Related Pain

A total of 24 subjects (12 males, 12 females) were treated in the 31 treatment sessions. There were six subjects each treated in the 7.5 μg b.i.d., 15 μg b.i.d., 30 μg b.i.d., and 30 μg t.i.d. dose groups, and seven subjects were treated in the 22.5 μg b.i.d. dose group. All 24 subjects enrolled in the first four dose groups completed the study. Three subjects in the 30 μg t.i.d. dose group discontinued treatment due to adverse events (AEs). There were no major protocol deviations.

The results of the study demonstrate that, in subjects with intractable cancer pain, TTX was effective and well tolerated at doses up to 30 μg b.i.d.

An intent-to-treat (ITT) analysis yielded the following results:

Primary Objective:

- Reductions of subjects' pain intensity were reported for all doses of TTX tested on all the pain scales assessed.
- 55% (17/31) of subjects were classified as Responders or Partial-Responders based on objective criteria.
- 71% (22/31) of subjects were considered to have responded to TTX treatment based on objective criteria or clinical judgement (clinical meaningful response).
- Of the nine subjects who were judged not to have responded to TTX treatment (objective criteria or clinical judgement), two discontinued, and four of seven remaining subjects had pain relief and/or improvement in their neuropathic pain subscales.

Secondary Objectives:

- Four days of TTX treatment resulted in prolonged reduction in pain intensity that was observed during treatment and persisted for a variable length of time during the 11-day post-treatment period. Two subjects had complete analgesic response to at least Day 14.
- Although investigators were encouraged to avoid changes in opioid dose during treatment, a reduction or change in opioid dose was noted in five subjects.
- A clear dose-response relationship for the primary efficacy endpoints was not evident.
- The minimum efficacious dose could not unequivocally be determined since a dose response relationship was not observed.
- No specific pattern of response was observed for cancer type, or pain pathophysiology.

A safety analysis yielded the following results:

- One SAE was reported in this study (ataxia at 30 μg t.i.d). This event resolved without sequalae, however the subject discontinued treatment.
- A total of 531 treatment-emergent adverse events were reported in 24 subjects (31 treatment sessions) with 98% AEs reported as mild or moderate.
- Adverse events with an incidence of ≥ 1%, regardless of relationship to TTX treatment and dose, are: abnormal sensation in eye, hypoaesthesia oral, nausea, vomiting, asthenia, feeling hot, injection site burning, abnormal intraocular pressure test, dizziness, dysguesia, headache, hypoaesthesia, paraesthesia, paraesthesia oral, somnolence, nasal congestion and flushing.

- The most common adverse events reported were related to the known pharmacologic effect of TTX. Paraesthesia and hypoaesthesia appeared to increase in frequency in a dose-dependent manner and were either classified under gastrointestinal disorders (oral) or neurological disorder but are representative of the effects of TTX. They are not considered to pose a safety concern.
- No clinically significant haematology or urinalysis findings were observed.
- The vital sign and ECG results indicate that TTX is well tolerated and does not exert an effect on these measures.
- Doses of TTX up to 30 μg b.i.d. were shown to be safe and tolerable.
- Dose limiting side effects were observed in the 30 μg t.i.d. dose group.

In summary, the 30 μg b.i.d. dosing regimen, which is associated with a high response rate and an acceptable safety tolerability profile, is an appropriate dose for future studies.

WEX-014: A Multicentre, Randomized, Double-blind, Placebo-controlled, Parallel-design Trial of the Efficacy and Safety of Subcutaneous Tetrodotoxin (TTX) for Moderate to Severe Inadequately Controlled Cancer-related Pain

The study population included male or female subjects 18 years of age and over with a diagnosis of cancer, with stable but inadequately controlled pain with current therapy for at least two weeks and with a life expectancy of at least 3 months. Of the 89 enrolled subjects, 89 (100%) received at least one injection. Male subjects represented approximately 55% and 50% of the TTX and Placebo groups, respectively.

An intent-to-treat (ITT) analysis yielded the following results:

As the study was terminated prematurely, the study lacks statistical power and only a trend in favor of TTX over Placebo for the primary endpoint (i.e. responders over the Post-Injection Period (Day 5-15)) was observed (31.1% of responders in TTX group vs. 29.5% in Placebo group, p=0.588). Similar trends were observed for the Injection (IP), Early Post-Injection (EPIP) and Late Post-Injection Period (LPIP).

The composite endpoint defined a response as a mean reduction in pain intensity of at least 30% or a decrease of at least 50% of opioid use from baseline and an improvement greater than 30% of quality of life in at least one descriptor of both emotional and physical functioning during the EPIP or LPIP. The composite endpoint showed a larger trend in favor of TTX over Placebo (27.9% vs. 17.9%, p=0.369). When focusing the analysis on the individual components of the composite endpoint, the pain component did not show a trend in favour of TTX over Placebo (37.2% vs. 43.6%) but there was a trend in favour of TTX for the Physical Functioning QoL Component (55% and 43.6%, respectively, p=0.305) and Emotional Functioning QoL Component (58.5% and 41.0%, respectively, p=0.173). When the high opioid subjects were removed from the ITT population, these trends improved.

A safety analysis yielded the following results:

In the TTX group, 84.1% of the subjects experienced at least one Treatment-Related Treatment Emergent Adverse Event (TEAE) (69.8% in the Placebo group). In the TTX group, the most common TEAEs were nausea, oral hypoaesthesia, oral paraesthesia and vomiting. These TEAEs were part of the known safety profile of TTX and were therefore expected.

Three subjects discontinued the study drug due to Adverse Events. Of these 3 subjects, 2 had metastasis and 1 was an in-patient.

Treatment Emergent Serious Adverse Events (SAE) were experienced by 3 subjects (2 Males, 1 Female) in the TTX group (6.8%) and by 1 subject (Female) in the Placebo group (2.3%). These SAEs were deemed not related to the study drug in all cases.

Three deaths occurred during the course of the study. Of these 3 deaths, 2 were reported in the Placebo group and 1 in the TTX group. The deaths in the Placebo group were deemed not related to the study drug and were caused by the progression of the disease under the study. The cause of the death reported in the TTX group was reported to be progression of disease.

After taking all the points above into consideration, no significant safety trends or concerns were found.

In summary, due to the early termination of the WEX-014 trial at 50% of the recruitment, the results do not demonstrate a clear benefit of TTX in cancer pain management for moderate to severe cancer pain, although a pain reduction has been shown with the proposed dosing. In addition, many of the subjects (~35-40%) experienced a protocol violation which also may have affected the efficacy outcomes in the study.

This study provided evidence that TTX has good tolerability with no SAEs leading to study drug discontinuation or death related to the study drug. The safety data were consistent with the known safety profile of TTX established in previous studies.

In consequence, because of its early termination this study did not demonstrate that TTX has a favorable benefit-risk profile in the treatment of uncontrolled moderate to severe cancer-related pain since its efficacy has not been demonstrated within the scope of the study.

TEC-006: A Multicentre, Randomized, Double-blind, Placebo-controlled, Parallel-design Trial of the Efficacy and Safety of Subcutaneous Tetrodotoxin (TTX) for Moderate to Severe Inadequately Controlled Cancer-related Pain

The planned total sample size was approximately 254 subjects, 127 subjects per group (TTX and Placebo). In total, there were 165 subjects randomized, 77 subjects in the TTX arm and 88 in the Placebo arm. The study population included male and female subjects 18 years of age or more with relatively stable but inadequately controlled moderate to severe cancer-related pain of at least 2 weeks duration. Subjects may have been experiencing visceral, somatic, and/or neuropathic pain.

In total, 147 subjects completed the study, 64 in the TTX arm and 83 in the Placebo arm. In the TTX group, 13 subjects did not complete the study due to AEs and consent withdrawal. In the

Placebo group, 5 subjects did not complete the study due to AEs, consent withdrawal, and non-compliance. The median age was identical in both treatment groups. The average age in both treatment groups was similar in the TTX group compared with the Placebo group.

An intent-to-treat (ITT) analysis yielded the following results:

The primary analysis of the efficacy data from this study supports a clinical benefit of TTX over Placebo on the pre-specified pain intensity endpoint (Co-primary #2) with a clinically significant estimated effect size of 16.2% (p=0.0460) and a number-needed-to-treat (NNT) value of 6.2. However, the proportion of responders to treatment with TTX during EPIP or LPIP was not significantly different from Placebo for the composite endpoint (Co-primary #1) with a response difference of 9.0% (p=0.2035) and a NNT value of 11.1 and for the impact of pain on QoL (physical functioning, difference of 4.6%, p=0.5651 and emotional functioning, difference of 6.9%, p=0.4011).

Upon adjustment for the Baseline factors of age, opioid level, and pain level (VRS), the analysis of the pain intensity endpoint showed a greater effect size and statistical significance with an estimated response difference of 23.1% (TTX – Placebo), nominal p=0.0127 and NNT of 4.3. Baseline factors of age, opioid level, and pain level (VRS) were the only cofactors remaining in a standard forward selection logistic regression based on 6 Baseline factors thought to be possibly clinically relevant and an entry threshold of 0.2. Marginal evidence of an interaction between treatment and Baseline opioid level on the composite endpoint (Co-primary #1) was found (p=0.2188 unadjusted, p=0.0702 adjusted/Firth).

Unadjusted analysis of the primary efficacy endpoints and adjusted analyses with the primary model in the subgroup of subjects on Low Baseline doses of opioids (daily opioid use <500 mg) displayed clinically and nominally statistically significant results.

As demonstrated below in Table 2, if the high-dose patients are removed from the data set, the data show a very significant response for (i) the primary pain endpoint and (ii) the composite endpoint.

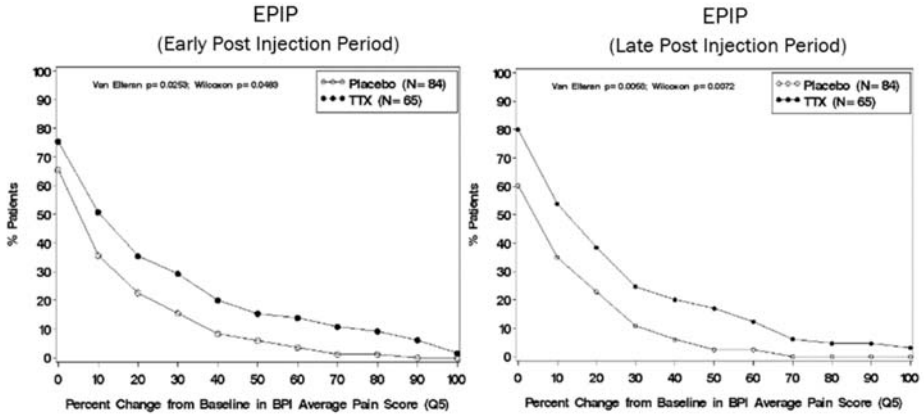
Table 2: Removal of patients receiving high-dose morphine further enhances the effect of Halneuron

	TTX (N=61) n (%)	PLB (N=65) n (%)	Diff (T-P) [95% CI] NNT	P-value*
Pain Primary				
Responder	31 (50.8%)	17 (26.2%)	24.7% [8.2 – 41.1] 4.0	0.0044
Non-Responder	30 (49.2%)	48 (73.8%)		
Composite Primary				
Responder	19 (31.1%)	9 (13.8%)	17.3% [3.0 – 31.6] 5.8	0.0196
Non-Responder	42 (68.9%)	56 (86.2%)		

For the composite endpoint, the difference in responders between TTX and Placebo was 17.3% (nominal p=0.0196) with a corresponding NNT of 5.8 in the unadjusted analysis. In the adjusted analysis, NNT was 5.1 (Odds ratio [OR] 3.128; 95% Confidence interval [CI] 1.209-8.090; nominal p=0.0187). For the pain intensity endpoint, the difference in responders between TTX and Placebo was 24.7% (nominal p=0.0044) with a NNT of 4.0 in the unadjusted analysis. In the adjusted analysis, NNT was 3.7 (OR 3.166; 95% CI 1.428-7.022; nominal p=0.0046).

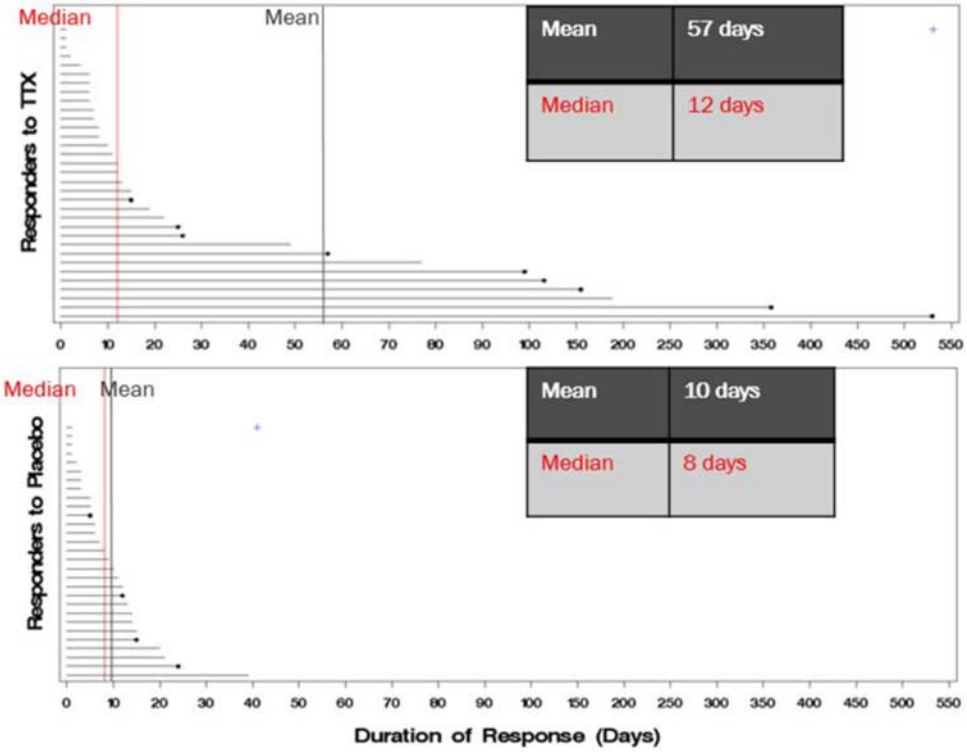
In Figure 4, the percent change of baseline pain was significantly improved in patients given Halneuron. Using the Brief Pain Inventory (BPI) score, a higher percentage of patients that received Halneuron reported an improvement in perceived pain as compared to each patient's baseline pain. These data indicate that in the early or late period, Halneuron's separation from placebo is significant.

Figure 4: Halneuron improves the percentage of patients who perceive an improvement in pain



In Figure 5, the mean and median duration of pain relief are shown on a patient by patient basis for TTX and Placebo. A mean of 57 days of therapeutic effect in the Halneuron treated group versus a mean of 10 days of therapeutic effect in the placebo group. No other therapy has such a long-lasting effect and represents a highly differentiating benefit between Halneuron and other pain drugs.

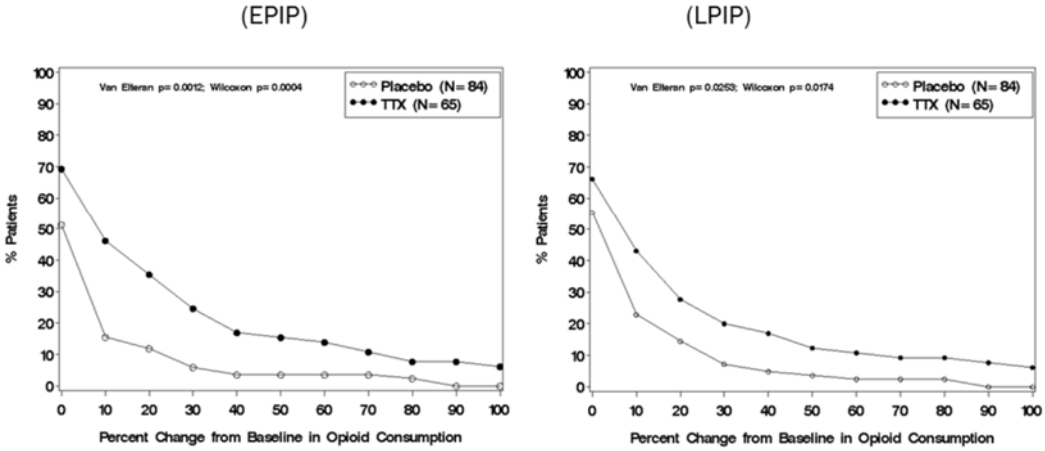
Figure 5: Halneuron provides a more substantial duration in therapeutic benefit over placebo



Halneuron's median pain response was about 20 days and approximately 1/4 of the patients experienced an exceptionally prolonged relief of pain lasting 30, 60, 90, or 120 days.

As Figure 6 shows, these same patients showed a reduced opioid consumption, which provides tangible support for the outcome of the reduction in perceived pain as described above.

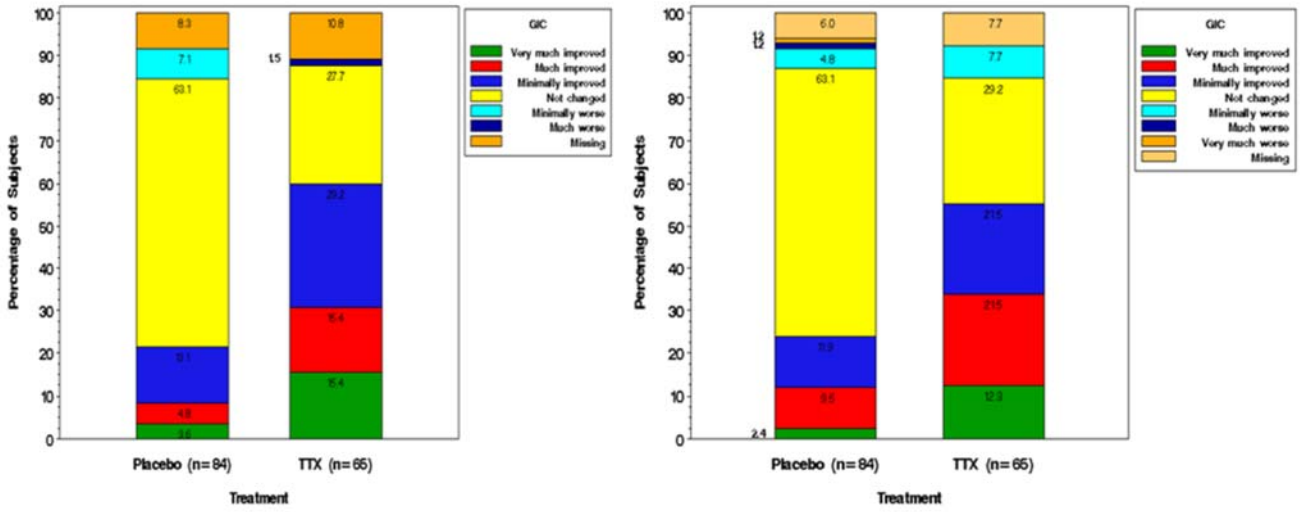
Figure 6: Halneuron treatment reduces overall opioid consumption



Analyses of the subject GIC supported the primary results of nominally statistically and clinically significant benefit of TTX on pain both at EPIP and LPIP. The distribution of GIC was clinically different between TTX and Placebo at EPIP and LPIP with the majority of subjects in the Placebo group reporting no change (63.1%) for the first most bothersome pain and the majority of subjects in TTX reporting improvement (55.4%). Response analyses of GIC supported the primary results with nominally statistically (Chi-square) and clinically significant benefit on pain both at EPIP and LPIP. GIC Strong response (impression defined as Much improved or Very much improved) was significantly higher in TTX-treated subjects than in Placebo-treated subjects at EPIP (30.8% vs 8.3%, nominal p=0.0004, NNT 4.4), LPIP (32.3% vs. 11.9%, nominal p=0.0023, NNT 4.9), and EPIP or LPIP (40.0% vs. 11.9%, nominal p<0.0001, NNT 3.6). When analyzing GIC response including the additional response category of Minimally improved, the proportion of subjects reporting an improvement was higher: 60.0% and 21.4% at EPIP (nominal p<0.0001, NNT 2.6), 55.4% and 23.8% at LPIP (nominal p<0.0001, NNT 3.2), and 67.7% and 31.0% at EPIP or LPIP (nominal p<0.0001, NNT 2.7) in TTX and Placebo respectively. Similar results were obtained in the Low Baseline opioids subgroup.

As seen in Figure 7, patients receiving Halneuron (right hand column) reported favorable results in both the early period (left panel) and the late period (right panel).

Figure 7: Summary figure based on Global Impression of Change showing that patients treated with Halneuron had an overall improvement in positive changes



A safety analysis yielded the following results:

In the TTX group, all subjects (100%) experienced at least 1 TEAE considered related to study drug while 77 subjects (88%) in the Placebo group reported at least 1 TEAE related to study drug. The most common TEAEs and study drug-related TEAEs were in the gastrointestinal disorders body system (nausea, hypoaesthesia oral, paraesthesia oral, and vomiting), nervous system disorders body system (dizziness, hypoaesthesia, paraesthesia, somnolence, headache, and ataxia), and general disorders and administration site conditions body system (injection site irritation, fatigue, injection site pain, and gait disturbance). These TEAEs were expected (part of the known safety profile of TTX). The majority of these most common TEAEs were shown to have a quick onset and a short duration and did not last beyond the 4-day IP.

The analysis of safety in subgroups of the safety population based on subjects' baseline characteristics indicative of their health status (hospital vs. non hospital site, metastases vs. no metastases) suggested that SAEs, drug-related SAEs, and discontinuations due to an AE occurred in a higher proportion in less healthy subjects (hospital sites or metastases subgroups). However, no safety concerns were generally detected in any of these subgroups when examining the incidence of AEs and the type of AEs.

A total of 12 SAEs were experienced by 9 subjects, 6 subjects in the TTX group and 3 subjects in the Placebo group. Of the 12 SAEs reported in the study, 5 were considered related to TTX treatment: cerebral ataxia, neurotoxicity, ataxia, nystagmus, and pneumonia aspiration.
A total of 3 Suspected Unexpected Serious Adverse Reactions (SUSARs) were reported for 2 subjects in the TTX group. One subject experienced 2 SUSARs in the nervous system disorders body system (central nervous toxicity and sensory ataxia) and another subject experienced a SUSAR in the Respiratory, thoracic and mediastinal system disorders (aspirating pneumonia). Additionally, 1 event in the Placebo group (Infections and infestations system disorders, pneumonia) was initially reported as a SUSAR and then reassessed by the investigator and

confirmed by the Sponsor, based on additional information, as not related to the study medication but to disease progression.

The most common TEAEs leading to study termination were nausea, vomiting, dizziness, and fatigue. Three of the events leading to study termination in the TTX group were also SAEs: cerebral ataxia and neurotoxicity for 1 subject and sepsis for another.

After review of the medications initiated after randomization for all randomized subjects, no significant safety trends or concerns were found.

The results from the TEC-006 study provide clinically relevant evidence that TTX can be of potential benefit in cancer pain management for moderate to severe cancer pain, particularly in subjects receiving low daily doses of opioids (<500 mg), as an adjunct to opioid therapy or in opioid-intolerant subjects. The safety data were consistent with the known safety profile of TTX established in previous studies.

TTX demonstrates a favorable benefit-risk profile in the treatment of uncontrolled moderate to severe cancer-related pain and may play an important role to address a major unmet medical need.

Phase II: A Randomized, Double-Blind, Dose-Finding, Placebo-Controlled, Phase II, Multicenter Study of Tetrodotoxin in the Treatment of Chemotherapy-Induced Neuropathic Pain

The trial was originally intended to have two parts: Part I, dose-ranging; and Part II, confirmatory proof of concept trial. The results of the dose-ranging trial, although not powered for statistical significance, were sufficiently clear and consistent with prior knowledge from the dosing of the TEC-006 Cancer Pain trial, that the trial was terminated early. Interim analysis was completed and thereafter WEX decided to proceed to a Phase III trial. The Part I study included 5 dosing cohorts of 25 subjects each (four active and one placebo) and involved 30 days screening and washout with a single 28 day sequence of treatment (four days of BID injections) and patient follow-up (total approximately 58 days) intended to identify up to two doses/regimens of TTX to bring forward to Part II for further evaluation.

Primary outcome measures were efficacy and safety. The study is currently in the process of being published.

Halneuron Overall Safety Profile

Halneuron has been administered to 531 patients in the course of its overall clinical development to date. The extent of data concerning Halneuron's safety is large:

- 13 completed safety studies
- 531 patients and healthy subjects exposed to Halneuron to date
- 348 cancer patients received Halneuron
- 157 cancer patients received placebo

Table 3 to Table 5 below describe the adverse events ("AEs") for healthy volunteers, CINP and CRP patients. The AE's have been contemporaneous with the time of injection and have been mild to moderate in severity. The most common reported side effect is a transient numbness and/or tingling sensation:

Table 3: Summary of Single Dose Healthy Volunteer Groups Ten Most Frequent Adverse Events Ranked by Preferred Terms

AE Preferred Term	Rank	System Organ Class	Total TTX AEs (%)	TTX 30 – 45 µg		Placebo	
				# AEs (%)	# Subjects (%)	# AEs (%)	# Subjects (%)
			N=519	N=363	N=76	N=41	N=43
Hypoesthesia	1	Nervous system disorders	121 (23.3)	103(28.4)	39 (51.3)	0 (0.0)	0 (0.0)
Paraesthesia	2	Nervous system disorders	61 (11.8)	46 (12.7)	21 (27.6)	0 (0.0)	0 (0.0)
Paraesthesia oral	3	Gastrointestinal disorders	55 (10.6)	35 (9.6)	19 (25.0)	0 (0.0)	0 (0.0)
Hypoesthesia oral	4	Gastrointestinal disorders	42 (8.1)	26 (7.2)	18 (23.7)	1 (2.4)	1 (3.6)
Nausea	5	Gastrointestinal disorders	28 (5.4)	21 (5.8)	14 (18.4)	2 (4.9)	2 (7.1)
Dizziness	6	Nervous system disorders	24 (4.6)	15 (4.1)	4 (5.3)	2 (4.9)	2 (7.1)
Headache	7	Nervous system disorders	18 (3.5)	14 (3.9)	6 (7.9)	5 (12.2)	4 (14.3)
Injection site pain	8	General disorders and administration site conditions	11 (2.1)	11 (3.0)	11 (14.5)	2 (4.9)	2 (7.1)
Hyporeflexia	9	Nervous system disorders	9 (1.7)	0 (0.0)	0 (0.0)	1 (2.4)	1 (3.6)
Feeling abnormal	10	General disorders and administration site conditions	7 (1.3)	6 (1.7)	1 (1.3)	0 (0.0)	0 (0.0)
Feeling hot	10	General disorders and administration site conditions	7 (1.3)	4 (1.1)	1 (1.3)	1 (2.4)	1 3.6)

Table 4: Summary of CINP Ten Most Frequent Adverse Events Ranked by Preferred Terms

AE Preferred Term	Rank	System Organ Class	Total TTX AEs (%)	120 µg cumulative (30 µg q.d. x 4 d)		240 µg cumulative (30 µg b.i.d. x 4 d)		Placebo	
				# AEs (%)	# Subjects (%)	# AEs (%)	# Subjects (%)	# AEs (%)	# Subjects (%)
			N=894	N=159	N=25	N=304	N=26	N=181	N=25
Paraesthesia oral	1	Gastrointestinal disorders	141 (15.8)	25 (15.7)	10 (40.0)	61 (20.1)	11 (42.3)	8 (4.4)	3 (12.0)
Hypoaesthesia oral	2	Gastrointestinal disorders	131 (14.7)	23 (14.5)	6 (24.0)	33 (10.9)	10 (38.5)	9 (5.0)	3 (12.0)
Paraesthesia	3	Nervous system disorders	87 (9.7)	17 (10.7)	5 (20.0)	30 (9.9)	7 (26.9)	11 (6.1)	6 (24.0)
Headache	4	Nervous system disorders	44 (4.9)	4 (2.5)	1 (4.0)	19 (6.3)	9 (32.6)	22 (12.2)	5 (20.0)
Nausea	5	Gastroinstestinal disorders	37 (4.1)	8 (5.0)	1 (4.0)	9 (3.0)	6 (23.1)	10 (5.5)	6 (24.0)
Dizziness	6	Nervouse system disorders	35 (3.9)	3 (1.9)	3 (12.0)	17 (5.6)	8 (30.8)	6 (3.3)	5 (20.0)
Oral dysesthesia	7	Nervous system disorders	30 (3.4)	4 (2.5)	1 (4.0)	12 (3.9)	2 (7.7)	0 (0.0)	0 (0.0)
Pain in extremity	8	Musculoskeletal and connective tissue disorders	27 (3.0)	9 (5.7)	4 (16.0)	8 (2.6)	3 (11.5)	16 (8.8)	2 (8.0)
Injection site pain	9	General disorders and adminstration site conditions	23 (2.6)	0 (0.0)	0 (0.0)	1 (0.3)	1 (3.8)	0 (0.0)	0 (0.0)
Dysgeusia	10	Nervouse system disorders	21 (2.3)	3 (1.9)	2 (8.0)	7 (2.3)	3 (11.5)	0 (0.0)	0 (0.0)
Fatigue	10	General disorders and adminstration site conditions	21 (2.3)	8 (5.0)	5 (20.0)	3 (1.0)	3 (11.5)	5 (2.8)	4 (16.0)

Table 5: Summary of Single Cycling Dosing Cancer Related Pain Ten Most Frequent Adverse Event Preferred Terms by Group

AE Preferred Term	Rank	System Organ Class	Total TTX AEs (%)	240 - 360 µg cumulative (30 µg b.i.d. and 30 µg t.i.d. x 4 d)		Placebo	
				# AEs (%)	# Subjects (%)	# AEs (%)	# Subjects (%)
			N=2918	N=2652	N=133	N=1203	N=121
Hypoaesthesia oral	1	Gastrointestinal disorders	514 (17.6)	460 (17.3)	72 (54.1)	35 (2.9)	12 (9.9)
Paraesthesia oral	2	Gastrointestinal disorders	311 (10.7)	280 (10.6)	59 (44.4)	11 (0.9)	6 (5.0)
Injection site irritation	3	General disorders and adminstration site conditions	223 (7.6)	223 (8.4)	47 (35.3)	355 (29.5)	62 (51.2)
Hypoaesthsesia	4	Nervous system disorders	221 (7.6)	216 (8.1)	61 (45.9)	23 (1.9)	14 (11.6)
Nausea	5	Gastroinstestinal disorders	200 (6.9)	190 (7.2)	84 (63.2)	61 (5.1)	31 (25.6)
Dizziness	6	Nervouse system disorders	152 (5.2)	147 (5.5)	72 (54.1)	43 (3.6)	22 (18.2)
Paraesthesia	7	Nervous system disorders	148 (5.1)	144 (5.4)	44 (33.1)	26 (2.2)	11 (9.1)
Injection site pain	8	General disorders and adminstration site conditions	102 (3.5)	102 (3.8)	23 (17.3)	120 (10.0)	32 (26.4)
Vomiting	9	Gastrointestinal disorders	75 (2.6)	71 (7.2)	39 (29.3)	15 (1.2)	13 (10.7)
Headache	10	Nervous system disorders	55 (1.9)	51 (1.9)	29 (21.8)	30 (2.5)	23 (19.0)

It is noteworthy that vomiting in *Halneuron* treatment in Table 5 is overwhelmingly a phenomenon seen in CRP patients on significant doses of opioids, drugs that predispose patients to nausea and vomiting. Rates in the CINP patient population and healthy volunteer studies are much lower. There has been no need to pre-treat or treat patients in clinical trials with anti-emetic agents.