TETRODOTOXIN FOR MODERATE TO SEVERE CANCER-RELATED PAIN
A MULTICENTRE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-DESIGN TRIAL

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INTRODUCTION

Pain related to cancer is highly prevalent, and existing treatments do not always work. Additional analgesic approaches are needed. Tetrodotoxin (TTX) is a small molecule that blocks voltage-gated sodium channels (VGSCs) on neurons, and likely exerts its analgesic properties by inhibiting the initiation and conduction of impulses in the peripheral nervous system. Clinical trials have been ongoing to evaluate the analgesic effect of TTX in cancer pain.

OBJECTIVES

Primary Objectives:
- To compare the efficacy of subcutaneous TTX with that of placebo as measured by:
  - Pain outcome (pain intensity reduction by ≥ 30%) or use of opioids (decrease by >50%).
  - Improvement in quality of life (≥30% physical AND emotional functioning).
- To compare the safety of subcutaneous TTX with that of placebo.

Secondary Objective:
- To determine the duration of analgesic response associated with subcutaneous TTX treatment.

METHODS

FOUR STUDY PERIODS

Screening	Up to 28 days
Baseline	Up to 7 days (minimum 4 days)
Treatment	4 days of b.i.d. TTX 30 µg or placebo
Follow-up	Days 5-8: Early post injection period
	Days 9-15: Late post injection period
	> Day 15: Weekly

Main Inclusion Criteria
- ≥ 18 years of age
- Patients with a diagnosis of cancer
- Stable baseline pain intensity score of ≥4 (/10) as assessed by numeric rating scale

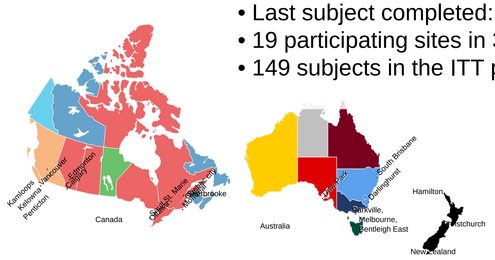
Main Exclusion Criteria
- History of significant respiratory disease, renal impairment, or positive pregnancy test

Data Analysis

Efficacy and safety analyses were performed on the modified Intent-to-Treat (mITT) population defined as all randomized subjects who had at least 1 injection of study medication and at least 1 post-Baseline efficacy assessment (n = 149).

RESULTS: CO-PRIMARY ENDPOINTS

- 165 subjects were randomized
- First subject enrolled: April 2008
- Last subject completed: August 2012
- 19 participating sites in 3 countries
- 149 subjects in the ITT population



PRIMARY ANALYSIS
All completed patients with Full Data (n=149)

	QOL plus Pain Composite Endpoint	Pain Co-Primary Endpoint
% responder:		
TTX	**29.2**	**50.8**
Placebo	**20.2**	**34.5**
TTX–Placebo: Difference	**9.0**	**16.2**
P-value	**0.2035**	**0.0460**
NNT	**11.1**	**6.2**

Efficacy: Unadjusted responder rate analysis on all completed 149 patients with full data supports a clinical benefit on the primary pain endpoint, significant at the one-sided 5% level (p=0.0460) but not at the pre-specified two-sided 5% level.

RESULTS: ADVERSE EVENTS

	TTX	Placebo
Most common AEs		
Nausea	68% (10% severe)	23% (2% severe)
Dizziness	61% (4% severe)	18% (0% severe)
Oral hypoesthesia	61% (0% severe)	9% (0% severe)
Hypoesthesia	48% (0% severe)	10% (0% severe)
Oral paresthesia	44% (0% severe)	2% (0% severe)
Vomiting	34% (3% severe)	8% (0% severe)
Injection site irritation	52% (6% severe)	53% (7% severe)
SAEs (n=12)	6 patients	3 patients

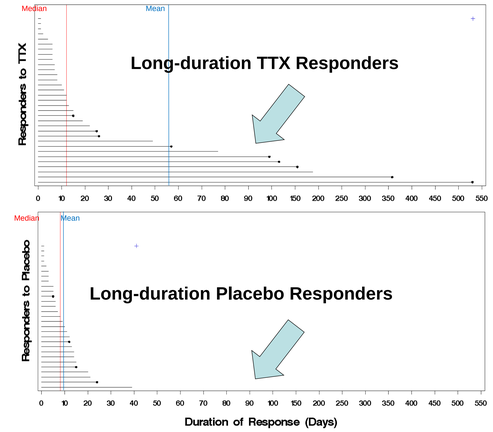
SAEs related to TTX (after unblinding): 5 events from 3 subjects: cerebral ataxia, neurotoxicity, ataxia, nystagmus, and aspiration pneumonia

Safety: Most treatment-emergent adverse events (TEAEs) were mild to moderate, transient, self-limiting, and could be managed with standard supportive care.

RESULTS: FOUR SECONDARY ENDPOINTS

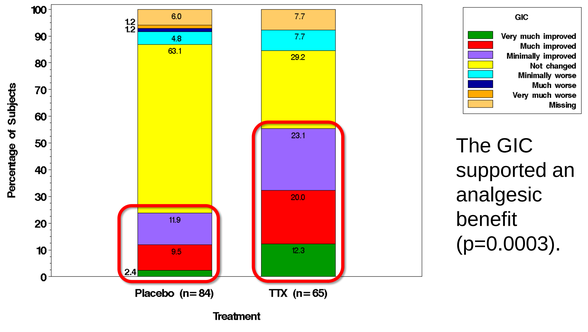
Several secondary endpoints and analyses were achieved, consistent with an analgesic effect.

A. Duration of Analgesic Response



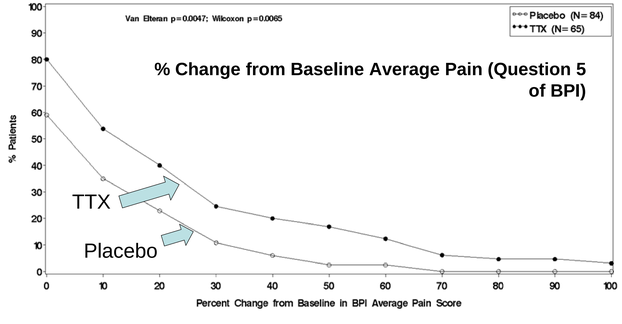
The median duration of pain response was 12 days with TTX vs 8 days for placebo (p=0.0345). There were more long duration responders in the TTX group.

B. Patient Global Impression of Change (GIC)



The GIC supported an analgesic benefit (p=0.0003).

C. Cumulative Proportion of Responders Analyses (ITT) at Late Post-Injection Period, Days 9-15



D. Low Opioid Subgroup Results

Original (n=126)	Unadjusted	Covariate-Adjusted
% responder (pain endpoint):		
TTX	**50.8**	**52.9**
Placebo	**26.2**	**26.2**
TTX–Placebo: Difference	**24.7**	**26.7**
P-value	**0.004**	**0.005**
NNT	**4.0**	**3.7**

This Figure shows the analgesic response in the subgroup of patients who received <500 mg mean equivalent dose opioids per day (n=126 out of a total of138 in the subgroup, or 84% of overall cohort)

CONCLUSIONS

Co-Primary Endpoints
- Composite Pain and QOL: missed (as have most analgesic trials with this design!)
- Pain: close (significant at one-sided but not 2-sided t-test).
- Magnitude of effect: NNT is about 4-6.

Secondary Endpoints and Analyses

An analgesic signal is present:
- ✓ Duration of Analgesic Response.
- ✓ Patient Global impression of Change.
- ✓ Low Opioid Dose Subgroup.
- ✓ Cumulative Proportion of Responders Analyses.

This multicentre, randomized, double-blind, placebo-controlled, parallel-design trial shows a clinically important analgesic effect (NNT about 4-6) in a cohort of patients with advanced illness and otherwise poorly controlled cancer pain.

Acknowledgements

We wish to acknowledge the many cancer patients with advanced illness and poorly controlled symptoms who selflessly enrolled in this trial.

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