Tetrodotoxin for Chemotherapy Induced Neuropathic Pain

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Background

Tetrodotoxin (TTX) is a small molecule inhibitor of voltage-gated sodium channels. It is postulated that the compound causes analgesia via inhibition of initiation and conduction of action potentials in the peripheral nervous system. TTX is under investigation for the treatment of chemotherapy induced neuropathic pain (CINP) and cancer pain.

Study Design

Phase II randomized, double-blind, dose-finding, placebo-controlled, multicenter study of the potential efficacy and safety of TTX in subjects with chemotherapy induced neuropathic pain (CINP).

Objectives

Primary: To identify up to 2 doses / regimens of TTX for phase III evaluation

Secondary: To determine the safety and tolerability of multiple doses / regimens of TTX

Key Inclusion Criteria

- Adults (≥ 18 years) with moderate to severe CINP attributed to a taxane or platinum chemotherapy
- Stable baseline pain intensity ≥ 4 (/10), for at least one week
- Thirty day washout from chemotherapy
- ECOG 0 or 1
- No evidence of progressive disease

Key Exclusion Criteria

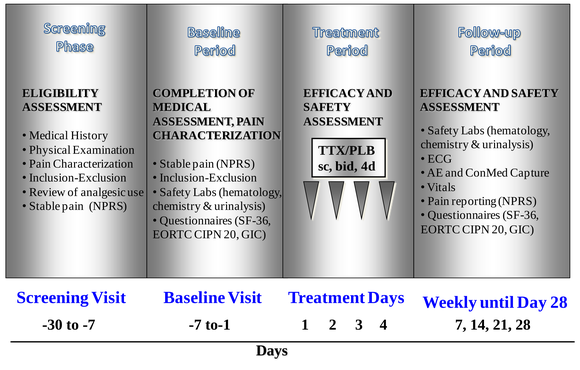
- History of peripheral neuropathy due to causes other than chemotherapy, or receiving concurrent agents known to cause peripheral neuropathy
- Concurrent cancer treatment
- Use of other sodium channel blocking agents, alternative therapies, or investigational agents
- Significant respiratory disease, renal impairment, cardiac arrhythmia, or pregnancy

Dosing Cohorts

Patients with taxane or platinum induced CINP were randomized to one of five cohorts. TTX or placebo was injected subcutaneously for four consecutive days.

Cohort	n	Drug Dose (TTX/Placebo)	Dosing Schedule		Dosing Duration	Cumulative Dose
			TTX	Placebo		
1	25	Placebo	NA	BID	4 days	NA
2	25	7.5 µg	BID	NA	4 days	60 µg
3	25	15 µg	BID	NA	4 days	120 µg
4	25	30 µg	QD	QD	4 days	120 µg
5	25	30 µg	BID	NA	4 days	240 µg

Study Procedures



Study Populations

- 125 subjects randomized
- 125 in the ITT population
- 107 subjects in the PP population

Results

Primary Endpoint – Week 4 NPRS Pain Score

	Cohort 1 (7.5 µg BID)	Cohort 2 (15 µg BID)	Cohort 3 (30 µg QD)	Cohort 4 (30 µg BID)	Placebo
Week 1	-0.836 (0.9553)	-0.891 (0.8396)	-1.006 (1.6116)	-1.244 (1.5911)	-0.906 (1.1193)
Week 2	-1.164 (1.3583)	-1.218 (1.1188)	-1.508 (1.8307)	-1.433 (1.7853)	-1.423 (1.7218)
Week 3	-1.197 (1.4770)	-1.277 (1.6375)	-1.670 (2.0198)	-1.555 (1.5565)	-1.365 (1.8792)
Week 4	-1.269 (1.3959)	-1.052 (1.5742)	-1.682 (2.3231)	-1.529 (1.8203)	-1.339 (2.0681)

Change from baseline in the average scores at Week 4 is largest in Cohorts 3 and 4.

Responder Analyses: 30% reduction in average NPRS score from baseline to any week

	Cohort 1 (7.5 µg BID)	Cohort 2 (15 µg BID)	Cohort 3 (30 µg QD)	Cohort 4 (30 µg BID)	Placebo
Yes	9 (36.0%)	11 (45.8%)	10 (40.0%)	15 (57.7%)	8 (32.0%)
No	16 (64.0%)	13 (54.2%)	15 (60.0%)	11 (42.3%)	17 (68.0%)
P-value	0.333	0.0657	0.992	0.072	

	Cohort 1 (7.5 µg BID)	Cohort 2 (15 µg BID)	Cohort 3 (30 µg QD)	Cohort 4 (30 µg BID)
Odds Ratio (vs. placebo)	1.12	1.99	1.65	3.39
95% CI for Odds Ratio	(0.32, 3.96)	(0.56, 7.13)	(0.46, 5.90)	(0.96, 11.97)

Responder Analyses: 30% reduction in average NPRS score from baseline to any 10 consecutive days

	Cohort 1 (7.5 µg BID)	Cohort 2 (15 µg BID)	Cohort 3 (30 µg QD)	Cohort 4 (30 µg BID)	Placebo
Yes	8 (32.0%)	10 (41.7%)	10 (40.0%)	15 (57.7%)	8 (32.0%)
No	17 (68.0%)	14 (58.3%)	15 (60.0%)	11 (42.3%)	17 (68.0%)
P-value	0.178	0.871	0.935	0.027	

	Cohort 1 (7.5 µg BID)	Cohort 2 (15 µg BID)	Cohort 3 (30 µg QD)	Cohort 4 (30 µg BID)
Odds Ratio (vs. placebo)	0.90	1.68	1.63	3.90
95% CI for Odds Ratio	(0.25, 3.24)	(0.47, 6.06)	(0.45, 5.83)	(1.08, 14.09)

Treatment Emergent Adverse Events

Parameter	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Placebo
Number of Subjects with at least 1 AE	21 (84.0%)	22 (91.7%)	20 (80.0%)	24 (92.3%)	18 (72.0%)
Number of SAE	0	1 (4.2%)	0	1 (3.8%)	1 (4.0%)

- Three patients suffered SAEs, two unrelated and one unlikely related to TTX
- Most AE reported were mild or moderate in severity
- Four subjects (all from Cohort 4) experienced a total of seven grade 3 AE (paresthesia, burning sensation, pain, hypertension, viral URI
- There were no grade 4 AE

Nervous system AE

System Organ Class Preferred Term	Cohort1 (N=25)	Cohort2 (N=24)	Cohort3 (N=25)	Cohort4 (N=26)	Placebo (N=25)
Nervous system disorders	13 (52.0%)	16 (66.7%)	17 (68.0%)	20 (76.9%)	11 (44.0%)
Paresthesia oral	4 (16.0%)	9 (37.5%)	10 (40.0%)	11 (42.3%)	3 (12.0%)
Hypesthesia oral	5 (20.0%)	7 (29.2%)	6 (24.0%)	10 (38.5%)	3 (12.0%)
Paresthesia	5 (20.0%)	7 (29.2%)	5 (20.0%)	7 (26.9%)	6 (24.0%)
Headache	6 (24.0%)	3 (12.5%)	1 (4.0%)	9 (34.6%)	5 (20.0%)
Dizziness	3 (12.0%)	4 (16.7%)	3 (12.0%)	8 (30.8%)	5 (20.0%)
Hypesthesia	2 (8.0%)	1 (4.2%)	2 (8.0%)	1 (3.8%)	2 (8.0%)

*All grade 1 or 2 save for one event of grade 3 paresthesia.

Conclusions

- TTX was safe and well-tolerated in all cohorts
- 30 µg BID is the most promising dose / schedule
- Phase III trial of TTX for CINP is in development

Disclosure

This study was funded by WEX Pharmaceuticals Inc.