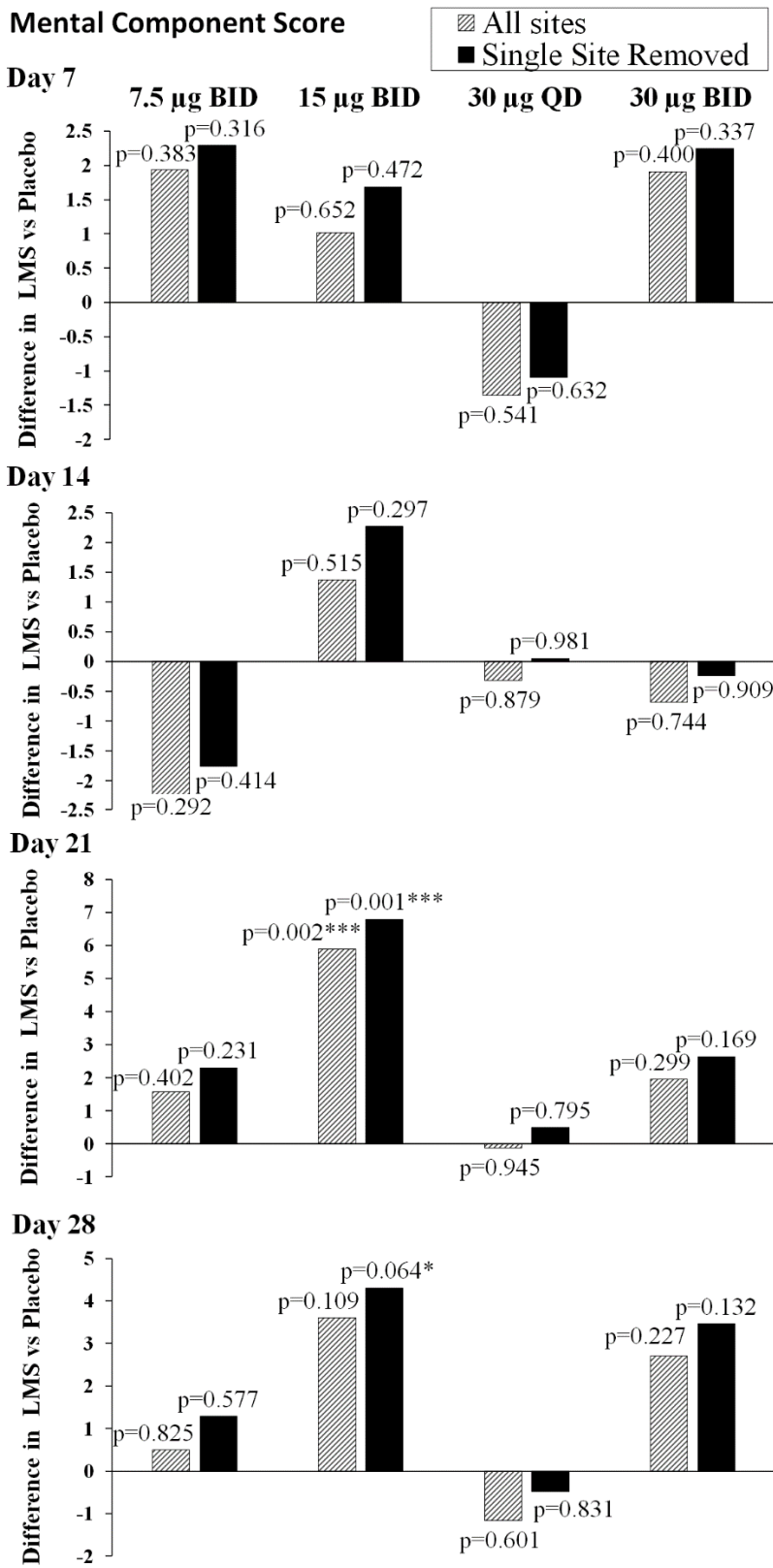
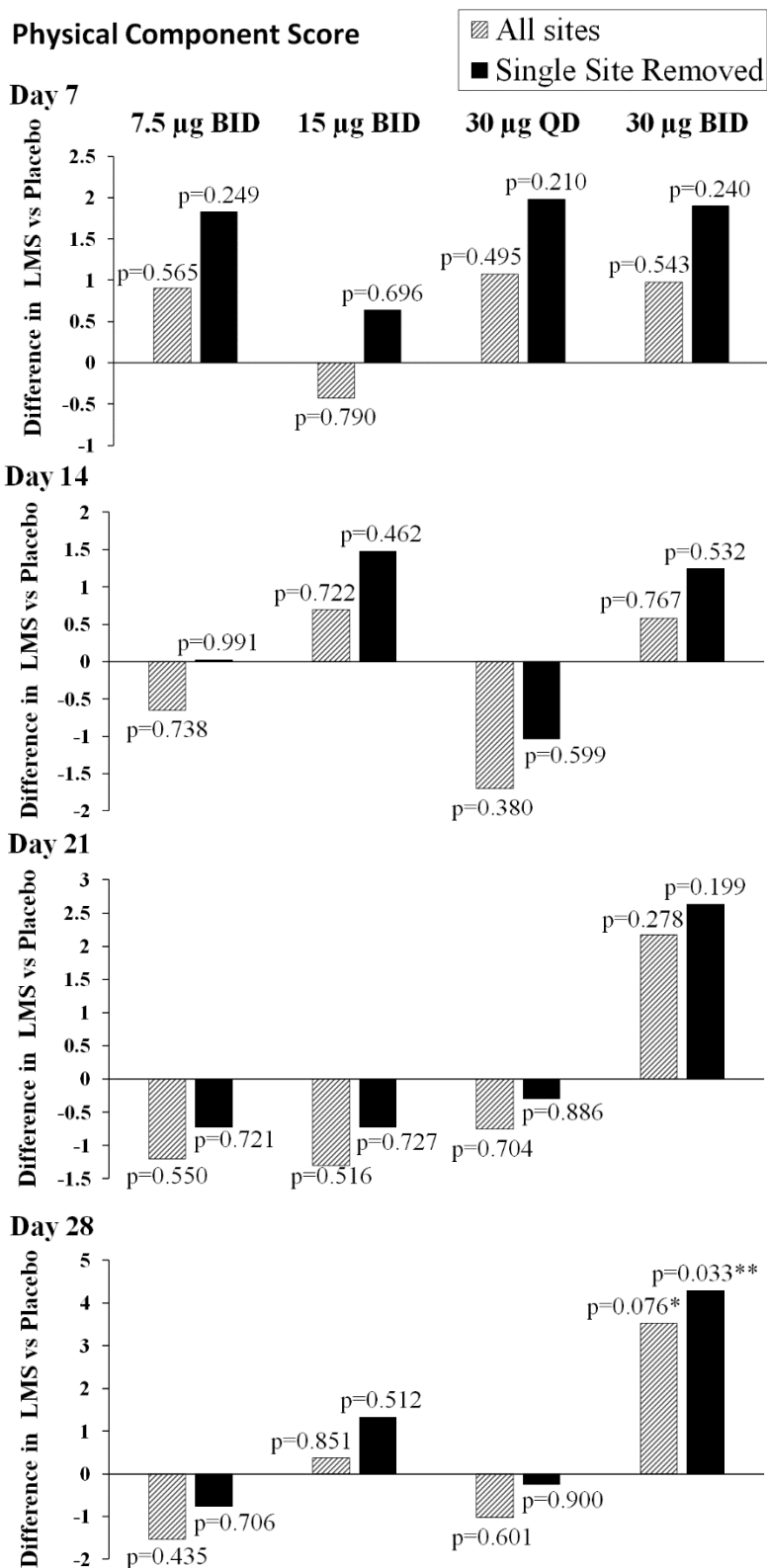


---

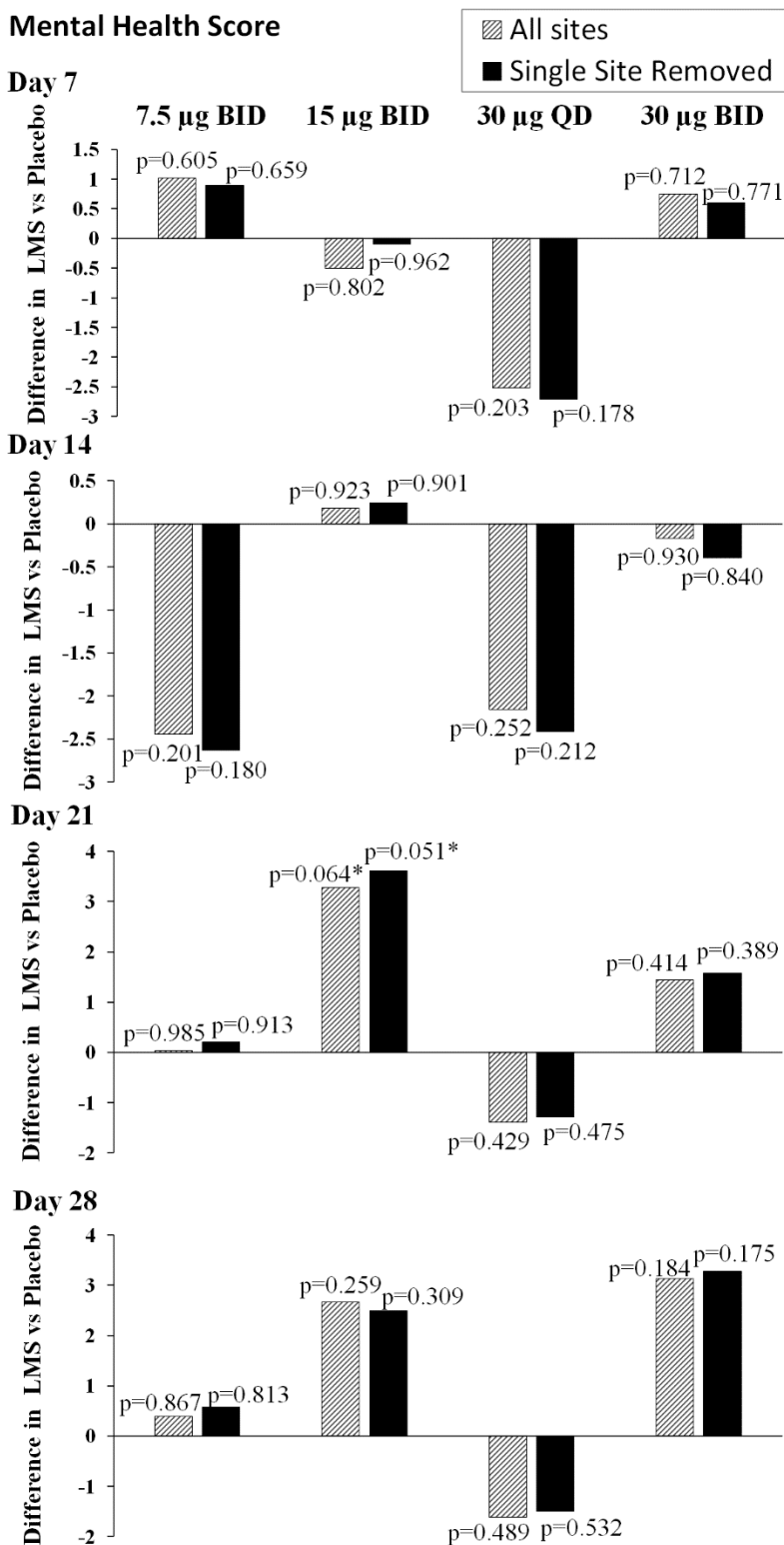
# **Supplementary Materials: Tetrodotoxin for Chemotherapy-Induced Neuropathic Pain: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Dose Finding Trial**

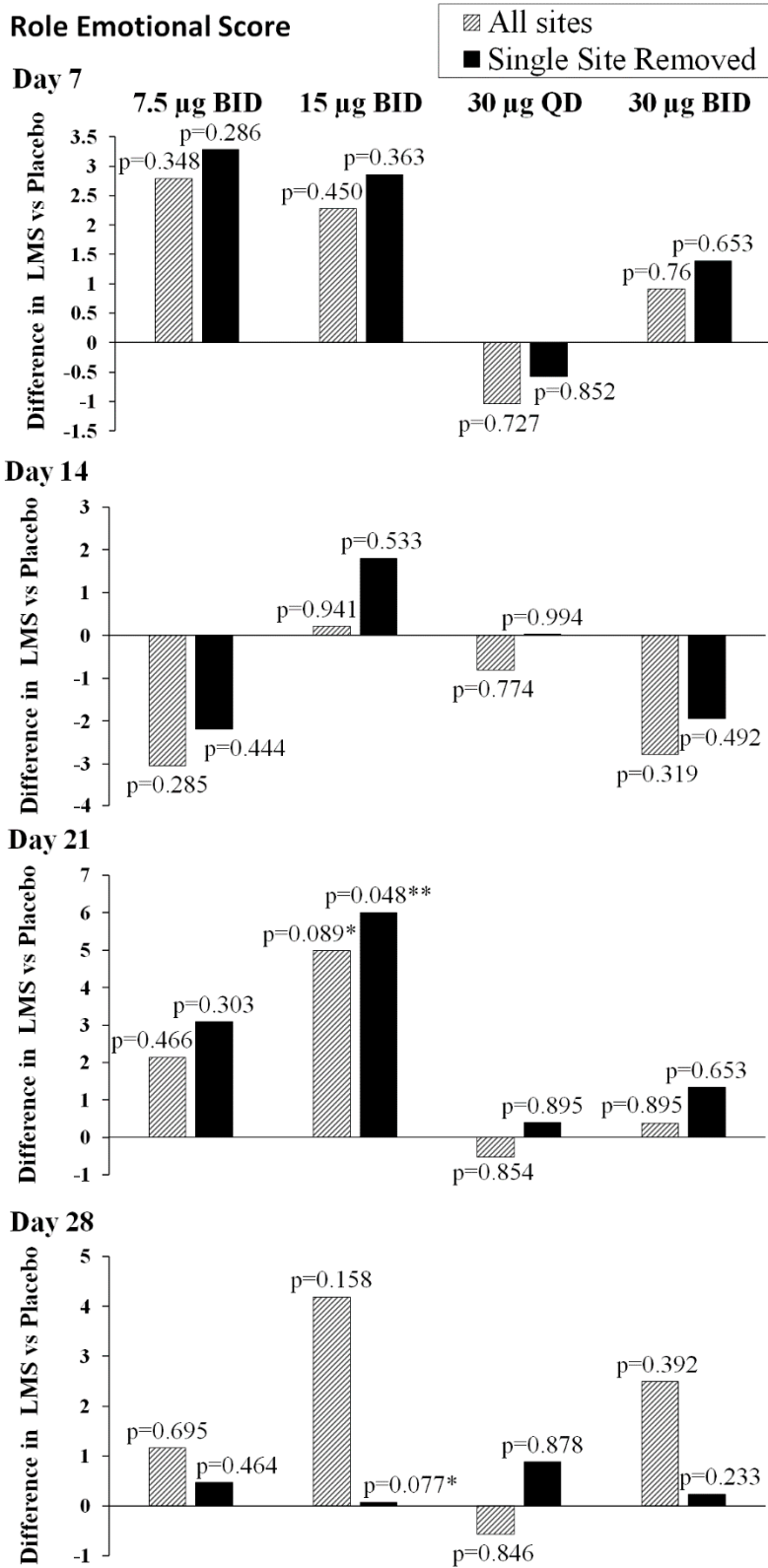
Samuel A. Goldlust, Mojgan Kavooosi, Jennifer Nezzar, Mehran Kavooosi, Walter Korz and Kenneth Deck

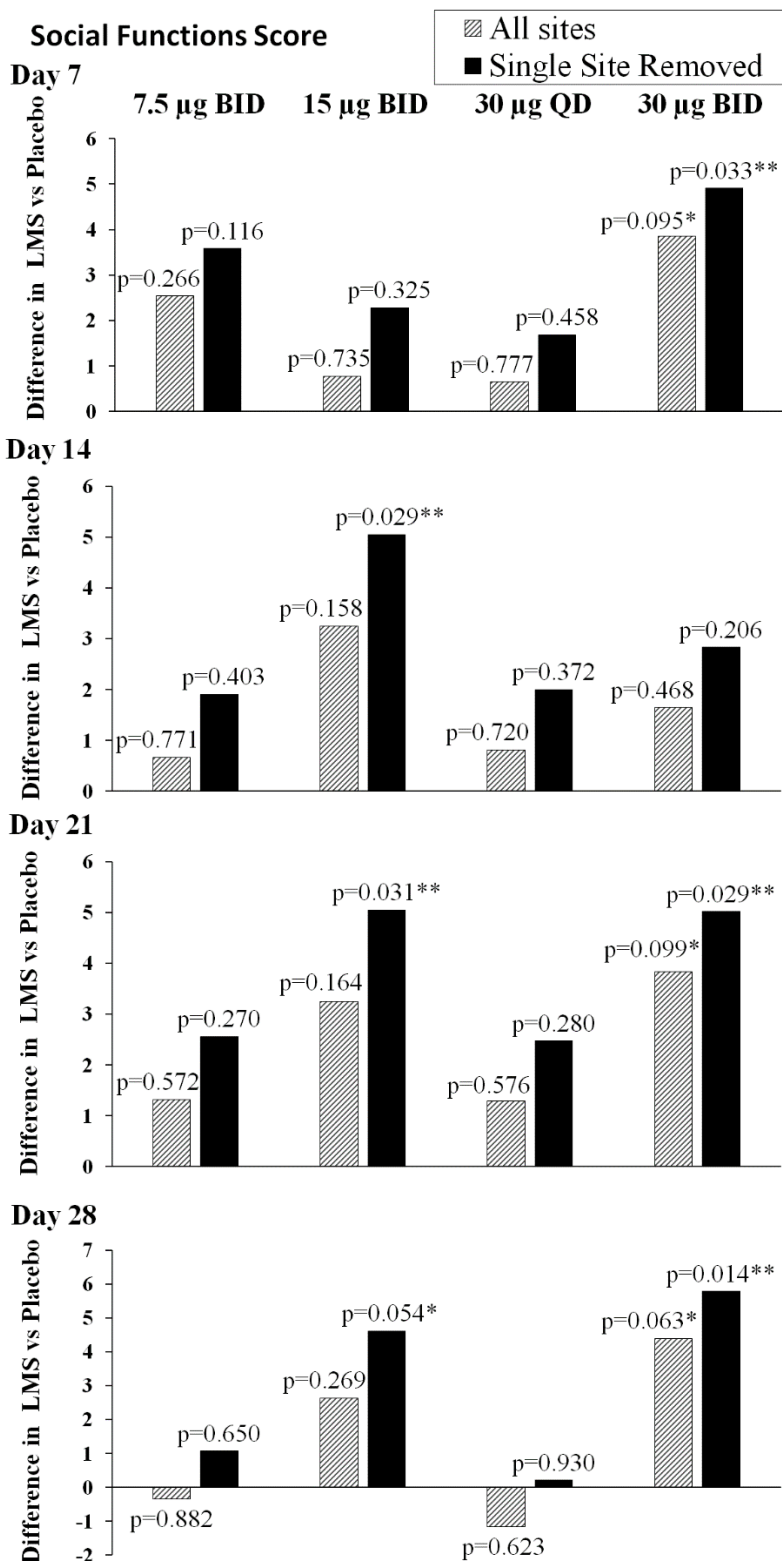


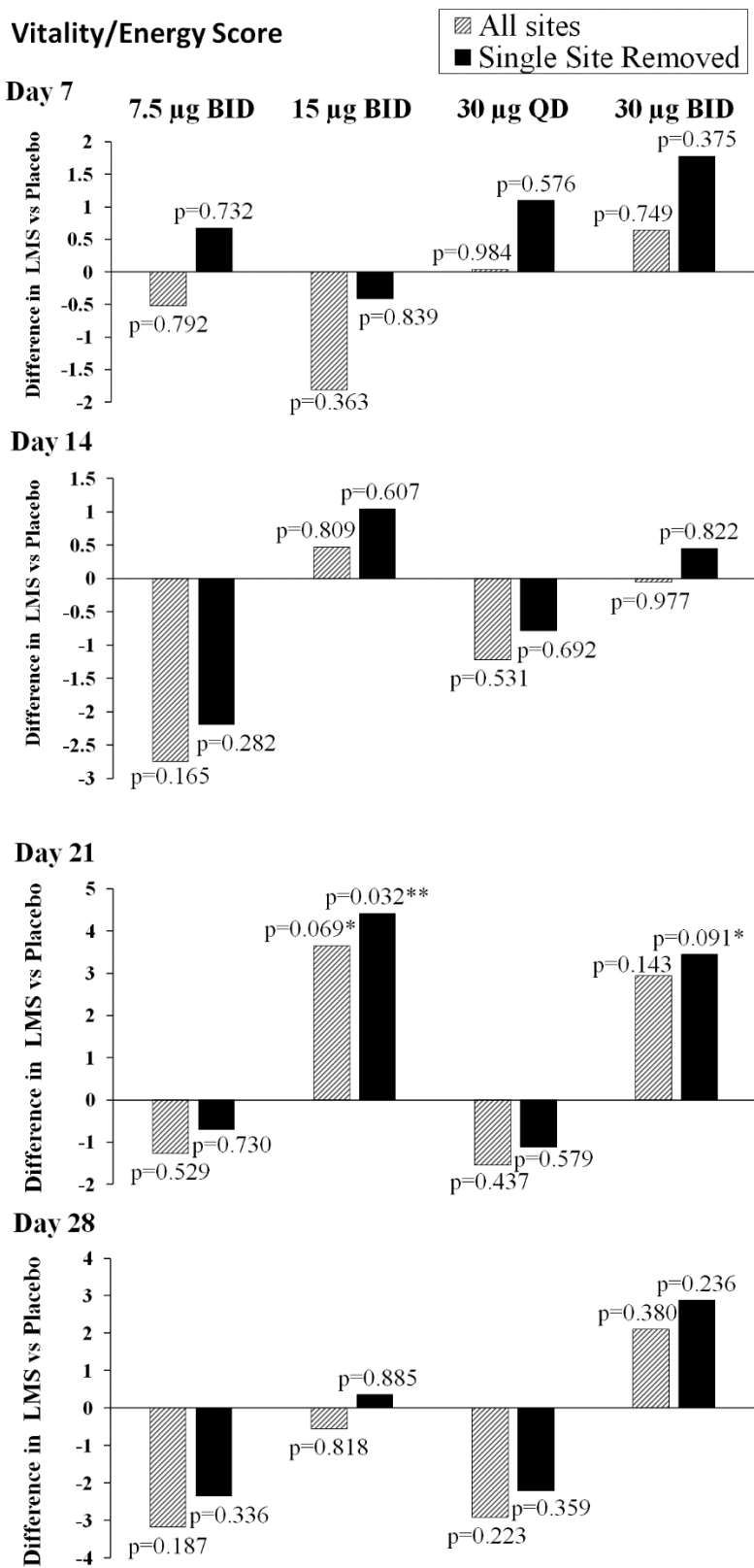


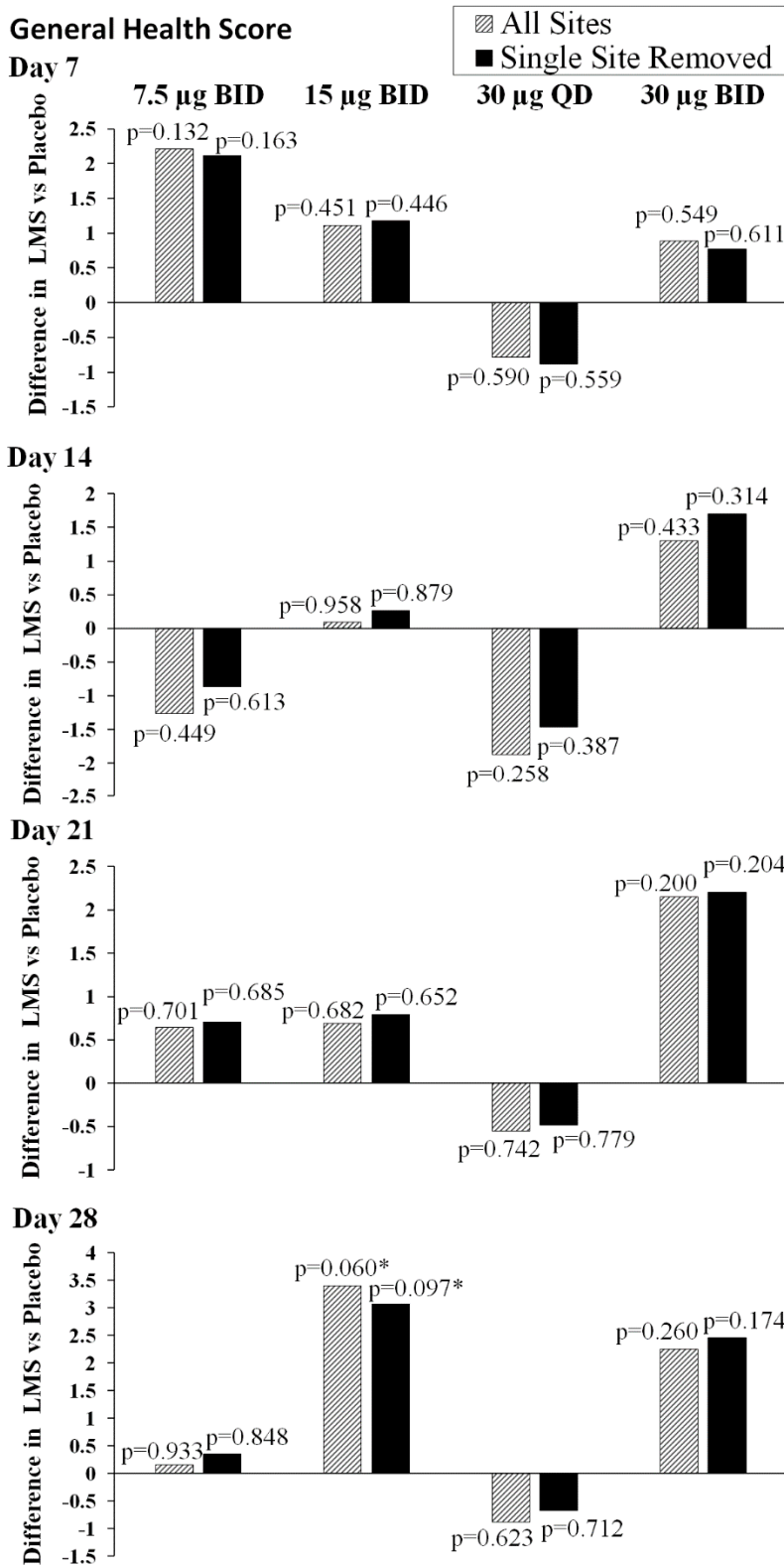
### Mental Health Score



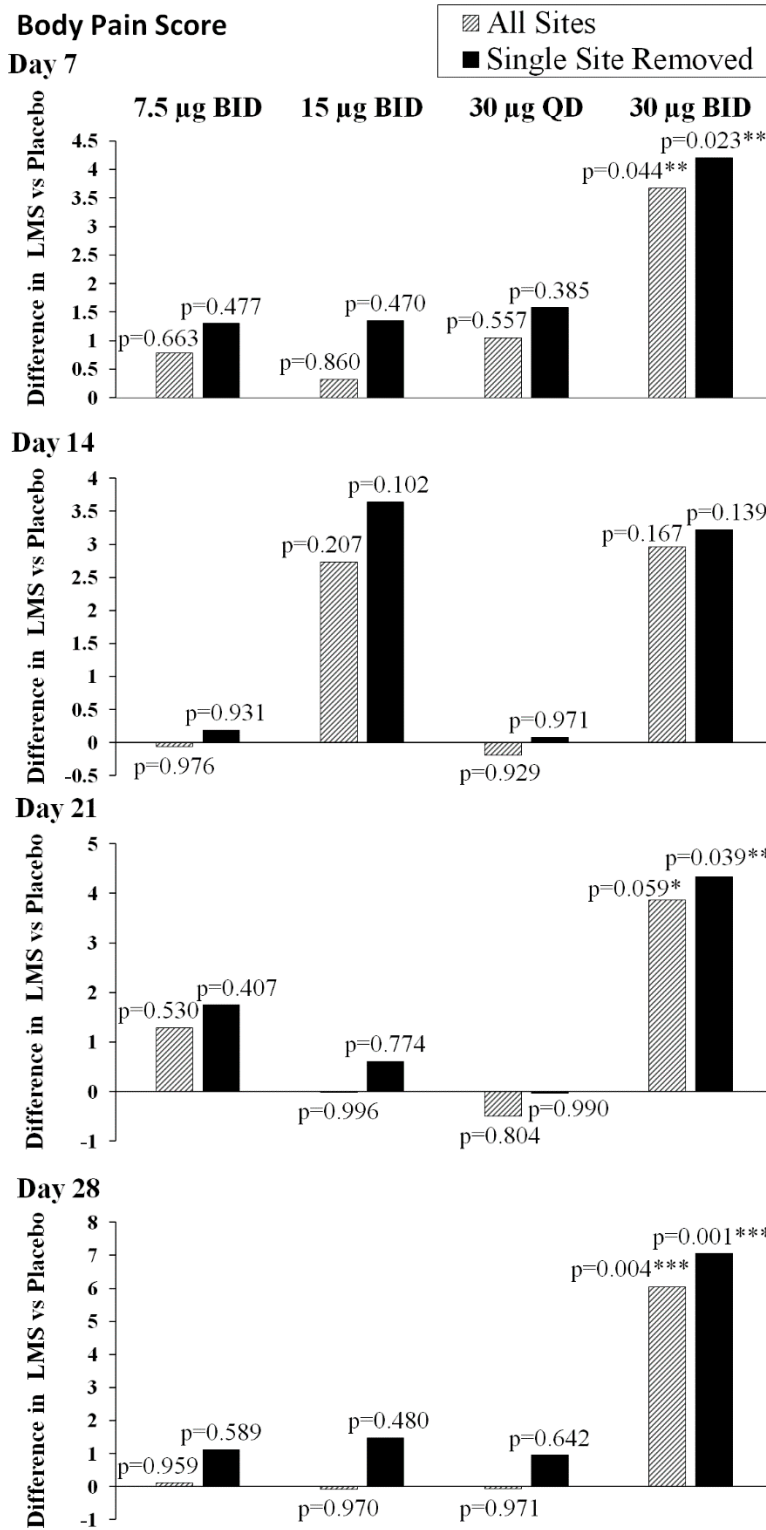




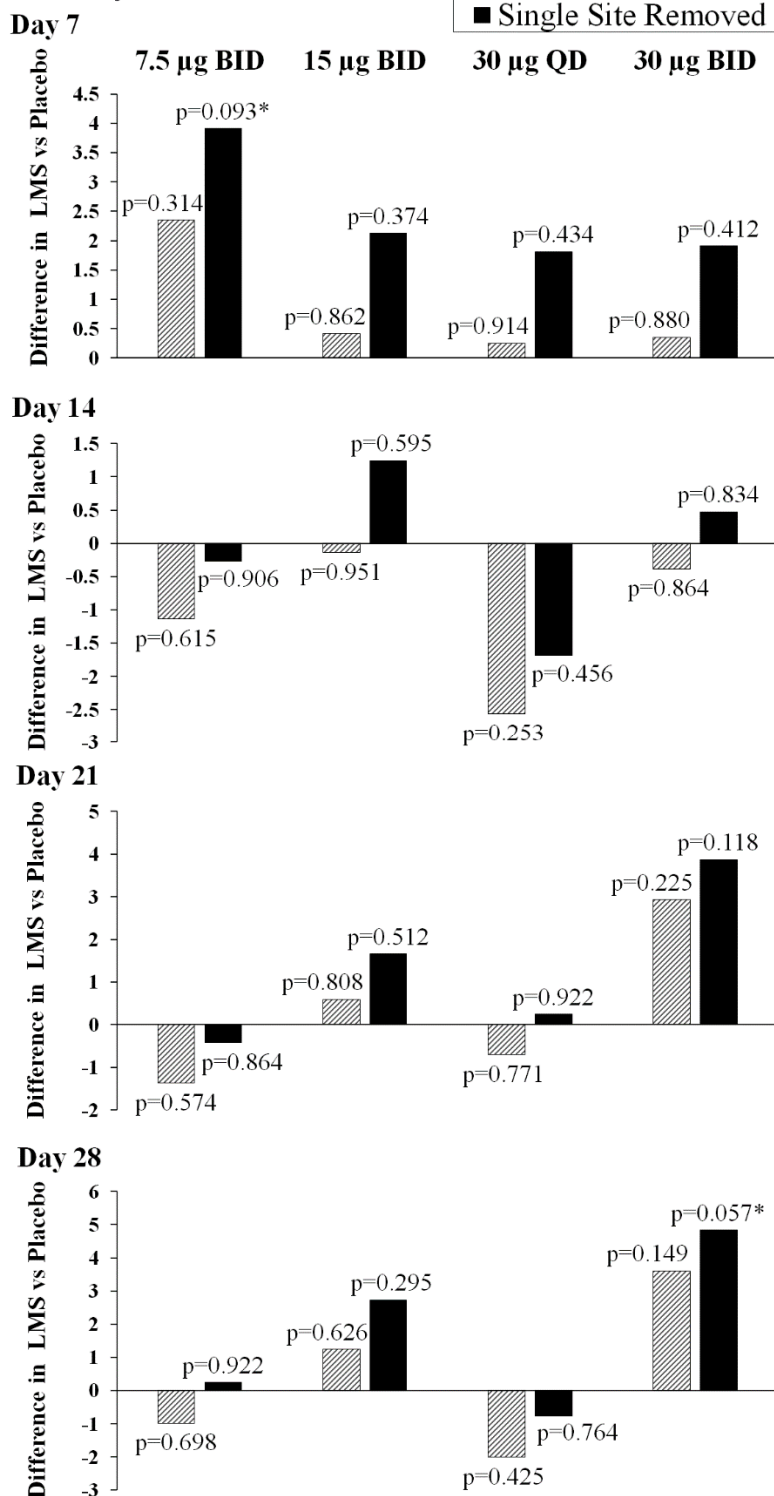


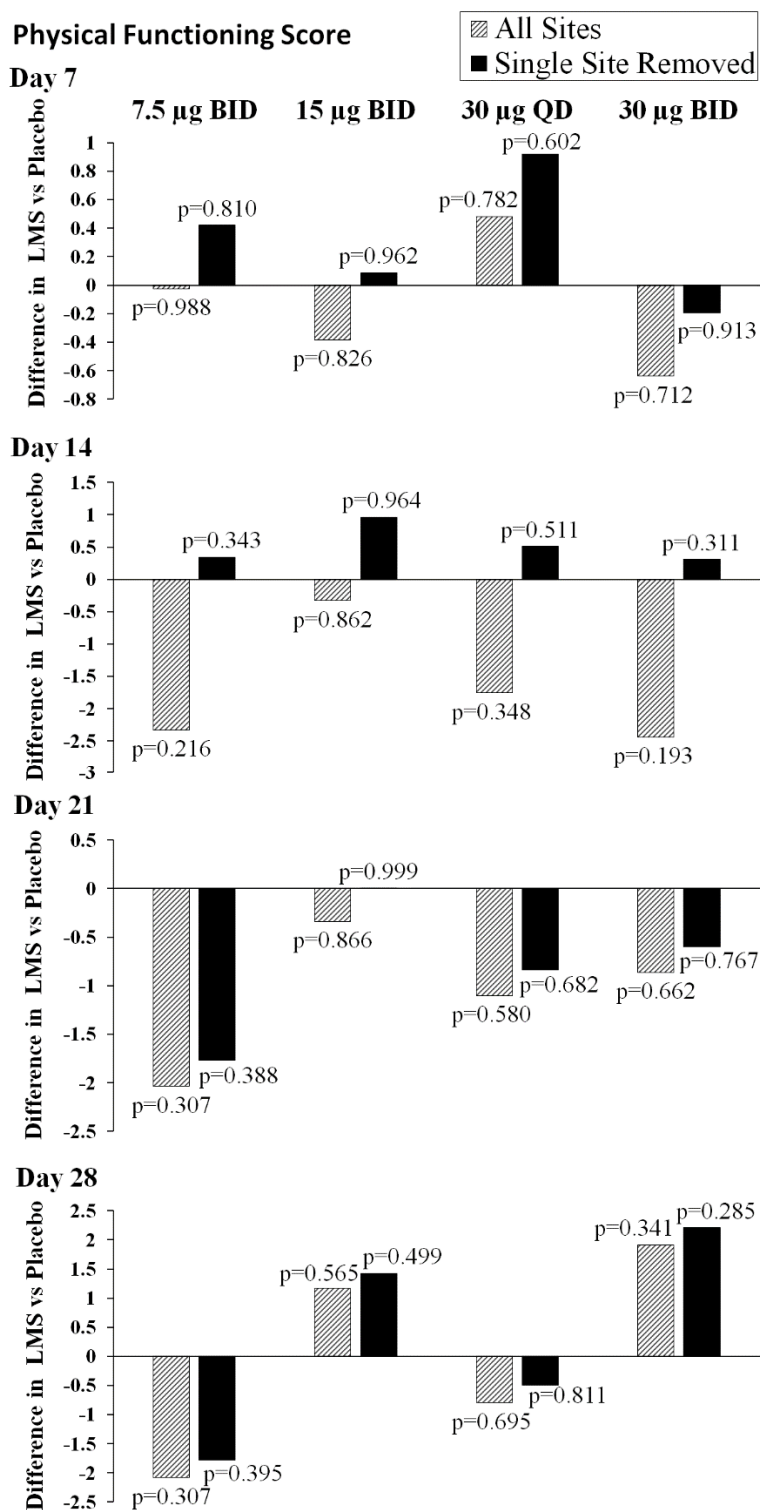




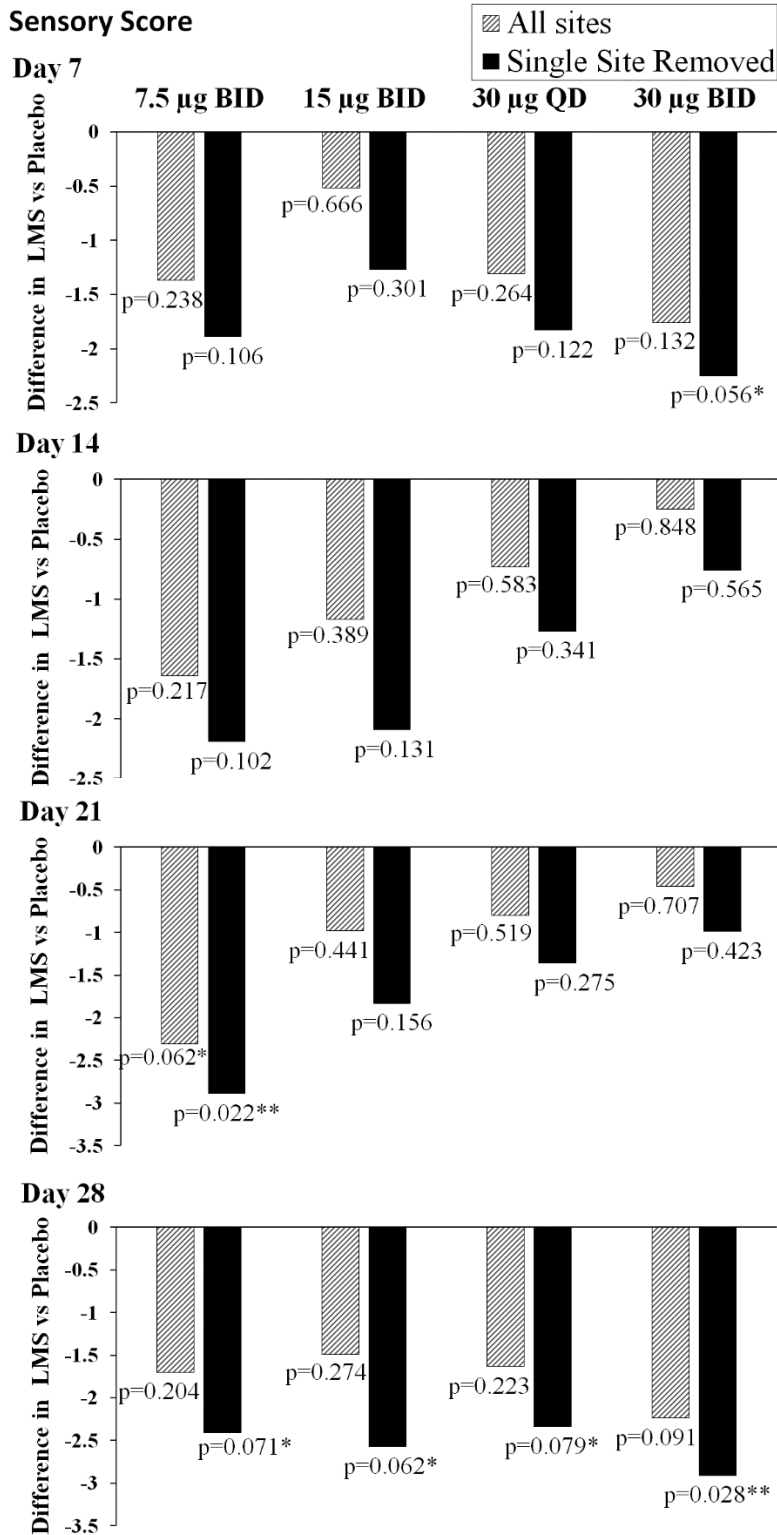


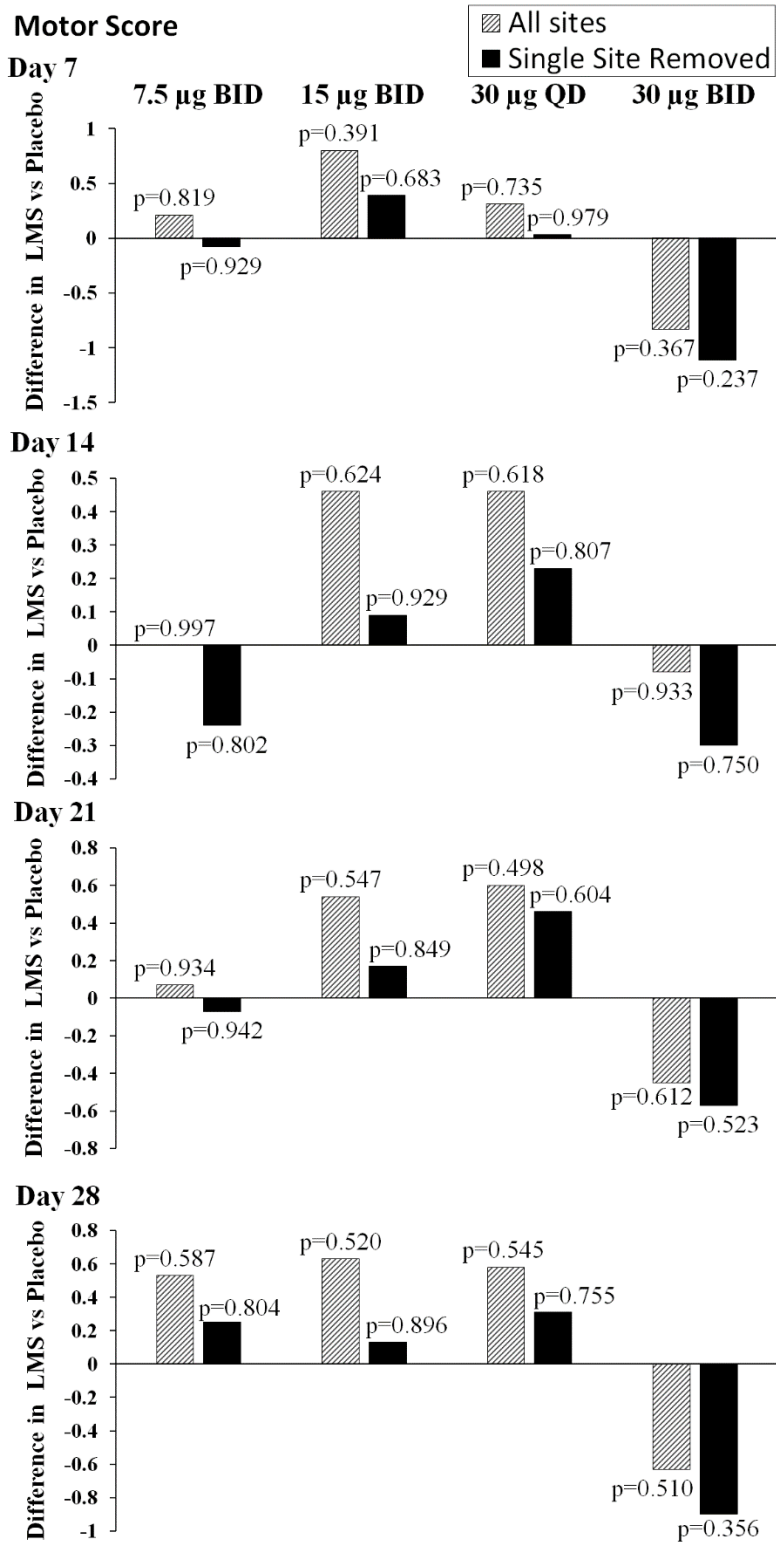
### Role Physical Score

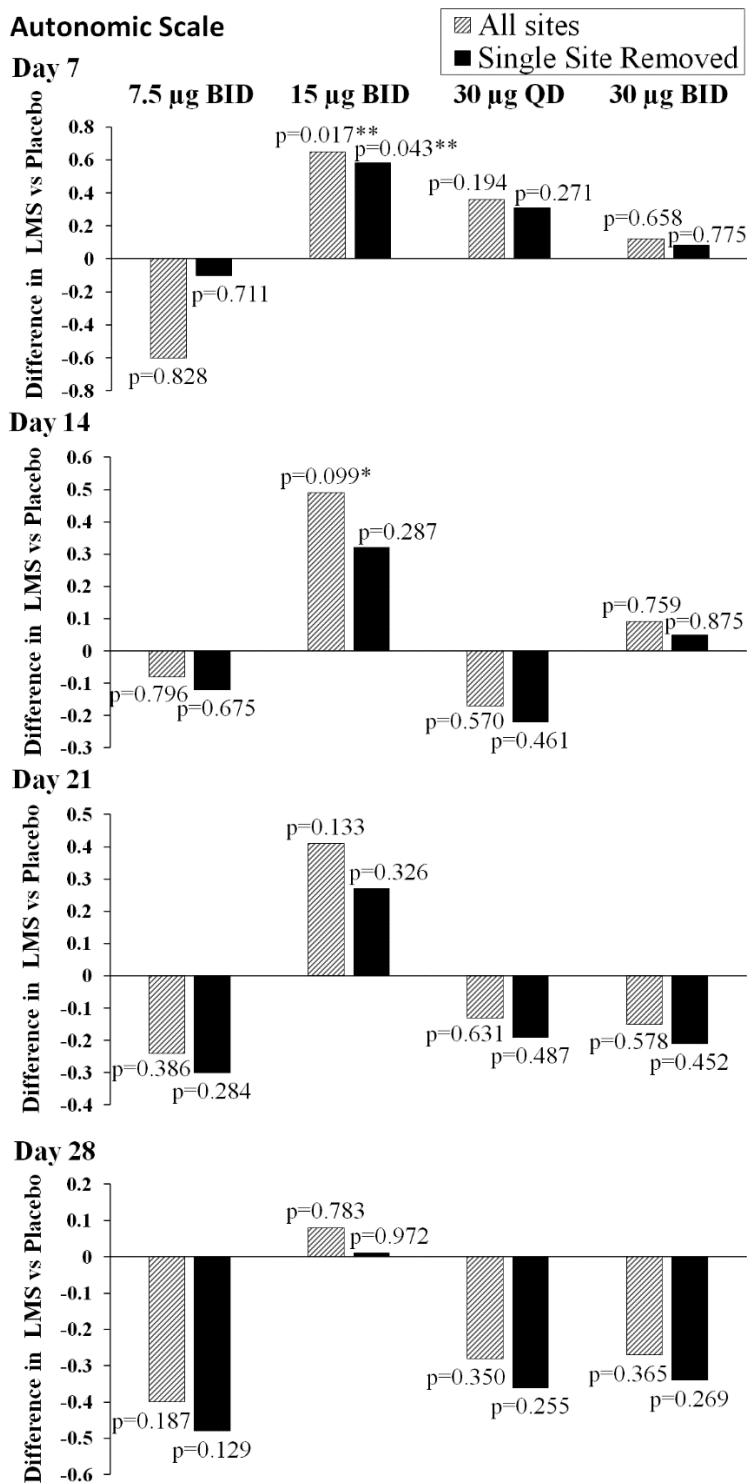




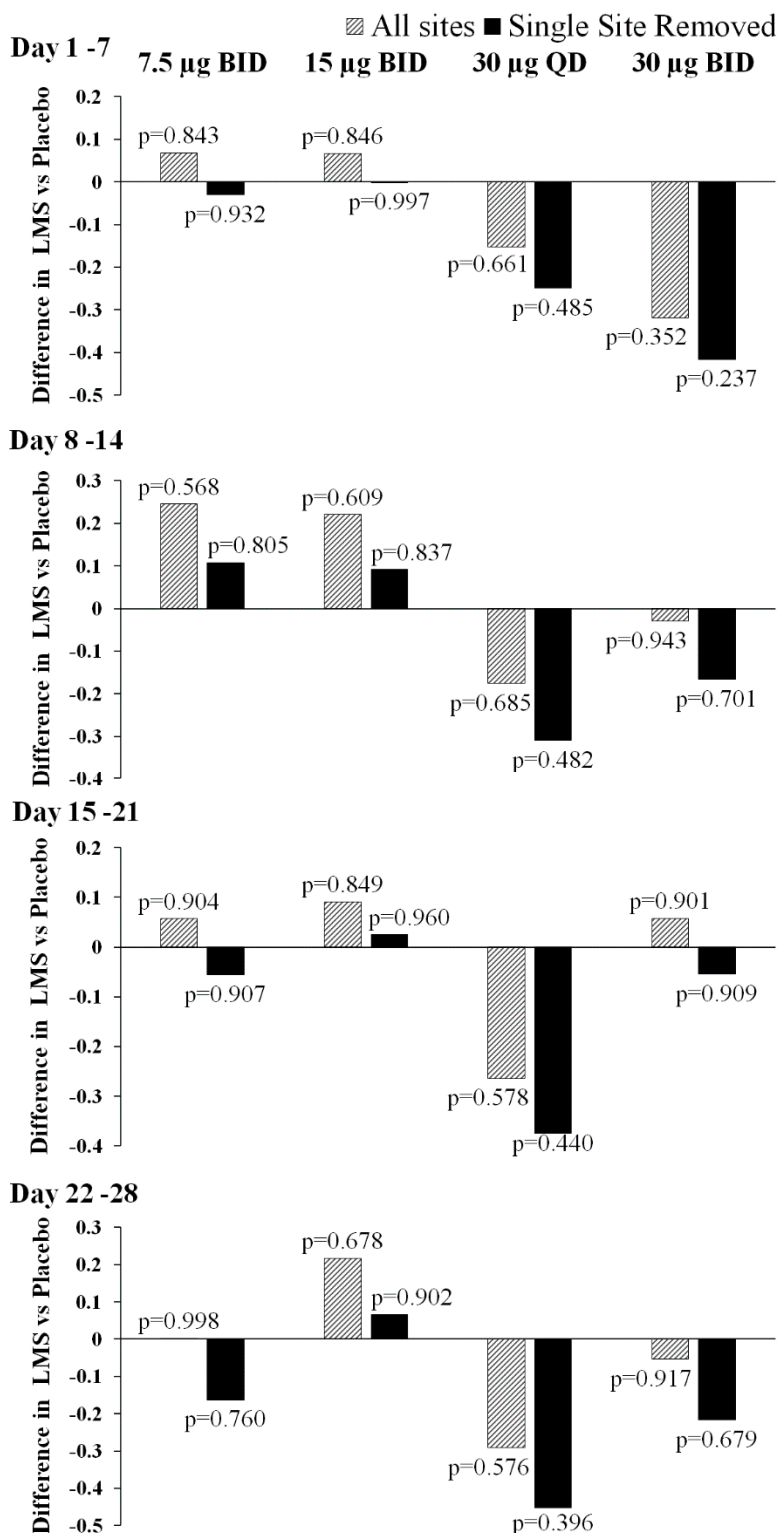
**Figure S1.** SF-36 Secondary Outcome Measures. The least squares mean (LMS) differences (treatment—placebo) from baseline to Day 7, Day 14, Day 21, and Day 28 are shown. *P*-values for the difference in means are shown with \* indicates  $p < 0.1$ , \*\* indicates  $p < 0.05$ , and \*\*\* indicates  $p < 0.01$ .







**Figure S2:** EORTC CIPN20 Secondary Outcome Measures. The least squares mean (LMS) differences (treatment – placebo) from baseline to Day 7, Day 14, Day 21, and Day 28 are shown. *P*-values for the difference in means are shown with \* indicates  $p < 0.1$ , \*\* indicates  $p < 0.05$ , and \*\*\* indicates  $p < 0.01$ .



**Figure S3:** Numerical Pain Rating Scale (NPRS) Scores. The change from baseline in average least squares mean (LMS) differences (treatment – placebo) for each week are shown. P-values represent the significant difference from placebo.

**Table S1:** Patient Global Impression of Change (PGIC) at Day 28

Since starting this study:	TTX Dosage				Placebo (N = 25) n (%)
	7.5 µg BID (N = 25) n (%)	15 µg BID (N = 24) n (%)	30 µg QD (N = 25) n (%)	30 µg BID (N = 26) n (%)	
<b>Overall QoL:</b>					
Very much worse	0	0	0	0	1 (4.0%)
Moderately worse	0	0	1 (4.0%)	1 (3.8%)	1 (4.0%)
A little worse	1 (4.0%)	2 (8.3%)	2 (8.0%)	1 (3.8%)	0
About the same	11 (44.0%)	8 (33.3%)	9 (36.0%)	9 (34.6%)	9 (36.0%)
A little better	5 (20.0%)	5 (20.8%)	2 (8.0%)	2 (7.7%)	5 (20.0%)
Moderately better	5 (20.0%)	6 (25.0%)	6 (24.0%)	10 (38.5%)	5 (20.0%)
Very much better	1 (4.0%)	3 (12.5%)	3 (12.0%)	2 (7.7%)	4 (16.0%)
<i>p</i> -value <sup>a</sup>	0.148	0.402	0.927	1.000	
<b>Physical Condition:</b>					
Very much worse	0	0	0	0	0
Moderately worse	0	1 (4.2%)	1 (4.0%)	0	2 (8.0%)
A little worse	1 (4.0%)	1 (4.2%)	1 (4.0%)	2 (7.7%)	0
About the same	13 (52.0%)	8 (33.3%)	10 (40.0%)	8 (30.8%)	11 (44.0%)
A little better	3 (12.0%)	8 (33.3%)	3 (12.0%)	5 (19.2%)	5 (20.0%)
Moderately better	5 (20.0%)	4 (16.7%)	5 (20.0%)	9 (34.6%)	3 (12.0%)
Very much better	1 (4.0%)	2 (8.3%)	3 (12.0%)	1 (3.8%)	4 (16.0%)
<i>p</i> -value <sup>a</sup>	0.433	0.219	0.943	0.385	
<b>Emotional State:</b>					
Very much worse	0	1 (4.2%)	1 (4.0%)	0	0
Moderately worse	0	0	0	1 (3.8%)	0
A little worse	0	0	1 (4.0%)	0	4 (16.0%)
About the same	17 (68.0%)	15 (62.5%)	14 (56.0%)	12 (46.2%)	11 (44.0%)
A little better	3 (12.0%)	5 (20.8%)	2 (8.0%)	4 (15.4%)	4 (16.0%)
Moderately better	2 (8.0%)	2 (8.3%)	4 (16.0%)	3 (11.5%)	2 (8.0%)
Very much better	1 (4.0%)	1 (4.2%)	1 (4.0%)	5 (19.2%)	4 (16.0%)
<i>p</i> -value <sup>a</sup>	0.982	0.898	0.451	0.370	
<b>Enjoy Social Life:</b>					
Very much worse	0	0	0	0	0
Moderately worse	0	0	0	0	1 (4.0%)
A little worse	0	0	0	1 (3.8%)	1 (4.0%)
About the same	16 (64.0%)	15 (62.5%)	15 (60.0%)	12 (46.2%)	12 (48.0%)
A little better	2 (8.0%)	5 (20.8%)	3 (12.0%)	3 (11.5%)	4 (16.0%)
Moderately better	4 (16.0%)	3 (12.5%)	3 (12.0%)	5 (19.2%)	3 (12.0%)
Very much better	1 (4.0%)	1 (4.2%)	2 (8.0%)	4 (15.4%)	4 (16.0%)
<i>p</i> -value <sup>a</sup>	0.612	0.218	0.636	0.849	
<b>Numbness, Tingling or Pain in Hands or Feet:</b>					
Very much worse	0	0	1 (4.0%)	1 (3.8%)	1 (4.0%)
Moderately worse	0	1 (4.2%)	2 (8.0%)	1 (3.8%)	2 (8.0%)
A little worse	1 (4.0%)	2 (8.3%)	1 (4.0%)	3 (11.5%)	0
About the same	10 (40.0%)	8 (33.3%)	8 (32.0%)	6 (23.1%)	9 (36.0%)



A little better	4 (16.0%)	7 (29.2%)	3 (12.0%)	5 (19.2%)	7 (28.0%)
Moderately better	6 (24.0%)	6 (25.0%)	3 (12.0%)	6 (23.1%)	2 (8.0%)
Very much better	2 (8.0%)	0	5 (20.0%)	3 (11.5%)	4 (16.0%)
<i>p</i> -value <sup>a</sup>	0.691	0.165	0.342	1.000	
<b>Believe Receiving Active Agent:</b>					
Yes	15 (60.0%)	15 (62.5%)	14 (56.0%)	22 (84.6%)	13 (52.0%)
No	8 (32.0%)	9 (37.5%)	8 (32.0%)	3 (11.5%)	12 (48.0%)

QoL: quality of life; BID: twice daily; QD: once daily; *n*: number of subjects. <sup>a</sup> Nominal *p*-values were obtained from Cochran-Mantel-Haenszel tests for comparing difference between active treatment and placebo cohorts.

**Table S2:** Study Adverse Events

System Organ Class Preferred Term	TTX 7.5 µg BID (N = 25) <i>n</i> (%)		TTX 15 µg BID (N = 24) <i>n</i> (%)		TTX 30 µg QD (N = 25) <i>n</i> (%)		TTX 30 µg BID (N = 26) <i>n</i> (%)		Placebo (N = 25) <i>n</i> (%)	
Number of Subjects with ≥1 AE	21 (84.0%)		22 (91.7%)		20 (80.0%)		24 (92.3%)		18 (72.0%)	
<b>Nervous system disorders</b>										
Paraesthesia oral	4 (16.0%) 3× Mild 1× Moderate		9 (37.5%) 8× Mild 1× Moderate		10 (40.0%) 10× Mild 7× Related		11 (42.3%) 11× Mild 2× Not Related 5× Possibly 4× Related		3 (12.0%) 3× Mild 2× Possibly 1× Related	
Hypoaesthesia oral	5 (20.0%) 4× Mild 1× Moderate		7 (29.2%) 6× Mild 1× Moderate		6 (24.0%) 6× Mild 3× Related		10 (38.5%) 9× Mild 1× Moderate 3× Possibly 6× Related		3 (12.0%) 3× Mild 2× Possibly 1× Related	
Paraesthesia	5 (20.0%) 4× Mild 1× Moderate		7 (29.2%) 6× Mild 1× Moderate		5 (20.0%) 5× Mild 1× Not Related 4× Related		7 (26.9%) 6× Mild 1× Severe 3× Possibly 3× Related		6 (24.0%) 5× Mild 1× Moderate 4× Possibly 1× Related	
Headache	6 (24.0%) 5× Mild 1× Moderate		3 (12.5%) 3 × Mild 1× Unlikely 1× Possibly 1× Related		1 (4.0%) 1× Mild 1× Not Related		9 (34.6%) 8× Mild 1× Moderate 4× Not Related 2× Possibly 3× Related		5 (20.0%) 4× Mild 1× Moderate 4× Possibly 1× Related	
Dizziness	3 (12.0%) 3× Mild 3× Possibly		4 (16.7%) 4× Mild 4× Possibly		3 (12.0%) 3× Mild 1× Not Related 1× Possibly 1× Related		8 (30.8%) 8× Mild 1× Not Related 4× Possibly 3× Related		5 (20.0%) 4× Mild 1× Moderate 1× Unlikely 2× Possibly 1× Related	
Hypoaesthesia	2 (8.0%) 1× Mild 2× Related 1× Moderate		1 (4.2%) 1× Mild 1× Possibly		2 (8.0%) 1× Mild 2× Related 1× Moderate		1 (3.8%) 1× Mild 1× Possibly		2 (8.0%) 1× Mild 2× Not Related 1× Moderate	
Dysgeusia	2 (8.0%)		0		2 (8.0%)		3 (11.5%)		0	

	2× Mild	2× Related			2× Mild	1× Not Related 1× Possibly	3× Mild	1× Not Related 1× Possibly 1× Related		
Burning sensation	0		1 (4.2%) 1× Mild	1× Possibly	1 (4.0%) 1× Mild	1× Possibly	2 (7.7%) 1× Mild 1× Severe	1× Possibly 1× Related	2 (8.0%) 2× Mild	2× Possibly
Hypoaesthesia facial	1 (4.0%) 1× Mild	1× Related	1 (4.2%) 1× Mild	1× Possibly	2 (8.0%) 2× Mild	1× Possibly 1× Related	0		1 (4.0%) 1× Mild	1× Possibly
Oral dysaesthesia	1 (4.0%) 1× Mild	1× Related	1 (4.2%) 1× Mild	1× Related	1 (4.0%) 1× Mild	1× Related	2 (7.7%) 2× Mild	2× Not Related	0	
Somnolence	1 (4.0%) 1× Mild	3× Possibly	0		0		1 (3.8%) 1× Mild	1× Related	2 (8.0%) 2× Mild	2× Possibly
Hyperaesthesia	1 (4.0%) 1× Moderate	1× Related	0		0		1 (3.8%) 1× Mild	1× Possibly	1 (4.0%) 1× Mild	1× Related
Neuropathy peripheral	0		1 (4.2%) 1× Mild	1× Related	0		2 (7.7%) 2× Moderate	1× Not Related 1× Related	0	
Pharyngeal hypoaesthesia	1 (4.0%) 1× Mild	1× Related	0		1 (4.0%) 1× Mild	1× Related	1 (3.8%) 1× Mild	1× Not Related	0	
Hypoaesthesia teeth	0		0		0		2 (7.7%) 2× Mild	2× Possibly	0	
Neuralgia	1 (4.0%) 1× Mild	1× Not Related	0		0		1 (3.8%) 1× Moderate	1× Related	0	
Peripheral sensory neuropathy	0		0		1 (4.0%)		1 (3.8%)		0	
					1× Moderate	1× Not Related	1× Moderate	1× Related		
Sensory disturbance	0		1 (4.2%) 1× Mild	1× Unlikely	0		0		1 (4.0%) 1× Mild	1× Possibly

Amnesia	0	0	1 (4.0%)	0	0	0	0	0	0
			1× Mild	1× Not Related					
Ataxia	0	0	0	1 (3.8%)	0	0	0	0	0
				1× Moderate	1× Related				
Dysaesthesia	0	0	1 (4.0%)	0	0	0	0	0	0
			1× Mild	1× Related					
Dyscalculia	0	0	1 (4.0%)	0	0	0	0	0	0
			1× Mild	1× Not Related					
Head discomfort	0	0	0	1 (3.8%)	0	0	0	0	0
				1× Mild	1× Related				
Hypersomnia	0	0	0	1 (3.8%)	0	0	0	0	0
				1× Moderate	1× Unlikely				
Hyporeflexia	0	0	0	0	0	0	0	1 (4.0%)	0
								1× Mild	1× Possibly
Lethargy	0	0	0	0	0	0	0	1 (4.0%)	0
								1× Moderate	1× Possibly
Motor dysfunction	0	1 (4.2%)	0	0	0	0	0	0	0
		1× Mild	1× Possibly						
Post-traumatic headache	0	1 (4.2%)	0	0	0	0	0	0	0
		1× Mild	1× Not Related						
<b>General disorders and administration site conditions</b>									
Fatigue	4 (16.0%)	5 (20.8%)	5 (20.0%)	3 (11.5%)	4 (16.0%)	0	0	0	0
	4× Mild	1× Unlikely	4× Mild	1× Not Related	5× Mild	3× Not Related	3× Mild	1× Not Related	3× Mild
		1× Possibly	1× Moderate	3× Possibly		1× Unlikely		1× Unlikely	1× Moderate
		2× Related		1× Related		1× Possibly		1× Possibly	2× Possibly
Feeling hot	1 (4.0%)	1 (4.2%)	1 (4.0%)	2 (7.7%)	2 (8.0%)	0	0	0	0
	1× Mild	1× Related	1× Mild	1× Possibly	1× Mild	1× Possibly	2× Mild	1× Related	2× Mild
								1× Related	2× Possibly
								1× Possibly	
Pain	1 (4.0%)	2 (8.3%)	1 (4.0%)	1 (3.8%)	1 (4.0%)	0	0	0	0
	1× Moderate	1× Related	2× Mild	1× Unlikely	1× Moderate	1× Not Related	1× Severe	1× Related	1× Mild
				1× Possibly					1× Not Related
Feeling abnormal	0	1 (4.2%)	2 (8.0%)	1 (3.8%)	1 (4.0%)	0	0	0	0
		1× Mild	1× Possibly	2× Mild	2× Related	1× Mild	1× Possibly	1× Mild	1× Possibly
Injection site pain	2 (8.0%)	2 (8.3%)	0	1 (3.8%)	0	0	0	0	0

	2× Mild	2× Possibly	2× Mild	2× Possibly		1× Mild	1× Possibly			
Feeling drunk	1 (4.0%)		1 (4.2%)		0	1 (3.8%)		1 (4.0%)		
	1× Mild	1× Possibly	1× Mild	1× Related		1× Mild	1× Related	1× Mild	1× Possibly	
Oedema peripheral	1 (4.0%)		1 (4.2%)		0	1 (3.8%)		1 (4.0%)		
	1× Mild	1× Not Related	1× Mild	1× Possibly		1× Mild	1× Not Related	1× Mild	1× Possibly	
Chest discomfort	0		1 (4.2%)		1 (4.0%)	0		0		
			1× Mild	1× Related	1× Mild	1× Related				
Influenza like illness	0		0		0	2 (7.7%)		0		
						1× Mild	1× Not Related			
						1× Moderate	1× Possibly			
Facial pain	0		0		0	0		1 (4.0%)		
								1× Mild	1× Possibly	
Feeling cold	1 (4.0%)		0		0	0		0		
	1× Mild	1× Possibly								
Gait disturbance	1 (4.0%)		0		0	0		0		
	1× Mild	1× Possibly								
Injection site erythema	1 (4.0%)		0		0	0		0		
	1× Mild	1× Possibly								
Local swelling	0		0		0	1 (3.8%)		0		
						1× Mild	1× Not Related			
Therapeutic response unexpected	0		0		0	1 (3.8%)		0		
						1× Mild	1× Possibly			
<b>Gastrointestinal disorders</b>										
Nausea	1 (4.0%)		5 (20.8%)		1 (4.0%)	6 (23.1%)		6 (24.0%)		
	1× Moderate	1× Possibly	3× Mild	1× Not Related	1× Mild	1× Possibly	4× Mild	1× Unlikely	5× Mild	1× Not Related
			2× Moderate	3× Possibly			2× Moderate	3× Possibly	1× Moderate	1× Unlikely
				1× Related				2× Related		3× Possibly
										1× Related
Diarrhoea	2 (8.0%)		1 (4.2%)		0	2 (7.7%)		0		
	2× Mild	1× Unlikely	1× Mild	1× Not Related		1× Mild	1× Unlikely			
		1× Possibly				1× Moderate	1× Related			

Abdominal discomfort	1 (4.0%)		1 (4.2%)		0		1 (3.8%)		1 (4.0%)	
	1× Mild	1× Not Related	1× Moderate	1× Not Related			1× Mild	1× Possibly	1× Mild	1× Possibly
Constipation	0		1 (4.2%)		1 (4.0%)		1 (3.8%)		0	
			1× Moderate	1× Unlikely	1× Mild	1× Not Related	1× Mild	1× Related		
Abdominal distension	1 (4.0%)		0		0		0		1 (4.0%)	
	1× Moderate	1× Not Related							1× Mild	1× Unlikely
Abdominal pain	1 (4.0%)		0		0		1 (3.8%)		0	
	1× Mild	1× Unlikely					1× Mild	1× Not Related		
Abdominal pain upper	1 (4.0%)		0		0		0		1 (4.0%)	
	1× Mild	1× Possibly							1× Moderate	1× Not Related
Lip swelling	0		0		0		1 (3.8%)		1 (4.0%)	
							1× Mild	1× Not Related	1× Mild	1× Possibly
Tongue disorder	1 (4.0%)		0		1 (4.0%)		0		0	
	1× Mild	1× Related			1× Mild	1× Not Related				
Vomiting	0		0		0		1 (3.8%)		1 (4.0%)	
							1× Moderate	1× Related	1× Mild	1× Unlikely
Abdominal rigidity	1 (4.0%)		0		0		0		0	
	1× Mild	1× Possibly								
Aphthous stomatitis	0		0		1 (4.0%)		0		0	
					1× Mild	1× Not Related				
Dry mouth	0		0		0		1 (3.8%)		0	
							1× Mild	1× Possibly		
Flatulence	1 (4.0%)		0		0		0		0	
	1× Mild	1× Possibly								
Lip dry	0		1 (4.2%)		0		0		0	
			1× Mild	1× Related						
Lip oedema	0		0		0		0		1 (4.0%)	
									1× Mild	1× Possibly
Salivary hypersecretion	0		0		1 (4.0%)		0		0	
					1× Mild	1× Not Related				
<b>Musculoskeletal and connective tissue disorders</b>										

Pain in extremity	1 (4.0%) 1× Mild 1× Not Related		5 (20.8%) 4× Mild 1× Unlikely 1× Moderate 3× Possibly 1× Related		4 (16.0%) 1× Mild 2× Not Related 3× Moderate 1× Possibly 1× Related		3 (11.5%) 2× Mild 1× Not Related 1× Severe 1× Possibly 1× Related		2 (8.0%) 1× Mild 1× Possibly 1× Moderate 1× Related	
Back pain	2 (8.0%) 2× Moderate 2× Not Related		1 (4.2%) 1× Mild 1× Not Related		1 (4.0%) 1× Moderate 1× Not Related		3 (11.5%) 2× Mild 2× Unlikely 1× Moderate 1× Not Related		3 (12.0%) 2× Mild 1× Unlikely 1× Moderate 2× Not Related	
Arthralgia	1 (4.0%) 1× Mild 1× Not Related		1 (4.2%) 1× Moderate 1× Not Related		1 (4.0%) 1× Moderate 1× Not Related		2 (7.7%) 2× Mild 1× Not Related 1× Related		2 (8.0%) 2× Mild 1× Unlikely 1× Related	
Muscle spasms	0		1 (4.2%) 1× Mild 1× Not Related		0		2 (7.7%) 1× Mild 1× Not Related 1× Moderate 1× Related		1 (4.0%) 1× Mild 1× Related	
Musculoskeletal stiffness	0		1 (4.2%) 1× Mild 1× Possibly		0		1 (3.8%) 1× Mild 1× Possibly		1 (4.0%) 1× Mild 1× Possibly	
Myalgia	1 (4.0%) 1× Moderate 1× Not Related		0		0		0		1 (4.0%) 1× Mild 1× Possibly	
Neck pain	0		0		0		0		2 (8.0%) 2× Mild 1× not Related 1× Possibly	
Sensation of heaviness	0		0		0		1 (3.8%) 1× Mild 1× Unlikely		1 (4.0%) 1× Mild 1× Possibly	
Flank pain	0		0		1 (4.0%) 1× Mild 1× Not Related		0		0	
Joint stiffness	0		1 (4.2%) 1× Mild 1× Possibly		0		0		0	
Limb discomfort	0		1 (4.2%) 1× Mild 1× Possibly		0		0		0	
Muscle tightness	0		0		0		0		1 (4.0%) 1× Mild 1× Possibly	
Muscle twitching	0		0		0		0		1 (4.0%) 1× Mild 1× Related	



Musculoskeletal chest pain	0	1 (4.2%)	0	0	0	0
		1× Mild	1× Not Related			
Musculoskeletal pain	0	0	0	0	0	1 (4.0%)
						1× Mild
						1× Not Related
Osteoarthritis	1 (4.0%)	0	0	0	0	0
	1× Mild	1× Not Related				
Pain in jaw	0	0	0	0	1 (3.8%)	0
					1× Moderate	1× Not Related
<b>Respiratory, thoracic and mediastinal disorders</b>						
Cough	1 (4.0%)	0	0	0	1 (3.8%)	1 (4.0%)
	1× Mild	1× Not Related			1× Moderate	1× Unlikely
					1× Moderate	1× Not Related
Oropharyngeal pain	1 (4.0%)	0	0	1 (4.0%)	0	1 (4.0%)
	1× Mild	1× Not Related		1× Mild	1× Not Related	1× Moderate
						1× Not Related
Rhinitis allergic	0	1 (4.2%)	0	1 (4.0%)	0	0
		1× Moderate	1× Not Related	1× Mild	1× Not Related	1× Moderate
					1× Not Related	
Dyspnoea	0	0	0	0	1 (3.8%)	1 (4.0%)
					1× Mild	1× Unlikely
					1× Mild	1× Not Related
Nasal congestion	0	0	0	0	1 (3.8%)	1 (4.0%)
					1× Moderate	1× Not Related
					1× Mild	1× Not Related
Bronchial hyperreactivity	0	0	0	0	1 (3.8%)	0
					1× Mild	1× Not Related
Chronic obstructive pulmonary disease	0	0	0	0	1 (3.8%)	0
					1× Moderate	1× Unlikely
Oropharyngeal discomfort	0	0	0	0	0	1 (4.0%)
						1× Mild
						1× Related
Pharyngeal oedema	0	0	0	1 (4.0%)	0	0
				1× Mild	1× Possibly	
Rhinorrhoea	0	0	0	1 (4.0%)	0	0
				1× Mild	1× Not Related	
Sneezing	0	1 (4.2%)	0	0	0	0

Throat tightness	0		1× Mild	1× Not Related	1 (4.2%)	0	0	0
			1× Mild	1× Related				
<b>Infections and infestations</b>								
Urinary tract infection	2 (8.0%)				0	1 (4.0%)	0	1 (4.0%)
	2× Moderate	2× Not Related				1× Mild	1× Not Related	1× Moderate 1× Not Related
Nasopharyngitis	1 (4.0%)				0	1 (4.0%)	0	0
	1× Mild	1× Not Related				1× Mild	1× Not Related	
Upper respiratory tract infection	0				1 (4.2%)	0	0	1 (4.0%)
			1× Mild	1× Not Related				1× Moderate 1× Not Related
Cystitis	0				1 (4.2%)	0	0	0
			1× Mild	1× Not Related				
Influenza	1 (4.0%)				0	0	0	0
	1× Moderate	1× Not Related						
Oral herpes	0				0	1 (4.0%)	0	0
						1× Moderate	1× Not Related	
Pharyngitis	0				1 (4.2%)	0	0	0
			1× Mild	1× Not Related				
Pneumonia	1 (4.0%)				0	0	0	0
	1× Moderate	1× Not Related						
Viral upper respiratory tract infection	0				0	0	1 (3.8%)	0
							1× Severe	1× Unlikely
<b>Vascular disorders</b>								
Hot flush	1 (4.0%)				1 (4.2%)	0	2 (7.7%)	1 (4.0%)
	1× Mild	1× Related	1× Mild	1× Related			1× Mild 1× Not Related	1× Mild 1× Possibly
							1× Moderate 1× Related	
Flushing	0				0	2 (8.0%)	1 (3.8%)	1 (4.0%)
						2× Mild 2× Related	1× Mild 1× Related	1× Mild 1× Possibly
Hypertension	0				0	0	2 (7.7%)	0
							1× Mild 2× Possibly	
							1× Severe	

Intra-abdominal haematoma	0		1 (4.2%)	0	0	0
		1× Mild	1× Possibly			
Peripheral coldness	0		0	0	1 (3.8%)	0
					1× Mild	1× Possibly
<b>Skin and subcutaneous tissue disorders</b>						
Pruritus	3 (12.0%)		1 (4.2%)	0	0	0
	3× Mild	1× Possibly	1× Mild	1× Possibly		
		2× Related				
Hyperhidrosis	0		1 (4.2%)	0	0	1 (4.0%)
						1× Mild
						1× Unlikely
Blister	0		0	0	1 (3.8%)	0
					1× Moderate	1× Not Related
Dry skin	0		0	1 (4.0%)	0	0
				1× Mild	1× Not Related	
Erythema	0		0	0	0	1 (4.0%)
						1× Mild
						1× Possibly
Rash	0		1 (4.2%)	0	0	0
		1× Mild	1× Possibly			
Scar	0		0	0	0	1 (4.0%)
						1× Mild
						1× Not Related
Skin discoloration	1 (4.0%)		0	0	0	0
	1× Mild	1× Possibly				
<b>Injury, poisoning and procedural complications</b>						
Fall	0		2 (8.3%)	0	0	1 (4.0%)
		2× Mild	2× Not Related			1× Mild
						1× Not Related
Contusion	0		0	1 (4.0%)	0	0
				1× Mild	1× Not Related	
Joint sprain	0		0	0	1 (3.8%)	0
					1× Mild	1× Not Related
Meniscus lesion	1 (4.0%)		0	0	0	0
	1× Mild	1× Not Related				
Pelvic fracture	1 (4.0%)		0	0	0	0
	1× Moderate	1× Not Related				

Post procedural discomfort	0	0	0	0	1 (3.8%)	0		
					1× Mild	1× Not Related		
Procedural pain	0	0	0	0	0	1 (4.0%)	1× Mild	1× Not Related
<b>Ear and labyrinth disorders</b>								
Ear pain	0	0	1 (4.0%)	1 (3.8%)	0			
			1× Mild	1× Not Related	1× Mild	1× Not Related		
Tinnitus	0	0	0	1 (3.8%)	1 (4.0%)			
				1× Mild	1× Not Related	1× Mild	1× Related	
Vertigo	0	1 (4.2%)	0	1 (3.8%)	0			
		1× Moderate	1× Related	1× Moderate	1× Possibly			
Ear pruritus	1 (4.0%)	0	0	0	0	0		
	1× Mild	1× Possibly						
<b>Psychiatric disorders</b>								
Thinking abnormal	1 (4.0%)	1 (4.2%)	0	0	1 (4.0%)			
	1× Mild	1× Possibly	1× Mild	1× Possibly	1× Mild	1× Possibly		
Anxiety	0	0	0	0	1 (4.0%)			
					1× Moderate	1× Possibly		
Hypervigilance	1 (4.0%)	0	0	0	0	0		
	1× Moderate	1× Not Related						
Insomnia	0	1 (4.2%)	0	0	0	0		
		1× Moderate	1× Not Related					
Nightmare	1 (4.0%)	0	0	0	0	0		
	1× Moderate	1× Related						
<b>Eye disorders</b>								
Eye pain	1 (4.0%)	1 (4.2%)	0	0	0	0		
	1× Mild	1× Possibly	1× Mild	1× Unlikely				
Vision blurred	0	0	0	1 (3.8%)	1 (4.0%)			
				1× Mild	1× Related	1× Mild	1× Not Related	
Abnormal sensation in eye	1 (4.0%)	0	0	0	0	0		
	1× Mild	1× Possibly						
Chalazion	0	0	1 (4.0%)	0	0	0		
			1× Moderate	1× Not Related				

Diplopia	0	0	0	1 (3.8%)	0	0
				1× Mild	1× Related	
<b>Investigations</b>						
Body temperature increased	0	0	1 (4.0%)	0	1 (4.0%)	
			1× Mild	1× Not Related	1× Mild	1× Possibly
Blood glucose increased	0	0	1 (4.0%)	0	0	
			1× Mild	1× Not Related		
Blood pressure increased	0	0	1 (4.0%)	0	0	
			1× Mild	1× Possibly		
Electrocardiogram QT prolonged	0	0	1 (4.0%)	0	0	
			1× Mild	1× Possibly		
Weight increased	0	0	0	0	1 (4.0%)	
					1× Mild	1× Unlikely
<b>Renal and urinary disorders</b>						
Dysuria	0	1 (4.2%)	0	0	0	
		1× Moderate	1× Not Related			
Pollakiuria	0	1 (4.2%)	0	0	0	
		1× Moderate	1× Not Related			
Renal pain	0	0	1 (4.0%)	0	0	
			1× Mild	1× Not Related		
<b>Blood and lymphatic system disorders</b>						
Lymphadenopathy	0	0	1 (4.0%)	0	1 (4.0%)	
			1× Mild	1× Not Related	1× Mild	1× Not Related
<b>Cardiac disorders</b>						
Palpitations	1 (4.0%)	0	0	0	0	
	1× Mild	1× Not Related				
Tachycardia	0	0	0	0	1 (4.0%)	
					1× Mild	1× Unlikely
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>						
Colon cancer metastatic	0	0	0	0	1 (4.0%)	

Metastatic carcinoma of the bladder	0	1 (4.2%)	0	0	1× Moderate	1× Not Related
		1× Death	1× Not Related			
Prostate cancer	0	1 (4.2%)	0	0		0
		1× Death	1× Not Related			
<b>Metabolism and nutrition disorders</b>						
Decreased appetite	0	1 (4.2%)	0	0		0
		1× Moderate	1× Not Related			

TTX: tetrodotoxin; QoL: quality of life; BID: twice daily; QD: once daily; *n*: number of subjects