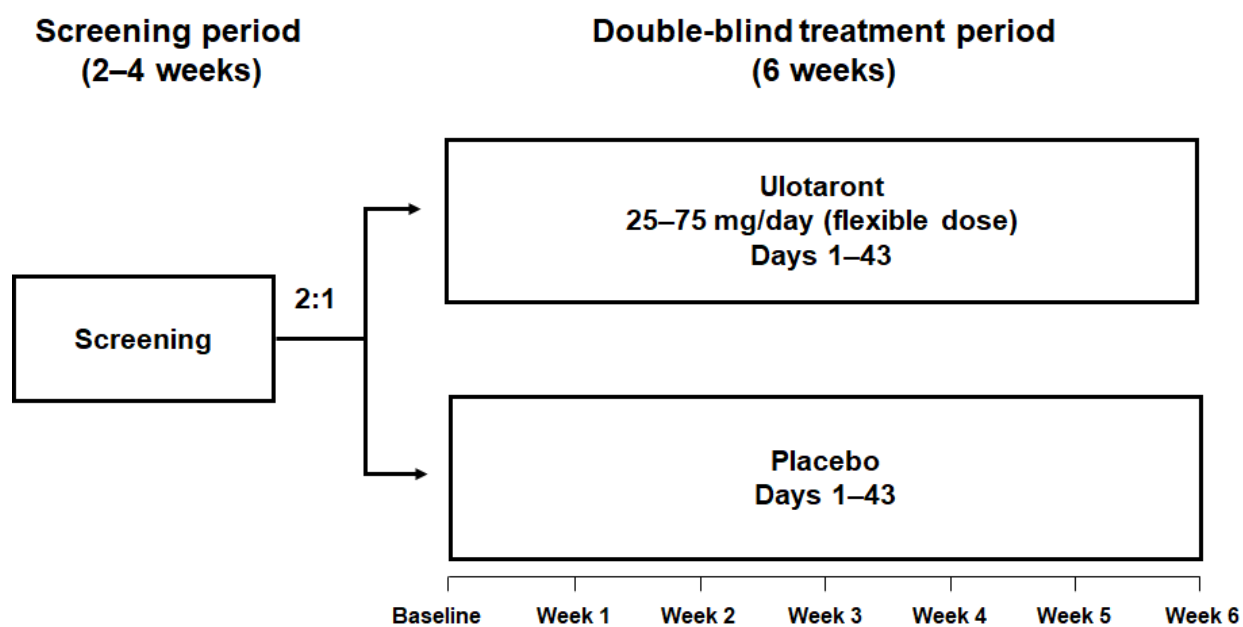
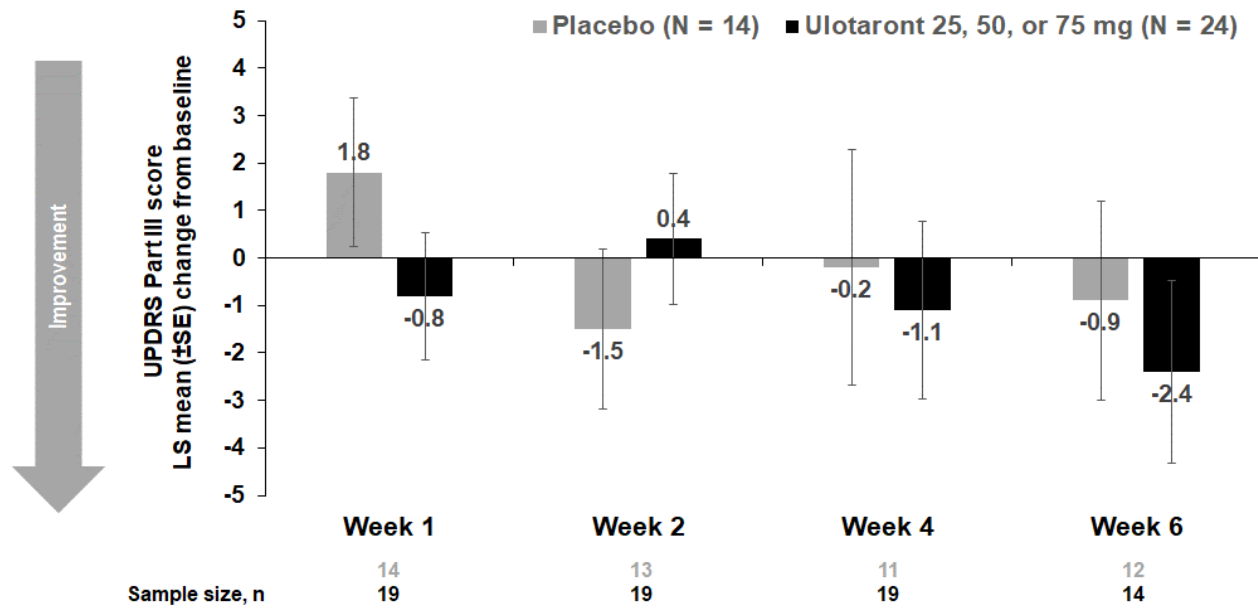


SUPPLEMENTAL APPENDIX

e-Figure 1 Study Design



e- Figure 2 Change From Baseline in UPDRS Part III Scores (mITT Population)



The mITT population includes all patients who received ≥ 1 dose and had a SAPS-PD assessment at baseline and ≥ 1 postbaseline. Lower scores indicate improvement.

Baseline mean (SD) UPDRS Part III scores for placebo and ulotaront were 35.9 (13.12) and 33.4 (10.28), respectively. Abbreviations: LS = least squares; mITT = modified intent-to-treat; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale.

eTable 1. Medical Comorbidity (Safety Population)

System organ class/preferred term ^{a,b,c} , n (%) ^d	Placebo (n = 14)	Ulotaront (n = 25)	Total (N = 39)
Subjects with any medical or surgical history	14 (100.0)	25 (100.0)	39 (100.0)
Blood and lymphatic system disorders	1 (7.1)	0	1 (2.6)
Anemia	1 (7.1)	0	1 (2.6)
Cardiac disorders	3 (21.4)	7 (28.0)	10 (25.6)
Coronary artery disease	3 (21.4)	4 (16.0)	7 (17.9)
Acute myocardial infarction	0	1 (4.0)	1 (2.6)
Aortic valve stenosis	0	1 (4.0)	1 (2.6)
Cardiac failure	0	1 (4.0)	1 (2.6)
Coronary artery disease	0	1 (4.0)	1 (2.6)
Mitral valve stenosis	0	1 (4.0)	1 (2.6)
Myocardial infarction	0	1 (4.0)	1 (2.6)
Congenital, familial, and genetic disorders	0	1 (4.0)	1 (2.6)
Ichthyosis	0	1 (4.0)	1 (2.6)
Ear and labyrinth disorders	1 (7.1)	3 (12.0)	4 (10.3)
Deafness bilateral	0	2 (8.0)	2 (5.1)
Deafness	1 (7.1)	0	1 (2.6)
Hypoacusis	0	1 (4.0)	1 (2.6)
Endocrine disorders	1 (7.1)	3 (12.0)	4 (10.3)
Hypothyroidism	1 (7.1)	3 (12.0)	4 (10.3)
Hypogonadism	0	1 (4.0)	1 (2.6)
Hypopituitarism	0	1 (4.0)	1 (2.6)
Eye disorders	7 (50.0)	9 (36.0)	16 (41.0)
Cataract	2 (14.3)	3 (12.0)	5 (12.8)
Presbyopia	2 (14.3)	3 (12.0)	5 (12.8)
Diplopia	2 (14.3)	1 (4.0)	3 (7.7)
Hypermetropia	1 (7.1)	2 (8.0)	3 (7.7)
Glaucoma	0	2 (8.0)	2 (5.1)
Macular degeneration	2 (14.3)	0	2 (5.1)
Myopia	0	2 (8.0)	2 (5.1)
Blindness unilateral	0	1 (4.0)	1 (2.6)
Retinal tear	0	1 (4.0)	1 (2.6)
Strabismus	0	1 (4.0)	1 (2.6)
Gastrointestinal disorders	8 (57.1)	19 (76.0)	27 (69.2)
Constipation	5 (35.7)	14 (56.0)	19 (48.7)

Gastroesophageal reflux disease	2 (14.3)	8 (32.0)	10 (25.6)
Inguinal hernia	3 (21.4)	3 (12.0)	6 (15.4)
Dysphagia	1 (7.1)	3 (12.0)	4 (10.3)
Salivary hypersecretion	1 (7.1)	3 (12.0)	4 (10.3)
Dyspepsia	0	2 (8.0)	2 (5.1)
Large intestine polyp	0	2 (8.0)	2 (5.1)
Esophagitis	1 (7.1)	1 (4.0)	2 (5.1)
Abdominal discomfort	0	1 (4.0)	1 (2.6)
Barrett's esophagus	0	1 (4.0)	1 (2.6)
Colitis	0	1 (4.0)	1 (2.6)
Colitis ulcerative	1 (7.1)	0	1 (2.6)
Diverticulum	1 (7.1)	0	1 (2.6)
Gastritis	0	1 (4.0)	1 (2.6)
Hiatus hernia	0	1 (4.0)	1 (2.6)
Intestinal obstruction	0	1 (4.0)	1 (2.6)
Irritable bowel syndrome	0	1 (4.0)	1 (2.6)
Nausea	0	1 (4.0)	1 (2.6)
Umbilical hernia	0	1 (4.0)	1 (2.6)
General disorders and administration site conditions	6 (42.9)	5 (20.0)	11 (28.2)
Edema peripheral	2 (14.3)	2 (8.0)	4 (10.3)
Fatigue	0	3 (12.0)	3 (7.7)
Gait disturbance	2 (14.3)	0	2 (5.1)
Pain	2 (14.3)	0	2 (5.1)
Asthenia	0	1 (4.0)	1 (2.6)
Hernia	0	1 (4.0)	1 (2.6)
Local swelling	1 (7.1)	0	1 (2.6)
Peripheral swelling	1 (7.1)	0	1 (2.6)
Hepatobiliary disorders	2 (14.3)	0	2 (5.1)
Cholelithiasis	2 (14.3)	0	2 (5.1)
Immune system disorders	3 (21.4)	5 (20.0)	8 (20.5)
Drug hypersensitivity	1 (7.1)	3 (12.0)	4 (10.3)
Seasonal allergy	2 (14.3)	1 (4.0)	3 (7.7)
Contrast media allergy	0	1 (4.0)	1 (2.6)
Dust allergy	0	1 (4.0)	1 (2.6)
Infections and infestations	4 (28.8)	11 (44.0)	15 (38.5)
Appendicitis	1 (7.1)	4 (16.0)	5 (12.8)
Tonsillitis	1 (7.1)	1 (4.0)	2 (5.1)
Angular cheilitis	0	1 (4.0)	1 (2.6)
Eye infection toxoplasmal	0	1 (4.0)	1 (2.6)
Hepatitis A	1 (7.1)	0	1 (2.6)
Infection parasitic	0	1 (4.0)	1 (2.6)
Infectious pleural effusion	0	1 (4.0)	1 (2.6)

Lyme disease	1 (7.1)	0	1 (2.6)
Onychomycosis	1 (7.1)	0	1 (2.6)
Paronychia	0	1 (4.0)	1 (2.6)
Rhinitis	0	1 (4.0)	1 (2.6)
Urinary tract infection	0	1 (4.0)	1 (2.6)
Injury, poisoning, and procedural complications	2 (14.3)	9 (36.0)	11 (28.2)
Joint injury	0	2 (8.0)	2 (5.1)
Cartilage injury	1 (7.1)	0	1 (2.6)
Facial bones fracture	0	1 (4.0)	1 (2.6)
Joint dislocation	0	1 (4.0)	1 (2.6)
Limb injury	0	1 (4.0)	1 (2.6)
Pelvic fracture	0	1 (4.0)	1 (2.6)
Rib fracture	0	1 (4.0)	1 (2.6)
Scapula fracture	0	1 (4.0)	1 (2.6)
Scar	0	1 (4.0)	1 (2.6)
Tendon rupture	1 (7.1)	0	1 (2.6)
Thoracic vertebral fracture	0	1 (4.0)	1 (2.6)
Investigations	0	5 (20.0)	5 (12.8)
Colonoscopy	0	2 (8.0)	2 (5.1)
Blood cholesterol increased	0	1 (4.0)	1 (2.6)
Blood homocysteine increased	0	1 (4.0)	1 (2.6)
Cardiac murmur	0	1 (4.0)	1 (2.6)
Prostatic specific antigen increased	0	1 (4.0)	1 (2.6)
Metabolism and nutrition disorders	8 (57.1)	16 (64.0)	24 (61.5)
Hypercholesterolemia	2 (14.3)	6 (24.0)	8 (20.5)
Dyslipidemia	1 (7.1)	3 (12.0)	4 (10.3)
Hyperlipidemia	2 (14.3)	2 (8.0)	4 (10.3)
Type 2 diabetes mellitus	0	4 (16.0)	4 (10.3)
Vitamin D deficiency	1 (7.1)	2 (8.0)	3 (7.7)
Gout	0	2 (8.0)	2 (5.1)
Diabetes mellitus	1 (7.1)	0	1 (2.6)
Hypokalemia	1 (7.1)	0	1 (2.6)
Overweight	1 (7.1)	0	1 (2.6)
Type 1 diabetes mellitus	0	1 (4.0)	1 (2.6)
Vitamin B12 deficiency	0	1 (4.0)	1 (2.6)
Musculoskeletal and connective tissue disorders	7 (50.0)	18 (72.0)	25 (64.1)
Back pain	1 (7.1)	8 (32.0)	9 (23.1)
Osteoarthritis	0	6 (24.0)	6 (15.4)
Arthritis	4 (28.6)	1 (4.0)	5 (12.8)
Osteopenia	0	3 (12.0)	3 (7.7)
Arthralgia	0	2 (8.0)	2 (5.1)
Foot deformity	1 (7.1)	1 (4.0)	2 (5.1)

Lumbar spinal stenosis	1 (7.1)	1 (4.0)	2 (5.1)
Pain in extremity	0	2 (8.0)	2 (5.1)
Scoliosis	0	2 (8.0)	2 (5.1)
Camptocormia	1 (7.1)	0	1 (2.6)
Dupuytren's contracture	0	1 (4.0)	1 (2.6)
Fistula	1 (7.1)	0	1 (2.6)
Gouty arthritis	0	1 (4.0)	1 (2.6)
Intervertebral disc degeneration	0	1 (4.0)	1 (2.6)
Intervertebral disc disorder	1 (7.1)	0	1 (2.6)
Kyphosis	0	1 (4.0)	1 (2.6)
Muscle spasms	0	1 (4.0)	1 (2.6)
Osteoporosis	0	1 (4.0)	1 (2.6)
Spinal osteoarthritis	0	1 (4.0)	1 (2.6)
Tendonitis	1 (7.1)	0	1 (2.6)
Torticollis	0	1 (4.0)	1 (2.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (28.6)	8 (32.0)	12 (30.8)
Basal cell carcinoma	0	3 (12.0)	3 (7.7)
Prostate cancer	1 (7.1)	2 (8.0)	3 (7.7)
Seborrheic keratosis	1 (7.1)	1 (4.0)	2 (5.1)
Benign renal neoplasm	0	1 (4.0)	1 (2.6)
Bladder cancer	1 (7.1)	0	1 (2.6)
Cervix carcinoma	0	1 (4.0)	1 (2.6)
Lipoma	0	1 (4.0)	1 (2.6)
Malignant melanoma in situ	1 (7.1)	0	1 (2.6)
Polycythemia vera	1 (7.1)	0	1 (2.6)
Skin papilloma	0	1 (4.0)	1 (2.6)
Squamous cell carcinoma of skin	0	1 (4.0)	1 (2.6)
Nervous system disorders	11 (78.6)	17 (68.0)	28 (71.8)
Cognitive disorder	3 (21.4)	8 (32.0)	11 (28.2)
Somnolence	3 (21.4)	3 (12.0)	6 (15.4)
Anosmia	2 (14.3)	3 (12.0)	5 (12.8)
Neuropathy peripheral	1 (7.1)	3 (12.0)	4 (10.3)
Dementia	3 (21.4)	0	3 (7.7)
Drooling	2 (14.3)	1 (4.0)	3 (7.7)
Restless leg syndrome	1 (7.1)	2 (8.0)	3 (7.7)
Amnesia	2 (14.3)	0	2 (5.1)
Dystonia	1 (7.1)	1 (4.0)	2 (5.1)
Headache	2 (14.3)	0	2 (5.1)
Parkinsonian gait	1 (7.1)	1 (4.0)	2 (5.1)
Aphasia	1 (7.1)	0	1 (2.6)
Aphonia	1 (7.1)	0	1 (2.6)
Balance disorder	0	1 (4.0)	1 (2.6)

Carpal tunnel syndrome	1 (7.1)	0	1 (2.6)
Cerebral hemorrhage	0	1 (4.0)	1 (2.6)
Cerebrovascular accident	0	1 (4.0)	1 (2.6)
Diabetic neuropathy	0	1 (4.0)	1 (2.6)
Dizziness	0	1 (4.0)	1 (2.6)
Migraine	0	1 (4.0)	1 (2.6)
ON and OFF phenomenon	1 (7.1)	0	1 (2.6)
Paresthesia	0	1 (4.0)	1 (2.6)
Parkinsonism	1 (7.1)	0	1 (2.6)
Psychomotor hyperactivity	1 (7.1)	0	1 (2.6)
Sciatica	0	1 (4.0)	1 (2.6)
Sensory loss	0	1 (4.0)	1 (2.6)
Vlth nerve paralysis	0	1 (4.0)	1 (2.6)
Psychiatric disorders	8 (57.1)	21 (84.0)	29 (74.4)
Depression	5 (35.7)	17 (68.0)	22 (56.4)
Anxiety	2 (14.3)	12 (48.0)	14 (35.9)
Insomnia	2 (14.3)	8 (32.0)	10 (25.6)
Rapid eye movement sleep behavior disorder	1 (7.1)	8 (32.0)	9 (23.1)
Sleep disorder	1 (7.1)	2 (8.0)	3 (7.7)
Delusion	1 (7.1)	1 (4.0)	2 (5.1)
Hallucination	2 (14.3)	0	2 (5.1)
Affect lability	0	1 (4.0)	1 (2.6)
Aggression	0	1 (4.0)	1 (2.6)
Agitation	0	1 (4.0)	1 (2.6)
Agoraphobia	0	1 (4.0)	1 (2.6)
Anxiety disorder	0	1 (4.0)	1 (2.6)
Depressed mood	1 (7.1)	0	1 (2.6)
Hallucination, visual	0	1 (4.0)	1 (2.6)
Nightmare	0	1 (4.0)	1 (2.6)
Renal and urinary disorders	4 (28.6)	10 (40.0)	14 (35.9)
Urinary incontinence	2 (14.3)	3 (12.0)	5 (12.8)
Nephrolithiasis	2 (14.3)	1 (4.0)	3 (7.7)
Nocturia	0	3 (12.0)	3 (7.7)
Hypertonic bladder	0	2 (8.0)	2 (5.1)
Micturition urgency	0	2 (8.0)	2 (5.1)
Calculus bladder	0	1 (4.0)	1 (2.6)
Ketonuria	1 (7.1)	0	1 (2.6)
Pollakiuria	0	1 (4.0)	1 (2.6)
Reproductive system and breast disorders	5 (35.7)	11 (44.0)	16 (41.0)
Benign prostatic hyperplasia	4 (28.6)	4 (16.0)	8 (20.5)
Erectile dysfunction	0	5 (20.0)	5 (12.8)
Prostatomegaly	0	2 (8.0)	2 (5.1)
Breast mass	1 (7.1)	0	1 (2.6)

Peyronie's disease	0	1 (4.0)	1 (2.6)
Sexual dysfunction	1 (7.1)	0	1 (2.6)
Respiratory, thoracic and mediastinal disorders	7 (50.0)	13 (52.0)	20 (51.3)
Sleep apnea syndrome	2 (14.3)	2 (8.0)	4 (10.3)
Asthma	1 (7.1)	2 (8.0)	3 (7.7)
Dysphonia	2 (14.3)	1 (4.0)	3 (7.7)
Rhinorrhea	1 (7.1)	2 (8.0)	3 (7.7)
Pulmonary embolism	0	2 (8.0)	2 (5.1)
Rhinitis allergic	0	2 (8.0)	2 (5.1)
Acquired diaphragmatic eventration	0	1 (4.0)	1 (2.6)
Allergic sinusitis	0	1 (4.0)	1 (2.6)
Chronic obstructive pulmonary disease	0	1 (4.0)	1 (2.6)
Cough	0	1 (4.0)	1 (2.6)
Dyspnea	1 (7.1)	0	1 (2.6)
Pulmonary mass	0	1 (4.0)	1 (2.6)
Respiratory tract congestion	1 (7.1)	0	1 (2.6)
Wheezing	0	1 (4.0)	1 (2.6)
Skin and subcutaneous tissue disorders	2 (14.3)	7 (28.0)	9 (23.1)
Actinic keratosis	0	2 (8.0)	2 (5.1)
Dry skin	0	2 (8.0)	2 (5.1)
Acne	0	1 (4.0)	1 (2.6)
Decubitus ulcer	0	1 (4.0)	1 (2.6)
Dermatitis	0	1 (4.0)	1 (2.6)
Intertrigo	0	1 (4.0)	1 (2.6)
Pruritus	0	1 (4.0)	1 (2.6)
Psoriasis	1 (7.1)	0	1 (2.6)
Rosacea	0	1 (4.0)	1 (2.6)
Seborrheic dermatitis	0	1 (4.0)	1 (2.6)
Skin lesion	1 (7.1)	0	1 (2.6)
Social circumstances	1 (7.1)	2 (8.0)	3 (7.7)
Corrective lens user	1 (7.1)	0	1 (2.6)
Menopause	0	1 (4.0)	1 (2.6)
Vascular device user	0	1 (4.0)	1 (2.6)
Surgical and medical procedures	6 (42.9)	18 (72.0)	24 (61.5)
Appendectomy	2 (14.3)	5 (20.0)	7 (17.9)
Tonsillectomy	1 (7.1)	6 (24.0)	7 (17.9)
Hernia repair	1 (7.1)	3 (12.0)	4 (10.3)
Inguinal hernia repair	2 (14.3)	2 (8.0)	4 (10.3)
Cataract operation	1 (7.1)	2 (8.0)	3 (7.7)
Cholecystectomy	2 (14.3)	1 (4.0)	3 (7.7)
Coronary artery bypass	1 (7.1)	2 (8.0)	3 (7.7)
Knee arthroplasty	0	3 (12.0)	3 (7.7)

Skin neoplasm excision	1 (7.1)	2 (8.0)	3 (7.7)
Coronary arterial stent insertion	1 (7.1)	1 (4.0)	2 (5.1)
Deep brain stimulation	0	2 (8.0)	2 (5.1)
Hysterectomy	0	2 (8.0)	2 (5.1)
Knee operation	0	2 (8.0)	2 (5.1)
Spinal laminectomy	1 (7.1)	1 (4.0)	2 (5.1)
Ankle arthroplasty	0	1 (4.0)	1 (2.6)
Aortic bypass	0	1 (4.0)	1 (2.6)
Blepharoplasty	0	1 (4.0)	1 (2.6)
Brain tumor operation	0	1 (4.0)	1 (2.6)
Bunion operation	0	1 (4.0)	1 (2.6)
Gastric bypass	1 (7.1)	0	1 (2.6)
Hypophysectomy	0	1 (4.0)	1 (2.6)
Intra-aortic balloon placement	0	1 (4.0)	1 (2.6)
Micrographic skin surgery	0	1 (4.0)	1 (2.6)
Nasal septal operation	1 (7.1)	0	1 (2.6)
Nephrectomy	0	1 (4.0)	1 (2.6)
Photocoagulation	0	1 (4.0)	1 (2.6)
Prostate ablation	1 (7.1)	0	1 (2.6)
Spinal operation	0	1 (4.0)	1 (2.6)
Strabismus correction	0	1 (4.0)	1 (2.6)
Tenoplasty	1 (7.1)	0	1 (2.6)
Transurethral prostatectomy	0	1 (4.0)	1 (2.6)
Umbilical hernia repair	0	1 (4.0)	1 (2.6)
Uvulopalatopharyngoplasty	1 (7.1)	0	1 (2.6)
Vasectomy	0	1 (4.0)	1 (2.6)
Vena cava filter insertion	0	1 (4.0)	1 (2.6)
Vascular disorders	8 (57.1)	13 (52.0)	21 (53.8)
Hypertension	6 (42.9)	10 (40.0)	16 (41.0)
Orthostatic hypotension	2 (14.3)	4 (16.0)	6 (15.4)
Hypotension	2 (14.3)	0	2 (5.1)
Deep vein thrombosis	0	1 (4.0)	1 (2.6)
Peripheral coldness	1 (7.1)	0	1 (2.6)
Peripheral vascular disorder	0	1 (4.0)	1 (2.6)

^a A subject may appear in more than one system organ class or preferred term.

^bSubjects with multiple occurrences of a condition coded to the same system organ class or preferred term are counted only once for that system organ class and preferred term

^cMedical and surgical history is coded using MedDRA version 19.0.

^dPercentages are based on the number of subjects in the safety population in each treatment group.