

Supplementary Table S1. The schedule of visits and assessments conducted from screening to the end of study visit. In addition, participants and their study partners (caregivers) answered questions in an eDiary (electronic Patient Reported Outcome; ePRO) about mood and aggressive outbursts using a web application that was developed for this study.

Week	SC	BL	2	4	6	8	10	12	F/U
Visit Window	Day -30 to 0	Day 0	Day 14±5	Day 28±5	Day 42±5	Day 56±5	Day 70±5	Day 84±5	Day 91±5
Visit	SC	BL	01	T1	02	03	04	05	T2
Assessment	Dosing (BID)		120 mg		120 or 160mg				none
Review Study Drug Compliance			X	X	X	X	X	X	
Assessments for Adverse Events		X	X	X	X	X	X	X	X
Assessments for Concomitant Medication Use		X	X	X	X	X	X	X	X
Columbia Suicide Severity Rating Scale (CSSRS)	X	X	X		X	X	X	X	
Unified Huntington Disease Rating Scale (UHDRS)	X	X			X			X	
Clinical Global Impression-Severity of Illness (CGI-S)		X							
Clinical Global Impression-Improvement (CGI-I)					X			X	
Provide Diary and Instructions		X	R	R	R	R	R	R	
Aberrant Behavior Checklist (ABC), irritability subscale		X			X			X	
Cohen-Mansfield Aggression Inventory (CMAI)		X			X			X	
Problem Behaviors Assessment-short form (PBA-s)		X			X			X	
Irritability Scale		X			X			X	
HD QoL		X			X			X	
Caregiver Burden Questionnaire		X			X			X	
Participant/Study Partner/PI Blindedness Questionnaire								X	
Informed Consent (Subject)	X	R							
Informed Consent (Study Partner)	X	R ^a	R ^e	R ^e	R ^e	R ^e	R ^e	R ^e	
Assign Subject ID/ Unique Site ID number	X								
Inclusion/Exclusion Criteria	X	R							
Screening Demographics (Subject)	X								
Screening Demographics (Study Partner)	X	R ^a	R ^e	R ^e	R ^e	R ^e	R ^e	R ^e	
Medical & Surgical History	X	R							
Review methods of birth control with men and women	X	X							
Complete Physical Exam, including neurological	X							X	
Height, Weight (wt)	X				X(wt)			X(wt)	
Orthostatic Vital Signs (HR, BP), and Body Temperature	X	X ^b	X		X	X ^b	X	X	
Resting 12-Lead EKG	X	X	X		X	X	X	X	
Safety Labs (Hematology, Chemistry, Urinalysis, Study Drug Spot Check)	X	X ^h	X ^g		X ^g	X	X	X ^g	
Pregnancy Test (females only)	X(s)	X(u)			X(s)			X(s)	
Urine Drug Screen	X								
Blood Collections for CAGn Genotyping and storage		X	R ^f		R ^f	R ^f	R ^f	R ^f	
Randomization Assignment		X							
Dispense Study drug		X	X		X	X	X		
Instruct Subject and Study Partner about Study Drug		X	X		X	X	X	X ^c	
Administer Study Drug on Site		X				X	(X) ^d		

Supplementary Table S2. Adverse Events by System Organ Class and Treatment Group

Column 1	2	3	4	5	6	7	8	9	10	11	12	13
	Group											
System Organ Class	120 mg N = 36			Placebo N = 36			160 mg N = 34			RR (95% CI)		
	# (%) of Subjects	# of Events	Rate	# (%) of Subjects	# of Events	Rate	# (%) of Subjects	# of Events	Rate	Placebo vs 120 mg	Placebo vs 160 mg	120 mg vs 160 mg
Blood												
Lymph node pain	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Cardiac												
Angina pectoris	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Atrioventricular block first degree	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A
Bundle branch block left	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A
Palpitations	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A
Gastrointestinal												
Abdominal distension	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Abdominal pain	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Abdominal pain lower	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A
Abdominal pain upper	1 (2.8%)	1	.009	1 (2.8%)	1	.009	3 (8.8%)	3	.026	1.00 (0.07, 15.38)	0.31 (0.03, 2.88)	0.31 (0.03, 2.88)
Constipation	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A
Diarrhoea	1 (2.8%)	1	.009	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	0.94 (0.06, 14.51)
Dyspepsia	3 (8.3%)	3	.027	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Gastroesophageal reflux disease	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A
Nausea	3 (8.3%)	4	.036	0 (0.0%)	0	.000	5 (14.7%)	5	.043	N/A	N/A	0.57 (0.15, 2.19)
Tongue disorder	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Toothache	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A
Vomiting	1 (2.8%)	1	.009	0 (0.0%)	0	.000	2 (5.9%)	4	.035	N/A	N/A	0.47 (0.04, 4.97)
General												
Crying	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	2	.017	N/A	N/A	N/A
Fatigue	2 (5.6%)	2	.018	0 (0.0%)	0	.000	4 (11.8%)	4	.035	N/A	N/A	0.47 (0.09, 2.41)
Gait disturbance	0 (0.0%)	0	.000	1 (2.8%)	1	.009	1 (2.9%)	1	.009	N/A	0.94 (0.06, 14.51)	N/A
Influenza like illness	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Pyrexia	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A
Infections												
Bronchitis	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Conjunctivitis	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A
Cystitis	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A
Influenza	0 (0.0%)	0	.000	2 (5.6%)	2	.018	0 (0.0%)	0	.000	N/A	N/A	N/A
Nasopharyngitis	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Pharyngitis	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A
streptococcal												
Pyelonephritis	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Sinusitis	0 (0.0%)	0	.000	1 (2.8%)	1	.009	1 (2.9%)	1	.009	N/A	0.94 (0.06, 14.51)	N/A
Staphylococcal skin infection	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A
Upper respiratory tract infection	1 (2.8%)	1	.009	3 (8.3%)	3	.027	2 (5.9%)	2	.017	0.33 (0.04, 3.06)	1.42 (0.25, 7.96)	0.47 (0.04, 4.97)
Urinary tract infection	2 (5.6%)	3	.027	1 (2.8%)	2	.018	0 (0.0%)	0	.000	2.00 (0.19, 21.09)	N/A	N/A
Injury, Poisoning, and Procedural Comp.												
Ankle fracture	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Contusion	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Fall	3 (8.3%)	3	.027	1 (2.8%)	1	.009	3 (8.8%)	6	.052	3.00 (0.33, 27.50)	0.31 (0.03, 2.88)	0.94 (0.20, 4.36)

Joint injury	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A
Ligament sprain	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A
Limb injury	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A
Muscle strain	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A
Post concussion syndrome	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Tooth fracture	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A
Investigations												
Alanine aminotransferase increased	0 (0.0%)	0	.000	0 (0.0%)	0	.000	2 (5.9%)	2	.017	N/A	N/A	N/A
Blood bilirubin increased	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Blood creatinine increased	1 (2.8%)	1	.009	2 (5.6%)	2	.018	0 (0.0%)	0	.000	0.50 (0.05, 5.27)	N/A	N/A
Electrocardiogram QT prolonged	0 (0.0%)	0	.000	1 (2.8%)	1	.009	1 (2.9%)	1	.009	N/A	0.94 (0.06, 14.51)	N/A
Electrocardiogram T wave abnormal	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Electrocardiogram abnormal	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A
Eosinophil count increased	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A
Glucose urine	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Glucose urine present	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A
Hepatic enzyme increased	3 (8.3%)	3	.027	1 (2.8%)	1	.009	1 (2.9%)	1	.009	3.00 (0.33, 27.50)	0.94 (0.06, 14.51)	2.83 (0.31, 25.94)
Platelet count decreased	0 (0.0%)	0	.000	1 (2.8%)	1	.009	1 (2.9%)	1	.009	N/A	0.94 (0.06, 14.51)	N/A
Urine leukocyte esterase positive	0 (0.0%)	0	.000	0 (0.0%)	0	.000	2 (5.9%)	2	.017	N/A	N/A	N/A
Weight increased	1 (2.8%)	1	.009	1 (2.8%)	1	.009	1 (2.9%)	1	.009	1.00 (0.07, 15.38)	0.94 (0.06, 14.51)	0.94 (0.06, 14.51)
Metabolic												
Dehydration	1 (2.8%)	1	.009	1 (2.8%)	1	.009	0 (0.0%)	0	.000	1.00 (0.07, 15.38)	N/A	N/A
Musculoskeletal												
Arthralgia	1 (2.8%)	1	.009	1 (2.8%)	1	.009	2 (5.9%)	2	.017	1.00 (0.07, 15.38)	0.47 (0.04, 4.97)	0.47 (0.04, 4.97)
Back pain	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A
Costochondritis	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Muscular weakness	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Musculoskeletal chest pain	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Neck pain	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Osteoporosis	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A
Pain in extremity	0 (0.0%)	0	.000	0 (0.0%)	0	.000	2 (5.9%)	2	.017	N/A	N/A	N/A
Neoplasms												
Renal neoplasm	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Squamous cell carcinoma	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A
Nervous System												
Anosmia	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Chorea	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A
Dizziness	2 (5.6%)	2	.018	1 (2.8%)	1	.009	1 (2.9%)	1	.009	2.00 (0.19, 21.09)	0.94 (0.06, 14.51)	1.89 (0.18, 19.89)
Dysarthria	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A
Headache	3 (8.3%)	3	.027	1 (2.8%)	1	.009	3 (8.8%)	3	.026	3.00 (0.33, 27.50)	0.31 (0.03, 2.88)	0.94 (0.20, 4.36)
Hypersomnia	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A
Lethargy	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A
Paraesthesia	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A
Somnolence	0 (0.0%)	0	.000	4 (11.1%)	4	.035	1 (2.9%)	1	.009	N/A	3.78 (0.44, 32.13)	N/A

Psychiatric													
Abnormal dreams	0 (0.0%)	0	.000	3 (8.3%)	3	.027	0 (0.0%)	0	.000	N/A	N/A	N/A	N/A
Aggression	0 (0.0%)	0	.000	1 (2.8%)	1	.009	1 (2.9%)	1	.009	N/A	0.94 (0.06, 14.51)	N/A	N/A
Agitation	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A	N/A
Anxiety	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A	N/A
Apathy	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A	N/A
Depressed mood	2 (5.6%)	2	.018	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	1.89 (0.18, 19.89)	N/A
Hallucination, auditory	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A	N/A
Hypervigilance	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A	N/A
Indifference	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A	N/A
Insomnia	2 (5.6%)	2	.018	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	1.89 (0.18, 19.89)	N/A
Intentional self-injury	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A	N/A
Irritability	1 (2.8%)	1	.009	1 (2.8%)	1	.009	1 (2.9%)	1	.009	1.00 (0.07, 15.38)	0.94 (0.06, 14.51)	0.94 (0.06, 14.51)	N/A
Psychotic disorder	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A	N/A
Sleep disorder	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A	N/A
Suicidal ideation	1 (2.8%)	1	.009	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	0.94 (0.06, 14.51)	N/A
Suicide attempt	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A	N/A
Renal													
Dysuria	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A	N/A
Proteinuria	1 (2.8%)	1	.009	1 (2.8%)	1	.009	0 (0.0%)	0	.000	1.00 (0.07, 15.38)	N/A	N/A	N/A
Renal cyst	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A	N/A
Urinary hesitation	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A	N/A
Reproductive													
Dysmenorrhoea	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A	N/A
Respiratory													
Asthma	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A	N/A
Cough	2 (5.6%)	2	.018	1 (2.8%)	1	.009	0 (0.0%)	0	.000	2.00 (0.19, 21.09)	N/A	N/A	N/A
Dry throat	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A	N/A
Dyspnoea	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A	N/A
Nasal congestion	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A	N/A
Oropharyngeal pain	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A	N/A
Rhinitis allergic	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A	N/A
Sleep apnoea syndrome	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A	N/A
Skin													
Dermatitis acneiform	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A	N/A
Hyperhidrosis	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A	N/A
Night sweats	0 (0.0%)	0	.000	1 (2.8%)	1	.009	0 (0.0%)	0	.000	N/A	N/A	N/A	N/A
Precancerous skin lesion	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A	N/A
Vascular													
Hot flush	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A	N/A
Hypertension	0 (0.0%)	0	.000	0 (0.0%)	0	.000	1 (2.9%)	1	.009	N/A	N/A	N/A	N/A
Hypotension	1 (2.8%)	1	.009	0 (0.0%)	0	.000	0 (0.0%)	0	.000	N/A	N/A	N/A	N/A
Total	29 (80.6%)	75	.676	26 (72.2%)	52	.460	30 (88.2%)	73	.635	1.12 (0.86, 1.44)	0.82 (0.65, 1.04)	0.91 (0.75, 1.12)	

Column Definitions:

1: System Organ Class of AE; bold terms are the System Organ Class of AE

2,5,8: Number and percentage of subjects who have ever had AE

3,6,9: Total number of AEs; includes multiple AEs of same type per subject

4,7,10: Number of AEs per 30 days

11: Relative Risk (120 mg relative to Placebo) and 95% confidence interval

12: Relative Risk (Placebo relative to 160 mg) and 95% confidence interval

13: Relative Risk (120 mg relative to 160 mg) and 95% confidence interval

Supplementary Figure S1. The power analysis is shown for the placebo single-arm sample size (n_p) as a function of the difference of the group completer proportions ($\pi_p - \pi_T$) and the marginal placebo proportion (π_p). Paneling is by α -level, with 80% power. In the left-hand panel, the upper red line shows that conducting two tests each at $\alpha = .025$ and 80% power requires approximately 36 participants per group for the smallest proposed control proportion ($\pi_p = .80$) and the largest proportion difference ($\pi_p - \pi_T = .20$). Therefore, the projected total sample size of $N = 3n_p =$ was 108, and a sample size of $2n_p = 72$ for each comparison (120mg vs placebo, 160mg vs placebo). The right panel shows the n's for conducting two tests at $\alpha = .05$.

