

Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods. Statistical Analysis

Efficacy was analyzed in the modified intention-to-treat (efficacy) sample, comprising all patients who took at least one dose of study drug and who had a baseline and at least one post-baseline CMAI total score measurement. CMAI total (primary endpoint) and CGI-S (key secondary endpoint) score changes were separately analyzed using MMRM, with change from baseline at each scheduled post-baseline timepoint as the dependent variable. The model for the fixed effects included the following terms: treatment, site, and visit week, an interaction term of treatment by visit week, and the interaction term of baseline score by visit week. The repeated measures across time were treated categorically. An unstructured variance–covariance structure for change from baseline scores among scheduled post-baseline timepoints was used in each MMRM model. The contrast (i.e., least squares mean difference between brexpiprazole and placebo) at the Week 12 visit was estimated from the interaction term and served as the primary treatment comparison. The point estimate and 95% confidence interval estimate of the contrast at Week 12 are reported. The models assumed missing data to be missing at random, with a sensitivity analysis under the missing not at random assumption. Small sites that did not have ≥ 1 evaluable patient in each treatment arm (brexpiprazole and placebo) were pooled by region (US, Europe) to form collected sites for the purpose of analysis.

A planned sample size of 330 patients was estimated to achieve 89% power at a two-sided alpha level of 0.05 for detecting a treatment effect of 6.5 points (standard deviation: 16.5) in CMAI total score change from baseline to Week 12, after accounting for early dropouts (12–13% for brexpiprazole in the two prior Phase 3 trials¹). The target sample size and number of trial sites were increased in protocol amendments to account for the potential impact of the COVID-19 pandemic on patient living situations and clinical outcomes, as well as to compensate for site termination (described below). The treatment effect of 6.5 points was selected to support statistical powering and ensure that the study could be completed within a 4-year timeframe, rather than to represent a threshold for clinical relevance. An interim analysis of efficacy data was performed by an independent data monitoring committee after the first 255 randomized patients had either completed the Week 12 visit or discontinued from the trial. Possible outcomes of the interim analysis were stopping the trial for superiority in efficacy, stopping for futility, or continuing to the final analysis. To control the overall type I error rate at 0.05, a conservative Bonferroni critical boundary was applied, meaning that the significance level was set at 0.015 (two-sided) for the interim analysis, leaving 0.035 (two-sided) for the final analysis, with 87% power. Based on the interim analysis, the committee recommended continuing the trial to the planned sample size (the sponsor remained blinded to the interim results until completion of the trial).

Subgroup analyses of the primary efficacy endpoint were performed by region (US, Europe), sex (female, male), race (White, all other races), age group (<75, ≥ 75 years), baseline dementia severity (*post hoc*: mild/moderate, severe), and baseline psychosis status (*post hoc*: present, absent).

Secondary efficacy endpoints of change from baseline in CGI-S score as related to agitation (key secondary), CMAI Factor 1 ‘aggressive behavior’ score (12 items), Factor 2 ‘physically non-aggressive behavior’ score (6 items), and Factor 3 ‘verbally agitated behavior’ score (4 items)² were analyzed using equivalent MMRM analyses to the primary analysis. Secondary efficacy endpoints of CGI-I score, CMAI response ($\geq 20\%$, $\geq 30\%$, $\geq 40\%$ improvement in total score; and improvement in agitation status [i.e., agitated at baseline on any of Factors 1–3, and changing to non-agitated for the same factor, while not becoming agitated on another factor]), and CGI-I response (score of 1 “very much improved” or 2 “much improved”) at Week 12 were analyzed using a last-observation-carried-forward approach with Cochran–Mantel–Haenszel statistics controlling for site. Prespecified exploratory efficacy endpoints included change from baseline in NPI-NH total score, as well as change from baseline in CMAI total score and CGI-S score by dose (brexpiprazole 2 mg versus placebo; brexpiprazole 3 mg versus placebo), which were analyzed using equivalent MMRM analyses to the primary analysis.

The safety sample was composed of all patients who took at least one dose of study drug. Safety results are presented using descriptive statistics.

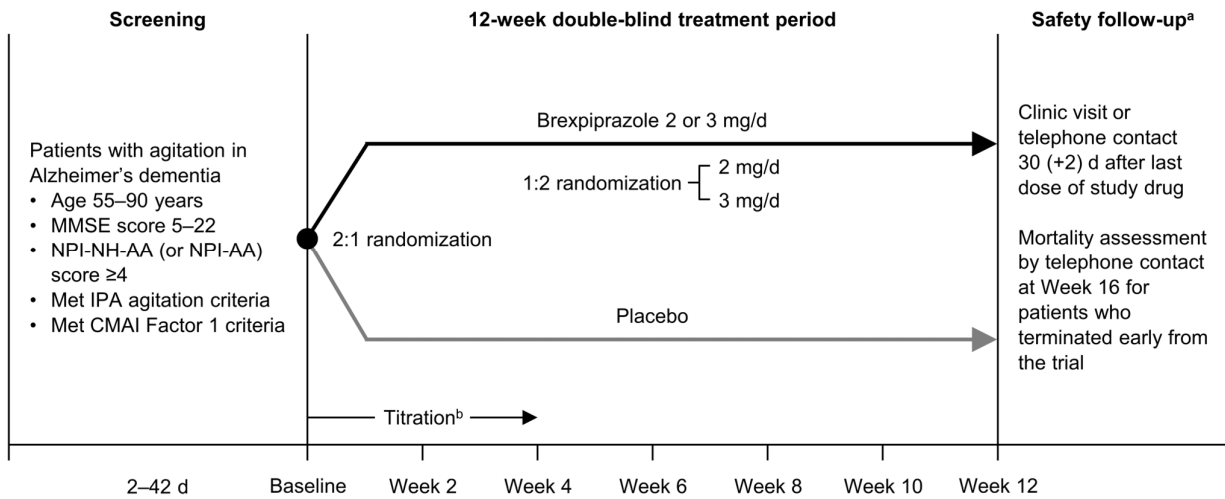
Two sites were terminated during the trial because good clinical practices were not followed; ongoing patients at these sites were discontinued from the trial. Patient data collected prior to site termination (19 patients) were included in the efficacy and safety analyses.

All analyses were performed using SAS Enterprise Guide version 8.1 (SAS Institute Inc; Cary, NC).

eReferences

1. Grossberg GT, Kohegyi E, Mergel V, et al. Efficacy and safety of brexpiprazole for the treatment of agitation in Alzheimer's dementia: two 12-week, randomized, double-blind, placebo-controlled trials. *Am J Geriatr Psychiatry*. 2020;28(4):383-400. doi:10.1016/j.jagp.2019.09.009
2. Rabinowitz J, Davidson M, De Deyn PP, Katz I, Brodaty H, Cohen-Mansfield J. Factor analysis of the Cohen-Mansfield Agitation Inventory in three large samples of nursing home patients with dementia and behavioral disturbance. *Am J Geriatr Psychiatry*. 2005;13(11):991-998. doi:10.1176/appi.ajgp.13.11.991

eFigure 1. Study Design

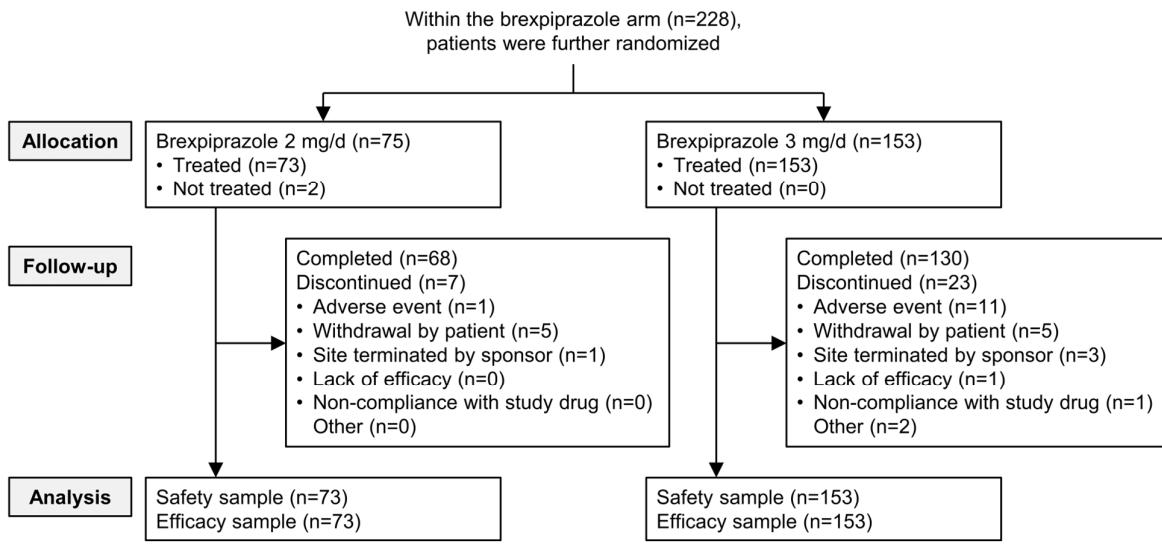


CMAI, Cohen-Mansfield Agitation Inventory; IPA, International Psychogeriatric Association; MMSE, Mini Mental State Examination; NPI-AA, Neuropsychiatric Inventory Agitation/Aggression domain; NPI-NH-AA, Neuropsychiatric Inventory – Nursing Home version Agitation/Aggression domain.

^aPatients who completed the 12-week double-blind treatment period were offered entry into a 12-week extension trial, as an alternative to the safety follow-up.

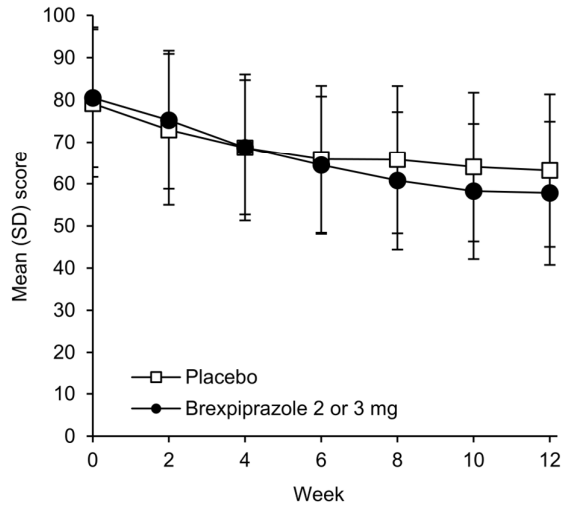
^bFirst week, 0.5 mg/d; second week, 1 mg/d; third and fourth weeks, 2 mg/d; beyond fourth week, 2 or 3 mg/d (fixed doses).

eFigure 2. Patient Disposition by Dose



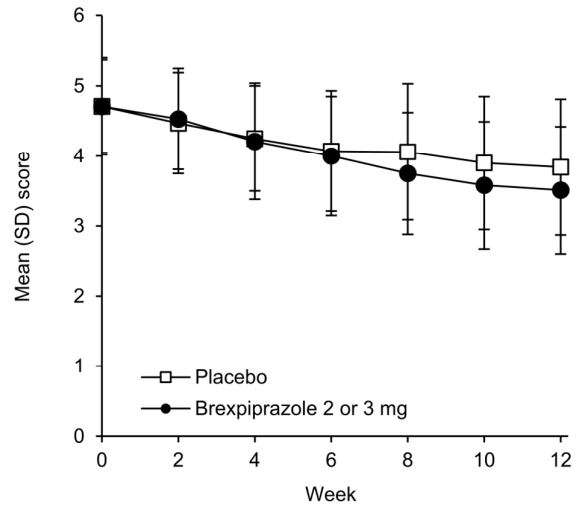
eFigure 3. CMAI Total Score and CGI-S Score as Related to Agitation (Efficacy Sample)

A. CMAI total score



Placebo, n=	116	114	114	112	105	105	103
Brex, n=	225	221	216	213	208	198	192

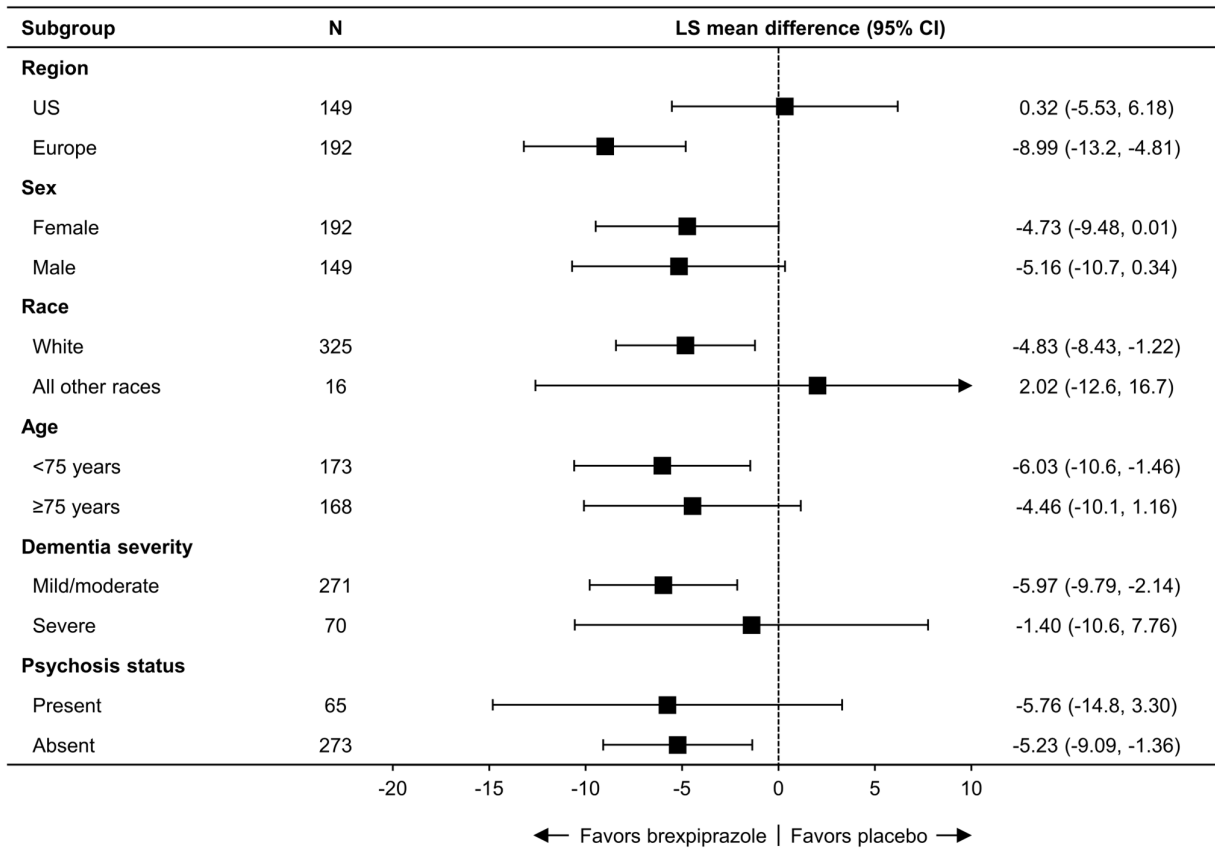
B. CGI-S score as related to agitation



Placebo, n=	116	114	114	112	105	105	103
Brex, n=	225	221	215	214	208	199	193

CGI-S, Clinical Global Impression – Severity of illness; CMAI, Cohen-Mansfield Agitation Inventory; SD, standard deviation.

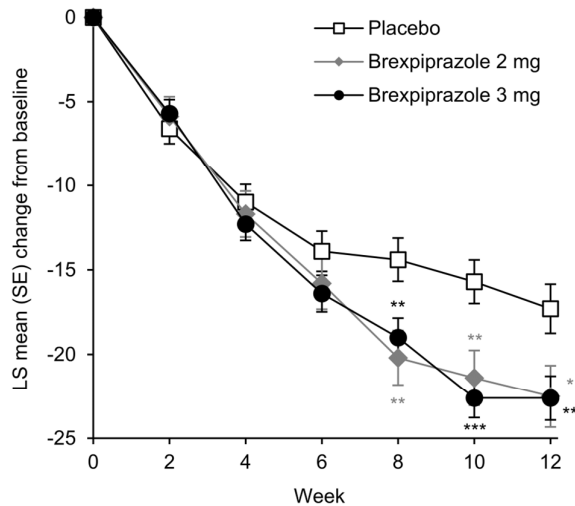
eFigure 4. Change From Baseline in CMAI Total Score at Week 12 by Subgroup (Efficacy Sample)



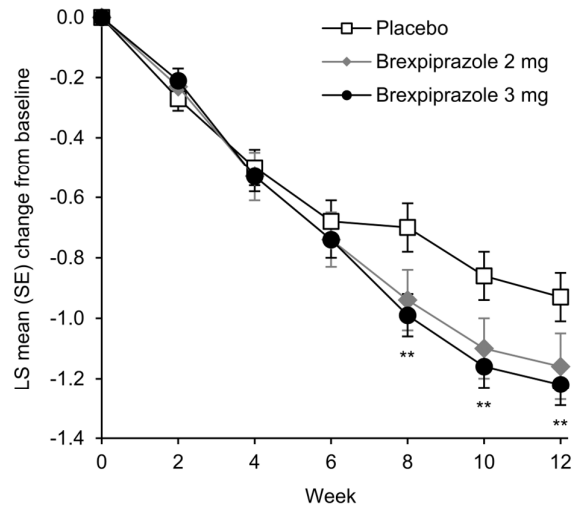
MMRM. In the subgroup analysis by region, the brexpiprazole response was consistent in the US (n=100; LS mean [SE] change, -21.8 [1.7]) and Europe (n=125; LS mean [SE] change, -22.5 [1.3]). However, a numerically higher placebo response was observed in the US (n=49; LS mean [SE] change, -22.1 [2.4]) versus Europe (n=67; LS mean [SE] change, -13.5 [1.7]). In the subgroup analysis by race, the 'all other races' subgroup was too small to be interpretable (n=16). CI, confidence interval; CMAI, Cohen-Mansfield Agitation Inventory; LS, least squares; MMRM, mixed model for repeated measures; SE, standard error.

eFigure 5. Change From Baseline in CMAI Total Score and CGI-S Score as Related to Agitation by Dose (Exploratory Analysis, Efficacy Sample)

A. CMAI total score by dose (exploratory endpoint)



B. CGI-S score as related to agitation by dose (exploratory endpoint)



Placebo, n=	116	114	114	112	105	105	103	Placebo, n=	116	114	114	112	105	105	103
Brex 2 mg, n=	73	71	70	70	70	67	66	Brex 2 mg, n=	73	71	69	70	70	67	66
Brex 3 mg, n=	152	150	146	143	138	131	126	Brex 3 mg, n=	152	150	146	144	138	132	127

Baseline mean CMAI total scores: brexpiprazole 3 mg, 81.3; brexpiprazole 2 mg, 79.1; placebo, 79.2. Baseline mean CGI-S scores: brexpiprazole 3 mg, 4.7; brexpiprazole 2 mg, 4.6; placebo, 4.7. Asterisks indicate nominal *P* values with no adjustment for multiplicity: **P*<.05, ***P*<.01, ****P*<.001 versus placebo; MMRM. CGI-S, Clinical Global Impression – Severity of illness; CMAI, Cohen-Mansfield Agitation Inventory; LS, least squares; MMRM, mixed model for repeated measures; SE, standard error.

eTable 1. List of Principal Investigators and Trial Sites

Site #	Principal Investigator Name	Address	# Screened ^a	# Enrolled	# Discontinued
100	Rajaprabhakaran Rajarethinam	Michigan Clinical Research Institute PC 3001 Plymouth Road Suite 107 Ann Arbor MI 48105 US	2	0	0
101	Emilio Mantero-Atienza	Premier Clinical Research Institute, Inc 3100 NW 72nd Avenue Suite 125 Miami FL 33122 US	55	7	2
102	Hemant Pandey ^b	MD First Research, LLC 3190 S. Gilbert Road Suite 5 Chandler AZ 85286 US	18	4	0
103	Anthony Ciabarra	Neurology Center of North Orange County 381 E. Imperial Hwy Fullerton CA 92835 US	1	0	0
104	Jose Gamez	Galiz Research 7100 W 20 Avenue Suite 802 Hialeah FL 33016 US	23	10	0
105	Ziad Hawatmeh (Daniel Mandri) ^c	Maxblue Institute Inc. 3408 West 84 Street Suite 209 Hialeah FL 33018 US	11	2	0
106	Gustavo Alva	ATP Clinical Research, Inc. 3151 Airway Avenue Ste T-3 Costa Mesa CA 92626 US	6	2	0
107	Heber Varela	Clinovation Research, LLC 2700 Glades Circle Suite 142 Weston FL 33327 US	0	0	0
108	Malini Nair (Anil Nair) ^c	Alzheimer Disease Center 173 Forest St Winchester MA 01890 US	13	1	0
109	Michael Pfeffer	Allied Biomedical Research Institute 7100 SW 47th Street Miami FL 33155 US	16	3	1
110	Richard Weisler	Richard H Weisler, MD, PA 700 Spring Forest Road Suite 125 Raleigh NC 27609 US	2	0	0

Site #	Principal Investigator Name	Address	# Screened ^a	# Enrolled	# Discontinued
111	Evelyn Lopez-Brignoni	IMIC Inc 18320 Franjo Road Palmetto Bay FL 33157 US	9	1	0
112	Ashok Patel	Bio Behavioral Health 20 Hospital Drive Suite 12 Toms River NJ 08755 US	18	3	1
113	David Lesch	Georgia Neurology and Sleep Medicine Associates 4385 Johns Creek Pkwy Ste 230 Suwanee GA 30024 US	14	0	0
114	Gnyandev Patel	Shreenath Clinical Service 3300 E. South Street Suite 206 Lakewood CA 90805 US	24	15	1
115	Dolores Sanchez-Cazau	Research in Miami Inc 777 East 25 Street Suite 516 Hialeah FL 33013 US	7	3	1
116	Emelina Arocha	Arocha Research Center 2000 SW 27 Avenue Suite 101 Miami FL 33145 US	11	2	0
117	Gil Fernandez-Year	Advanced Clinical Research 3940 West Flagler Street Coral Gables FL 33134 US	9	3	0
118	Junaid Syed	Arch Clinical Trials, LLC 1400 Lemay Ferry Road St. Louis MO 63125 US	14	1	1
119	Joe Pouzar (Amro El Feki) ^c	Centex Studies, Inc. 1045 Gemini Avenue Ste. 200-A Houston TX 77058 US	9	0	0
122	Jeanette Wendt	Territory Neurology & Research Institute 1631 W Ina Road #151 Tucson AZ 85704 US	0	0	0
123	Jason Mensah	Gadolin Research, LLC 2965 Harrison Avenue Suite 317 Beaumont TX 77702 US	2	0	0
124	Rodney Guttman	University of West Florida (UWF) Clinical Trials 8800 N. 9th Avenue Ste. A Pensacola FL 32514 US	1	0	0

Site #	Principal Investigator Name	Address	# Screened ^a	# Enrolled	# Discontinued
125	Paul Gross	Lehigh Center for Clinical Research 401 N 17th Street Suite 207 Allentown PA 18104 US	0	0	0
126	Syed Zaidi (Ashok Jain, Ata Rehman) ^c	Bio Pharma Informatic Inc. 19255 Park Row Drive Suite 205 Houston, TX 77084 US	5	0	0
127	Richard Shubin	SC3 Research 50 Alessandro Place Ste 240 Pasadena CA 91105 US	1	0	0
128	Francisco Esparza	Nova Clinical Research, LLC 2010 59th Street West Suite 3800 Bradenton FL 34209 US	6	0	0
129	Jason Kellogg	Global Clinical Trials 275 Victoria Street Suite 1G Costa Mesa CA 92627 US	2	0	0
130	Joseph Kwentus	Precise Research Centers 3531 Lakeland Drive Brentwood Plaza Suite 1060 Flowood MS 39232 US	8	0	0
131	Inna Yuryev-Golger	Integrative Clinical Trials LLC 2409 Ocean Avenue Unit # 1F Brooklyn NY 11229 US	6	3	1
132	Lydia Hazan	Axis Clinical Trials 5800 Wilshire Blvd. Los Angeles CA 90036 US	6	0	0
133	Antonio Terrelonge (Richard Dreize) ^c	Ocean Blue Medical Research 286 Westward Drive Miami Springs FL 33166 US	2	0	0
134	Adolfo Cueli	ICR Sites, LLC 3901 Nw 79th Avenue Suite 120 Doral FL 33166 US	18	11	6
135	Syed Mumtaz	SIH Research 724 W Vine Street Kissimmee FL 34741 US	15	8	1
137	Elly Lee	Irvine Clinical Research 2515 McCabe Way Suite 350 Irvine CA 92614 US	3	0	0

Site #	Principal Investigator Name	Address	# Screened ^a	# Enrolled	# Discontinued
138	Richard Holub	Neurological Associates of Albany, PC 760 Madison Avenue Albany NY 12208 US	7	2	0
139	Asad Islam	Northpointe Psychiatry 860 Hebron Pkwy Suite 1101 Lewisville TX 75057 US	16	1	0
140	David Steiner	Five Towns Neurology PC/Village 923 Broadway Woodmere NY 11598 US	8	0	0
141	Nader Armanious	California Neurological Services 8780 Van Nuys Blvd Suite B. Panorama City CA 91402 US	3	0	0
142	Jose Lopez Escobar (Elizabeth Mones) ^c	Health Care Family Rehab & Research 5901 NW 183 Street Suite 311 Miami FL 33015 US	62	15	0
143	Vaughn Whittaker	NY Clinical Trials 59 E 54th Street Room 93 New York NY 10022 US	0	0	0
144	Manuel Fernandez	Direct Helpers Research Center 425 W 51 Place Hialeah FL 33012 US	74	9	0
145	Oscar Hernandez	Janus Clinical Research 13500 SW 88th Street Suite 295 Miami FL 33186 US	0	0	0
146	Enrique Hanabergh	LC Professional Medical Research Institute 5965-5975 SW 8th Street Suite B Miami FL 33144 US	2	1	0
147	Seema Gupta (Bradley Musser) ^c	Relaro Medical Trials 12801 N. Central Expressway Suite 350 Dallas TX 75243 US	4	1	0
148	Leonardo Alonso	Central Miami Medical Institute 719 NW 13th Avenue Miami FL 33125 US	21	3	0

Site #	Principal Investigator Name	Address	# Screened ^a	# Enrolled	# Discontinued
149	Shahin Shirzadi	Mercury Clinical Research Inc. 1415 Highway 6, Suite A-200 Sugar Land TX 77478 US	7	2	0
150	Jacobo Mintzer	Roper St. Francis Healthcare 316 Calhoun Street Charleston SC 29401 US	9	4	1
151	Patrick Sciara	Mariposa Point of Surprise/CCT Research 16650 North Stadium Way Surprise AZ 85374 US	1	0	0
152	Sandeep Vaishnavi	Mind Path Care Centers North Carolina, PLLC 1130 Situs Court Suite 190 Raleigh NC 27606 US	3	0	0
154	Kalvin Kapoor	Humanity Clinical Research 2231 N University Drive Suite B Pembroke Pines FL 33024 US	13	3	0
155	Michael Mahdad	HB Clinical Trials, Inc. 11100 Warner Avenue Suite 150B Fountain Valley CA 92708 US	2	0	0
156	Mohammed Asim Nisar	Health Synergy Clinical Research 308 NW 5th Avenue Suite 125 Okeechobee FL 34972 US	5	1	0
157	John Puente	West Omaha Family Physicians/CCT Research 401 East Gold Coast Road Suite 215 Papillion NE 68046 US	1	0	0
158	Jeffrey Shy	Neurological Physicians of Arizona 726 S Greenfield Road Suite 110 Gilbert AZ 85234 US	0	0	0
159	Jay Sandberg	Oakland Medical Research 115 E Long Lake Road Troy MI 48085 US	5	1	1
161	Michael Killpack	Wasatch Clinical Research, LLC 310 East 4500 South Suite 360 Salt Lake City UT 84107 US	0	0	0

Site #	Principal Investigator Name	Address	# Screened ^a	# Enrolled	# Discontinued
162	Siddharth Kaul	Clinical Research Professionals 17998 Chesterfield Airport Road Suite 100 Chesterfield MO 63005 US	3	0	0
163	Judith Joseph	Manhattan Behavioral Medicine PPLC 2 W 46th Street Ste 405 New York NY 10036 US	1	0	0
164	Jose DeLaGandara	Quantum Laboratories 50 E Sample Road Suite 201 Pompano Beach FL 33064 US	2	0	0
166	Perminder Bhatia	Neuro Pain Medical Center 736 E Bullard Avenue #101 Fresno CA 93710 US	6	3	0
168	Myron Reiff	CItrials Inc 17800 Woodruff Avenue Suite B Bellflower CA 90706 US	4	0	0
169	Alfredo Torres	Clinical Trials of America 300 Washington Street Suite 208 Monroe LA 71201 US	0	0	0
170	Eric Carbonell	Combined Research Orlando 1417 N Semoran Blvd, Suite 106 Orlando FL 32807 US	11	1	0
172	Silvia Silva-Duluc	South Florida Research Phase I-IV, Inc. 4487 NW 36th Street Miami Springs FL 33166 US	10	5	1
174	Hareesh Boghara	Epic Medical Research 106 Plaza Drive Red Oak TX 75154 US	3	0	0
175	Zaheer Aslam	Gulfcoast Clinical Research Center 6150 Diamond Centre Ct Building 500 Fort Myers FL 33912 US	0	0	0
176	Lourdes Selem	New Life Medical Research Center, Inc. 3750 W 16th Avenue Suite 226 U Hialeah FL 33012 US	11	7	0

Site #	Principal Investigator Name	Address	# Screened ^a	# Enrolled	# Discontinued
177	Tatiana Hernandez	Bayside Medical Group 2155 Little Road Trinity FL 34655 US	6	1	0
178	Ibrahim Menendez-Perez	Project4Research, Inc. 1281 NW 6 Street Miami FL 33125 US	10	4	0
179	David Purselle	Advanced Discovery Research 652 Bellemeade Avenue NW Atlanta GA 30318 US	2	1	0
180	Luis Merced	VICIS Clinical Research 6107 Memorial Highway Suite G Tampa FL 33615 US	4	2	0
181	John De Beixedon	Havana Research Institute LLC 675 S. Arroyo Parkway Suite 320 Pasadena CA 91105 US	0	0	0
182	Cyrus Khorrami	Ocean Medical Research 328 Commons Way, Bldg. C Toms River NJ 08755 US	0	0	0
184	Mark DiBuono (Eli Shalenberg) ^c	Evolution Research Group 4349 Hylan Blvd Staten Island NY 10312 US	2	1	1
185	Miguel Flores	International Research Associates, LLC 8200 SW 117th Avenue # 210 Miami FL 33183 US	0	0	0
186	Rafael Gonzalez	P&S Research, LLC 12905 SW 42 Street Ste: 201 Miami FL 33175 US	2	0	0
188	Karen Figueredo Reyes	Innovation Medical Research Center 9299 SW 152nd Street Suite 205 Palmetto Bay FL 33157 US	11	5	1
189	Alan Jacobson	Miami Health Center 19001 SW 106 Avenue Suite C-109 Cutler Bay FL 33157 US	0	0	0
190	Brad Herskowitz	Brainstorm Research 9090 SW 87th Court Suite 200 Miami FL 33176 US	2	0	0

Site #	Principal Investigator Name	Address	# Screened ^a	# Enrolled	# Discontinued
200	Veselin Palazov	Mental Health Center Prof. Dr Ivan Temkov – Burgas EOOD Department for Treatment of Emergency Psychiatric Conditions Complex Lazur Park Ezero Burgas 8000 BG	5	4	0
201	Temenuzhka Dechkova-Novakova	Mental Health Centre-Ruse EOOD, Daily Unit 20 Tutrakan Blvd. Ruse 7003 BG	10	7	1
202	Hristo Kozhuharov	Diagnostic and Consultative Centre Mladost – M Varna OOD Unit V, Office 521 15 “Republika” Blvd. Varna 9020 BG	7	6	0
203	Rozaliya Rangelova	State Psychiatry Hospital – Kardzhali Third Male Department, 44 Dobrich Str. Kardzhali 6600 BG	6	3	2
204	Petar Petrov	Diagnostic and Consultative Centre Mladost – M Varna OOD Unit G, Office 312 15 “Republika” Blvd Varna 9020 BG	5	5	0
205	Nadya Ivanova	Mental Health Center – Vratsa EOOD Department of Psychiatry, 1 Belasitsa Str. Vratza Vratza 3000 BG	11	7	0
206	Assen Karadaliiev	Medical Center Sveti Naum EOOD Izgrev district, 1 Lyuben Rusev Str. Sofia 1113 BG	11	2	0
208	Toni Donchev	Medical Center Intermedica OOD 62 Nishava Str. Sofia 1680 BG	8	3	0
300	Angel Luis Montejo-Gonzalez	Centro de Salud San Juan First Floor Unidad de Investigación Neurociencias Avenida de Portugal, 83 Salamanca 37005 ES	3	2	1

Site #	Principal Investigator Name	Address	# Screened ^a	# Enrolled	# Discontinued
301	Manuel Franco Martin	Complejo Asistencial de Zamora. Servicio de Psiquiatria C Hernan Cortes 40 Zamora 49021 ES	9	3	0
302	Juan Luis Munoz Sanchez	Hospital Universitario Rio Hortega Servicio de Psiquiatria C Dulzaina 2 Valladolid 47012 ES	12	6	2
303	Miguel Baquero Toledo	Hospital Universitari i Politecnic La Fe Service de Neurologia Avda Fernando Abril Martorell 109 Torre C, Planta 5 Valencia 46026 ES	0	0	0
304	Jose Miguel Lainez Andres	Hospital Clinico Universitario de Valencia Blasco Ibañez, 17 Valencia 46010 ES	0	0	0
400	Valentyna Kozydubova	Public Non-profit Enterprise within Kharkiv Regional Council Regional Clinical Psychiatric Hospital No. 3, #14 psychiatric department for adults 46, Acad. Pavlov Vul Kharkiv 61068 UA	21	14	4
401	Svitlana Moroz	Communal Company "Dnipropetrovsk Regional Clinical Hospital named after I.I. Mechnikov" Dnipropetrovsk Regional Council 14, Ploscha Soborna Dnipro 49005 UA	10	9	0
402	Andrii Skrypnikov	Communal Enterprise "Regional Institution of Mental Psychiatric Care of the Poltava Regional Council". Higher State Educational Establishment of Ukraine "Ukrainian Medical and Dental Academy", Chair of Psychiatry, Narcology and Medical Psychology 1, Medychna St. Poltava 36013 UA	21	17	0
403	Iryna Vrublevska	Kiev City Psychoneurological hospital # 3, Department of nursing care #6 7 Pavlova Str. Glevakha Kiev region 08631 UA	9	9	0

Site #	Principal Investigator Name	Address	# Screened ^a	# Enrolled	# Discontinued
404	Kateryna Zakal	Communal Institution of Lviv Regional Council "Lviv Regional Clinical Psychiatric Hospital", Department #20 95 Kulparkivska str. Lviv 79021 UA	15	10	2
405	Pavlo Palamarchuk	Public nonprofit enterprise "Kherson Regional Institution of Mental Care" of Kherson Regional Council, Male Psychiatric Department #3 and Female Psychiatric Department #10 65, Govarda Vul. Kherson Kherson 73488 UA	29	19	3
406	Oksana Serebrennikova	Communal Noncommercial Enterprise "Vinnytsia Regional Clinical Psychoneurological Hospital" named after Acad. O. I. Yushchenko of Vinnytsia regional Council Male Department #14, Female Department #15, M.I. Pirogov Vinnytsia National Medical University, Chair of Psychiatry, Narcology and Psychotherapy with Postgraduate Studies Course 109 Pyrogov St Vinnytsia 21005 UA	18	12	0
407	Andriy Dubenko	Public Non-profit Enterprise within Kharkiv Regional Council Regional Clinical Psychiatric Hospital No. 3, #23 psychiatric department for war veterans 46, Acad. Pavlov Vul. Kharkiv 61068 UA	11	9	1
408	Yuliya Blazhevych	Municipal uncommercial enterprise "Clinical Hospital" PSYCHIATRY of the executive agency of the Kyiv city council (Kyiv city state administration), Center for Novel Treatment and Rehabilitation of Psychotic disorders Department 29 (Men's), Department 30 (Women's), Outpatient Clinic Office of Department 30 103 Kyrulivska str. Kyiv, Kyiv Region 04080 UA	9	8	1

Site #	Principal Investigator Name	Address	# Screened ^a	# Enrolled	# Discontinued
409	Valerii Pidkorytov	State Institution "Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine", Clinic of Department of Clinical, Social and Pediatric Psychiatry 46, Acad. Pavlova Vul. Kharkiv 61068 UA	0	0	0
500	Vladimir Diligenski	Clinical Hospital Center "Dr. Dragisa Misovic - Dedinje" Clinic of Psychiatry, Heroja Milana Tepica 1 Belgrade 11000 RS	8	7	0
501	Vladimir Janjic	Clinical Center Kragujevac Clinic of Psychiatry, Zmaj Jovina 30 Kragujevac 34000 RS	4	1	0
502	Jovanka Petrovic	Special Hospital for Psychiatric Diseases "Kovin" Cara Lazara 253 Kovin 26220 RS	17	11	1
503	Marija Semnic	Clinical Center of Vojvodina Clinic of Neurology, Hajduk Veljkova 1-9 Novi Sad 21000 RS	2	0	0
504	Vrsac Voskresenski	Special Hospital for Psychiatric Diseases "Dr Slavoljub Bakalovic" Vrsac Podvrsanska 13 Vrsac 26300 RS	0	0	0
700	Magdolna Abraham	Bekes Megyei Kozponti Korhaz Pzichiatra Simmelweis utca 1. Gyula 5700 HU	0	0	0
701	Gabor Feller	Petz Aladar County Teaching Hospital Department of Psychiatry Mental Hygiene and Addictology Vasvari P. str. 2-4. Gyor 9024 HU	2	0	0
703	Agnes Kertesz	Balassa Janos Hospital Psychiatry Beri Balogh A. u. 5-7. Szekszard 7100 HU	2	0	0
704	Eva Mathé	Dr. Mathe es Tarsa Bt Szechenyi str 8. Kalocsa 6300 HU	6	3	0

Site #	Principal Investigator Name	Address	# Screened ^a	# Enrolled	# Discontinued
706	Magdolna Pakaski (Kalman Janos) ^c	Szegedi Tudományegyetem AOK, Pszichiatriai Klinika, Vasas Szent Peter u. 1-3. Szeged 6724 HU	0	0	0
707	Viktor Voros	PsychoTech Kft. 2/2. Endresz Gyorgy str. Pecs 7633 HU	6	1	0
708	Janos Rethelyi	Semmelweis University Medical School, Department of Psychiatry and Psychotherapy Balassa Janos utca 6. Budapest 1083 HU	3	2	0
709	Tibor Kovacs	Semmelweis University Medical School, Department of Neurology Balassa Janos utca 6. Budapest 1083 HU	1	0	0
800	Beata Dupejova	Neurologicka Ambulancia MUDr.Dupejova Nová 21 Banská Bystrica 974 04 SK	11	5	1
801	Eva Palova	EPAMED s.r.o. Department of Psychiatry - Outpatient Unit, Topasova 9, Hlavná 68 Kosice 040 11 SK	10	2	0
802	Martina Hanzelova	KRANKAS s.r.o. Vojtecha Spanyola 43 Zilina 012 07 SK	0	0	0
804	Peter Molcan	Mentum s.r.o. Ruzinovska 10 Bratislava 820 07 SK	1	0	0
805	Magdalena Perichtova	Medicinske Centrum Konzilium s.r.o. - Dubnica nad Vahom Andreja Kmeťa 370 Dubnica nad Váhom 018 41 SK	10	6	4
806	Veronika Reznakova	Centrum MEMORY n.o Mlynarovicova 2571/21 Bratislava 851 01 SK	3	0	0
807	Livia Vavrusova	Psychiatricka ambulancia - Vavrusova Consulting, s.r.o Zaporozská 12 Bratislava 851 01 SK	1	0	0

^aA total of 900 unique patients were screened (987 screenings; 87 patients were rescreened).

^bCoordinating investigator.

^cFormer principal investigator.

eTable 2. CMAI Total Score Sensitivity Analysis – MNAR Using Pattern Mixture Model With Multiple Imputation and Dropout Due to Adverse Event or Withdrawal By Patient as MNAR (Efficacy Sample)

Shifted from the MAR ^a	Treatment difference versus placebo	
	Difference (95% CI) ^b	P value ^b
0	-4.79 (-8.16, -1.41)	.005
0.65	-4.73 (-8.11, -1.36)	.006
1.3	-4.68 (-8.06, -1.31)	.007
1.95	-4.63 (-8.01, -1.25)	.007
2.6	-4.58 (-7.96, -1.20)	.008
3.25	-4.53 (-7.92, -1.15)	.009
3.9	-4.48 (-7.87, -1.10)	.01
4.55	-4.43 (-7.82, -1.04)	.01
5.2	-4.38 (-7.77, -0.99)	.01
5.85	-4.33 (-7.73, -0.93)	.01
6.5	-4.28 (-7.68, -0.88)	.01
7.15	-4.23 (-7.63, -0.82)	.01
7.8	-4.18 (-7.59, -0.77)	.02
8.45	-4.13 (-7.54, -0.71)	.02
9.1	-4.08 (-7.50, -0.66)	.02
9.75	-4.03 (-7.45, -0.60)	.02
10.4	-3.98 (-7.41, -0.54)	.02
11.05	-3.93 (-7.36, -0.49)	.03
11.7	-3.87 (-7.32, -0.43)	.03
12.35	-3.82 (-7.28, -0.37)	.03
13	-3.77 (-7.23, -0.31)	.03
13.65	-3.72 (-7.19, -0.26)	.04
14.3	-3.67 (-7.15, -0.20)	.04
14.95	-3.62 (-7.10, -0.14)	.04
15.6	-3.57 (-7.06, -0.08)	.05
16.25	-3.52 (-7.02, -0.02)	.05
16.9	-3.47 (-6.98, 0.04)	.05

Abbreviations: CI, confidence interval; CMAI, Cohen-Mansfield Agitation Inventory; MAR, missing at random; MNAR, missing not at random.

^aAnalysis departs from MAR assumption by progressively increasing the delta (treatment effect) until the conclusion from the primary analysis is overturned. When delta is 0 the missing data are assumed to be MAR; when delta is >0 the missing data are assumed to be MNAR.

^bDerived based on 100 imputations.

eTable 3. Suicidality, EPS, Cognitive Dysfunction, Body Weight, Metabolic Parameters, and QT Interval (Safety Sample)

Endpoint	Placebo	Brexiprazole 2 or 3 mg	Treatment difference versus placebo	
			LS mean difference (95% CI)	P value
LS mean change from baseline to last visit				
Sheehan-STS total score ^a	-0.01 (n=110)	-0.02 (n=214)	0.00 (-0.03 to 0.03)	.83
SAS total score ^a	0.07 (n=109)	0.47 (n=211)	0.40 (0.09 to 0.71)	.01
AIMS Movement rating score ^a	0.05 (n=110)	0.05 (n=212)	0.00 (-0.08 to 0.08)	>.99
BARS Global score ^a	-0.04 (n=110)	-0.04 (n=213)	0.00 (-0.04 to 0.04)	.96
MMSE score ^a	0.31 (n=110)	0.30 (n=212)	-0.01 (-0.59 to 0.56)	.97
Body weight, kg ^b	-0.03 (n=111)	0.18 (n=220)	0.22 (-0.35 to 0.79)	.45
Mean change from baseline to last visit				
Fasting metabolic parameters, mg/dL				
Glucose	-2.29 (n=108)	5.64 (n=196)	–	–
HDL cholesterol	-1.21 (n=107)	-0.64 (n=196)	–	–
LDL cholesterol	3.16 (n=105)	-0.84 (n=193)	–	–
Total cholesterol	2.84 (n=107)	-2.08 (n=196)	–	–
Triglycerides	10.69 (n=107)	-1.53 (n=196)	–	–
QTcF, ms	0.3 (n=112)	1.3 (n=221)	–	–
QTcF prolongation, No. (%) ^c	3/112 (2.7)	3/221 (1.4)	–	–

Abbreviations: ANCOVA, analysis of covariance; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; CI, confidence interval; EPS, extrapyramidal symptoms; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LS, least squares; MMSE, Mini Mental State Examination; QTcF, QT interval as corrected by Fridericia's formula; SAS, Simpson–Angus Scale; STS, Suicidality Tracking Scale.

^aANCOVA model, with treatment and trial site as main effects and baseline value as covariate.

^bANCOVA model, with treatment as main effect and baseline value as covariate.

^cNew onset, ≥450 ms (men), ≥470 ms (women), at any post-baseline visit.