

Supplementary information

Efficacy of brexpiprazole in participants with agitation associated with dementia due to Alzheimer's disease: pooled analysis of randomized controlled trials

Clinical Drug Investigation

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Contents

Additional results (two trials)

Fig. S1 Change from baseline to Week 12 in Cohen-Mansfield Agitation Inventory (CMAI) total score, stratified by demographic subgroups 2

Table S1 Change from baseline to Week 12 in Cohen-Mansfield Agitation Inventory (CMAI) item scores 3

Sensitivity analysis (three trials) 6

Table S2 Baseline demographic and clinical characteristics, and concomitant medications – sensitivity analysis 7

Fig. S2 Change from baseline in Cohen-Mansfield Agitation Inventory (CMAI) total score – sensitivity analysis 8

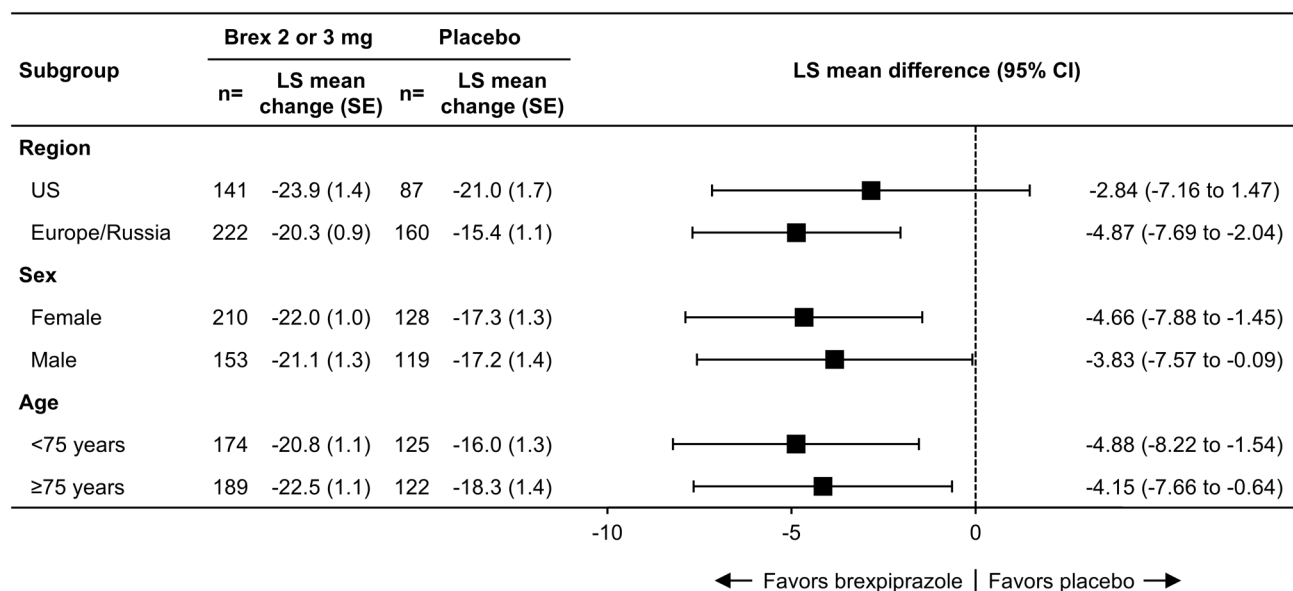
Fig. S3 Change from baseline in Clinical Global Impression – Severity of illness (CGI-S) score as related to agitation – sensitivity analysis 9

Fig. S4 Change from baseline in Cohen-Mansfield Agitation Inventory (CMAI) factor scores – sensitivity analysis 10

Table S3 Summary of efficacy results – sensitivity analysis 11

Additional results (two trials)

Fig. S1 Change from baseline to Week 12 in Cohen-Mansfield Agitation Inventory (CMAI) total score, stratified by demographic subgroups



Efficacy sample; mixed model for repeated measures; n-values are for baseline.

Abbreviations: Brex, brexpiprazole; CI, confidence interval; LS, least squares; SE, standard error.

Table S1 Change from baseline to Week 12 in Cohen-Mansfield Agitation Inventory (CMAI) item scores

CMAI item ^a	Treatment group	N	Mean (SD) at baseline	LS mean (SE) change from baseline to Week 12	Treatment difference at Week 12		
					LS mean (95% CI)	p-value	Cohen's <i>d</i>
Factor 1: aggressive behavior							
3. Spitting (including at meals)	Brexpiprazole 2 or 3 mg	363	1.8 (1.4)	-0.6 (0.0)	-0.04 (-0.16 to 0.09)	0.54	0.05
	Placebo	247	1.8 (1.4)	-0.5 (0.1)			
4. Cursing or verbal aggression	Brexpiprazole 2 or 3 mg	363	4.0 (1.6)	-1.8 (0.1)	-0.41 (-0.64 to -0.19)	<0.001	0.30
	Placebo	247	3.9 (1.6)	-1.4 (0.1)			
7. Hitting (including self)	Brexpiprazole 2 or 3 mg	363	2.0 (1.4)	-0.7 (0.1)	-0.09 (-0.24 to 0.06)	0.22	0.10
	Placebo	247	2.0 (1.4)	-0.6 (0.1)			
8. Kicking	Brexpiprazole 2 or 3 mg	363	1.7 (1.2)	-0.5 (0.0)	-0.05 (-0.16 to 0.05)	0.30	0.09
	Placebo	247	1.7 (1.1)	-0.5 (0.0)			
9. Grabbing onto people	Brexpiprazole 2 or 3 mg	363	2.4 (1.6)	-0.9 (0.1)	-0.17 (-0.33 to -0.01)	0.041	0.17
	Placebo	247	2.4 (1.6)	-0.8 (0.1)			
10. Pushing	Brexpiprazole 2 or 3 mg	363	2.3 (1.6)	-0.9 (0.1)	-0.12 (-0.27 to 0.03)	0.12	0.13
	Placebo	247	2.3 (1.5)	-0.8 (0.1)			
11. Throwing things	Brexpiprazole 2 or 3 mg	363	2.2 (1.4)	-0.8 (0.1)	-0.02 (-0.17 to 0.13)	0.77	0.02
	Placebo	247	2.3 (1.5)	-0.8 (0.1)			
13. Screaming	Brexpiprazole 2 or 3 mg	363	2.8 (1.8)	-1.3 (0.1)	-0.20 (-0.37 to -0.03)	0.023	0.19
	Placebo	247	2.8 (1.7)	-1.1 (0.1)			
14. Biting	Brexpiprazole 2 or 3 mg	363	1.1 (0.5)	-0.1 (0.0)	-0.01 (-0.09 to 0.06)	0.70	0.03
	Placebo	247	1.2 (0.8)	-0.1 (0.0)			
15. Scratching	Brexpiprazole 2 or 3 mg	363	1.6 (1.3)	-0.3 (0.0)	-0.11 (-0.25 to 0.04)	0.14	0.12
	Placebo	247	1.5 (1.1)	-0.2 (0.1)			

CMAI item ^a	Treatment group	N	Mean (SD) at baseline	LS mean (SE) change from baseline to Week 12	Treatment difference at Week 12		
					LS mean (95% CI)	p-value	Cohen's <i>d</i>
21. Hurting self or others	Brexpiprazole 2 or 3 mg	363	1.3 (0.8)	-0.2 (0.0)	-0.14 (-0.22 to -0.05)	0.001	0.27
	Placebo	247	1.3 (0.9)	-0.1 (0.0)			
25. Tearing things/destroying property	Brexpiprazole 2 or 3 mg	363	1.8 (1.3)	-0.6 (0.0)	-0.23 (-0.35 to -0.12)	<0.001	0.32
	Placebo	247	1.8 (1.3)	-0.3 (0.0)			
Factor 2: physically non-aggressive behavior							
1. Pacing, aimless wandering	Brexpiprazole 2 or 3 mg	363	4.6 (1.8)	-1.4 (0.1)	-0.23 (-0.45 to 0.00)	0.051	0.16
	Placebo	247	4.6 (1.7)	-1.2 (0.1)			
2. Inappropriate dressing or disrobing	Brexpiprazole 2 or 3 mg	363	2.7 (1.7)	-0.6 (0.1)	0.06 (-0.12 to 0.23)	0.54	0.05
	Placebo	247	2.6 (1.6)	-0.7 (0.1)			
16. Trying to get to a different place	Brexpiprazole 2 or 3 mg	363	3.8 (1.9)	-1.3 (0.1)	-0.26 (-0.47 to -0.04)	0.019	0.19
	Placebo	247	4.0 (1.8)	-1.0 (0.1)			
22. Handling things inappropriately	Brexpiprazole 2 or 3 mg	363	3.0 (1.9)	-0.8 (0.1)	-0.14 (-0.34 to 0.06)	0.17	0.11
	Placebo	247	2.8 (1.9)	-0.6 (0.1)			
26. Performing repetitious mannerisms	Brexpiprazole 2 or 3 mg	363	3.7 (2.1)	-0.8 (0.1)	-0.22 (-0.44 to 0.01)	0.056	0.16
	Placebo	247	3.4 (2.1)	-0.6 (0.1)			
29. General restlessness	Brexpiprazole 2 or 3 mg	363	5.1 (1.5)	-1.8 (0.1)	-0.35 (-0.60 to -0.10)	0.007	0.22
	Placebo	247	4.9 (1.5)	-1.4 (0.1)			
Factor 3: verbally agitated behavior							
5. Constant unwarranted requests for attention/help	Brexpiprazole 2 or 3 mg	363	3.8 (1.9)	-1.1 (0.1)	-0.21 (-0.44 to 0.02)	0.079	0.14
	Placebo	247	3.6 (1.9)	-0.9 (0.1)			
6. Repetitive sentences or questions	Brexpiprazole 2 or 3 mg	363	4.3 (2.0)	-1.1 (0.1)	-0.37 (-0.59 to -0.15)	0.001	0.27
	Placebo	247	4.1 (2.0)	-0.7 (0.1)			

CMAI item ^a	Treatment group	N	Mean (SD) at baseline	LS mean (SE) change from baseline to Week 12	Treatment difference at Week 12		
					LS mean (95% CI)	p-value	Cohen's <i>d</i>
18. Complaining	Brexpiprazole 2 or 3 mg	363	3.9 (1.9)	-1.2 (0.1)	-0.36 (-0.59 to -0.14)	0.002	0.26
	Placebo	247	3.9 (2.0)	-0.8 (0.1)			
19. Negativism	Brexpiprazole 2 or 3 mg	363	3.9 (1.8)	-1.2 (0.1)	-0.29 (-0.52 to -0.06)	0.013	0.21
	Placebo	247	3.8 (1.9)	-0.9 (0.1)			
Other items							
12. Making strange noises	Brexpiprazole 2 or 3 mg	363	2.2 (1.7)	-0.7 (0.1)	-0.32 (-0.49 to -0.15)	<0.001	0.31
	Placebo	247	2.2 (1.7)	-0.4 (0.1)			
17. Intentional falling	Brexpiprazole 2 or 3 mg	363	1.2 (0.7)	-0.1 (0.0)	0.00 (-0.05 to 0.06)	0.87	0.01
	Placebo	247	1.1 (0.6)	-0.1 (0.0)			
20. Eating or drinking inappropriate substances	Brexpiprazole 2 or 3 mg	363	1.3 (0.9)	-0.2 (0.0)	-0.10 (-0.19 to -0.02)	0.018	0.20
	Placebo	247	1.2 (0.8)	-0.1 (0.0)			
23. Hiding things	Brexpiprazole 2 or 3 mg	363	3.1 (1.9)	-0.9 (0.1)	-0.13 (-0.34 to 0.07)	0.21	0.10
	Placebo	247	2.9 (1.8)	-0.8 (0.1)			
24. Hoarding things	Brexpiprazole 2 or 3 mg	363	2.9 (1.9)	-0.7 (0.1)	-0.09 (-0.30 to 0.11)	0.37	0.07
	Placebo	247	2.7 (1.7)	-0.6 (0.1)			
27. Making verbal sexual advances	Brexpiprazole 2 or 3 mg	363	1.4 (1.0)	-0.2 (0.0)	-0.04 (-0.13 to 0.05)	0.36	0.08
	Placebo	247	1.3 (0.9)	-0.2 (0.0)			
28. Making physical sexual advances	Brexpiprazole 2 or 3 mg	363	1.1 (0.6)	-0.1 (0.0)	0.02 (-0.02 to 0.06)	0.35	0.08
	Placebo	247	1.2 (0.7)	-0.1 (0.0)			

^aEfficacy sample; mixed model for repeated measures; n-values are for baseline.

Abbreviations: CMAI, Cohen-Mansfield Agitation Inventory; CI, confidence interval; LS, least-squares; SD, standard deviation; SE, standard error.

Sensitivity analysis (three trials)

Methods

The sensitivity analysis included data from Trial 283, Trial 213, and a third Phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-arm trial: Trial 284 (ClinicalTrials.gov identifier: NCT01922258) [1]. Trial 284 was conducted between 2013 and 2017 at 62 clinical trial sites in Europe, Russia, the US, and Canada.

Detailed methodology for Trial 284 has been published [1]. Enrolment criteria were the same as for Trial 283. However, Trial 284 employed flexible dosing rather than fixed dosing, and had a target dose lower than the US FDA-approved doses (see below).

In Trial 284, participants were randomized 1:1 to brexpiprazole 0.5–2 mg/day or placebo. The target brexpiprazole dose was 1 mg/day. However, the dose could be reduced to 0.5 mg/day or increased to 2 mg/day at the Week 4 visit, if medically needed.

This pooled sensitivity analysis included the sample from the main analysis plus the subset of participants from Trial 284 who were titrated to the maximum 2 mg dose (or equivalent placebo) at the Week 4 visit. The statistical analysis followed the same approach as for the main analysis.

Results

Trial 284 screened 394 participants for eligibility, of whom 270 (68.5%) were randomized: 133 to brexpiprazole 0.5–2 mg/day and 137 to placebo [1]. Of these participants, 77 were titrated to brexpiprazole 2 mg at Week 4, and 74 were “titrated” to the maximum dose of placebo at Week 4 [1]. Thus, the sensitivity analysis included an additional 151 participants, which increased the total efficacy sample from 611 to 762 (prior to excluding 1 participant with no post-baseline visits within the eligible window).

Baseline characteristics are presented in Table S2, and were similar to the main analysis.

Efficacy results are shown in Figures S2–S4 and Table S3, and were similar to the main analysis.

Reference

1. Grossberg GT, Kohegyi E, Mergel V, Josiassen MK, Meulien D, Hobart M, 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. <https://doi.org/10.1016/j.jagp.2019.09.009>

Table S2 Baseline demographic and clinical characteristics, and concomitant medications – sensitivity analysis

Characteristic^a	Brexpiprazole 2 or 3 mg (n=441)	Placebo (n=321)
Age (years)	73.9 (8.0)	74.0 (7.6)
Sex, n (%)	-	-
Female	262 (59.4)	176 (54.8)
Male	179 (40.6)	145 (45.2)
Race, n (%)	-	-
Asian	5 (1.1)	4 (1.2)
Black or African American	16 (3.6)	10 (3.1)
White	419 (95.0)	307 (95.6)
BMI (kg/m ²)	25.7 (4.4)	25.9 (4.7)
Living situation, n (%)	-	-
Care facility	234 (53.1)	184 (57.3)
Community-based setting	207 (46.9)	137 (42.7)
Time since Alzheimer's disease diagnosis (months)	32.9 (33.0)	33.7 (32.3)
Time since onset of current episode of agitation associated with Alzheimer's disease (months)	8.6 (16.7) ^b	6.4 (8.9) ^c
MMSE score	15.0 (3.7)	14.7 (4.0)
CMAI total score	75.6 (17.1)	73.8 (17.8)
CGI-S score as related to agitation	4.6 (0.7)	4.6 (0.7)
Took medication for Alzheimer's disease during trial, n (%)	345 (78.2)	260 (81.0)
Memantine	216 (49.0)	161 (50.2)
Donepezil	143 (32.4)	104 (32.4)
Took concomitant medication for agitation during trial, n (%)	59 (13.4)	40 (12.5)

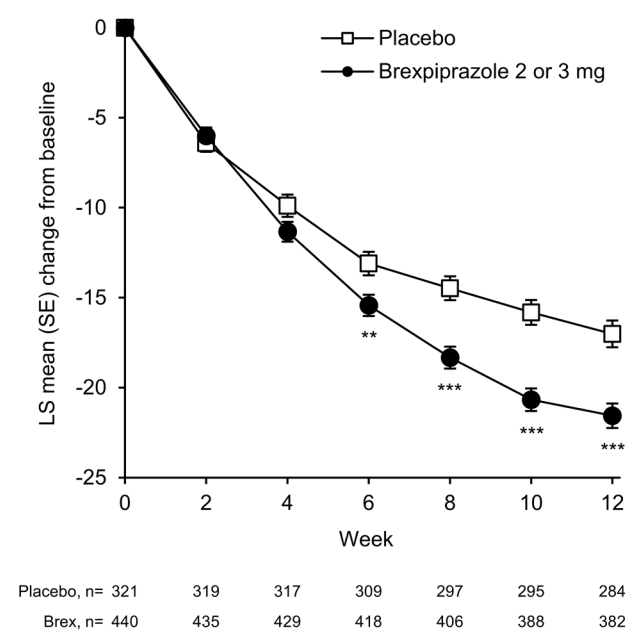
^aEfficacy sample. Data are mean (SD) unless otherwise stated.

^bn=439.

^cn=320.

Abbreviations: BMI, body mass index; CGI-S, Clinical Global Impression – Severity of illness; CMAI, Cohen-Mansfield Agitation Inventory; MMSE, Mini-Mental State Examination; SD, standard deviation.

Fig. S2 Change from baseline in Cohen-Mansfield Agitation Inventory (CMAI) total score^a
– sensitivity analysis

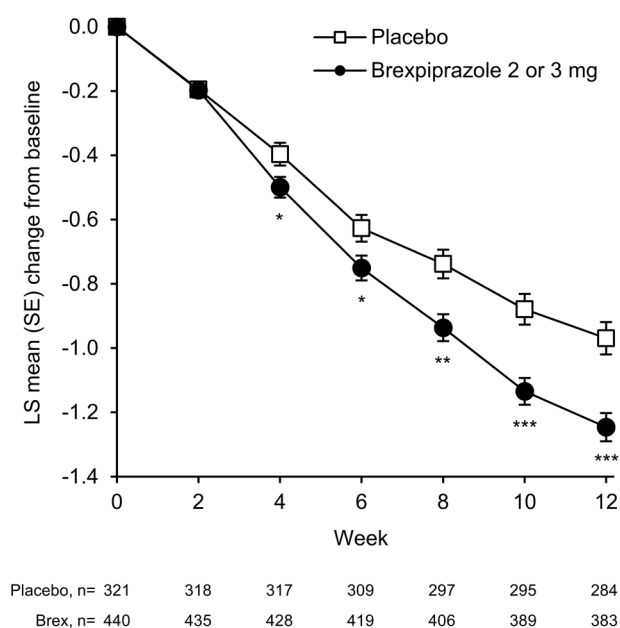


p<0.01, *p<0.001 versus placebo; efficacy sample; mixed model for repeated measures.

^aBaseline mean CMAI total scores: brexpiprazole, 75.6; placebo, 73.8.

Abbreviations: CMAI, Cohen-Mansfield Agitation Inventory; LS, least squares; SE, standard error.

Fig. S3 Change from baseline in Clinical Global Impression – Severity of illness (CGI-S) score as related to agitation^a – sensitivity analysis



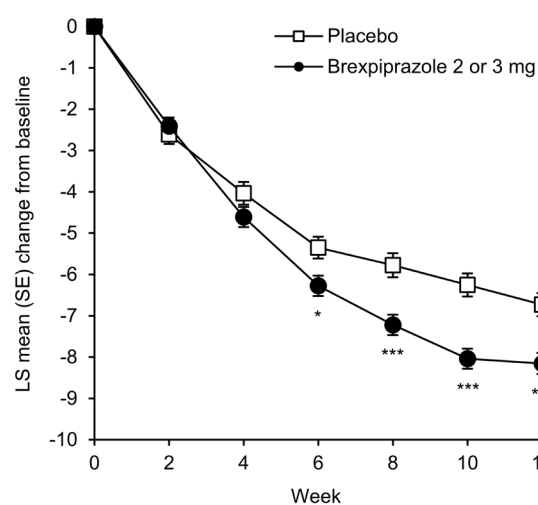
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus placebo; efficacy sample; mixed model for repeated measures.

^aBaseline mean CGI-S scores: brexpiprazole, 4.6; placebo, 4.6.

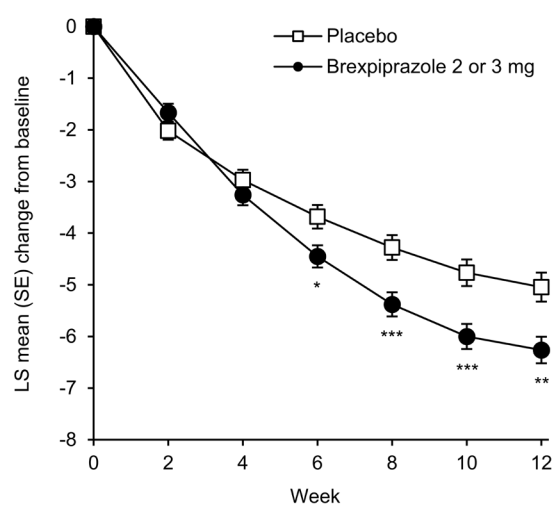
Abbreviations: CGI-S, Clinical Global Impression – Severity of illness; LS, least squares; SE, standard error.

Fig. S4 Change from baseline in Cohen-Mansfield Agitation Inventory (CMAI) factor scores^a – sensitivity analysis

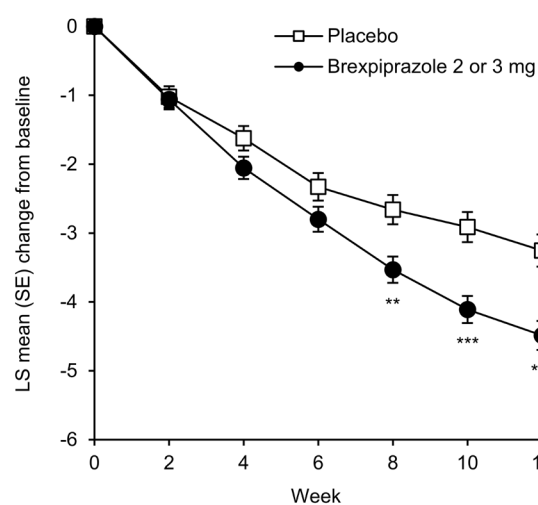
a CMAI factor 1: aggressive behavior score



b CMAI factor 2: physically non-aggressive behavior score



c CMAI factor 3: verbally agitated behavior score



* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus placebo; efficacy sample; mixed model for repeated measures.

^aBaseline mean scores (brexpiprazole, placebo): a) CMAI factor 1 aggressive behavior: 24.7, 24.2; b) CMAI factor 2 physically non-aggressive behavior: 22.5, 21.8; c) CMAI factor 3 verbally agitated behavior: 15.7, 15.3.

Abbreviations: CMAI, Cohen-Mansfield Agitation Inventory; LS, least squares; SE, standard error.

Table S3 Summary of efficacy results – sensitivity analysis

Endpoint ^a	Treatment group	N	Mean (SD) at baseline	LS mean (SE) change from baseline to Week 12	Treatment difference at Week 12		
					LS mean (95% CI)	p-value	Cohen's <i>d</i>
CMAI total score	Brexipiprazole 2 or 3 mg	440	75.6 (17.2)	-21.6 (0.7)	-4.55 (-6.49 to -2.62)	<0.001	0.34
	Placebo	321	73.8 (17.8)	-17.0 (0.7)			
CGI-S score as related to agitation	Brexipiprazole 2 or 3 mg	440	4.6 (0.7)	-1.2 (0.0)	-0.28 (-0.41 to -0.15)	<0.001	0.31
	Placebo	321	4.6 (0.7)	-1.0 (0.1)			
CMAI factor 1: aggressive behavior score	Brexipiprazole 2 or 3 mg	440	24.7 (8.0)	-8.2 (0.3)	-1.42 (-2.17 to -0.68)	<0.001	0.27
	Placebo	321	24.2 (8.8)	-6.7 (0.3)			
CMAI factor 2: physically non-aggressive behavior score	Brexipiprazole 2 or 3 mg	440	22.5 (7.1)	-6.3 (0.3)	-1.22 (-1.95 to -0.49)	0.001	0.24
	Placebo	321	21.8 (7.1)	-5.0 (0.3)			
CMAI factor 3: verbally agitated behavior score	Brexipiprazole 2 or 3 mg	440	15.7 (5.0)	-4.5 (0.2)	-1.23 (-1.82 to -0.64)	<0.001	0.30
	Placebo	321	15.3 (5.7)	-3.3 (0.2)			
Endpoint ^b	Treatment group	N	-	Mean (SD) at Week 12	Adjusted mean (95% CI)	p-value	-
CGI-I score	Brexipiprazole 2 or 3 mg	440	-	2.6 (1.1)	-0.33 (-0.49 to -0.17)	<0.001	-
	Placebo	321	-	2.9 (1.1)			
Endpoint ^c	Treatment group	N	-	n (%)	Relative risk (95% CI)	p-value	-
CMAI response: ≥20% improvement	Brexipiprazole 2 or 3 mg	440	-	281 (63.9)	1.28 (1.11 to 1.47)	<0.001	-
	Placebo	321	-	159 (49.5)			
CMAI response: ≥30% improvement	Brexipiprazole 2 or 3 mg	440	-	184 (41.8)	1.44 (1.17 to 1.77)	<0.001	-
	Placebo	321	-	98 (30.5)			
CMAI response: ≥40% improvement	Brexipiprazole 2 or 3 mg	440	-	103 (23.4)	1.84 (1.32 to 2.56)	<0.001	-
	Placebo	321	-	41 (12.8)			

Endpoint ^c	Treatment group	N	-	n (%)	Relative risk (95% CI)	p-value	-
CMAI response: improvement in agitation status	Brexpiprazole 2 or 3 mg	440	-	245 (55.7)	1.41 (1.20 to 1.65)	<0.001	-
	Placebo	321	-	131 (40.8)			
CGI-I response: very much improved or much improved	Brexpiprazole 2 or 3 mg	440	-	231 (52.5)	1.25 (1.06 to 1.48)	0.004	-
	Placebo	321	-	132 (41.1)			

^aEfficacy sample; mixed model for repeated measures; n-values are for baseline.

^bEfficacy sample; last observation carried forward; CMH row mean scores statistics.

^cEfficacy sample; last observation carried forward; CMH general association test.

Abbreviations: CGI-I, Clinical Global Impression – Improvement; CGI-S, Clinical Global Impression – Severity of illness; CI, confidence interval; CMAI, Cohen-Mansfield Agitation Inventory; CMH, Cochran-Mantel-Haenszel; LS, least-squares; SD, standard deviation; SE, standard error.