Supplemental Material 1: Methods

Details of outcome measures

The CMAI is a questionnaire that measures how often 29 different agitation symptoms occurred over the past 2 weeks.[1,2] The 29 agitation symptoms include aggressive behaviors, physically non-aggressive behaviors, and verbally agitated behaviors[2] – this aligns with the International Psychogeriatric Association criteria for agitation.[3] Each agitation symptom is scored on a 7-point scale from 1 (never occurs) to 7 (occurs several times an hour).[1] CMAI Total scores range from 29 (no agitation) to 203 (worst possible agitation), where a ≥20-point reduction is a meaningful within-patient change.[4] The CMAI was the primary efficacy measure in the randomized trials. It was completed at 2-week intervals by the clinician based on an interview with the patient's caregiver.

Safety was assessed by TEAEs, which were recorded by the clinician at 2-week intervals (also at Day 3 for Trial 283). TEAEs were coded using Medical Dictionary for Regulatory Activities version 25.0 preferred terms.

12-week sensitivity analysis

The 12-week sensitivity analysis included data from Trial 283, Trial 213, and a third Phase 3, randomized, double-blind, placebo-controlled, parallel-arm trial: Trial 284 (ClinicalTrials.gov identifier: NCT01922258).[5] Trial 284 had a different design to the other trials (flexible dose rather than fixed dose), and had a target dose lower than the United States FDA-approved doses (see below).

The design and primary results of Trial 284 are published.[5] Enrollment criteria were the same as for Trial 283.

Participants were randomly allocated to flexibly dosed brexpiprazole or placebo, for 12 weeks (with titration over 4 weeks). The target brexpiprazole dose was 1 mg/day; the dose could be reduced to 0.5 mg/day or increased to 2 mg/day if medically needed.

This post hoc sensitivity analysis included the subset of participants from Trial 284 who were titrated to the maximum 2 mg dose (or equivalent placebo) at the Week 4 visit (n=151).

24-week analysis

The 24-week analysis included data from randomized Trial 213 and a Phase 3, 12-week, active-treatment, single-arm extension trial (Trial 182; ClinicalTrials.gov identifier: NCT03594123).[6]

Participants who completed randomized Trial 213 were eligible to enroll in extension Trial 182. All participants in Trial 182 received brexpiprazole 2 or 3 mg/day. One dose decrease (to 2 mg) and one dose increase (to 3 mg) were permitted. The primary endpoint was the frequency and severity of TEAEs.

A 24-week sample was created by combining data for participants who received brexpiprazole 2 or 3 mg/day in Trial 213 and who continued to receive brexpiprazole 2 or 3 mg/day in Trial 182. This enabled the analysis of up to 24 weeks of continuous brexpiprazole treatment. Participants who received placebo in Trial 213 were excluded from this analysis.

In this post hoc analysis, participants were stratified into two subgroups: those with co-occurring psychosis at baseline of Trial 213, and those without. Co-occurring psychosis was defined as a score ≥4 on the NPI Delusions domain, the NPI Hallucinations domain, or both. Outcomes were the mean change in CMAI Total score from baseline of Trial 213 to Week 24 (descriptive statistics, observed cases), and the incidence of TEAEs. Participants with a CMAI assessment at baseline of Trial 213 and at any post-baseline visit of Trial 182 were analyzed.

Supplemental references

1. Cohen-Mansfield J, Marx MS, Rosenthal AS. A description of agitation in a nursing home. *J Gerontol*. 1989;44(3):M77-M84. doi:10.1093/geronj/44.3.m77

2. Cohen-Mansfield J. *Instruction Manual for the Cohen-Mansfield Agitation Inventory (CMAI)*. Rockville, MD: The Research Institute of the Hebrew Home of Greater Washington; 1991.

3. Sano M, Cummings J, Auer S, et al. Agitation in cognitive disorders: progress in the International Psychogeriatric Association consensus clinical and research definition. *Int Psychogeriatr*. 2024;36(4):238-250. doi:10.1017/S1041610222001041

4. Meunier J, Creel K, Loubert A, et al. Defining a clinically meaningful within-patient change threshold for the Cohen-Mansfield Agitation Inventory in Alzheimer's dementia. *Front Neurol*. 2024;15:1379062. doi:10.3389/fneur.2024.1379062

5. 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

6. Behl S, Slomkowski M, Chen D, et al. Brexpiprazole for the treatment of agitation associated with dementia due to Alzheimer's disease: a 12-week, active-treatment, extension trial. *J Alzheimers Dis*. 2024;102(2):520-529. doi:10.3233/JAD-240491

Supplemental Material 2: Results

12-week sensitivity analysis

Participants

Across the three randomized trials, 761 participants had a baseline and post-baseline CMAI assessment, and 758 also had data to determine baseline psychosis status and were included in the sensitivity analysis (brexpiprazole 2 or 3 mg/day, N=438; placebo, N=320).

Efficacy for agitation

In the subgroup with co-occurring psychosis, mean (standard deviation) baseline CMAI Total score was 80.6 (20.7) for brexpiprazole (n=102) and 82.6 (19.6) for placebo (n=71). LS mean (standard error) CMAI Total score change from baseline to Week 12 was -25.9 (1.8) for brexpiprazole and -18.0 (2.0) for placebo. The LS mean difference (95% confidence interval) at Week 12 was -7.89 (-13.3 to -2.53); *P*=0.004; Cohen's *d*=0.45.

In the subgroup without co-occurring psychosis, mean (standard deviation) baseline CMAI Total score was 74.0 (15.7) for brexpiprazole (n=336) and 71.3 (16.5) for placebo (n=249). LS mean (standard error) CMAI Total score change from baseline to Week 12 was -20.3 (0.8) for brexpiprazole and -16.0 (0.9) for placebo. The LS mean difference (95% confidence interval) at Week 12 was -4.32 (-6.61 to -2.03); *P*<0.001; Cohen's *d*=0.31.

24-week analysis

Participants

The extension trial (Trial 182) enrolled 259 participants, of whom 163 had received brexpiprazole in Trial 213. Of these participants, 159 had a baseline and post-baseline CMAI assessment, and 157 also had baseline psychosis status and were included in the present analysis. Thirty-five of 157 participants (22.3%) on brexpiprazole had co-occurring psychosis at baseline. The full 24 weeks of treatment was completed by 30 of 35 participants (85.7%) with co-occurring psychosis and 109 of 122 participants (89.3%) without co-occurring psychosis.

Co-occurring psychosis was more common in females than males, and was associated with a higher frequency of agitation symptoms at baseline (CMAI Total score) (Supplemental Table 1). Otherwise, baseline demographic and clinical characteristics (baseline of Trial 213) were generally similar between the subgroups (Supplemental Table 1).

Efficacy for agitation

In the subgroup with co-occurring psychosis, mean (standard deviation) CMAI Total score change from baseline to Week 24 was -28.5 (14.1) (Supplemental Figure 1A).

In the subgroup without co-occurring psychosis, mean (standard deviation) CMAI Total score change from baseline to Week 24 was -31.4 (16.1) (Supplemental Figure 1B).

Safety

Small subgroup sizes limit comparisons of TEAEs between subgroups (Supplemental Table 2). No particular concerns were noted when taking brexpiprazole with co-occurring psychosis.

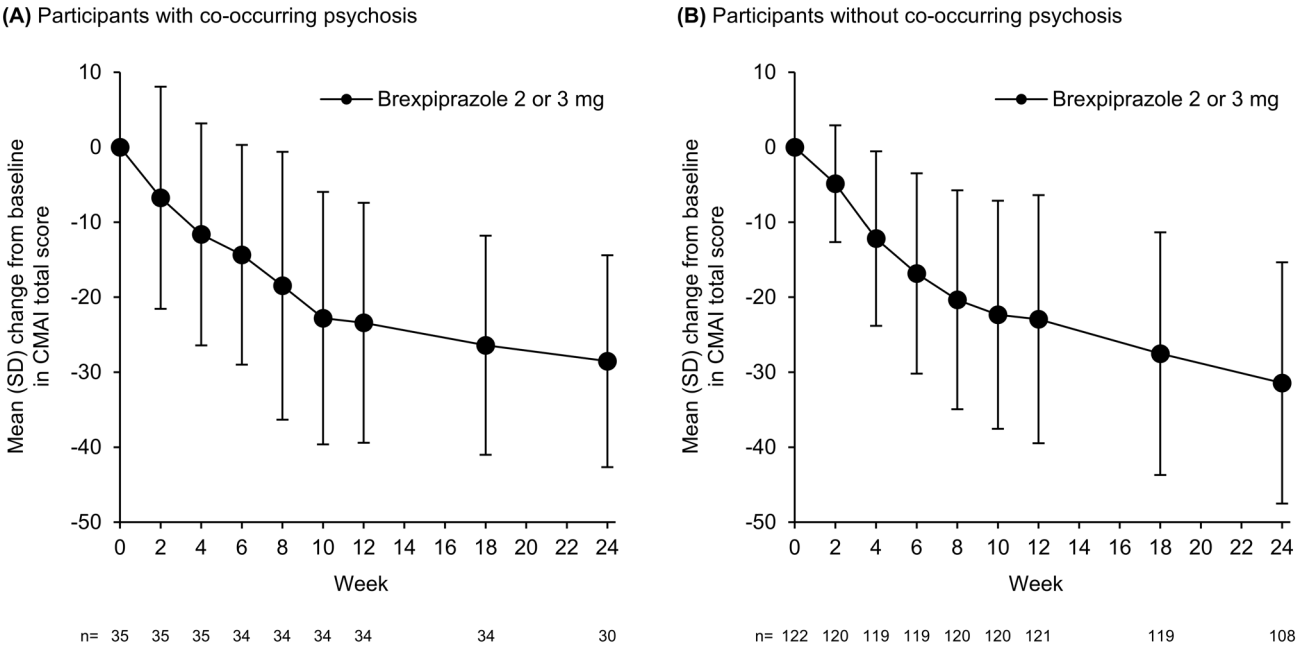
Supplemental Table 1 Baseline demographic and clinical characteristics (24-week analysis).

	With co-occurring psychosis	Without co-occurring psychosis
Characteristic[a]	**Brexpiprazole 2 or 3 mg (N=35)**	**Brexpiprazole 2 or 3 mg (N=122)**
Demographic characteristics		
Age, years	76.5 (8.1)	73.8 (7.8)
Sex, n (%)		
Female	27 (77.1)	69 (56.6)
Male	8 (22.9)	53 (43.4)
BMI, kg/m^2	26.1 (5.3)	26.3 (4.4)
Race, n (%)		
Asian	1 (2.9)	1 (0.8)
Black or African American	3 (8.6)	4 (3.3)
White	31 (88.6)	117 (95.9)
Clinical characteristics		
Time since Alzheimer's disease diagnosis, months	33.4 (30.1)	35.8 (34.0)
MMSE score	16.0 (3.8)	15.9 (3.4)
CMAI Total score	89.2 (14.7)	78.1 (14.9)
CGI-S score	4.8 (0.7)	4.7 (0.6)

[a]Data are for baseline of Trial 213, and are mean (standard deviation) unless otherwise specified.

BMI, body mass index; CMAI, Cohen-Mansfield Agitation Inventory; CGI-S, Clinical Global Impression – Severity; MMSE, Mini-Mental State Examination.

Supplemental Figure 1 Change from baseline in agitation symptoms (CMAI Total score; 24-week analysis). **Notes:** Mean (SD) baseline score (baseline of Trial 213): (A) 89.2 (14.7); (B) 78.1 (14.9). **Abbreviations:** CMAI, Cohen-Mansfield Agitation Inventory; SD, standard deviation.



Supplemental Table 2 Summary of TEAEs (24-week analysis).

	With co-occurring psychosis	Without co-occurring psychosis
Event, n (%)	**Brexpiprazole 2 or 3 mg (N=35)**	**Brexpiprazole 2 or 3 mg (N=122)**
Any TEAE	11 (31.4)	48 (39.3)
Any serious TEAE	0	1 (0.8)
Discontinued due to TEAE	0	0
Death	0	0
TEAEs with incidence ≥2% in either subgroup		
Headache	2 (5.7)	11 (9.0)
Back pain	1 (2.9)	1 (0.8)
Depression	1 (2.9)	0
Dizziness	1 (2.9)	3 (2.5)
Dry mouth	1 (2.9)	2 (1.6)
Extrapyramidal disorder	1 (2.9)	1 (0.8)
Gastroesophageal reflux disease	1 (2.9)	0
Nasopharyngitis	1 (2.9)	6 (4.9)
Somnolence	1 (2.9)	4 (3.3)
Tooth infection	1 (2.9)	0
Urinary tract infection	1 (2.9)	2 (1.6)
Alopecia	1 (2.9)	0
Diarrhea	0	3 (2.5)
TEAE categories of specific interest		
Any cerebrovascular event	0	0
Any cardiovascular event	0	1 (0.8)
Any EPS-related event	1 (2.9)	4 (3.3)
Any akathisia event[a]	1 (2.9)	2 (1.6)
Any orthostatic hypotension/ dizziness/syncope event	1 (2.9)	3 (2.5)
Falls	0	1 (0.8)
Insomnia	0	1 (0.8)
Somnolence including sedation	1 (2.9)[b]	4 (3.3)[b]

[a]A subcategory of EPS that includes akathisia, extrapyramidal disorder, and restlessness.

[b]All events were somnolence.

EPS, extrapyramidal symptom; TEAE, treatment-emergent adverse event.