Research Article

Journal of Alzheimer's Disease Reports
Volume 9: 1–11

DOI: 10.1177/25424823251334054
journals.sagepub.com/home/alr

Long-term safety and tolerability of brexpiprazole for Japanese patients with agitation in Alzheimer's disease dementia: A multicenter, open-label study

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Abstract

Background: The long-term safety and efficacy of brexpiprazole in Asian patients with agitation associated with dementia due to Alzheimer's disease are unknown.

Objectives: To evaluate the safety of 14-week treatment with brexpiprazole 1 or 2 mg/day in Japanese patients who completed the 10-week double-blind treatment period in a parent phase 2/3 study, and to explore the efficacy of brexpiprazole.

Methods: This was a phase 3 multicenter, open-label study (ClinicalTrials.gov Identifier NCT03724942, registered on 28 October 2018). Patients who had completed 10-week treatment of placebo, 1 or 2 mg/day of brexpiprazole in a parent study were rolled over into this extended study. The primary endpoint was the frequency of adverse events.

Results: Of 183 patients with informed consent, 164 were treated with brexpiprazole 1 or 2 mg/day for 14 weeks (prior brexpiprazole subgroup: 102 patients, prior placebo subgroup: 62 patients), and the overall study completion rate was 71.3%. The overall incidence of treatment-emergent adverse events was 90.2% (in each subgroup, 90.2% and 90.3%, respectively). Most treatment-emergent adverse events were mild or moderate in severity, and no new safety signals were observed. Regarding the Cohen-Mansfield Agitation Inventory total score at Week 14 (last observation carried forward), the mean change from baseline (standard deviation) was −4.0 (9.8).

Conclusions: The extended 14-week treatment with brexpiprazole 1 or 2 mg/day after 10-week treatment was generally well tolerated in Japanese patients with agitation associated with dementia due to Alzheimer's disease, and the efficacy was maintained.

Keywords

Alzheimer's disease, brexpiprazole, Japan, long-term, safety

Received: 25 November 2024; accepted: 12 March 2025

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Introduction

As the world's population ages,[1] the number of patients with dementia is estimated to increase from 55 million in 2019 to 139 million in 2050.[2] In line with this trend, the number of Japanese patients with dementia is expected to increase from 4.6 million (15% of elderly people, defined as ≥65 years old) in 2012 to 8.0–10.1 million (21.1%–27.0%) in 2050.[3] Of dementia, Alzheimer's disease (AD) is the most common type,[3] and its symptoms include cognitive impairment, and behavioral and psychological symptoms of dementia (BPSD).[4]

Agitation is one of BPSD and is observed in 40%–80% patients.[5,6] According to the International Psychogeriatric Association, agitation is defined by excessive motor activity, verbal aggression, or physical aggression; behaviors produce excess disability; and agitation is not solely attributable to another disorder (psychiatric, medical, or substance-related).[7] Agitation is not only related to declining cognitive and physical functions, worsening AD dementia, and shorter survival time,[8–10] but also increasing caregiver's distress and time for caring patients, accelerating institutionalization into a care facility, and increasing healthcare cost.[8,11–16] These reports demonstrate that agitation is causing a wide range of problems in multifaceted ways.

In the United States (U.S.), despite the international and local recommendations of non-pharmacological therapy as first-line approach,[17–19] the data from a retrospective chart review showed that the most patients started an antipsychotic treatment for agitation before non-pharmacological intervention.[20] Similarly in Japan, Clinical Practice Guideline for Dementia 2017 states "if non-pharmacological therapies do not provide adequate effect, consider pharmacotherapy".[4] However, in the case of patients with AD dementia combined with agitation, aggressive behaviors endanger both patients themselves and people around them, such as families and caregivers, and thus pharmacotherapy may need to be considered immediately.

Brexpiprazole is an antipsychotic known as a partial agonist at serotonin 5-hydroxytryptamine$_{1A}$ and dopamine D_2 receptors, and at the same time as an antagonist at serotonin 5-hydroxytryptamine$_{2A}$ and noradrenaline α_{1B}/α_{2C} receptors.[21] Neurotransmitters like serotonin, dopamine, and noradrenaline are considered related to agitation.[22] As of the third quarter of 2024, brexpiprazole is approved only in a limited number of countries (the U.S., Canada, the Philippines, Taiwan, and Japan) for the treatment of agitation in Alzheimer's dementia (AAD), and its clinical profile is still evolving globally. In patients with AAD, three short-term multinational studies with 12-week treatment of brexpiprazole were conducted (NCT01862640, NCT01922258, and NCT03548584),[23,24] one short-term study with 10-week regimen was conducted in Japanese patients (NCT03620981),[25] and all of these studies reported the favorable efficacy and safety of brexpiprazole treatment. As for the long-term safety and efficacy, one multinational study with extended 12-week regimen was conducted (NCT03594123),[26] in which the patients were rolled over from the parent study,[24] and the favorable safety and efficacy of brexpiprazole treatment were reported. However, this multinational extended study was conducted in the U.S. and Europe and had a very low representation of Asian populations.

Therefore, we considered it important to provide the long-term safety and efficacy data in Asian population, in this case Japanese patients, and conducted the first long-term study with extended 14-week regimen after the parent study with 10-week regimen (NCT03620981).[25] We report here the results of a phase 3 multicenter, open-label study that investigated the long-term safety and efficacy of brexpiprazole 1 or 2 mg/day treatment for 14 weeks, which in combination of 10 weeks of the parent study led to 24 weeks in total.

Methods

Patients

The patients were rolled over into this study after completion of a randomized, double-blind, placebo-controlled study of brexpiprazole in patients with AAD (NCT03620981). For the details of the parent study, refer to the Nakamura et al.[25] In brief, the parent study enrolled patients aged 55–90 years with diagnoses of AD dementia by Diagnostic and Statistical Manual of Mental Disorders Fifth Edition[27] and probable AD by National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association.[28] In the parent study, these patients were randomized in a 3:4:4 ratio to brexpiprazole 1 or 2 mg, or placebo for 10 weeks. The patients who completed 10-week treatment period and all assessments at Week 10 of the parent study were rolled over into this extended study with informed consent. The patients from the brexpiprazole 1 or 2 mg groups were defined as the prior brexpiprazole subgroup and those from the placebo group were defined as the prior placebo subgroup. The patients who had serious treatment-emergent adverse events (TEAEs) considered related to the study treatment by the investigator in the parent study were excluded from this extended study.

This study was registered in ClinicalTrials.gov (NCT03724942) on 28 October 2018 and conducted in compliance with the International Council for Harmonisation Good Clinical Practice and local regulations. The protocol, its amendments, and informed consent forms were reviewed and approved by each site's institutional review boards (for the list of the institutional review boards including its approval date, see the

Supplemental Material). Written informed consent was obtained from patients and/or their legal representatives and caregivers after the procedures had been fully explained. This study was conducted at 77 sites across the country, including not only large hospitals but also small clinics, with diversity, equity, and inclusion in consideration.

Study design

This study was a phase 3 multicenter, open-label study conducted in Japan. The study comprised a screening period of up to 10 days, a treatment period of 14 weeks, and a follow-up period of 28 days. Eligible patients were rolled over from the parent double-blind study to this extended study. Brexpiprazole was initiated at 0.5 mg (Day 1), increased to 1 mg in Week 1 (Day 8), and further to 2 mg in Week 2 (Day 15) when the investigators considered the dose increase to 2 mg was acceptable. After Week 2 (Day 15), a flexible dose adjustment at 1 or 2 mg was allowed at the discretion of the investigators. When the dose reduction to less than 1 mg was necessary, the patients were withdrawn from the study. Brexpiprazole was taken orally once daily, preferably at the same time each day, regardless of meals. Visits occurred at Day 1 (Week 10 of the parent study [baseline]), Day 8, Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, Day 99, or at study discontinuation, and within 28 days after Day 99 or study discontinuation for follow-up assessment (Figure 1). Concomitant medications of antidementia drugs, narcotic analgesics, beta blockers, and sleeping drugs were allowed with restrictions (Supplemental Table 1).

Assessments

Safety endpoints. The primary safety endpoint was the frequency of adverse events (AEs). The other safety endpoints included physical examination, laboratory tests, vital signs, body weight, 12-lead electrocardiogram, pregnancy test (only for patients with childbearing potential), Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS),[29] Abnormal Involuntary Movement Scale (AIMS),[30] Barnes Akathisia Rating Scale (BARS),[31] and Sheehan Suicidality Tracking Scale (S-STS).[32] The AE collection period was defined as from after the Week 10 assessment of the parent study to the completion of this extended study.

Efficacy endpoints. The efficacy endpoints were the change in Cohen-Mansfield Agitation Inventory (CMAI) total score from baseline to Week 4 and Week 14,[33–35] the change in Clinical Global Impression – Severity of Illness (CGI-S) score from baseline to Week 2 (Day 15), Week 4 (Day 29), Week 6 (Day 43), Week 10 (Day 71), and Week 14 (Day 99), and the Clinical Global Impression – Global Improvement (CGI-I) score at Week 2 (Day 15), Week 4 (Day 29), Week 6 (Day 43), Week 10 (Day 71), and Week 14 (Day 99).[30]

Other endpoints. The other endpoints were Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL),[36] and Mini-Mental State Examination (MMSE).[37]

Statistical analysis

The sample size was not calculated based on statistical power considerations. Based on the number of eligible patients who could roll over from the parent study, the sample size was targeted to enroll 100 patients in the prior brexpiprazole subgroup. Considering that the randomization ratio in the parent study was 3:4:4 to brexpiprazole 1 or 2 mg, or placebo, respectively, and the patients in the placebo group in the parent study were also to be rolled over into this extended study, 157 patients in total were planned as the sample size.

The safety analysis set consisted of patients who were administered at least one dose of study treatment. The incidences of TEAEs in each subgroup and total group were summarized. All analyses were performed using SAS® software version 9.4 (SAS Institute, Cary, NC, USA). The efficacy analysis set consisted of patients who were administered at least one dose of study treatment and had a CMAI total score at baseline and at least one occasion after baseline.

The baselines of endpoints were defined as the last data before the start of study treatment in this extended study. For Week 14, the analysis with the dataset of the last observation carried forward (LOCF) was also conducted.

Results

Patients

This study was conducted from 9 November 2018 to 5 January 2022. Of 183 patients who provided informed consent, 164 patients were enrolled in the study. Of these, the patients who rolled over from the brexpiprazole 1 mg and 2 mg groups in the parent study were 28.7% (47/164) and 33.5% (55/164), respectively, and those from the placebo group in the parent study were 37.8% (62/164), i.e., in this study, the prior brexpiprazole subgroup had 102 patients and the prior placebo subgroup had 62 patients. The overall study completion rate was 71.3% (117/164), which was similar in the prior brexpiprazole (71.6% [73/102]) and placebo (71.0% [44/62]) subgroups. The most common reason for study discontinuation was AEs and its percentage was 20.1% (33/164); in breakdown, that in the

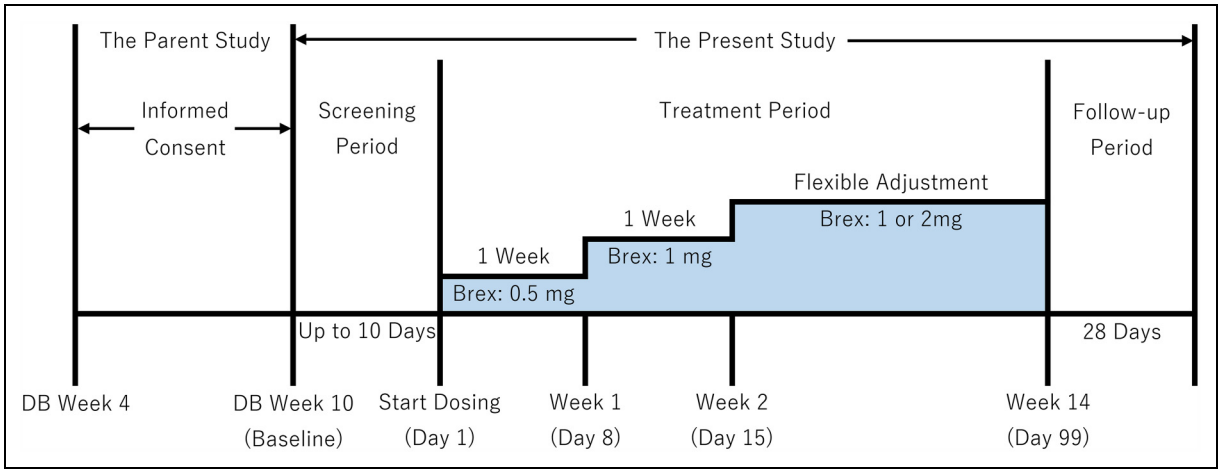

Figure 1. Study design. Eligible patients who provided informed consent were rolled over from the parent double-blind study to this study. Brexpiprazole was initiated at 0.5 mg (Day 1), increased to 1 mg in Week 1 (Day 8), and was flexibly administered at 1 or 2 mg onwards until Week 14 (Day 99). Brexpiprazole was taken orally once daily, preferably at the same time each day, regardless of meals. Visits occurred at Day 1 (Week 10 of the parent study [baseline]), Day 8, Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, Day 99, or at study discontinuation, and within 28 days after Day 99 or study discontinuation for follow-up assessment. Concomitant medications of antidementia drugs, narcotic analgesics, beta blockers, and sleeping drugs were allowed with restrictions (Supplemental Table 1). Brex: brexpiprazole; DB: double-blind.

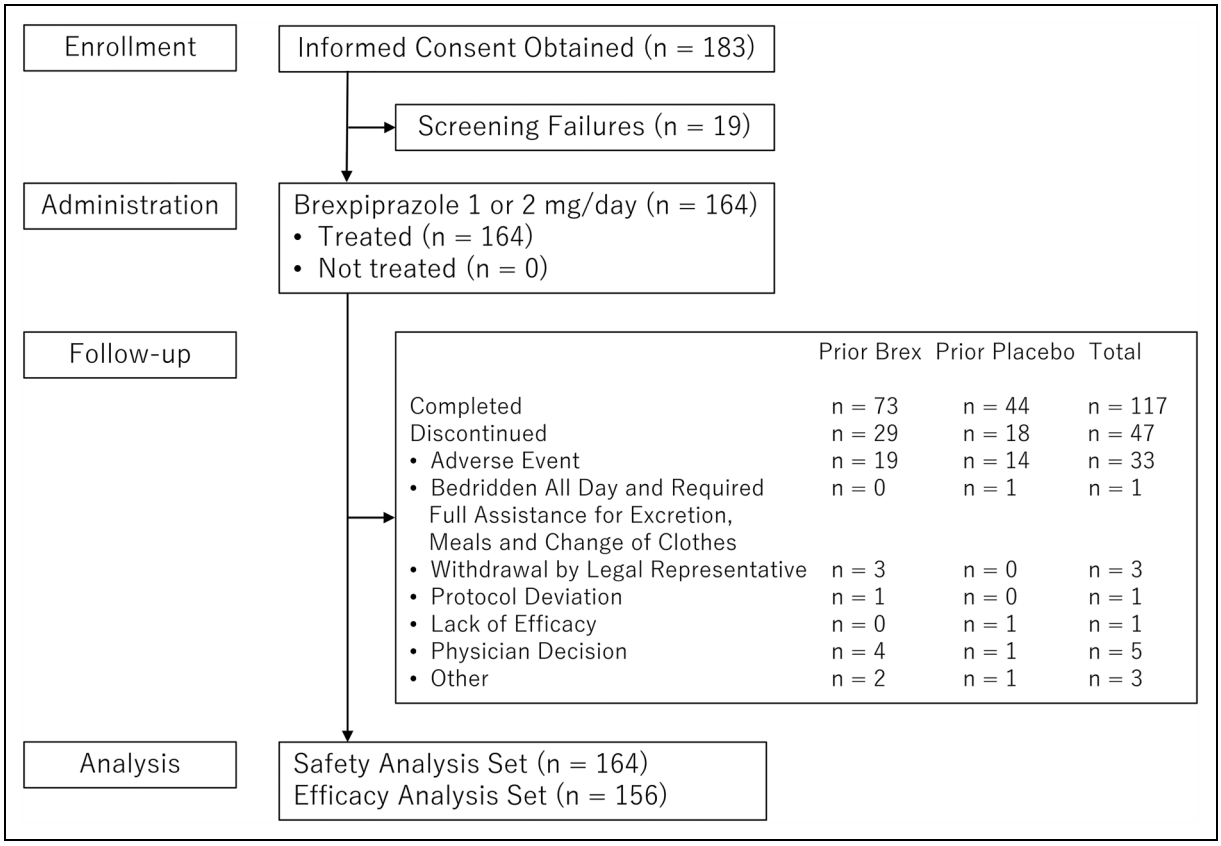

Figure 2. Patient disposition. The safety analysis set consisted of patients who were administered at least one dose of study treatment. The efficacy analysis set consisted of patients who were administered at least one dose of study treatment and had a CMAI total score at baseline and at least one occasion after baseline. Brex: brexpiprazole; CMAI: Cohen-Mansfield Agitation Inventory.

Table 1. Demographic and baseline clinical characteristics (safety analysis set).

Characteristics	Prior Brex (N = 102)		Prior Placebo (N = 62)		Total (N = 164)	
Demographic						
Age (y), Mean (SD)	79.0	(6.8)	80.2	(6.9)	79.5	(6.8)
Sex						
Male, n (%)	37	(36.3)	26	(41.9)	63	(38.4)
Female, n (%)	65	(63.7)	36	(58.1)	101	(61.6)
Weight (kg), Mean (SD)	48.88	(9.97)	48.55	(8.80)	48.76	(9.52)
BMI (kg/m^2), Mean (SD)	20.86	(3.32)	20.76	(2.99)	20.82	(3.19)
Clinical						
Duration[a]						
AD (months)[b], Mean (SD)	63.4	(39.6)	64.9	(43.9)	64.0	(41.1)
Agitation from AD (months)[b], Mean (SD)	27.1	(25.6)	26.7	(24.7)	26.9	(25.2)
CGI-S Score[c], Mean (SD)	3.3	(0.9)	3.9	(1.0)	3.5	(1.0)
CMAI Total Score[c], Mean (SD)	48.5	(13.0)	52.9	(13.1)	50.2	(13.2)
Medical Care Category[c]						
Hospital n (%)	69	(67.6)	38	(61.3)	107	(65.2)
Care Facility n (%)	3	(2.9)	7	(11.3)	10	(6.1)
Home n (%)	30	(29.4)	17	(27.4)	47	(28.7)
Dose of Parent Study (mg)						
0 n (%)	0	(0.0)	62	(100.0)	62	(37.8)
1 n (%)	47	(46.1)	0	(0.0)	47	(28.7)
2 n (%)	55	(53.9)	0	(0.0)	55	(33.5)
Prior Medications (Antipsychotic)[a]	68	(66.7)	36	(58.1)	104	(63.4)

Percentages are based on the number of patients in the subgroup (Prior Brex or Placebo means the patients who were randomized to brexpiprazole or placebo, respectively, in the parent study). AD: Alzheimer's disease; BMI: body mass index; Brex: brexpiprazole; CGI-S: Clinical Global Impression – Severity of Illness; CMAI: Cohen-Mansfield Agitation Inventory; SD: standard deviation.

[a]Screening of the parent study.

[b]Months derived based on the calculation: (date of assessment – estimated date of onset + 1)/30. Any unknown month or day of onset is imputed with June or 15, respectively.

[c]Baseline of this study.

prior brexpiprazole subgroup (18.6% [19/102]) was slightly lower than that in the prior placebo subgroup (22.6% [14/62]). All treated patients were analyzed for safety, and 96 and 60 patients in each subgroup were analyzed for efficacy (Figure 2).

At baseline, the mean age (standard deviation [SD]) was 79.5 (6.8), and 61.6% of patients were female. In terms of the medical care category, 65.2% of patients were in hospital, 6.1% were in care facility, and 28.7% were at home. The mean CMAI total scores in the prior brexpiprazole and placebo subgroups were 48.5 and 52.9, and the mean CGI-S scores in these subgroups were 3.3 and 3.9, respectively (Table 1).

In the prior brexpiprazole and placebo subgroups, the mean days of exposure were 82.5 and 83.4; the proportions of patients who had treatment duration of ≥84 days were 74.5% and 72.6%; and the mean exposures per day were 1.42 mg and 1.45 mg, respectively. The proportions of patients who had the most frequent dose at 0.5 mg were 4.9% and 3.2%, those at 1.0 mg were 42.2% and 40.3%, and those at 2 mg were 52.9% and 56.5%, respectively. The proportions of patients who had the last dose at 0.5 mg were 2.0% and 1.6%, those at 1 mg were 45.1% and 54.8%, and those at 2 mg were 52.9% and 43.5%, respectively. The proportions of patients who achieved ≥90% treatment compliance were 97.9% and 100%, respectively. Concomitant use of antidementia drugs in the prior brexpiprazole and placebo subgroups were 61.8% and 50.0%, respectively.

Safety endpoints

The incidence of TEAEs was 90.2% (148/164), which was similar in the prior brexpiprazole (90.2% [92/102]) and placebo (90.3% [56/62]) subgroups. One TEAE with an outcome of death occurred in the prior placebo subgroup, whereas no death was observed in the prior brexpiprazole subgroup. Overall, the resulting incidence of deaths was 0.6% (1/164). The incidence of serious TEAEs was 7.3% (12/164), that of severe TEAEs was 7.3% (12/164), that of TEAEs leading to discontinuation of study treatment was 20.1% (33/164), and that of TEAEs leading to dose reduction of study treatment was 36.0% (59/164) (Table 2).

The TEAEs with an incidence of ≥10% were somnolence and insomnia, those in the prior brexpiprazole subgroup were somnolence, fall, and skin abrasion, and those in the prior placebo subgroup were insomnia, sedation

Table 2. Summary of treatment-emergent adverse events (safety analysis set).

	Prior Brex (N = 102)		Prior Placebo (N = 62)		Total (N = 164)	
	n	(%)[a]	n	(%)[a]	n	(%)[a]
Patients with TEAEs[b]	92	(90.2)	56	(90.3)	148	(90.2)
Patients with TEAEs with an Outcome of Death	0	(0.0)	1	(1.6)	1	(0.6)
Patients with Serious TEAEs	7	(6.9)	5	(8.1)	12	(7.3)
Patients with Severe TEAEs	6	(5.9)	6	(9.7)	12	(7.3)
Patients with Discontinuation of Study Treatment Due to TEAEs	19	(18.6)	14	(22.6)	33	(20.1)
Patients with Dose Reduction of Study Treatment Due to TEAEs	31	(30.4)	28	(45.2)	59	(36.0)
TEAEs with an Incidence ≥10% in the prior Brex or Placebo Subgroup (Preferred Term)						
Somnolence	13	(12.7)	7	(11.3)	20	(12.2)
Insomnia	5	(4.9)	12	(19.4)	17	(10.4)
Fall	12	(11.8)	4	(6.5)	16	(9.8)
Sedation complication	7	(6.9)	9	(14.5)	16	(9.8)
Skin abrasion	11	(10.8)	2	(3.2)	13	(7.9)
Adverse Events of Interest						
EPS-related TEAEs	29	(28.4)	21	(33.9)	50	(30.5)
Accident and injury-related TEAEs	25	(24.5)	17	(27.4)	42	(25.6)
Cerebrovascular-related TEAEs	1	(1.0)	0	(0.0)	1	(0.6)
Cardiovascular-related TEAEs	4	(3.9)	3	(4.8)	7	(4.3)
Oversedation-related TEAEs	22	(21.6)	17	(27.4)	39	(23.8)
Pneumonia-related TEAEs	6	(5.9)	5	(8.1)	11	(6.7)

Medical Dictionary for Regulatory Activities v25.0 was used. Brex: brexpiprazole; EPS: extrapyramidal symptoms; TEAE: treatment-emergent adverse event.

[a]Percentages are based on the number of patients treated with study medication.

[b]All adverse events that started after the start of study drug treatment. Adverse events are counted once, per term, for the most severe of multiple occurrences of a specific Medical Dictionary for Regulatory Activities preferred term.

complication, and somnolence. The severity of most TEAEs was mild or moderate, and similarly to the parent study, no new safety signals were observed (Table 2). In terms of the time to onset of TEAEs, the period with the highest incidence of TEAEs was Day 15 to 21 with 20.4% (20/98) in the prior brexpiprazole and 23.3% (14/60) in the prior placebo subgroups. The incidences in the subsequent periods remained in the range of 0.0% to 14.1% and 0.0% to 12.5%, respectively. There were no TEAEs whose incidences increased over time.

The one TEAE that resulted in death was metastatic pancreatic carcinoma and was considered not related to brexpiprazole by the investigator. Serious TEAEs that occurred in ≥2 patients in the prior brexpiprazole subgroup were gait disturbance (2.0% [2/102], both of which were considered by the investigator to be treatment-related), and those in the prior placebo subgroup were pneumonia aspiration (3.2% [2/62], one of which was treatment-related). Regarding the outcome, one gait disturbance was not recovered and another gait disturbance was recovered with sequelae at the end of study, whereas both of pneumonia aspiration were recovered. TEAEs leading to discontinuation of study treatment that occurred in ≥2% of patients in the prior brexpiprazole subgroup were gait disturbance, muscle rigidity, and bradykinesia (2.9% [3/102] each), hepatic function abnormal, dystonia, and tremor (2.0% [2/102] each), and those in the prior placebo subgroup were pneumonia aspiration, akathisia, dystonia, and extrapyramidal disorder (3.2% [2/62] each). TEAEs leading to dose reduction of study treatment that occurred in ≥5% of patients in the prior brexpiprazole subgroup were somnolence (7.8% [8/102]) and sedation complication (5.9% [6/102]), and those in the prior placebo subgroup were sedation complication (11.3% [7/62]) and somnolence (8.1% [5/62]).

As for AEs of interest, the incidence of extrapyramidal symptoms (EPS)-related TEAEs was 30.5%. The EPS-related TEAEs that occurred in ≥5% of patients were muscle rigidity (8.5%), bradykinesia (7.9%), salivary hypersecretion (6.1%), gait disturbance (6.1%), and extrapyramidal disorder (5.5%). Severe EPS-related TEAEs were observed in two patients in the prior brexpiprazole subgroup: tremor in one patient, and akathisia and gait disturbance in another patient. The incidence of accident and injury-related TEAEs was 25.6%. The accident and injury-related TEAEs that occurred in ≥5% of patients were fall (9.8%), contusion (7.9%), and skin abrasion (7.9%). The incidence of cerebrovascular-related TEAEs was 0.6%. There were no cerebrovascular-related TEAEs that occurred in ≥5% of patients. The incidence of cardiovascular-related TEAEs was 4.3%. There were no cardiovascular-related TEAEs that occurred in ≥5% of

Table 3. CMAI total scores over time (efficacy analysis set).

					Change from baseline	
Visit	Subgroup	n	Mean	(SD)	Mean	(SD)
Baseline	Prior Brexpiprazole	96	48.1	(12.7)		
	Prior Placebo	60	52.9	(13.2)		
	Total	156	49.9	(13.1)		
Week 4	Prior Brexpiprazole	96	47.3	(12.5)	−0.7	(7.7)
	Prior Placebo	60	49.1	(12.8)	−3.8	(9.0)
	Total	156	48.0	(12.6)	−1.9	(8.3)
Week 14	Prior Brexpiprazole	73	44.6	(12.5)	−3.5	(8.4)
	Prior Placebo	44	45.6	(12.6)	−7.6	(9.4)
	Total	117	45.0	(12.5)	−5.0	(9.0)
Week 14 (LOCF)[a]	Prior Brexpiprazole	96	45.5	(12.8)	−2.5	(9.9)
	Prior Placebo	60	46.5	(12.8)	−6.4	(9.3)
	Total	156	45.9	(12.8)	−4.0	(9.8)

LOCF: last observation carried forward; SD: standard deviation.
[a]Week 14 (LOCF) = last post-baseline evaluation.

patients. The incidence of oversedation-related TEAEs was 23.8%. The oversedation-related TEAEs that occurred in ≥5% of patients were somnolence (12.2%) and sedation complication (9.8%). The incidence of pneumonia-related TEAEs was 6.7%. There were no pneumonia-related TEAEs that occurred in ≥5% of patients.

There were no clinically relevant findings (i.e., leading to treatment intervention) for events related to prolactin, lipids, and glucose, or QT prolongation, including the incidence of shifts to abnormal levels. No clinically meaningful changes were observed in laboratory values, vital signs, body weight, body mass index, and 12-lead electrocardiogram.

In the prior brexpiprazole and placebo subgroups, the DIEPSS total scores at baseline were 2.2 (2.7) and 1.1 (1.9), and those at Week 14 (LOCF) were 3.3 (3.5) and 2.4 (3.0), i.e., the mean changes (SD) from baseline to Week 14 (LOCF) were 1.1 (2.4) and 1.3 (2.1), respectively. The AIMS total scores at baseline were 0.2 (0.8) and 0.1 (0.6), and those at Week 14 (LOCF) were 0.2 (0.8) and 0.2 (1.0), i.e., the mean changes (SD) from baseline to Week 14 (LOCF) were 0.0 (0.5) and 0.1 (0.9), respectively. The BARS "Global Clinical Assessment of Akathisia" scores at baseline were 0.0 (0.2) and 0.0 (0.3), and those at Week 14 (LOCF) were 0.1 (0.3) and 0.0 (0.3), i.e., the mean changes (SD) from baseline to Week 14 (LOCF) were 0.0 (0.4) and 0.0 (0.4), respectively. The S-STS total scores at baseline were 0.0 (0.2) and 0.1 (0.2), and those at Week 14 (LOCF) were 0.1 (0.3) and 0.1 (0.3), i.e., the mean changes (SD) from baseline to Week 14 (LOCF) were 0.0 (0.4) and 0.0 (0.3), respectively.

Efficacy endpoints

At baseline of this study (at Week 10 of the parent study), the CMAI total scores (mean [SD]) in the prior brexpiprazole and placebo subgroups were 48.1 (12.7) and 52.9 (13.2), and those at Week 14 (LOCF) were 45.5 (12.8) and 46.5 (12.8), respectively, i.e., the mean changes (SD) from baseline to Week 14 (LOCF) were −2.5 (9.9) and −6.4 (9.3), respectively (Table 3). Similarly, the CGI-S scores (mean [SD]) at baseline were 3.2 (0.9) and 3.9 (1.0), and those at Week 14 (LOCF) were 3.1 (0.9) and 3.1 (1.1), i.e., the mean changes (SD) from baseline to Week 14 (LOCF) were −0.2 (0.8) and −0.7 (1.1), respectively. The CGI-I scores (mean [SD]) at Week 14 (LOCF) were 3.1 (1.2) and 2.7 (1.1), respectively.

Other endpoints

Regarding ADCS-ADL and MMSE, the mean changes (SD) from baseline to Week 14 (LOCF) of total score were small, and no clinically meaningful changes were observed: in the order of the prior brexpiprazole and placebo subgroups, −2.6 (5.8) and −1.6 (4.9) for ADCS-ADL; −1.1 (2.4) and −0.8 (2.5) for MMSE, respectively.

Discussion

The results of our study showed that the 14-week treatment of brexpiprazole 1 or 2 mg/day was generally well tolerated, and its efficacy was maintained in patients with AAD who were rolled over from the 10-week treatment regimen in the parent double-blind study. As of the third quarter of 2024, brexpiprazole is approved for AAD in the U.S., Canada, the Philippines, Taiwan, and Japan, but brexpiprazole for this indication is not yet approved in many other countries. Considering the huge burden on patients, families/caregivers, and healthcare cost, further accumulation of clinical knowledge of brexpiprazole is necessary and will contribute

to the healthcare not only in Japan but also the world in multidirectional ways. Additionally, the long-term safety data of brexpiprazole in other indications, e.g., major depressive disorder and schizophrenia, have already been reported,[38,39] but such data in AAD had never been reported until 2023. In 2024, the first multinational study to evaluate the long-term safety of brexpiprazole in AAD was reported as an extended study from its parent study, in which the treatment periods in the parent and extended studies were 12 weeks each, i.e., 24 weeks in total.[24,26] Similarly, the first Japanese study in AAD with a treatment period for 10 weeks was reported in 2024,[25] and the study we report here was the extended study with treatment period of 14 weeks, i.e., 24 weeks in total.

For the safety endpoint, the incidence of TEAEs was similar in the prior brexpiprazole and placebo subgroups (90.2% and 90.3%, respectively). Most TEAEs were mild to moderate in severity and brexpiprazole was generally well tolerated in both subgroups. It should be noted that there were no TEAEs whose incidences increased over time. Additionally, the incidences of serious TEAEs and severe TEAEs were slightly lower in the prior brexpiprazole subgroup than in the prior placebo subgroup (serious TEAEs: 6.9% and 8.1%, severe TEAEs: 5.9% and 9.7%), respectively. A similar tendency was observed in incidences of TEAEs leading to discontinuation (18.6% and 22.6%) and dose reduction (30.4% and 45.2%), respectively. The reason for these lower incidences in the prior brexpiprazole subgroup could be because the patients with tolerability were enriched in the prior brexpiprazole subgroup (the patients who had drug-related serious TEAEs in the parent study were excluded from this study, and the patients who discontinued the parent study due to TEAEs were not included in this study).

In the parent study, sedation complication was the most common TEAE leading to discontinuation of study treatment (brexpiprazole 1 mg: 0.9%, 2 mg: 6.0%, placebo: 0.7%]), whereas in this extended study, the incidences of sedation complication leading to discontinuation were lower (prior brexpiprazole: 1.0%, prior placebo: 1.6%), suggesting that the study design with flexible dose reduction might have contributed to the lower incidences. It should also be noted that, in a large-scale prospective cohort study with Japanese patients, there were no differences in the mortality risk in the antipsychotic exposed and unexposed groups, but a subgroup of patients who newly started antipsychotic drug represented a higher risk for mortality during the 11-week to 24-week period.[40] On the other hand, although this comparison has limitations due to the different study designs and populations, our study showed no such tendency of increasing mortality risk, which demonstrated favorable tolerability of brexpiprazole 1 or 2 mg/day treatment for the same 24-week study period in total of the 10-week parent study and this 14-week extended study. In the 12-week extended study in non-Japanese patients too, brexpiprazole was well tolerated and no tendency of higher mortality risk was reported.[26]

Tardive dyskinesia is associated with the long-term blocking of dopamine D_2 receptors and the resulting dopamine hypersensitivity.[41] Given that brexpiprazole is a partial agonist at dopamine D_2 receptors, brexpiprazole is also considered to have an antagonistic function, and its long-term impact on tardive dyskinesia was unknown in the parent study.[25] In this extension study, tardive dyskinesia was reported in one patient in the prior brexpiprazole subgroup. This tardive dyskinesia occurred during a follow up period. The investigator assessed the causality as treatment-related and the severity as mild.

For the efficacy endpoint, the mean changes (SD) in CMAI total score from baseline to Week 14 (LOCF) in the prior brexpiprazole and placebo subgroups were −2.5 (9.9) and −6.4 (9.3), respectively, indicating continued improvement of agitation behavior in both subgroups. Of note, the baseline in this extended study was defined as the last data before the start of study treatment in this study, and at baseline the prior placebo subgroup had a higher score than the prior brexpiprazole subgroup, i.e., the means (SD) in CMAI total score at baseline in the prior brexpiprazole and placebo subgroups were 48.1 (12.7) and 52.9 (13.2), respectively. Notably, the means (SD) in CMAI total score at Week 14 (LOCF) in the prior brexpiprazole and placebo subgroups were similar at 45.5 (12.8) and 46.5 (12.8), indicating the prior placebo subgroup could catch up with the prior brexpiprazole within 14 weeks treatment period of this extended study. CGI-S and CGI-I also showed similar tendencies and supported the results of CMAI total score.

Given that the safety results showed no new safety signals and that the efficacy was maintained for the extended 14 weeks, brexpiprazole appears to have a favorable benefit/risk profile for the long-term treatment of AAD in Japanese patients for 24 weeks in total.

Limitations of this study are as follows. This study was uncontrolled, and thus the comparison between brexpiprazole and placebo was not conducted. As this study was open-label, the possible bias towards the study assessments can't be excluded. Since this study was conducted in Japanese patients, caution is required when extrapolating the results to other racial/ethnic groups. CMAI and ADCS-ADL were completed by investigators, based on information from caregivers (to minimize the influences caused by different caregivers, the protocol defined requirements for setting a primary caregiver, such as available at least 4 days/week and 4 h/day for patient observation, etc.). Patients with certain concurrent diseases and concomitant medications were excluded, which limits the generalizability of the results. As the treatment period of this extended study was 14 weeks, and the total study period of the parent study and this study was 24 weeks, the

safety and efficacy over a longer period are unknown. Although the antipsychotic treatment period for patients with AAD should be as short as possible, it is conceivable that some patients may need treatment for more than 24 weeks. Thus, continuous data collection will be necessary in the post-marketing study and/or the real-world setting for longer treatment periods.

In conclusion, the 14-week treatment of brexpiprazole 1 or 2 mg/day was well tolerated in patients with AAD who were rolled over from the 10-week treatment regimen in the parent double-blind study. The efficacy of brexpiprazole was also maintained. In a combination of the parent study and this extended study, brexpiprazole treatment of 1 or 2 mg/day showed no remarkable safety concerns and demonstrated sustainable efficacy for up to 24 weeks in total.

Acknowledgments

The authors thank the investigators at the study sites and the patients who participated in this study. Writing support was provided by Yasuyuki Koh, M.S., with assistance from his colleague Moriyoshi Yasuda, PhD, at IQVIA Services Japan G.K.

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Statements and declarations

Ethical considerations

This study was registered in ClinicalTrials.gov (NCT03724942) on 28 October 2018 and conducted in compliance with the International Council for Harmonisation Good Clinical Practice and local regulations. The protocol, its amendments, and informed consent forms were reviewed and approved by each site's institutional review boards (for the list of the institutional review boards including its approval date, see the Supplemental Material).

Consent to participate

All patients provided written informed consent to participate in this study.

Consent for publication

Not applicable.

Author contributions/CRediT

Yu Nakamura (Conceptualization; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing); Jun Adachi (Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – original draft; Writing – review & editing); Naoki Hirota (Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Resources; Validation; Writing – original draft; Writing – review & editing); Katsuhiro Iba (Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Resources; Software; Validation; Writing – original draft; Writing – review & editing); Koichi Shimizu (Funding acquisition; Visualization; Writing – original draft; Writing – review & editing); Masami Nakai (Funding acquisition; Writing – original draft; Writing – review & editing); Naoki Mori (Funding acquisition; Writing – original draft; Writing – review & editing); Kaneyoshi Takahashi (Funding acquisition; Writing – original draft; Writing – review & editing).

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded and study drugs were supplied by Otsuka Pharmaceutical Co., Ltd The writing support was also funded by Otsuka Pharmaceutical Co., Ltd.

Conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Yu Nakamura has received speakers' honoraria, manuscript fee, research support, or scholarship donation from Otsuka Pharmaceutical Co., Ltd, Meiji Seika Pharma Co., Ltd, Viatris Pharmaceutical K.K., Eisai Co., Ltd, Takeda Pharmaceutical Co., Ltd, Teikoku Pharmaceutical K.K., Kowa Company Ltd, Mochida Pharmaceutical Co., Ltd, Towa Pharmaceutical Co., Ltd, MSD K.K., Biogen Japan Ltd, and Daiichi Sankyo Company Ltd. Jun Adachi, Naoki Hirota, Katsuhiro Iba, Koichi Shimizu, Masami Nakai, Naoki Mori, and Kaneyoshi Takahashi are full-time employees of Otsuka Pharmaceutical Co., Ltd.

Data availability

The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Supplemental material

Supplemental material for this article is available online.

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