Otsuka

BREXPIPRAZOLE FOR THE TREATMENT OF AGITATION ASSOCIATED WITH ALZHEIMER'S DEMENTIA

SPONSOR BRIEFING DOCUMENT

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List of Abbreviations

Abbreviation	Definition
5-HT_{1A}	Serotonin type 1A receptor
5-HT_{2A}	Serotonin type 2A receptor
α_{1B}	Noradrenaline receptor α_{1B}
α_{2C}	Noradrenaline receptor α_{2C}
AAD	Agitation associated with Alzheimer's dementia
AD	Alzheimer's dementia
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CGI-I	Clinical Global Impression-Improvement scale
CGI-S	Clinical Global Impression-Severity of Illness scale
CMAI	Cohen-Mansfield Agitation Inventory
CMH	Cochran-Mantel-Haenszel
CT	Computed tomography
D_2	Dopamine type 2 receptor
ECG	Electrocardiogram
EPS	Extrapyramidal symptoms
E-R	Exposure-response
EU	European Union
FDA	Food and Drug Administration
IND	Investigational New Drug
IPA	International Psychogeriatric Association
LOCF	Last observation carried forward
MAR	Missing at Random
MCID	Minimal clinically important difference
MDD	Major depressive disorder
MI	Multiple Imputation
MMRM	Mixed-effect model repeated measure
MMSE	Mini-Mental State Examination
MNAR	Missing not at Random
MRI	Magnetic resonance imaging
MWPC	Meaningful within-patient change

NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NPI-NH	Neuropsychiatric Inventory–Nursing Home
NPI-NH AA	Neuropsychiatric Inventory-Nursing Home Agitation/Aggression
NPI/NPI-NH	Neuropsychiatric Assessment for Noninstitutionalized Patients based on the NPI-NH
OC	Observed case
PK	Pharmacokinetic
PMM	Pattern Mixture Models
popPK	Population pharmacokinetics
QT	QT interval
REML	Restricted maximum likelihood
SAE(s)	Serious adverse event(s)
sNDA	Supplemental New Drug Application
UN	Unstructured
US	United States
USPI	United States Prescribing Information

1 EXECUTIVE SUMMARY

1.1 Introduction

Otsuka is seeking approval of brexpiprazole for the treatment of agitation associated with Alzheimer's dementia (AAD). Alzheimer's dementia (AD) is a progressive, neurodegenerative disorder characterized by cognitive decline and is associated with a shortened life-expectancy. Approximately, 6.5 million Americans aged ≥ 65 years have AD, with agitation occurring in about half of all individuals with AD (Alzheimer's Association 2022; Halpern et al 2019). Neuropsychiatric symptoms, including agitation, are common features of AD. Agitation has been associated with accelerated disease progression, increased risk of institutionalization, functional decline, and decreased quality of life (Banerjee et al 2006; Cloutier et al 2019; Lanctot et al 2017; Rockwood et al 2019; Scarmeas et al 2007; Wilcock et al 2008). Currently, there are no approved pharmacological treatments for AAD creating a significant unmet medical need for this patient population and a source of considerable caregiver distress.

Brexpiprazole is an atypical antipsychotic that targets noradrenergic, serotonergic, and dopaminergic system dysfunction in brain circuits that mediate agitation behaviors. Brexpiprazole (REXULTI) was first approved in the United States (US) in 2015 for the treatment of schizophrenia in adults and for use as adjunctive treatment to antidepressants for the treatment of major depressive disorder (MDD). Brexpiprazole has since been approved in over 60 countries.

Otsuka is seeking approval of brexpiprazole for the treatment of AAD based on 2 positive, randomized, placebo-controlled, Phase 3 clinical studies, Studies 283 (331-12-283) and 213 (331-14-213). These studies used a fixed once-daily dose and achieved statistically significant and clinically meaningful improvements in agitation compared to placebo. In both studies, the primary endpoint was met, demonstrating statistically significant improvements in Cohen-Mansfield Agitation Inventory (CMAI) total score with brexpiprazole 2 or 3 mg/day compared to placebo at Week 12 (Study 283, p=0.0404) (Study 213, p=0.0026). Further supportive data comes from a third flexible-dose Phase 3 randomized, placebo-controlled study, Study 284 (331-12-284), which did not meet the primary endpoint, and from a 12-week, active-treatment extension study, Study 182 (331-201-00182), for patients who completed Study 213. Across all 4 studies, treatment with brexpiprazole was safe and generally well tolerated in patients with AAD. The safety profile was consistent with the known brexpiprazole profile, and no new safety signals were identified. All studies were designed based on feedback from the Food and Drug Administration (FDA).

1.2 Current Treatment Options and Unmet Need

There are currently no approved pharmacological treatments in the US for the management of agitation in patients with AD. Treatment guidelines typically recommend a comprehensive treatment plan encompassing non-pharmacological and off-label pharmacological interventions (Jeste et al 2008; Kales et al 2015; Kales et al 2019;

Reus et al 2016; Scales et al 2018). Clinicians rely on off-label pharmacological use of drugs, including benzodiazepines, antihistamines, antidepressants, atypical antipsychotics, and antiepileptics that have mixed effectiveness and carry several notable safety considerations in patients with AAD, including increased risk of mortality, sedation, falls, and worsening of cognitive status (Caraci et al 2020; Hsu et al 2021; O'Gorman et al 2020; Moretti et al 2006; Schneider et al 2006). Currently, all antipsychotic medications, including brexpiprazole, carry a class boxed warning in their label for the increased risk of death in elderly patients with dementia-related psychosis which was based on an FDA meta-analysis of 17 placebo-controlled studies in elderly patients with dementia-related psychosis, mostly treated with atypical antipsychotics. Elderly patients showed a rate of death in drug-treated patients of about 4.5%, compared to a rate of about 2.6% in the placebo group (a 1.6- to 1.7-fold increased risk of death compared to placebo). Most deaths were caused by either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) events.

Agitation is also a leading cause of institutionalization into high-level residential care facilities for patients with AD, as caregiver distress along with burden of agitation, places the patients at a higher risk for institutionalization (Cloutier et al 2019; Fillit et al 2021; Gaugler et al 2011).

Given the serious consequences of AAD and lack of approved, effective, and safe treatment options, there is a significant unmet need for a therapeutic option with a positive benefit-risk profile.

1.3 Overview of Brexpiprazole

Brexpiprazole, if approved, would provide the first FDA approved treatment option with a distinct mechanistic approach to manage agitation in AD. Brexpiprazole, an atypical antipsychotic, is a partial agonist at serotonin type 1A receptor (5-HT_{1A}) and dopamine type 2 (D_2) receptors. Brexpiprazole is also an antagonist at serotonin type 2A receptor (5-HT_{2A}) and noradrenaline receptors (α_{1B} and α_{2C}). At clinical doses, brexpiprazole binds with similar affinities to these receptors (Maeda et al 2014). Brexpiprazole may reduce agitation by its α_{1B} receptor antagonism in combination with 5-HT_{1A} and D_2 receptor partial agonist activity (Beiderbeck et al 2012; Couppis and Kennedy 2008; Gannon and Wang 2019; Lindenmayer 2000; Nelson and Trainor 2007; Puig and Gulledge 2011).

The proposed indication of brexpiprazole is for the treatment of agitation associated with Alzheimer's dementia with a recommended target dose of 2 mg orally, once daily, with a maximum dose of 3 mg/day.

1.4 Agitation Associated with Alzheimer's Dementia Phase 3 Clinical Development Program

The AAD clinical development program for brexpiprazole consists of 3 randomized, double-blind, placebo-controlled Phase 3 studies, 2 pivotal (Studies 283 and 213), and

1 supportive, which did not meet its primary endpoint (Study 284; Table 1), and a 12-week, multicenter, active-treatment extension study (Study 182) in patients who completed Study 213. Overall, 1,048 patients with AAD participated in the clinical development program of brexpiprazole. Fixed-dose Study 283 and flexible-dose Study 284 were conducted concurrently and prior to Study 213. All three Phase 3 studies utilized the same primary and key secondary efficacy endpoints and were designed with feedback from the FDA. Based on the results of Studies 283 and 284, including post-hoc data (Sections 1.5.3 and 6.1.5), and discussions with FDA, higher doses were included in the subsequent Study 213, and adaptations were made to enroll patients with AAD who exhibited a higher baseline agitation level.

Table 1: Clinical Development Program for Brexpiprazole in Agitation Associated with Alzheimer's Dementia

	Study 283 Fixed-Dose	Study 284 Flexible-Dose	Study 213 Fixed-Dose
Number of patients randomized	433[a]	270	345
Brexpiprazole dose	1 or 2 mg/day	0.5–2 mg/day	2 or 3 mg/day
Duration of treatment	12 weeks	12 weeks	12 weeks

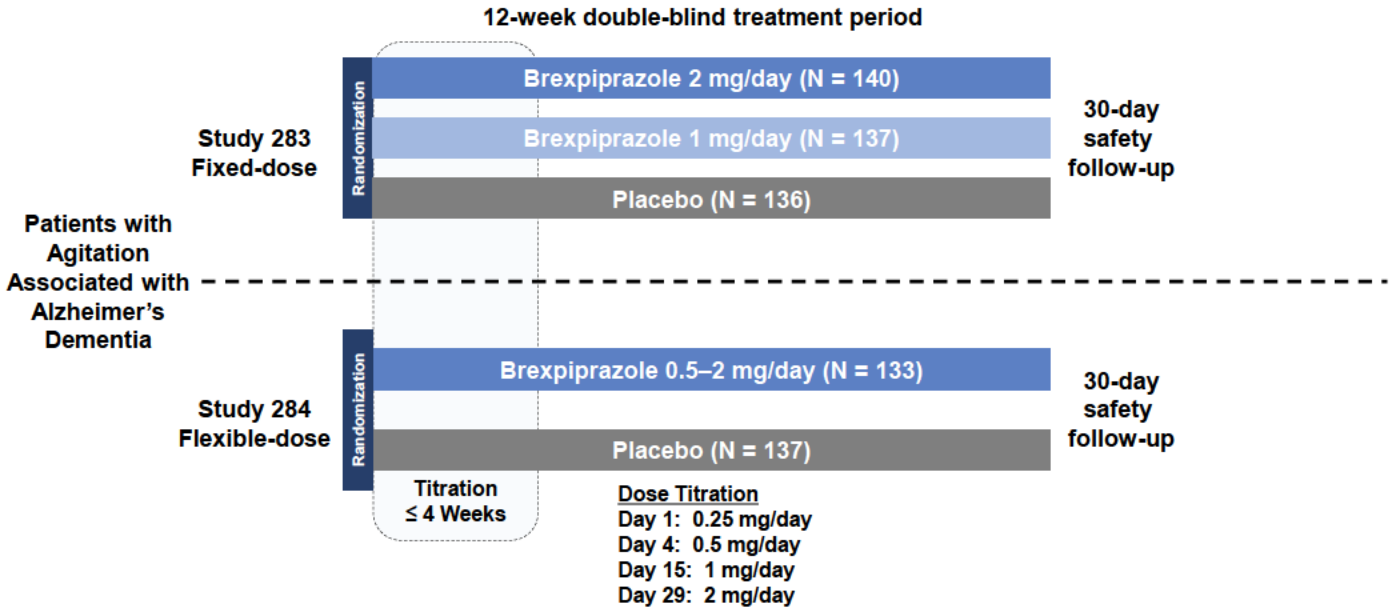
a. Twenty patients received brexpiprazole 0.5 mg/day. The 0.5 mg/day group in Study 283 was removed after initiation of the study based on new information from completed studies in other indications and recent pharmacokinetic data in elderly patients, supporting that doses lower than 1 mg/day were unlikely to be efficacious.

1.5 Pivotal Fixed-Dose Study 283 and Supportive Flexible-Dose Study 284

1.5.1 Studies 283 and 284 Design

Studies 283 and 284 were designed to assess the efficacy, safety, and tolerability of brexpiprazole in the treatment of patients with AAD (Figure 1). The design of Studies 283 and 284 were similar with the exception that Study 283 was a fixed-dose design with 3 arms (brexpiprazole 1 mg/day, 2 mg/day, and placebo; 1:1:1) while Study 284 consisted of a flexible-dose group (0.5–2 mg/day) and a placebo group (1:1). For Study 284, at the Week 4 visit, if the Investigator determined the patient had an inadequate response and was tolerating the treatment, the dose could be increased to 2 mg/day. Each study had a 30-day safety follow-up.

Figure 1: Studies 283 and 284: Study Design



Note: The 0.5 mg/day group in Study 283 was removed based on new information from completed studies in other indications and recent pharmacokinetic data in elderly patients, supporting that doses lower than 1 mg/day were unlikely to be efficacious.
Note: For patients who were terminated early from the study for any reason, the caregiver was contacted by telephone at Week 16 to collect follow-up information on mortality status.

Eligible patients were between 55 and 90 years of age, who were living in either an institutionalized (residential) or non-institutionalized (community) setting. All patients had a diagnosis of probable Alzheimer's disease according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria and a magnetic resonance imaging (MRI) or computed tomography (CT) scan with findings consistent with a diagnosis of Alzheimer's disease. Additionally, patients must have had a Mini-Mental State Examination (MMSE) score of 5–22, and a total score of ≥ 4 on the agitation/aggression item of the Neuropsychiatric Inventory–Nursing Home (NPI-NH) for institutionalized patients or on the Neuropsychiatric Inventory for Non-institutionalized Patients (NPI/NPI-NH) with the onset of symptoms occurring at least 2 weeks prior to screening. Patients with dementia or other memory impairment not due to AD were not eligible for study enrollment. A full list of enrollment criteria is provided in Appendix 11.1.1.

Studies 283 and 284 utilized the same primary and key secondary efficacy endpoints. The primary endpoint was change from baseline to Week 12 in the CMAI total score. CMAI is a well-established questionnaire that measures the frequency of 29 different agitated behaviors in elderly persons (Cohen-Mansfield 1995; Cohen-Mansfield 2008; Cohen-Mansfield et al 1989).

The CMAI has been judged to be appropriate for this patient population and has become the scale of choice in assessing agitation in clinical studies. Psychometric analysis further characterizes behaviors into 3 key CMAI subscale domains or factors: verbally and physically aggressive behavior (Factor 1), physically nonaggressive behavior (Factor 2), and verbally agitated behavior (Factor 3) (Rabinowitz et al 2005) (additional details are provided in Appendix 11.2). Each behavior is rated on a 7-point scale of frequency with higher ratings corresponding to higher frequency of agitated behavior. A score of 1 represents that the symptom does not occur; a score of 2 represents occurrence less than once a week; a score of 4 represents occurrence several times a week and a score of 7 represents occurrence several times an hour. Therefore, results will range from the lowest, non-agitated score of 29 to a maximum score of 203.

The key secondary endpoint was change from baseline to Week 12 in the Clinical Global Impression-Severity of Illness scale (CGI-S) score, as related to agitation. The CGI-S was used to assess the severity of agitation.

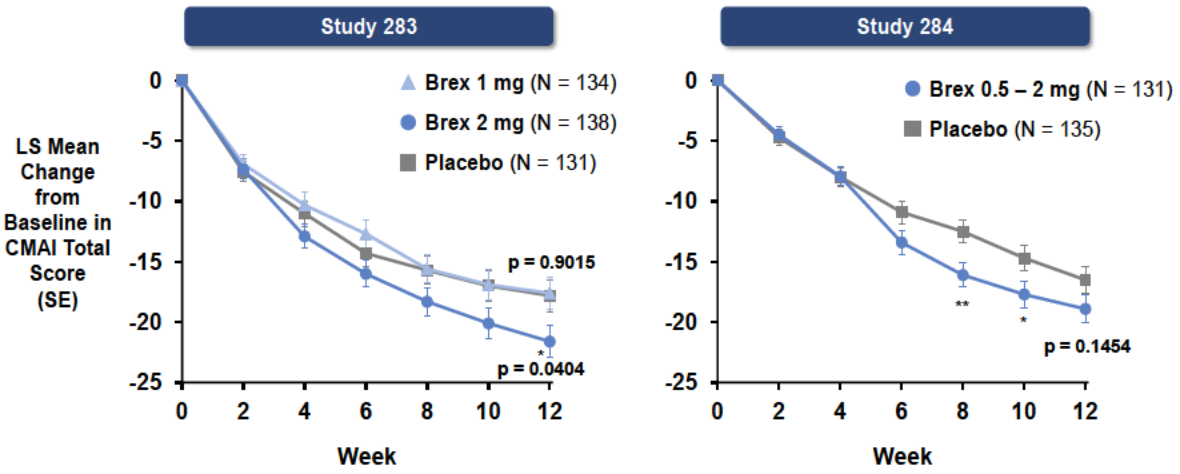
CMAI response rate, where response is defined as ≥ 40%, ≥ 30%, and ≥ 20% reduction in CMAI total score, was a secondary endpoint. Additional endpoints included change from baseline in CMAI total score and CGI-S for every scheduled study visit in the double-blind treatment period other than the Week 12 visit.

All efficacy analyses were conducted on the Efficacy Sample. For Studies 283 and 284, the Efficacy Sample consisted of all randomized patients who took ≥ 1 dose of study drug treatment (excluding patients randomized to brexpiprazole 0.5 mg/day [n=20] in Study 283) and had a baseline and ≥ 1 post-baseline evaluation for the CMAI total score.

1.5.2 Studies 283 and 284 Efficacy Results

The results from the pivotal fixed-dose Study 283 demonstrated the efficacy of brexpiprazole 2 mg/day in the treatment of adult patients with AAD. Brexpiprazole 2 mg/day was statistically superior to placebo resulting in improvement in CMAI total score (least squares mean difference [LSMD]=−3.77 [95% confidence interval (CI): −7.38, −0.17], p=0.0404; Figure 2, left panel). Separation from placebo started to emerge after patients began receiving the 2 mg/day dose of brexpiprazole at Week 4. The lower dose group, 1 mg/day brexpiprazole, did not show any meaningful separation relative to placebo. Study 284 did not meet the primary endpoint; the brexpiprazole 0.5–2 mg/day group (mean dose: 1.54 mg/day) did not show statistical superiority relative to placebo on the CMAI total score at Week 12 (LSMD=−2.34 [95% CI: −5.49, 0.82], p=0.1454; Figure 2, right panel).

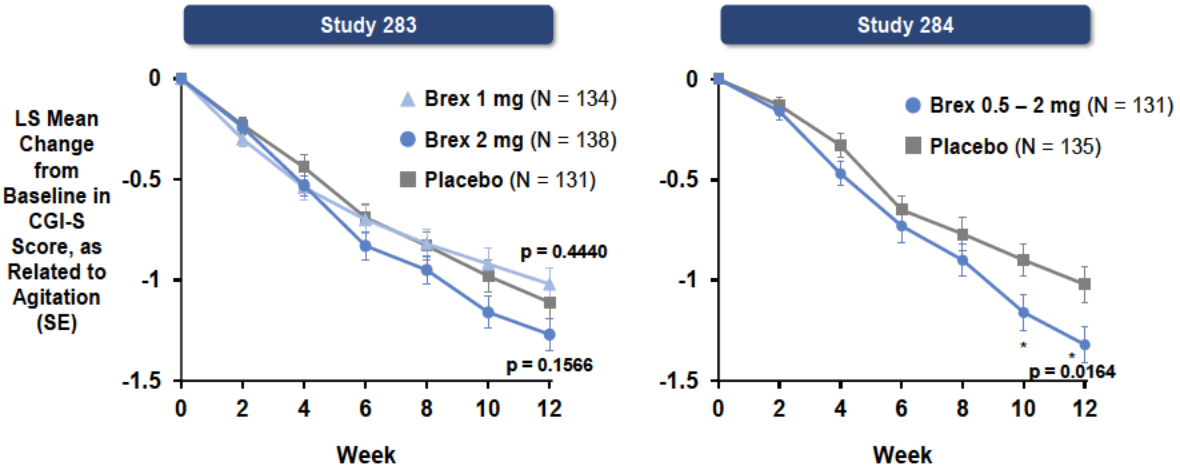
Figure 2: Studies 283 and 284: Change from Baseline in CMAI Total Score After 12 Weeks of Treatment (Efficacy Sample)



*p < 0.05, **p < 0.01 vs placebo; MMRM.
Note: Error bars are LS Mean ± standard error.
Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory; MMRM=mixed-effect model repeated measure.

In Study 283, a numerically greater improvement for the key secondary efficacy endpoint of the mean change in CGI-S as related to agitation from baseline to Week 12 was also observed for the 2 mg/day dose but the treatment difference did not reach statistical significance (LSMD=−0.16 [95% CI: −0.39, 0.06], p=0.1566; Figure 3, left panel). In Study 284, improvement was observed for the mean change of CGI-S score as related to agitation from baseline to Week 12 with brexpiprazole 0.5–2 mg/day vs placebo (LSMD=−0.31, nominal p=0.0164; Figure 3, right panel).

Figure 3: Studies 283 and 284: Change from Baseline in CGI-S Score After 12 Weeks of Treatment (Efficacy Sample)



*p < 0.05 vs placebo; MMRM.
Note: Error bars are LS Mean ± standard error.
Brex=brexpiprazole; CGI-S=Clinical Global Impression-Severity of Illness scale; MMRM=mixed-effect model repeated measure.

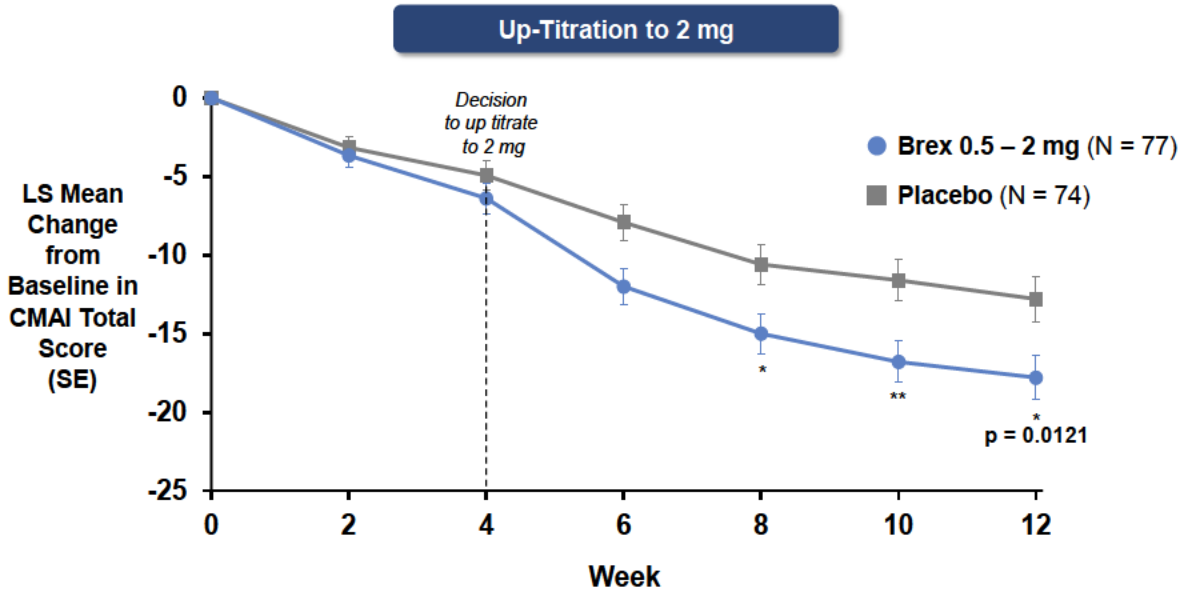
1.5.3 Studies 283 and 284 Post-Hoc Analyses

1.5.3.1 Brexpiprazole Dose Up-Titration to 2 mg/day

Based on results of fixed-dose Study 283 which showed that doses lower than 2 mg/day did not confer statistical superiority relative to placebo, post-hoc analyses of Study 284 were conducted for patients who were up-titrated to 2 mg vs those who were not.

In total, 77/131 patients in the brexpiprazole group and 74/135 patients in the placebo group had their dose increased from 1 to 2 mg/day at the Week 4 visit. At Week 12, a numerically greater improvement in mean change in CMAI total score from baseline was demonstrated with brexpiprazole over placebo in the up-titrated subgroup (LSMD=−5.06 [95% CI: −8.99, −1.13], nominal p=0.0121; Figure 4). No improvement was observed with brexpiprazole over placebo in the subgroup that did not implement an increase in dose at Visit 4 (p=0.5506). Taken together, the results from Study 283 and results from the subgroup of patients who were up-titrated to 2 mg/day in Study 284 support the conclusion that the minimum effective dose of brexpiprazole in patients with AAD may be 2 mg/day.

Figure 4: Study 284 Post-Hoc Analysis: Change from Baseline in CMAI Total Score After 12 Weeks of Treatment in Patients Up-Titrated to 2 mg/day at Week 4



*p < 0.05, **p < 0.01 vs placebo; nominal p-values presented; MMRM.
*Nominal p-values were not adjusted for multiple comparisons.
Note: Error bars are LS Mean ± standard error.
Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory; MMRM=mixed-effect model repeated measure.

1.5.3.2 Patients Meeting Criteria for CMAI Factor 1 at Baseline

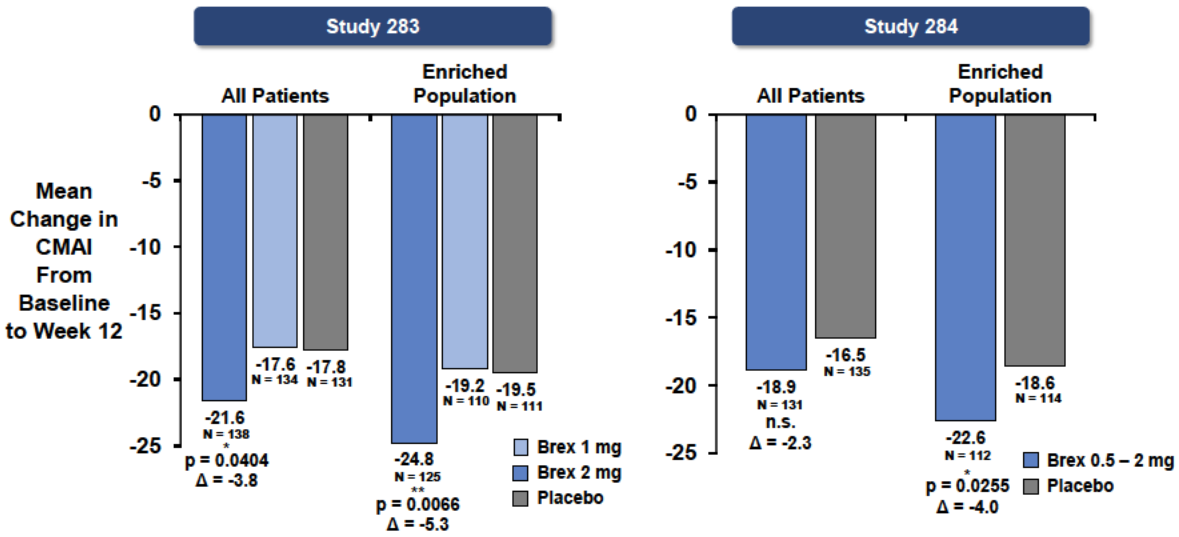
Additional post-hoc analyses were conducted for Studies 283 and 284 to test the hypothesis that baseline frequency of agitation, as based primarily on a Neuropsychiatric Inventory (NPI) agitation/aggression item score of ≥ 4, may not have been sufficiently high in a subset of patients to observe a separation from placebo over time. This was also a hypothesis offered by the FDA. Post-hoc analyses of the primary efficacy endpoint for Studies 283 and 284 for patients who met criteria for being positive for CMAI Factor 1 (Appendix 11.2) at baseline were conducted to test the hypothesis. Being positive for CMAI Factor 1 was defined as patients who exhibited ≥ 1 aggressive behavior(s) occurring several times per week, ≥ 2 aggressive behaviors occurring once or twice per week, or ≥ 3 aggressive behaviors occurring less than once per week (adapted from Cohen-Mansfield 1991).

Approximately 86% of all randomized patients in Study 283 and approximately 84% of all randomized patients in Study 284 met the criteria for CMAI Factor 1 at baseline (i.e., Enriched Population). Notable differences in the mean baseline CMAI total scores were observed in patients who met criteria for CMAI Factor 1 vs patients who did not meet this criterion (Study 283: 73.4 vs 56.4; Study 284: 72.3 vs 56.5). Of note, most patients who met CMAI Factor 1 criteria at baseline also met criteria for CMAI Factor 2 and Factor 3 at baseline (approximately 80% of patients) which includes physically nonaggressive and verbally agitated behaviors, demonstrating a generally higher level

of agitation at baseline when applying enrollment criteria that enriched for CMAI Factor 1.

In Study 283, the treatment difference in the Enriched Population with brexpiprazole 2 mg/day was more favorable with a mean change in CMAI total score from baseline to Week 12 of −5.35 (95% CI: −9.19, −1.50) vs placebo (nominal p=0.0066) than that observed in the full Efficacy Sample (Figure 5, left panel). Similarly, the post-hoc analysis results of Study 284 showed greater improvement in CMAI total score at Week 12 relative to placebo (LSMD=−4.04 [95% CI: −7.58, −0.50], nominal p=0.0255) than that observed in the full Efficacy Sample (Figure 5, right panel).

Figure 5: Studies 283 and 284 Post-Hoc Analyses[1]: Change from Baseline in CMAI Total Score After 12 Weeks of Treatment



*p < 0.05, **p < 0.01 vs placebo; nominal p-values presented; MMRM.
*Nominal p-values were not adjusted for multiple comparisons.
1. Patients meeting criteria for CMAI Factor 1 at baseline.
Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory; MMRM=mixed-effect model repeated measure; ns=not significant.

1.5.4 Key Learnings from Studies 283 and 284

Study 283 demonstrated the efficacy of brexpiprazole 2 mg/day in the treatment of adult patients with AAD. The lower dose group, 1 mg/day brexpiprazole, did not show any meaningful separation relative to placebo in Study 283, supporting brexpiprazole 2 mg/day as the minimal effective dose. Furthermore, a post-hoc analysis for Study 284 showed that patients who were up-titrated to 2 mg/day at Week 4 showed a greater treatment difference in CMAI total score vs placebo. In addition, results from post-hoc analyses from Studies 283 and 284 determined that a subset of patients enrolled in these 2 studies exhibited a higher level of baseline agitation symptoms and showed a better treatment difference with separation from placebo. Also, defining an agitated patient population based primarily on an NPI agitation/aggression item score of ≥ 4

likely led to enrollment of some patients with insufficient agitation behaviors at baseline, suggesting that patients with more prominent agitation behaviors should be recruited into future AAD studies to discern improvements between treatment arms. In addition, based on the favorable safety and tolerability profile demonstrated in Studies 283 and 284 (additional details provided in Section 1.10), patients could be titrated up to 2 mg/day two weeks earlier.

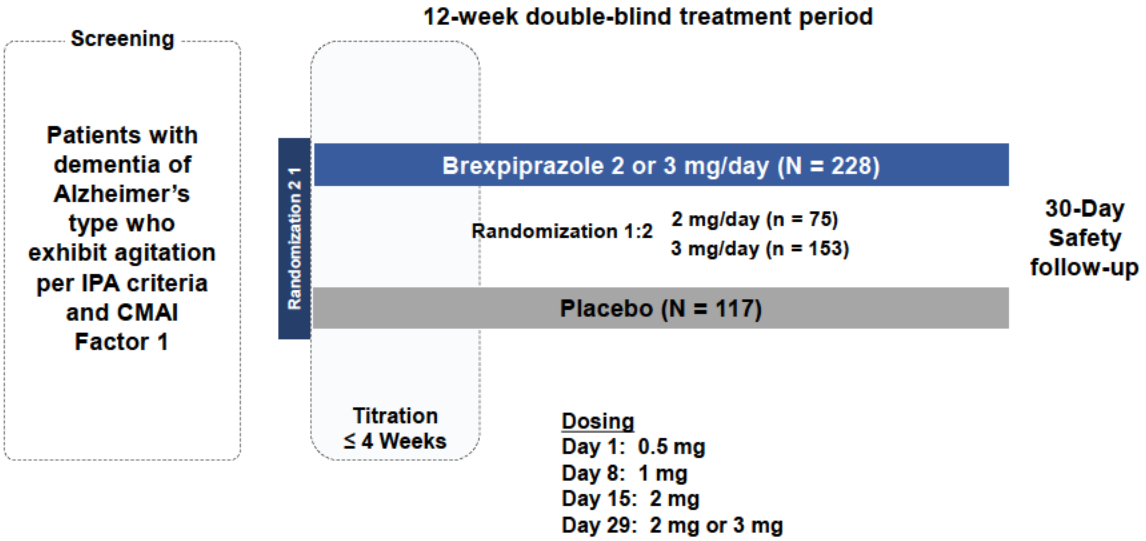
1.6 Pivotal Fixed-Dose Study 213

1.6.1 Study 213 Design

Study 213 was similarly designed to Studies 283 and 284 with identical primary and key secondary efficacy endpoints (Figure 6). Patients were randomized (2:1) to receive either brexpiprazole or placebo during the double-blind treatment period. Within the brexpiprazole arm, patients were further randomized (1:2) to 2 mg/day or 3 mg/day to ensure that a minimum of 100 patients were randomized to the higher dose (3 mg). In addition, per agreement with the FDA, the two brexpiprazole doses were combined into a single arm to enhance feasibility by ensuring a meaningful sample size whilst enabling enrollment to be completed within a reasonable timeframe. A faster titration was utilized in comparison to Studies 283 and 284, with patients up-titrated to 2 mg/day at Day 15.

Key inclusion and exclusion criteria for Study 213 were similar to those for Studies 283 and 284, with the exception of 2 additional inclusion criteria, to ensure enrollment of sufficiently agitated patients. During screening and at baseline, patients must have met the criteria for the provisional International Psychogeriatric Association (IPA) consensus definition of agitation in patients with cognitive disorders (which was not available at the time of Studies 283 and 284; additional details are provided in Section 2.1.4.1) and the CMAI Factor 1 criteria.

Figure 6: Study 213: Study Design



Note: The study had an interim analysis at 255 patients. Decision to move to full sample of 330. Alpha level for final analysis was 0.035.
Note: For patients who terminated early from the study, a mortality assessment was obtained from the patient's caregiver by telephone contact at Week 16.
CMAI=Cohen-Mansfield Agitation Inventory; IPA=International Psychogeriatric Association.

Screening for patients with CMAI Factor 1 criteria was blinded from the Investigator. Eligible patients had to exhibit ≥ 1 aggressive behavior(s) occurring several times per week, ≥ 2 aggressive behaviors occurring once or twice per week, or ≥ 3 aggressive behaviors occurring less than once per week. A full list of enrollment criteria is provided in Appendix 11.1.2. All patients who completed Study 213 were enrolled into an (optional) 12-week active-treatment extension study, Study 182.

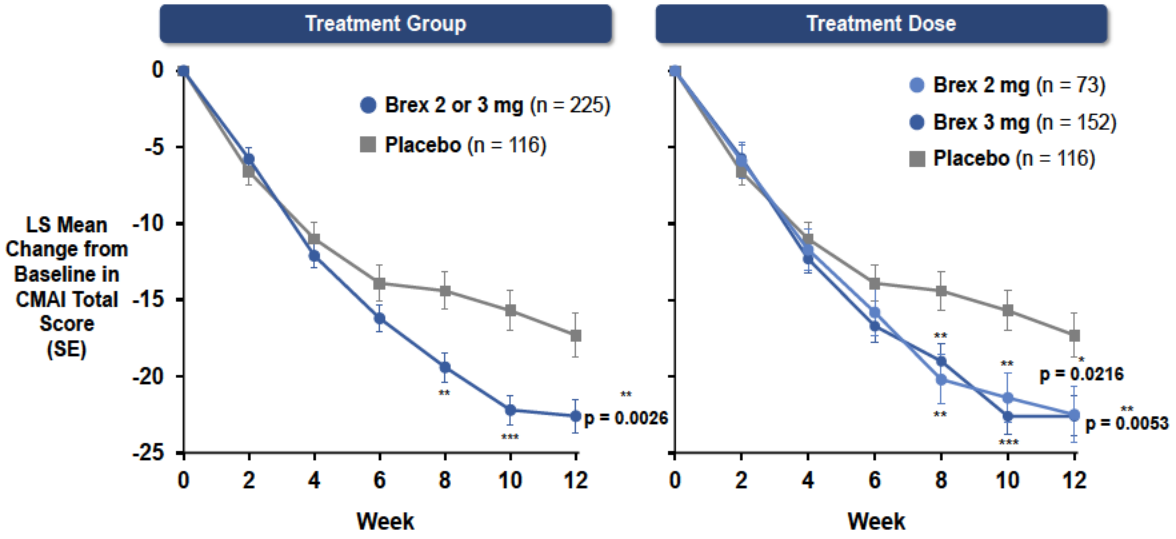
1.6.2 Study 213 Efficacy Results

Study 213 met its primary and key secondary efficacy endpoints. The brexpiprazole 2 or 3 mg/day group met the primary efficacy endpoint, demonstrating statistically significant improvement from baseline in CMAI total score compared with placebo at Week 12 (LSMD=−5.32 [95% CI: −8.77, −1.87], p=0.0026; Figure 7, left panel). The LSM change from baseline in CMAI total score between the brexpiprazole 2 or 3 mg/day group and the placebo group began to separate at Week 6 and showed a treatment difference vs placebo at Week 8 (LSMD=−5.08, nominal p=0.0011) and Week 10 (LSMD=−6.47, nominal p < 0.0001).

Additional exploratory analyses of the CMAI total score were performed on the 2 mg/day brexpiprazole group compared to placebo and 3 mg/day brexpiprazole group compared to placebo. The findings from these analyses at Week 12 were similar for both doses (2 mg/day vs placebo: LSMD=−5.28 [95% CI: −9.77, −0.78], nominal p=0.0216; 3 mg/day vs placebo: LSMD=−5.35 [95% CI: −9.09, −1.60], nominal

p=0.0053; Figure 7, right panel) and were consistent with the primary CMAI total score analyses (Figure 7, left panel).

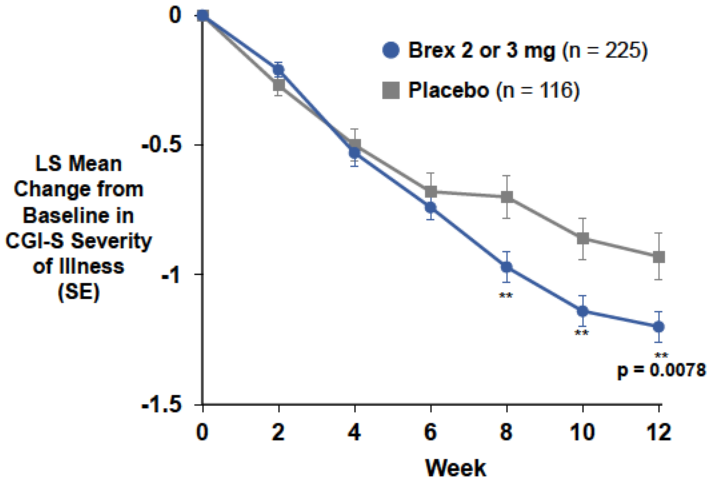
Figure 7: Study 213: Change from Baseline in CMAI Total Score Through 12 Weeks of Treatment by Treatment Group and Dose (Efficacy Sample)



*p<0.05, **p < 0.01, ***p < 0.001 vs placebo; MMRM.
*Nominal p-values were not adjusted for multiple comparisons.
Note: Error bars are LS Mean ± standard error.
Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory; MMRM=mixed-effect model repeated measure.

Study 213 also met its pre-specified key secondary efficacy endpoint. The brexpiprazole 2 or 3 mg/day group, demonstrated a statistically significant (p=0.0078) improvement in CGI-S score as related to agitation with −0.27-point (95% CI: −0.47, −0.07) change over placebo (Figure 8).

Figure 8: Study 213: Change from Baseline in CGI-S Score as Related to Agitation Through 12 Weeks of Treatment (Efficacy Sample)



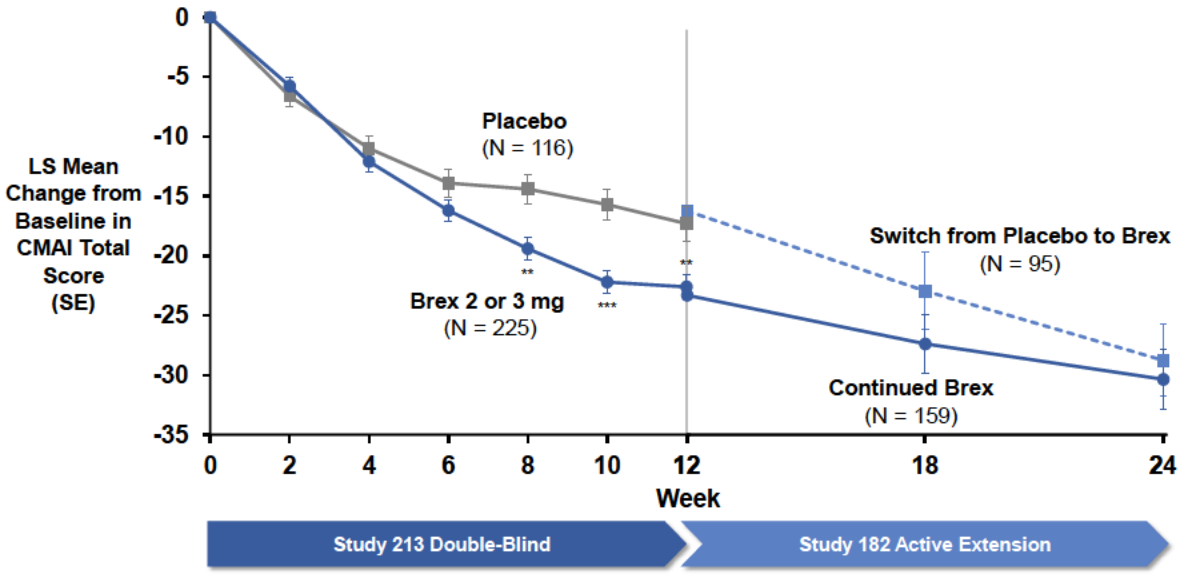
**p-value < 0.01 vs placebo; MMRM.
Note: Error bars are LS Mean ± standard error.
Brex=brexpiprazole; CGI-S=Clinical Global Impression-Severity of Illness scale; MMRM=mixed-effect model repeated measure.

1.7 Active-Treatment Extension Study 182

Study 182 was a multicenter, 12-week, active-treatment extension study designed to assess the long-term safety and tolerability of brexpiprazole (2 or 3 mg/day) in adults with AAD. Enrollment into the study consisted of eligible patients who completed 12 weeks of treatment in the double-blind Study 213. Patients randomized to the 2 or 3 mg/day doses of brexpiprazole in Study 213 began treatment on these same doses in the active-treatment extension. Prior treatment was blinded to the study Investigator. Patients who received placebo in Study 213 received 0.5 mg brexpiprazole once a day during Week 1, up-titrated to 1 mg during Week 2, and then up-titrated to 2 mg by Week 3. Efficacy was an exploratory objective and assessed by CMAI total score at 6 and 12 weeks of treatment.

Baseline for Study 182 was the last efficacy visit in the double-blind treatment period of Study 213. As expected, based on prior treatment, mean CMAI total scores at baseline for the prior placebo group were higher than those for the prior brexpiprazole group (62.9 vs 57.3). In Study 182, after 6 weeks of treatment with brexpiprazole 2 or 3 mg/day, mean change in CMAI total scores from baseline was greater in the 93 patients in the prior placebo group (−6.7) than in the 155 patients in the prior brexpiprazole group (−4.1; Figure 9). After 12 weeks of treatment, mean CMAI total scores remained similar between both groups, with mean change from baseline greater in the prior placebo group (−12.5) than in the prior brexpiprazole group (−7.1).

Figure 9: Studies 213 and 182: Change from Baseline in CMAI Total Score Through 24 Weeks of Treatment (Efficacy Sample)



**p-value < 0.01, ***p < 0.001 vs placebo; MMRM.
Note: 163 patients on brexpiprazole entered Study 182 and continued brexpiprazole.
Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory; MMRM=mixed-effect model repeated measure.

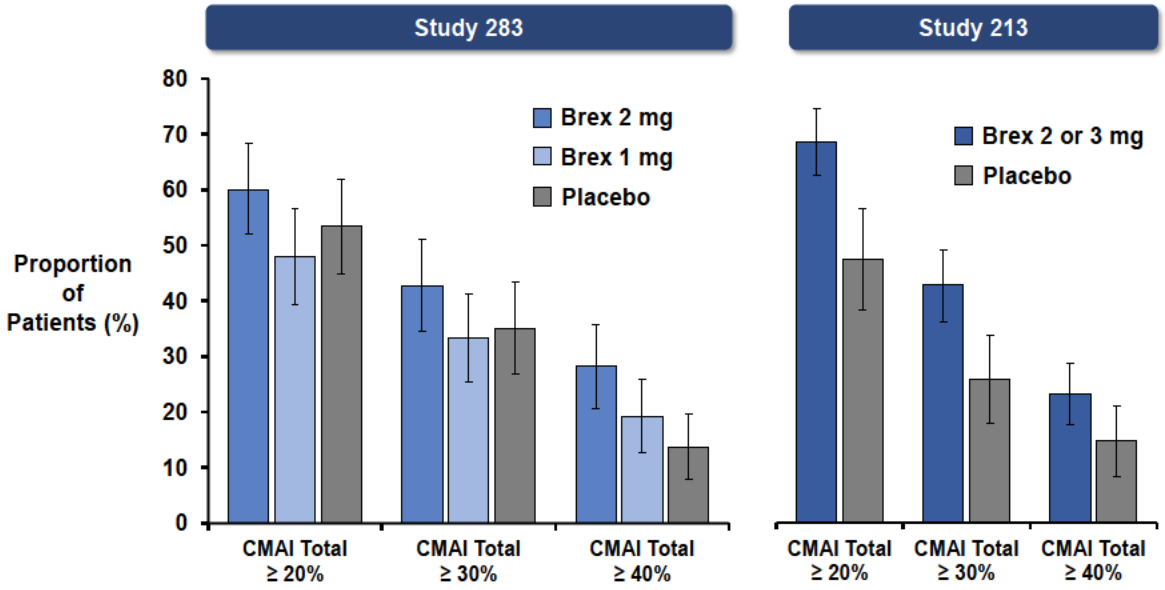
1.8 Clinical Meaningfulness of Efficacy Results

1.8.1 Proportion of Responders

In Study 283, the proportion of responders was numerically higher for brexpiprazole 2 mg/day (28.3%) compared to placebo (13.7%) for ≥ 40% reduction in CMAI total score at Week 12 (Figure 10, left panel).

In Study 213, approximately 23% of patients on brexpiprazole vs 15% of patients on placebo achieved a CMAI response (or reduction in CMAI total score) of ≥ 40% at Week 12 (Figure 10, right panel). Approximately 42.7% of patients on brexpiprazole and 25.9% of patients on placebo achieved a CMAI response of ≥ 30% at Week 12 (Figure 10, right panel).

Figure 10: Studies 283 and 213: Proportion of Patients with CMAI Reductions at Week 12 (Efficacy Sample)



Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory.
Note: Last observation carried forward (LOCF) method was used for missing data imputation.

1.8.2 Proportion of Patients Achieving Meaningful Within-Patient Change

Post-hoc analyses of Studies 283 and 284 were conducted to derive a meaningful within-patient change (MWPC) threshold for the CMAI, in accordance with methods outlined in FDA's PFDD Guidance 4 (FDA 2019), and this threshold was applied prospectively to Study 213. Based on this FDA guidance, a triangulation of methods, including anchoring the CMAI change to a 2-point improvement in the CGI-S, a decrease of 20 points in the CMAI total score was determined to constitute a meaningful improvement in agitation frequency. In Study 213, approximately 56% of patients treated with brexpiprazole 2 or 3 mg/day met this MWPC threshold as compared to 37% of patients receiving placebo. In the pooled analysis across both fixed-dose studies (Studies 283 and 213), similar values were obtained with 50% of brexpiprazole-treated patients achieving this MWPC threshold vs 38% of the patients treated with placebo (Table 2). Overall, the proportion of patients who met the threshold for clinically meaningful change in CMAI total score (i.e., a 20-point change from baseline) was consistently larger in the brexpiprazole treatment group compared with the placebo group (Study 213: 55.6% vs 37.1%; Studies 283 and 213: 50.1% vs 37.7%).

Table 2: Study 213 and Pooled Fixed-Dose Studies (283 and 213): Proportion of Patients Achieving MWPC Threshold by Treatment Arm (Efficacy Sample, LOCF)

	Study 213		Pooled Fixed-Dose Studies (283 and 213)	
	Brexpiprazole 2 or 3 mg/day (N=225)	Placebo (N=116)	Brexpiprazole 2 or 3 mg/day (N=363)	Placebo (N=247)
-20 Point Change in CMAI Total Score, n (%)	125 (55.6)	43 (37.1)	182 (50.1)	93 (37.7)

CMAI=Cohen-Mansfield Agitation Inventory; LOCF=last observation carried forward; MWPC=Meaningful within-patient change.

1.9 Efficacy Summary

Overall, across 2 randomized clinical studies using a fixed-dose, of brexpiprazole 2 or 3 mg/day achieved statistically significant and clinically meaningful improvements in agitation compared to placebo in patients with AAD (Figure 11). In addition, Studies 284 and 182 provided supportive data for 2 mg/day being the minimal effective dose and for benefits out to 24 weeks of treatment, respectively. Furthermore, post-hoc analyses that adjust for CMAI Factor 1, CMAI, and CGI-S showed improvements for both the primary and key secondary endpoints – with similar effect sizes across all three studies.

Figure 11: Brexpiprazole Efficacy Results Across Studies 283, 284, and 213

Trial Number and Analysis	Daily Dose	CMAI Result	CMAI p-value	CGI-S Result	CGI-S p-value
Pre-specified Analyses					
Study 283 ITT	**2 mg**	-3.77	**0.0404**	-0.16	0.1566
Study 213 ITT	**2 or 3 mg**	-5.32	**0.0026**	-0.27	**0.0078**
Study 284 ITT	**0.5 – 2 mg** (Mean dose 1.54 mg)	-2.34	0.1454	-0.31	**0.0164***
Analyses Using Factor 1 Enrichment					
Study 283 (Post-hoc)*	***2 mg***	*-5.35*	***0.007***	*-0.25*	***0.045***
Study 284 (Post-hoc)*	***0.5 – 2 mg***	*-4.04*	***0.026***	*-0.43*	***0.002***

Bold text designates p-values < 0.05.
*Nominal p-values were not adjusted for multiple comparisons.
CGI-S=Clinical Global Impression-Severity of Illness Scale; CMAI=Cohen-Mansfield Agitation Inventory; ITT=Intent to treat.

1.10 Safety Results

Since receiving marketing approval in 2015, the cumulative number of patient-years of treatment with brexpiprazole worldwide as of 30 June 2022 was an estimated 1,269,877. Additionally, 10,291 patients have been exposed to ≥ 1 dose of brexpiprazole in clinical studies, of which 892 were > 65 years of age. The safety of brexpiprazole was evaluated in 751 elderly patients (≥ 55 years of age) with AAD in the 12-week, placebo-controlled, Phase 3 studies (Studies 283, 284, and 213) and long-term active-treatment extension study with up to 24 weeks of treatment (Study 182). In these studies, use of brexpiprazole was safe and well tolerated and the safety results are consistent with the known safety profile of brexpiprazole from the many years of clinical experience in other indications.

1.10.1 Treatment Exposure

In the three 12-week controlled studies in AAD (Studies 283, 284, and 213), 655 patients were exposed to ≥ 1 dose of brexpiprazole. The all brexpiprazole group included all patients exposed to brexpiprazole in completed AAD studies. Mean treatment duration was similar between the all brexpiprazole (79.4 days) and placebo (80 days) groups and was also similar across the brexpiprazole dose groups (78.4–79.8 days).

In the active-extension study (Study 182), 259 rollover patients were enrolled from Study 213, including 163 patients who received brexpiprazole and 96 patients who received placebo in the parent study, were exposed to ≥ 1 dose of brexpiprazole in the double-blind treatment period with a mean duration of 170.7 days.

1.10.2 Overall Safety

A summary of the adverse events (AEs) in the three 12-week controlled studies in AAD is provided in Table 3. Most AEs were mild to moderate in intensity. A low incidence of serious AEs (SAEs) was observed. A total of 7 deaths occurred, during the double-blind treatment period or within the 30-day safety follow-up period in the 3 completed, 12-week controlled studies in AAD.

Six deaths (0.9%) were reported in a brexpiprazole group, and 1 death (0.3%) was reported in the placebo group. While incidence of death was numerically higher in brexpiprazole compared to the placebo group, the overall incidence was low (< 1%) with no pattern in cause of death and individual cases were confounded by underlying conditions and other factors, including advanced age, comorbidities, and concomitant medications consistent with the AD population. All deaths occurred at least 30 days after beginning administration, with a wide range of when deaths occurred following the last dose (2–67 days). The events resulting in death varied, and none were considered by the Investigator to be related to brexpiprazole (additional details are provided in Section 7.6 and Appendix 11.3).

Table 3: Studies 283, 284, and 213: Overall Summary of Adverse Events (Pooled Safety Sample)

Patients with any, n (%)	Brexpiprazole				Placebo (N=388)
	≤ 1 mg (N=157)	2 or 3 mg (N=366)	0.5–2 mg (N=132)	All (N=655)	
AE	77 (49.0)	183 (50.0)	75 (56.8)	335 (51.1)	178 (45.9)
AE leading to study drug discontinuation	14 (8.9)	18 (4.9)	9 (6.8)	41 (6.3)	13 (3.4)
Severe AE	10 (6.4)	19 (5.2)	9 (6.8)	38 (5.8)	16 (4.1)
SAE	16 (10.2)	19 (5.2)	7 (5.3)	42 (6.4)	16 (4.1)
Death	4 (2.5)	2 (0.5)	0	6 (0.9)	1 (0.3)

SAE=serious adverse event.
Note: Treatment groups consisted of brexpiprazole ≤ 1 mg consisting of 0.5 mg/day and 1 mg/day arms in Study 283; brexpiprazole 0.5–2 mg arm in Study 284; brexpiprazole 2 or 3 mg/day arms in Studies 283 and 213; and placebo arms in Studies 283, 284, and 213.

The most common AEs (that occurred in ≥ 2% of patients in the all brexpiprazole group and greater than placebo) in the brexpiprazole group were nasopharyngitis, urinary tract infection, somnolence, and insomnia (additional details are provided in Section 7.4.1). Of these events, nasopharyngitis and insomnia were reported by 2.5% and 3.3%, respectively, in the 2 or 3 mg/day group which was similar to the percentage of patients who reported these events in the placebo group (2.6% and 2.8%, respectively). Incidences of somnolence (3.3%) and urinary tract infection (3.3%) were higher in the 2 or 3 mg/day group compared with the placebo group (1.8% for somnolence and 1.5% for urinary tract infection).

Overall, 5.8% of patients in the all brexpiprazole group (N=655) and 4.1% of patients in the placebo group reported ≥ 1 severe AE (additional details are provided in Section 7.4.2). Only 3 severe events were reported by more than 2 patients in any treatment group: seizure in 3 patients (0.5%) in the brexpiprazole group, urinary tract infection in 3 patients (0.5%) in the brexpiprazole group, and agitation in 3 patients (0.8 %) in the placebo group.

Forty-two patients (6.4%) in the all brexpiprazole group reported at least 1 SAE compared to 16 patients (4.1%) in the placebo group (additional details are provided in Section 7.4.3). SAEs reported by ≥ 2 patients in the brexpiprazole group were urinary tract infection in 6 patients (0.9%); agitation in 3 patients (0.5%); and pneumonia, fall, dementia Alzheimer's type, seizure, and chronic obstructive pulmonary disease in 2 patients each (0.3%). None of these events were reported in the placebo group except pneumonia in 2 patients (0.5%) and urinary tract infection and seizure in 1 patient each (0.3%). In the brexpiprazole 2 or 3 mg/day group, 5.2% of patients reported ≥ 1 SAE. Urinary tract infection reported by 6 patients (1.6%) was the only event reported by ≥ 2 patients in this dose group.

Forty-one patients (6.3%) in the all brexpiprazole group (N=655) and 13 patients (3.4%) in the placebo group had AEs leading to study drug discontinuation (additional details are provided in Section 7.4.4). AEs leading to brexpiprazole discontinuation for ≥ 2 patients included agitation (n=4), seizure (n=3), pneumonia (n=3), and asthenia, fall, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, electrocardiogram (ECG) QT interval (QT) prolonged, and insomnia (n=2, each). In the brexpiprazole 2 or 3 mg/day dose group, 4.9% of patients reported an AE resulting in discontinuation. Asthenia was the only event resulting in discontinuation reported by 2 patients in this dose group. Overall, there were no clinically relevant differences in changes in vital signs, ECG parameters, and laboratory values between brexpiprazole and placebo groups.

1.10.3 Active-Treatment Extension Study 182

The overall safety results of Study 182 were consistent with that seen in the placebo-controlled Phase 3 studies. Brexpiprazole was well tolerated by patients in both the prior brexpiprazole and the prior placebo group in Study 182. The overall incidence of AEs in the active-treatment extension study was 26.3% (68/259) with 2.3% (6/259) SAEs. The most frequently reported AE was headache, in 6 patients (3.7%) who received brexpiprazole in the previous study and 3 patients (3.1%) who received prior placebo. Fall occurred in 5 patients (3.1%) in the prior brexpiprazole group and 1 patient (1.0%) in the prior placebo group, followed by nasopharyngitis occurring in 5 patients (5.2%) in the prior placebo group. Dizziness and somnolence each occurred in 4 patients (2.5%) in the prior brexpiprazole group and 1 patient (1.0%) in the prior placebo group. The overall incidence of study drug discontinuation due to an AE was 4.6% and was similar between patients who received brexpiprazole in the parent study (7 [4.3%] patients) and patients who received placebo in the parent study (5 [5.2%]). No deaths or cerebrovascular events were reported for Study 182.

1.10.4 Selected Safety Topics of Special Interest

Safety topics of special interest were identified for enhanced data investigation based on the known pharmacology of the drug class effects, the underlying patient population, and known safety areas of interest for approved atypical antipsychotic agents. Six major topics of interest included falls, cerebrovascular events, cardiovascular events, sedation and somnolence, cognitive worsening, and extrapyramidal symptoms (EPS). Rates of AEs for selected safety topics of special interest were generally low and similar between brexpiprazole and placebo; additional details are included in Appendix 11.4. No difference in cognitive deterioration, as evaluated by the MMSE, was observed during the studies between brexpiprazole and placebo.

1.11 Benefit-Risk Summary

Alzheimer's dementia is the most common cause of dementia, a neurodegenerative brain disorder. Majority of patients who develop AD are likely to experience neuropsychiatric symptoms, including agitation, that have been associated with

accelerated disease progression, functional decline, decreased quality of life, and increased risk of institutionalization (Banerjee et al 2006; Cloutier et al 2019; Fillit et al 2021; Gaugler et al 2011; Halpern et al 2019; Lanctot et al 2017; Rockwood et al 2019; Scarmeas et al 2007; Wilcock et al 2008). Despite significant morbidity and mortality associated with AAD, there are no approved treatments that ameliorate the symptoms of agitation, highlighting the urgent unmet medical need for patients with AAD.

Adequate treatment of behavioral disturbances is essential to increasing the quality of care and safety of patients with AAD and easing the burden of care borne by families and other caregivers. Published studies evaluating the effects of off-label treatments for AAD with drugs such as benzodiazepines, antihistamines, antidepressants, atypical antipsychotics, and antiepileptics show mixed results and carry several notable safety limitations such as potentially increased risk of mortality, sedation, falls, and worsening of cognitive status (Caraci et al 2020; Hsu et al 2021; O'Gorman et al 2020; Moretti et al 2006; Schneider et al 2006).

Brexpiprazole is a novel therapy for patients with AAD that resulted in significant and clinically meaningful improvements in measures of agitation compared to placebo. Brexpiprazole, if approved, would be the first pharmacological treatment option for the management of agitation in AD. Brexpiprazole has been approved and used for the treatment of schizophrenia and MDD since 2015 with an acceptable safety profile.

Pivotal fixed-dose Study 283 demonstrated brexpiprazole 2 mg as the minimum efficacious dose. Brexpiprazole 2 mg/day was statistically significant (p=0.0404) in improving symptoms related to AAD in the primary efficacy endpoint as compared to placebo, while brexpiprazole 1 mg/day showed no separation from placebo. Pivotal Study 213 met its primary and key secondary efficacy endpoints; treatment with brexpiprazole 2 or 3 mg/day significantly improved CMAI and CGI-S, as related to agitation, scores relative to placebo at Week 12 (p=0.0026 and p=0.0078). Flexible-dose Study 284 did not meet its primary endpoint; however, post-hoc analysis from this study provided meaningful information supporting brexpiprazole 2 mg/day as the minimum efficacious dose.

Collectively, results from pivotal Studies 283 and 213, demonstrated 2 or 3 mg/day brexpiprazole resulted in clinically meaningful improvements in key measures of agitation compared with placebo. The proportion of patients who met the threshold for clinically meaningful change in CMAI total score (i.e., a 20-point change from baseline; Section 1.8.2) was consistently larger in the brexpiprazole treatment group compared with the placebo group (Study 213: 55.6% vs 37.1%; Studies 283 and 213: 50.1% vs 37.7%).

The clinical safety profile of brexpiprazole has been studied in the three 12-week placebo-controlled studies and an active-treatment extension study for up to 24 weeks. Consistently, the results show an acceptable and manageable safety profile in patients with AAD. Brexpiprazole was generally well tolerated, with low discontinuation rates,

and low rates of SAEs. Importantly, no new safety signals have been detected in the active-treatment extension study.

Deaths in the studies were not unexpected as AD affects the elderly population and is associated with an increased risk of death. Seven deaths were reported on study: 6 deaths (0.9%) in the brexpiprazole group and 1 death (0.3%) in the placebo group. Although there were numerically more deaths in the brexpiprazole group, the overall incidence was low (< 1%) with no pattern in cause of death. There was no relationship with dose or duration of treatment, nor a unifying pathophysiological process, and the risk factors were consistent with risk factors associated with AAD medical comorbidities prevalent in the underlying population. All deaths were determined to be not related to study treatment by the site Investigators and the deaths were lower in all three randomized trials than those noted in current class labeling for atypical antipsychotics. Importantly, there were no further deaths among patients who entered the active-treatment extension study.

1.12 FDA Mandated Class Warning for Atypical Antipsychotics

In 2005, an FDA analysis of 17 placebo-controlled studies (not including brexpiprazole) resulted in a class (boxed) warning for all antipsychotics in the US Prescribing Information (USPI). FDA concluded that over the course of a typical 10-week controlled study in patients aged ≥ 65 years with dementia-related psychosis, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group. It was also noted that most of the deaths were due to cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) causes. Consequently, all antipsychotic medications carry a boxed warning in the USPI for the increased risk of death in patients aged ≥ 65 years with dementia-related psychosis. In addition, FDA also added a class warning for cerebrovascular AEs in patients aged ≥ 65 years with dementia-related psychosis, noting a higher incidence of stroke and transient ischemic attacks, including fatal stroke with atypical antipsychotics.

The boxed warning in the currently approved brexpiprazole label (REXULTI) indicates an increased risk of death in elderly patients with dementia-related psychosis. The Sponsor proposes that the black box remains. The Sponsor intends to discuss label wording with the FDA to guide healthcare professionals and patients in the safe use of Rexulti in patients with AAD and the exact labeling text will be discussed with FDA to appropriately address risks and to accommodate the AAD indication. As precedence, in 2016, FDA approved pimavanserin (NUPLAZID) for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis and modified the boxed warning language to accommodate this indication.

2 BACKGROUND ON AGITATION ASSOCIATED WITH ALZHEIMER'S DEMENTIA

Summary

- Neuropsychiatric symptoms, including agitation, are common features associated with AD and typically become more frequent and severe as the disease progresses.
- AAD is associated with a significant burden for patients and caregivers. Caregivers spend > 20 hours/week helping patients with clinically significant agitation. AAD is often a determining factor of institutionalization into high-level residential care facilities.
- There are currently no approved pharmacological treatments for AAD.
    - Published studies evaluating the effects of off-label treatments for AAD with drugs such as benzodiazepines, antihistamines, antidepressants, atypical antipsychotics, and antiepileptics have mixed efficacy results and carry several notable safety limitations such as increased risk of mortality, falls, sedation, and worsening of cognitive status.
    - In 2005, FDA meta-analyses resulted in a Boxed Warning in labeling for the atypical antipsychotic drug class for increased risk of mortality in elderly patients with dementia-related psychosis.
- Access to approved safe and effective AAD treatments remains an ongoing and serious unmet need in this patient population.

2.1 Overview of Agitation Associated with Alzheimer's Dementia

2.1.1 Condition and Pathophysiology of Disease

The defining clinical features of AD includes a progressive decline in cognition, functional abilities, and a range of behavioral symptoms (i.e., neuropsychiatric symptoms) – agitation, mood disturbances, psychotic symptoms, and sleep disturbances – that manifest throughout the disease process. Neuropsychiatric symptoms, including agitation, are common features and the majority of patients with Alzheimer's dementia are likely to experience them with increasing severity as the disease progresses (Antonsdottir et al 2015; Peters et al 2015).

Evidence from structural and functional imaging studies as well as postmortem tissue analysis in AD indicate that pathology within key brain regions, including the prefrontal cortex and amygdala, may give rise to monoaminergic dysregulation and increase the risk of agitation in patients with AD (Rosenberg et al 2015; Lanctot et al 2017). In support of this, noradrenergic hyperactivity along with serotonergic deficiency and dopamine dysregulation has been linked to agitated and aggressive behaviors (Gannon and Wang 2019; Liu et al 2018).

2.1.2 Epidemiology

Currently in the US, an estimated 6.5 million Americans aged ≥ 65 years have AD and by 2050 that number is expected to double to 12.7 million individuals aged ≥ 65 years (Alzheimer's Association 2022). While cognitive impairment is a key symptom of AD, agitation occurs in about half of the patient population across different care settings (community: 45%; institution: 53%; Fillit et al 2021; Halpern et al 2019).

2.1.3 Patient, Caregiver, and Societal Burden

Agitation, along with other neuropsychiatric symptoms in dementia, is associated with a significant burden for patients and caregivers (Cohen-Mansfield 2008; Scarmeas et al 2007). Agitated behaviors manifest as both physical and verbal aggression (including cursing, spitting, throwing objects, and hitting), repetitive sentences or questions, and constant unwarranted requests for attention, resulting in emotional distress for the patient and caregiver (Schein et al 2022). Caregivers spend > 20 hours/week helping patients with clinically significant agitation. Symptoms of agitation may continue to escalate as AAD progresses (Okura and Langa 2011).

Agitation is a leading cause of institutionalization into high-level residential care facilities for patients with AD (Cloutier et al 2019; Fillit et al 2021; Gaugler et al 2011). Aggressive behaviors such as combativeness, destroying property, and being a danger to oneself and others are significant predictors of time to nursing home placement (Gaugler et al 2011). These symptoms increase patient morbidity and demand more caregiver support and can force the need for sedation or restraining patients to prevent further harm to the patient or others, irrespective of care setting.

Furthermore, AAD has been associated with accelerated disease progression, functional decline, and decreased quality of life (Banerjee et al 2006; Cloutier et al 2019; Lanctot et al 2017; Rockwood et al 2019; Scarmeas et al 2007; Wilcock et al 2008).

2.1.4 Clinical Evaluation

2.1.4.1 Identification and Diagnosis

Agitated behaviors associated with cognitive impairment manifest as both physical and verbal aggression, as well as excessive motor activity. The IPA definition of agitation is a standardized and validated definition to facilitate research and communication among clinicians and patients. The final definition was presented in 2022 with minimal changes to the provisional definition. The provisional IPA definition of agitation applicable to patients with cognitive impairment requires the following:

a) Evidence of emotional distress as exhibited by ≥ 1 of the following observable types of behavior: excessive motor activity, verbal aggression, or physical aggression (examples provided in Table 4);
b) Behaviors severe enough to cause excess disability; and

c) That the behaviors cannot be solely attributable to a suboptimal care environment or other disorder such as a psychiatric illness, a medical illness, or physiological effects of a substance (Cummings et al 2015).

The IPA defines agitation in dementia as behaviors that are persistent or frequently recurrent for 2 or more weeks (Cummings et al 2015).

Table 4: Types of Agitation Behaviors

Excessive Motor Activity Behaviors	Verbal Aggression Behaviors	Physical Aggression Behaviors
• Pacing • Rocking • Gesturing • Pointing fingers • Restlessness • Performing repetitious mannerisms	• Yelling • Speaking in an excessively loud voice • Using profanity • Screaming • Shouting	• Grabbing • Shoving • Pushing • Resisting • Hitting others • Kicking objects or people • Scratching • Biting • Throwing objects • Hitting self • Slamming doors • Tearing things • Destroying property

2.2 Current Treatment Options

There are currently no approved pharmacological treatments in the US for the management of agitation in patients with AD. Treatment guidelines typically recommend a comprehensive treatment plan encompassing non-pharmacological and off-label pharmacological interventions (Jeste et al 2008; Kales et al 2015; Kales et al 2019; Reus et al 2016; Scales et al 2018).

2.2.1 Non-Pharmacological Interventions

Non-pharmacological strategies are first-line based on specific symptoms. Careful evaluation and treatment for general medical, psychiatric, environmental, or psychosocial problems that may underlie the disturbance, including minimizing polypharmacy, is recommended prior to other interventions. Environmental or behavioral measures, including behavioral management therapy or behavioral interventions, emotion-oriented approaches or stimulation-oriented treatments (recreational activity, art therapy, music therapy, and pet therapy) have shown efficacy in some patients (Reus et al 2016). Both non-pharmacological interventions and pharmacological treatments are often initiated only after a clinical emergency when the need becomes more urgent. This is generally due to poor recognition of agitation, a lack of indicated treatments, and a reluctance to treat early on the part of clinicians.

2.2.2 Off-Label Pharmacological Therapies

Off-label pharmacological use of drugs such as benzodiazepines, antihistamines, antidepressants, atypical antipsychotics, and antiepileptics occurs due to the absence of approved treatments for AAD. Clinicians decide based on individual patient need whether off-label use is an option and whether the benefit of such treatments outweigh the risks.Published studies evaluating the effects of off-label treatments for AAD show mixed results and carry several notable safety limitations such as potentially increased risk of mortality, sedation, falls, and worsening of cognitive status (Caraci et al 2020; Hsu et al 2021; O'Gorman et al 2020; Moretti et al 2006; Schneider et al 2006). Specifically, safety concerns with benzodiazepines and their use in the management of agitation, particularly in the elderly, include a potential risk of cognitive decline, and an increased risk of fractures and falls (Defrancesco et al 2015; Saarelainen et al 2017). Furthermore, treatment with select antipsychotics (risperidone, quetiapine, olanzapine, and aripiprazole) can result in sedating side effects (Farlow and Shamliyan 2017; Schneider et al 2006). Sedation in vulnerable patients may have unwanted consequences which include significant morbidity, such as increased risk of falls, cognitive impairment, and mortality (Caraci et al 2020; Moretti et al 2006).

2.3 Unmet Medical Need

AAD is a devastating, rapidly progressive disease with a significant unmet need due to the absence of approved treatments. For patients and their families, AAD has important negative consequences regarding the patient’s behavior, functional abilities, quality of life, and life expectancy. Due to limited treatment options, off-label use of benzodiazepines, antihistamines, antidepressants, atypical antipsychotics, and antiepileptics occurs, increasing the risk of falls, sedation, worsening of cognitive status, and mortality in patients with AAD (Hsu et al 2021; Caraci et al 2020; O'Gorman et al 2020; Moretti et al 2006; Schneider et al 2006). Access to approved treatment options for agitated behaviors is essential to increasing the quality of care and safety of patients with AAD and easing the burden of care borne by families and their caregivers.

There is a need for approved pharmacological therapies that treat the symptoms of AAD. These new therapies would improve patient health outcomes and potentially reduce the quality of life and socio-economic strain placed on patients, their caregivers and families, as well as the overall healthcare system.

3 BREXPIPRAZOLE PRODUCT DESCRIPTION

Summary

- Brexpiprazole, an atypical antipsychotic, is a partial agonist at serotonin 5-HT_{1A} receptor and dopamine D_2 receptors and an antagonist at serotonin 5-HT_{2A} and noradrenaline (α_{1B} and α_{2C}) receptors.
    - Brexpiprazole addresses noradrenergic, serotonergic, and dopaminergic system dysfunction in brain circuits that mediate agitation behaviors.
- Brexpiprazole (REXULTI) has been approved since 2015 in the US, and is currently approved for the treatment of:
    - Schizophrenia in adults and pediatric patients ≥ 13 years of age, and
    - MDD in adult patients as an adjunctive therapy to antidepressants.

3.1 Product Overview

3.1.1 Brexpiprazole Mechanism of Action

Brexpiprazole is a partial agonist at serotonin 5-HT_{1A} receptor and dopamine D_2 receptors and an antagonist at serotonin 5-HT_{2A} and noradrenaline receptors (α_{1B} and α_{2C}), all with similar subnanomolar affinities. While the precise mechanism of action of brexpiprazole in treating psychiatric conditions is unknown, the pharmacology of brexpiprazole is believed to be mediated by a combination of high binding affinity and functional activities at multiple monoaminergic receptors. Brexpiprazole may reduce agitation by its α_{1B} receptor antagonism in combination with 5-HT_{1A} and D_2 receptor partial agonist activity (Beiderbeck et al 2012; Couppis and Kennedy 2008; Gannon and Wang 2019; Lindenmayer 2000; Nelson and Trainor 2007; Puig and Gulledge 2011).

3.2 Approved Indications and Doses

Brexpiprazole (REXULTI), an atypical antipsychotic, is currently indicated for the treatment of:

- Schizophrenia in adults and pediatric patients ages 13 years and older, and
- Major depressive disorder (MDD) in adult patients as an adjunctive therapy to antidepressants (Rexulti USPI).

Recommended Dose

Indication	Dose
Adults with major depressive disorder	2–3 mg/day
Adults with schizophrenia	2–4 mg/day
Pediatric patients with schizophrenia (13–17 years)	2–4 mg/day

Brexpiprazole has been approved for the treatment of schizophrenia and, where applicable, MDD, in over 60 countries, including the European Union (EU), Canada, and Japan.

3.3 Proposed Indication and Dosing for Use in Agitation Associated with Alzheimer's Dementia

The proposed indication of brexpiprazole is for the treatment of agitation associated with Alzheimer's dementia (AAD).

The recommended target dose of brexpiprazole is 2 mg taken orally, once daily, with or without food with a maximum dose of 3 mg/day.

The following brexpiprazole dose titration is recommended for the treatment of AAD, which is consistent with the schedule used in Study 213:

The recommended starting dosage for brexpiprazole for the treatment of AAD is 0.5 mg taken orally once daily on Days 1 to 7. The dosage should be titrated on Days 8 through 14 to 1 mg, and on Day 15 to 2 mg. The recommended target dose is 2 mg once daily. After at least 14 days at 2 mg once daily, the dose can be increased to the maximum recommended daily dose of 3 mg, if clinically warranted.

4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- Brexpiprazole was first approved for the treatment of schizophrenia in adults and as adjunctive therapy for the treatment of MDD in July 2015, in the US.
- The primary evidence supporting approval of brexpiprazole in patients with AAD comes from two randomized, placebo-controlled Phase 3 studies (fixed-dose studies – Studies 283 and 213) and supportive evidence from flexible-dose Study 284 and active-treatment extension Study 182.
- Studies 283, 284, and 213 were designed with input from FDA to provide efficacy and safety data that could meet the evidentiary standard for a new drug approval.

4.1 Regulatory History

Brexpiprazole was approved in the US for the treatment of schizophrenia in adults and as adjunctive therapy for the treatment of MDD on 10 July 2015. On 27 December 2021, brexpiprazole was approved for the treatment of schizophrenia in pediatric patients (ages 13 years and older).

The Investigational New Drug (IND) application for brexpiprazole for AAD was submitted by Otsuka on 22 February 2013. The corresponding supplemental New Drug Application (sNDA) was submitted by Otsuka in November 2022 and was accepted for priority review.

4.2 Regulatory Milestones

- FDA granted Fast Track Designation for brexpiprazole in AAD on 16 March 2015.

4.3 Key Regulatory Interactions

Key regulatory interactions between FDA and Otsuka in the clinical development of brexpiprazole for the treatment of AAD are included in Table 5.

Table 5: Key Regulatory Interactions in Brexpiprazole Clinical Development for the Treatment of Agitation Associated with Alzheimer's Dementia

Regulatory Interaction Date	Key Outcomes
Pre-IND Meeting 06 Nov 2012	• Agreement that AAD is an important target for treatment. • Agreement on the designs of the fixed and flexible-dose Phase 3 studies when targeting AAD, including: o Primary endpoint: measure of CMAI total score, and o Selection criteria: probable Alzheimer's dementia according to the NINCDS-ADRDA criteria and a score ≥ 4 on the agitation/aggression item of the NPI-NH.
Fast-track Designation Granted 16 Mar 2015	• Fast-track designation granted for brexpiprazole in AAD.
Type C Meeting – Study 283/284 results 21 Sep 2017	• Acknowledgment of 2 adequate and well-controlled studies to support AAD indication; however, only Study 283 was positive with 1 of the 2 doses tested to be statistically superior to placebo on the pre-specified primary endpoint. • The Division recommended that the Sponsor conduct a 12-week, 3-arm, fixed-dose, double-blind, placebo-controlled study and plan for one arm to include a higher dose than previously studied (e.g., 3 mg). Potential enrichment strategies were also discussed. • FDA also noted that drug performance in Study 283/284 was likely undercut by NPI inclusion criteria. Specifically, defining a NPI score of ≥ 4 as the minimum necessary for inclusion likely led to enrollment of a number of patients with no or very mild agitation. • FDA recommended the Sponsor review the International Psychogeriatric Association's provisional consensus definition of agitation and plan the inclusion criteria carefully to ensure enrolled participants exhibit sufficient agitation at baseline to demonstrate greater change over time for brexpiprazole versus placebo. Patients do not need to exhibit aggressive behavior to be suitable for enrollment.
Type C Meeting – Study 213 design 31 Jan 2018	• FDA agreed with the proposed criteria to have CMAI Factor 1 aggressive behavior at baseline. • Agreement to randomize 100 patients to receive brexpiprazole 3 mg/day. • Agreement to combine 2 and 3 mg/day doses of brexpiprazole into one treatment arm.
Pre-sNDA Meeting 23 Sep 2022	• FDA agreed that based on information submitted in the meeting briefing package and their background familiarity with the program that there was sufficient information to support a supplemental marketing application.

AAD=agitation associated with Alzheimer's dementia; CMAI=Cohen-Mansfield Agitation Inventory; FDA=Food and Drug Administration; IND=Investigational New Drug; NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NPI-NH=Neuropsychiatric Inventory-Nursing Home; sNDA=supplemental New Drug Application.

4.4 Brexpiprazole Clinical Development Program in Agitation Associated with Alzheimer's Dementia

The clinical development program designed to demonstrate the efficacy and safety of brexpiprazole for the treatment of AAD is comprised of 7 clinical studies (Table 6). Data from three phase 3 clinical studies and 1 active-treatment extension study in 1,048 patients with AAD are summarized in Sections 6 and 7. The primary data supporting brexpiprazole efficacy and safety comes from the pivotal fixed-dose Studies 283 and 213.

Table 6: Clinical Development Program Overview of Brexpiprazole in Patients with Agitation Associated with Alzheimer's Dementia

Study Name Study Number NCT Number Status	Study Design	Brexpiprazole Dose	Study Duration	Number of Patients Enrolled
Study 283 331-12-283 NCT01862640 Completed	Pivotal study Randomized, double-blind, fixed-dose, placebo-controlled	1 mg/day 2 mg/day[a]	12-weeks of treatment plus 30 days off treatment	433
Study 284 331-12-284 NCT01922258 Completed	Randomized, double-blind, flexible-dose, placebo-controlled	0.5–2 mg/day	12-weeks of treatment plus 30 days off treatment	270
Study 213 331-14-213 NCT03548584 Completed	Pivotal study Randomized, double-blind, fixed-dose, placebo-controlled	2 mg/day 3 mg/day	12-weeks of treatment plus 30 days off treatment, if not rolled over in Study 182	345
Study 182 331-201-00182 Extension Study NCT03594123 Completed	Active-treatment extension	2 mg/day 3 mg/day	12-weeks of treatment plus 30 days off treatment	259 (rollover from Study 213)

Study 211 331-13-211 Observational Rollover Study NCT02192554 Completed	Observational rollover	No brexpiprazole administered	2-month observation	450 (rollover from Study 283 and 284)
Study 88 331-102-00088 Japanese Study NCT03620981 Ongoing	Double-blind, fixed-dose, placebo-controlled,	1 mg/day 2 mg/day	10-weeks of treatment	407 (estimated)
Study 184 331-102-00184 Japanese Study NCT03724942 Ongoing	Open-label	1 mg/day 2 mg/day	14-weeks of treatment	164 (rollover from Study 88)

a. Study 283 originally included a brexpiprazole 0.5 mg/day treatment group that was removed based on analyses supporting that doses lower than 1 mg/day were unlikely to be efficacious. A total of 20 patients were randomized in the 0.5 mg arm.

5 CLINICAL PHARMACOLOGY

Summary

- Brexpiprazole has affinity (K_i) for multiple monoaminergic receptors, including serotonin 5-HT_{1A} (0.12 nM), 5-HT_{2A} (0.47 nM), 5-HT_{2B} (1.9 nM), 5-HT_7 (3.7 nM), dopamine D_2 (0.30 nM), D_3 (1.1 nM), and noradrenergic α_{1A} (3.8 nM), α_{1B} (0.17 nM), α_{1D} (2.6 nM), and α_{2C} (0.59 nM) receptors.
- Brexpiprazole acts as a partial agonist at the 5-HT_{1A} and D_2 receptors and as an antagonist at 5-HT_{2A}, α_{1B}, and α_{2C} receptors.
- Brexpiprazole can be administered with or without food.
- Brexpiprazole has a long terminal elimination half-life of approximately 91 hours.
- Brexpiprazole is mainly metabolized by CYP2D6 and CYP3A4 and its major metabolite (DM-3411) does not contribute to its pharmacological effects.
- The brexpiprazole formulation used in the AAD clinical studies is identical to commercially available brexpiprazole (REXULTI) in the US, EU, Canada, and Japan.

5.1 Pharmacokinetics

After single dose administration of brexpiprazole tablets, peak plasma brexpiprazole concentrations occur within 4 hours after administration, and the absolute oral bioavailability is 95%. Brexpiprazole steady-state concentrations are attained within 10–12 days of dosing. Administration of a 4 mg brexpiprazole tablet with a standard high-fat meal does not significantly affect brexpiprazole exposure (C_{max} or AUC); therefore, brexpiprazole can be administered with or without food. After single and multiple once daily administration, brexpiprazole exposure (C_{max} and AUC) increases in a dose-proportional manner. After multiple once-daily administration of brexpiprazole, the terminal elimination half-life for brexpiprazole is approximately 91 hours.

Based on in vitro and in vivo metabolism studies of brexpiprazole, metabolism of brexpiprazole is mainly mediated by CYP3A4 and CYP2D6. After single- and multiple-dose administrations, brexpiprazole and its major metabolite, DM-3411, are the predominant drug moieties in the systemic circulation. At steady-state, DM-3411 represents 23–48% of brexpiprazole exposure (AUC) in plasma. DM-3411 is considered not to contribute to the therapeutic effects of brexpiprazole. Based on in vitro data, brexpiprazole showed little to no inhibition of CYP450 isozymes.

In vitro studies of brexpiprazole do not indicate that brexpiprazole is a substrate of efflux transporters (e.g., MDRI [P-gp] and BCRP).

Age or sex do not appear to have clinically relevant effects on the pharmacokinetics (PK) of brexpiprazole. In a previously conducted population PK (popPK) analysis, age

was identified as a statistically significant covariate on apparent volume of distribution of the central compartment (Vc/F); the effects of age within the 5th and 95th percentiles (23 years and 61 years) of the population were −19% to +14% and not considered clinically relevant. An external validation of the previously submitted popPK model using data from Studies 283 and 284 identified no difference in the PK of patients with AAD.

5.2 Pharmacodynamics

Brexpiprazole has affinity (expressed as K_i) for multiple monoaminergic receptors, including serotonin 5-HT_{1A} (0.12 nM), 5-HT_{2A} (0.47 nM), 5-HT_{2B} (1.9 nM), 5-HT_7 (3.7 nM), dopamine D_2 (0.30 nM), D_3 (1.1 nM), and noradrenergic α_{1A} (3.8 nM), α_{1B} (0.17 nM), α_{1D} (2.6 nM), and α_{2C} (0.59 nM) receptors. Brexpiprazole also exhibits affinity for histamine H1 (19 nM) and muscarinic M1 receptors (67% inhibition at 10 µM). Brexpiprazole acts as a partial agonist at the 5-HT_{1A} and D_2 receptors and as an antagonist at 5-HT_{2A}, α_{1B} and α_{2C} receptors.

5.3 Dosing in Agitation Associated with Alzheimer's Dementia

The brexpiprazole formulation used in the AAD clinical studies is identical to that used in previous registrational brexpiprazole (REXULTI) clinical studies that supported approval for the treatment of adults with schizophrenia and, where applicable, MDD (US, EU, Canada, and Japan).

An exposure-response (E-R) analysis based on the data from fixed-dose Studies 283 and 213 supports the current dosing recommendations in the AAD patient population.

6 CLINICAL EFFICACY

Summary

- Studies 283 and 213 demonstrate 2 or 3 mg/day brexpiprazole treatment results in statistically and clinically meaningful improvements in key measures of agitation compared with placebo, with supportive data from Study 284.
  - Pivotal Study 213 results demonstrated statistically significant improvements across the primary endpoint of mean change in CMAI total score from baseline to Week 12 (p=0.0026) and key secondary endpoint mean change in CGI-S score as related to agitation from baseline to Week 12 (p=0.0078) in the pre-specified statistical hierarchy. Patients dosed to 2 or 3 mg/day attained meaningful reduction in the signs and symptoms of agitation.
  - Pivotal Study 283 demonstrated statistically significant and clinically meaningful improvement for brexpiprazole 2 mg/day dose relative to placebo on the primary endpoint of CMAI total score (p=0.0404); along with numerical improvement in CGI-S compared to placebo, although the difference did not reach statistical significance (p=0.1566).
  - Study 284 did not achieve statistical superiority when using a flexible brexpiprazole 0.5–2 mg/day dosing schedule (mean daily dose: 1.54 mg; p=0.1454) relative to placebo in the primary efficacy endpoint of mean change in CMAI total score from baseline to Week 12; but did show improvement over placebo for the CGI-S (nominal p=0.0164).
  - In Study 284, post-hoc analyses of a subgroup of patients who were up-titrated to 2 mg/day brexpiprazole at Week 4 demonstrated higher numerical improvements in mean changes from baseline to Week 12 for the primary and key secondary efficacy endpoints in the brexpiprazole group compared with placebo, further supporting 2 mg/day as the minimum effective dose.
  - Furthermore, results from post-hoc analyses from Studies 283 and 284 determined that a subset of patients enrolled in these 2 studies who exhibited a higher level of baseline agitation showed a better treatment difference with separation from placebo on CMAI total and CGI-S scores.

6.1 Fixed-Dose Study 283 and Flexible-Dose Study 284

6.1.1 Study Designs

Studies 283 and 284 were designed based on feedback from FDA and were conducted concurrently. Both studies were Phase 3, 12-week, multicenter, randomized, double-

blind, placebo-controlled studies designed to assess the efficacy, safety, and tolerability of brexpiprazole in the treatment of patients with AAD. The design of Study 283 and Study 284 were similar with common primary and secondary endpoints and patient eligibility criteria with the exception that Study 283 was a fixed-dose design with 3 arms (brexpiprazole 1 mg/day, 2 mg/day, and placebo; 1:1:1) while Study 284 consisted of a flexible-dose group (0.5–2 mg/day) and a placebo group (1:1; Figure 1). Both studies utilized the same primary and key secondary efficacy endpoints: change from baseline to Week 12 in the CMAI total score and mean change from baseline to Week 12 on CGI-S score as related to agitation, respectively.Both studies consisted of a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment safety follow-up period.

Study 283 originally included a brexpiprazole 0.5 mg/day treatment group that was removed based on completed studies in other indications and recent pharmacokinetic data in patients aged ≥ 65 years, supporting that doses < 1 mg/day were unlikely to be efficacious.

6.1.1.1 Key Enrollment Criteria

Patients in Study 283 were enrolled at 81 study centers in Croatia, Germany, Serbia, Spain, Russia, Ukraine, and the US. Patients in Study 284 were enrolled at 62 study centers in Bulgaria, Canada, Finland, France, Russia, Slovenia, Ukraine, United Kingdom, and the US. Key enrollment criteria for Studies 283 and 284 were identical and included:

- ≥ 55 and ≤ 90 years of age,
- Living in either an institutionalized (residential) or in a non-institutionalized (community) setting where the patient was not living alone,
- Diagnosis of probable Alzheimer's disease according to the NINCDS-ADRDA criteria and an MRI or CT scan with findings consistent with a diagnosis of Alzheimer's disease, and with an onset of symptoms of agitation at least 2 weeks prior to the screening visit,
- At the screening and baseline visits, patients must have had an MMSE score of ≥ 5 and ≤ 22, and
- A total score (frequency x severity) of ≥ 4 on the agitation/aggression item of the NPI-NH for institutionalized patients or the NPI/NPI-NH for non-institutionalized patients.

Patients were ineligible if they had dementia or other memory impairment not due to Alzheimer's disease, such as mixed or vascular dementia, dementia with Lewy bodies, Parkinson's disease dementia, frontotemporal dementia, substance-induced dementia, HIV-dementia, traumatic brain injury, normal pressure hydrocephalus, or any other specific non-Alzheimer's-type dementia.

For Studies 283 and 284, a full list of eligibility criteria is provided in Appendix 11.1.1.

6.1.1.2 Endpoint Definitions

The primary efficacy endpoint for Studies 283 and 284 was the change from baseline to Week 12 in the CMAI total score.

The key secondary endpoint for both studies was change from baseline to Week 12 in the CGI-S score as related to agitation.

Other secondary endpoints included:

- Change from baseline to Week 12 in CMAI subscale scores (aggressive behavior, physically nonaggressive behavior, and verbally agitated behavior),
- Change from baseline to Week 12 in NPI-NH
    - 12-item total score, and
    - Agitation/aggression (AA) score, and
- Clinical Global Impression-Improvement (CGI-I) score as related to agitation at Week 12.

Exploratory endpoints included change from baseline in CMAI total score for every scheduled study visit in the double-blind treatment period other than the Week 12 visit and CMAI response rate at every scheduled study visit in the double-blind treatment period, where response was defined as ≥ 40%, ≥ 30%, and ≥ 20% reduction in CMAI total score from baseline.

6.1.1.2.1 Cohen-Mansfield Agitation Inventory Scale

The CMAI is a well-established rating questionnaire to assess the frequency of agitated behaviors in elderly persons. The CMAI consists of 29 items all rated on a frequency scale of 1–7 with 1 being the most favorable rating (representing a frequency of 'never') and 7 being the worst rating (representing a frequency of 'several times an hour'). Ratings pertain to the 2 weeks preceding the administration of the CMAI (i.e., 2-week recall period). The CMAI total score is a sum of the scores on all 29 items at the time of the assessment; therefore, the range of possible total scores for each timepoint is ≥ 29 and ≤ 203 (i.e., 7 x 29 = 203). A higher CMAI score represents more frequent agitated behaviors.

The individual items are further categorized to capture specific domains of agitated behaviors (Cohen-Mansfield 1991; Cohen-Mansfield et al 1989). An examination of the instrument factor structure suggests 3 key CMAI subscale domains or factors (Rabinowitz et al 2005):

- Aggressive behaviors (i.e., Factor 1; includes 12 behaviors),
- Physically non-aggressive behaviors (i.e., Factor 2; includes 6 behaviors), and
- Verbally agitated behaviors (i.e., Factor 3; includes 4 behaviors).

The primary CMAI factor compositions, definitions, and corresponding scores are provided in Appendix 11.2.

Cohen-Mansfield Agitation Inventory Scale Validation

The CMAI is well-established and commonly used in clinical studies to assess the frequency of agitated behaviors in elderly persons (Cohen-Mansfield et al 1989; Cohen-Mansfield 1995). The CMAI was administered as a Clinician Reported Outcome where interviews were conducted with the caregiver of the patient with AAD by a qualified and certified clinician.

6.1.1.2.2 Clinical Global Impression-Severity of Illness Scale

The severity of agitation for each patient was rated using the CGI-S (Guy 1976). The CGI-S scale is a well-recognized scale and used across multiple psychiatric disorders to rate the general severity of symptoms and improvements during clinical studies. To perform this assessment, the Investigator (or Designee) answered the following question: “Considering your total clinical experience with this particular population, how mentally ill (as related to agitation) is the patient at this time?” The CGI-S is a 7-point scale from 1–7. Response choices were 0=not assessed; 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; and 7=among the most extremely ill patients.

6.1.1.2.3 Clinical Global Impression Improvement Scale

The efficacy of brexpiprazole in the treatment of agitation was rated for each patient using the CGI-I (Guy 1976). The Investigator (or Designee) rated the patient’s total improvement based on the following question: “Rate total improvement (as related to agitation) whether or not it is due entirely to drug treatment. Compared to his/her condition at baseline, how much has the patient changed?”. This is also a 7-point scale (1–7), where the response choices were 0=not assessed, 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse.

6.1.1.2.4 Neuro-Psychiatric Inventory

The NPI was developed to assess specific behavioral disturbances occurring in dementia patients (Cummings et al 2015). The NPI consists of 12 items and the NPI total score is calculated by adding the individual 12-item scores (possible total scores range: 0–144). For each item, there is a screening question to determine if the behavioral disturbance is present (rated 1) or absent (rated 0). For each present item frequency (score 1–4) and severity (score 1–3) were assessed and the item score calculated by multiplying the 2 scores (ranging 1–12). In addition, the caregiver distress (NPI/NPI-NH) or occupational disruptiveness (NPI-NH) is rated as a separate score (0–5). For all items, low scores are better than high scores. Two different versions of NPI, the NPI/NPI-NH, (not institutionalized) and NPI-NH (institutionalized), were administered depending on where the patient was living. The items are identical between the 2 versions, but the information on agitated behaviors is provided by caregivers for non-institutionalized patients and by professional staff for institutionalized patients.

6.1.1.3 Data Sets Analyzed

The following datasets were defined in Studies 283 and 284:

Sample	Definition
Randomized	The Randomized Sample included all patients who were randomized into the study.
Safety	The Safety Sample included all patients who were administered ≥ 1 dose of brexpiprazole or placebo.
Efficacy	The Efficacy Sample included all patients in the randomized sample who took ≥ 1 dose of brexpiprazole or placebo and had a baseline and ≥ 1 post-baseline evaluation for the CMAI total score. All efficacy analyses were performed on the Efficacy Sample.

CMAI=Cohen-Mansfield Agitation Inventory.

6.1.1.4 Statistical Analyses

6.1.1.4.1 Primary and Secondary Efficacy Analyses

The primary efficacy endpoint mean change from baseline in CMAI total score was analyzed using a restricted maximum likelihood (REML)-based repeated measures approach. Under the assumption of Missing at Random (MAR), the analysis was performed by fitting the mixed-effect model repeated measure (MMRM) model with an unstructured (UN) variance-covariance structure in which the change from the baseline in CMAI total score (Week 2, 4, 6, 8, 10,12) was the dependent variable based on the observed cases (OC) data.

The key secondary efficacy endpoint and all continuous secondary endpoints (CGI-S and CMAI factor scores) were analyzed by fitting the same MMRM model as described for the primary analysis. Response rates were analyzed by the Cochran–Mantel–Haenszel (CMH) General Association Test controlling for study center in last observation carried forward (LOCF) analysis.

In both Studies 283 and 284, a hierarchical testing procedure was used to maintain the type I error at 0.05 for the analysis of the key secondary efficacy variable (CGI-S score as related to agitation). In addition, Study 283 also included a hierarchical testing procedure for comparison of the 2 mg dose vs placebo before the 1 mg dose vs placebo comparison.

6.1.1.4.2 Subgroup Analyses

The same MMRM model was used as for the primary efficacy analysis with the addition of terms for subgroup-by-week and treatment by-subgroup-by-week. All subgroup analyses were conducted using the same MMRM analysis as for the primary efficacy analysis except that the fixed class-effect terms for study center were not included in the model.

6.1.1.4.3 Handling of Missing Data

As sensitivity analyses for MAR assumption, analyses for Missing Not at Random (MNAR) will be carried out. Pattern Mixture Models (PMM) based on Multiple Imputation

(MI) with mixed missing data mechanisms will be used to investigate the response profile of dropout patients by last dropout reason under MNAR mechanism for the following three scenarios:

- Dropout reasons due to AE as MNAR,
- Dropout reasons due to either AE or patient withdrew consent as MNAR, and
- All dropouts as MNAR.

6.1.1.4.4 Supplementary Analyses When Applying Enrollment Criteria That Enriched for Agitation

Post-hoc analyses on primary and key secondary efficacy endpoints were conducted using the same MMRM model described in the primary efficacy analysis for the Efficacy Sample based on the Enriched Population. The subgroup of enriched patients consisted of patients who met the criteria for CMAI Factor 1 at baseline.

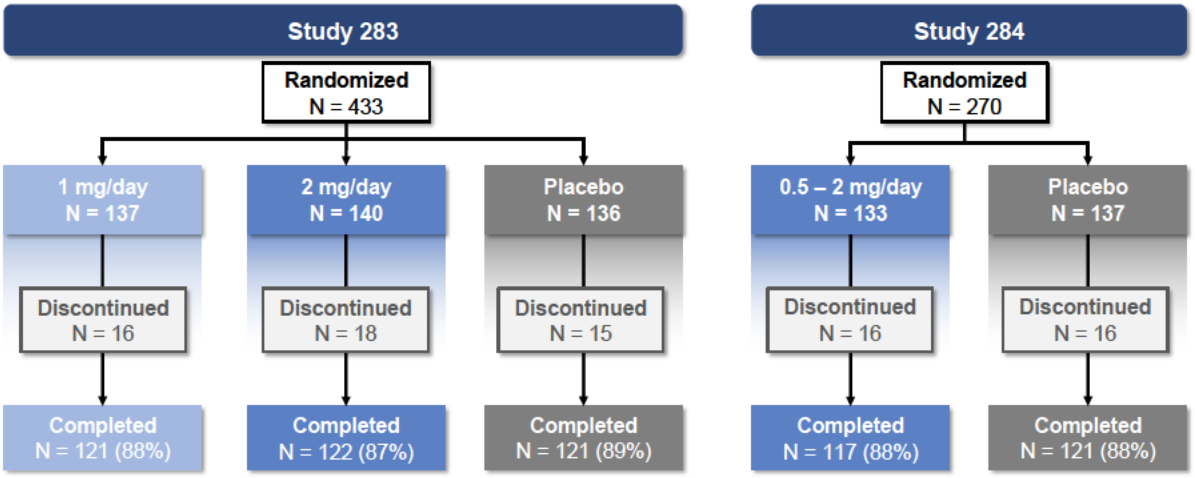
6.1.2 Patient Disposition and Baseline Characteristics

6.1.2.1 Disposition

In Study 283, a total of 433 patients were randomized (1:1:1:1) to either brexpiprazole (0.5 mg/day, 1 mg/day, or 2 mg/day) or placebo (Figure 12). In Study 284, a total of 270 patients were randomized (1:1) to either the brexpiprazole group (0.5–2 mg/day) or placebo. Completion rates among patients in Study 283 and Study 284 ranged from 87–89% across all treatment groups, with the exception of the 0.5 mg/day group in Study 283, which was terminated early.

In both studies, the 2 most frequently reported reasons for discontinuation from any treatment arm were AEs (4.3–7.3%) and withdrawal of consent by the patient (approximately 4%). In Study 283, all other reasons for discontinuation were reported at an incidence of ≤ 1.2% in all treatment groups. Similar results were observed in Study 284, except for reasons for patient discontinuation in the placebo group: patients meeting withdrawal criteria and withdrawn from participation by the Investigator (2.9%; n=4, each).

Figure 12: Studies 283 and 284: Patient Disposition (Randomized Sample)



Note: Patients randomized to the 0.5 mg/day brexpiprazole group (N=20) in Study 283 were excluded from the efficacy analyses presented; data are however included for demographics and extent of exposure to be inclusive of the total population prior to protocol amendment 3.

6.1.2.2 Baseline Demographics

Key baseline demographics were similar and generally well balanced across Studies 283 and 284 and between brexpiprazole and placebo groups for each study (Table 7). The mean age of patients was 74 years, and the majority of patients were female and white.

Across both studies, approximately 3–4% of patients were Black or African-American, but Black or African-American patients constituted approximately 8–11% of the US study population, which is consistent with the proportion of Black and African-Americans with AD in the US (Peroutka 2023).

Table 7: Studies 283 and 284: Baseline Demographics (Randomized Sample)

Characteristic	Study 283				Study 284	
	Brexpiprazole				Brexpiprazole	
	0.5 mg (N=20)	1 mg (N=137)	2 mg (N=140)	Placebo (N=136)	0.5–2 mg (N=133)	Placebo (N=137)
Age (years), mean (SD)	73.9 (9.1)	73.8 (8.8)	73.7 (8.1)	74.1 (8.0)	73.5 (8.5)	74.0 (7.8)
Age group, n (%)						
< 65	5 (25.0)	24 (17.5)	22 (15.7)	21 (15.4)	24 (18.0)	19 (13.9)
≥ 65 and < 75	4 (20.0)	35 (25.5)	48 (34.3)	41 (30.1)	46 (34.6)	49 (35.8)
≥ 75	11 (55.0)	78 (56.9)	70 (50.0)	74 (54.4)	63 (47.4)	69 (50.4)
Female, n (%)	12 (60.0)	78 (56.9)	79 (56.4)	70 (51.5)	82 (61.7)	88 (64.2)
Race, n (%)						
White	20 (100)	134 (97.8)	133 (95.0)	130 (95.6)	128 (96.2)	129 (94.2)
Black/African -American	0	2 (1.5)	5 (3.6)	5 (3.7)	4 (3.0)	5 (3.6)
Asian	0	1 (0.7)	2 (1.4)	1 (0.7)	0	3 (2.2)
Other	0	0	0	0	1 (0.8)	0
Hispanic or Latino, n (%)	1 (5.0)	24 (17.5)	23 (16.4)	23 (16.9)	6 (4.5)	9 (6.6)

6.1.2.3 Baseline Disease Characteristics

Across both studies, the distribution of baseline disease characteristics was similar across all treatment groups in the Randomized Sample (Table 8). The mean time since onset of the first episode of AAD was similar between Study 283 (excluding the 0.5 mg group) and Study 284. The majority of patients had mild/moderate dementia at baseline based on MMSE score > 12. Less than 31% of patients across all treatment groups were identified as having psychotic symptoms at baseline.

Table 8: Studies 283 and 284: Baseline Disease Characteristics (Randomized Sample)

Parameter	Study 283			Study 284	
	Brexpiprazole			Brexpiprazole	
	1 mg (N=137)	2 mg (N=140)	Placebo (N=136)	0.5–2mg (N=133)	Placebo (N=137)
CMAI total score, mean (SD)	70.7 (15.8)	71.0 (16.5)	72.0 (17.7)	71.4 (16.7)	68.5 (15.9)
CGI severity score, mean (SD)	4.5 (0.6)	4.5 (0.7)	4.5 (0.7)	4.5 (0.8)	4.5 (0.7)
Dementia severity (MMSE), n (%)					
Mild (>18)	7 (5.1)	11 (7.9)	19 (14.0)	28 (21.1)	34 (24.8)
Moderate (13–18)	76 (55.5)	87 (62.1)	74 (54.4)	64 (48.1)	65 (47.4)
Severe (≤12)	54 (39.4)	42 (30.0)	43 (31.6)	41 (30.8)	38 (27.7)
Baseline psychosis status, n (%)					
≤ 4 Absent[a]	104 (75.9)	97 (69.3)	100 (73.5)	101 (75.9)	108 (78.8)
≥ 4 Present	33 (24.1)	43 (30.7)	36 (26.5)	32 (24.1)	29 (21.2)
Institutionalized, n (%)	89 (65.0)	86 (61.4)	88 (64.7)	73 (54.9)	75 (54.7)
Time since diagnosis of AD, (months), mean (SD)	36.7 (40.7)	31.3 (30.4)	32.3 (35.9)	28.2 (28.3)	32.1 (27.2)
Time since onset of first episode of AAD, (months), mean (SD)	18.3 (21.5)	21.5 (24.7)	19.5 (20.6)	19.7 (23.4)	17.5 (19.8)
Time since onset of current agitation episode (months), mean	7.0 (17.9)	9.3 (22.5)	4.7 (6.3)	5.2 (16.5)	4.5 (7.1)

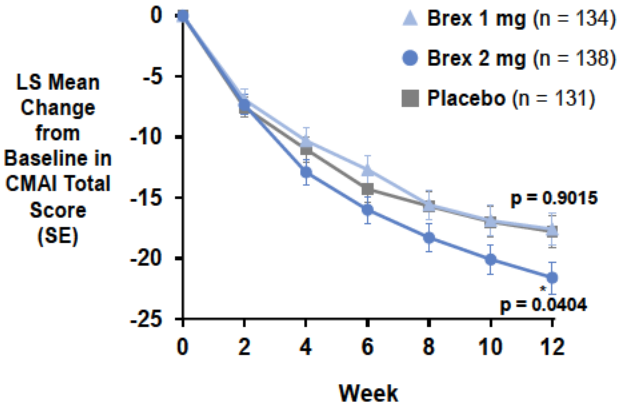
a. Defined as the absence of any ≥ 4 values, as in the absence of psychosis symptoms.
AD=Alzheimer's Dementia; AAD=Agitation associated with Alzheimer's Dementia; CGI=Clinical Global Impression; CMAI=Cohen-Mansfield Agitation Inventory; MMSE=Mini-Mental State Examination.

6.1.3 Efficacy Results of Pivotal Fixed-Dose Study 283

6.1.3.1 Primary Endpoint Results – Change from Baseline to Week 12 in CMAI Total Score

The brexpiprazole 2 mg/day group met the primary efficacy endpoint, demonstrating a statistically significant improvement from baseline in CMAI total score compared with placebo at Week 12 (LSMD=−3.77 [95% CI: −7.38, −0.17], p=0.0404; Figure 13). No improvement vs placebo was found for the brexpiprazole 1 mg/day group (LSMD=0.23 [95% CI: −3.40, 3.86], p=0.9015).

Figure 13: Study 283: Change from Baseline in CMAI Total Score After 12 Weeks of Treatment (Efficacy Sample)



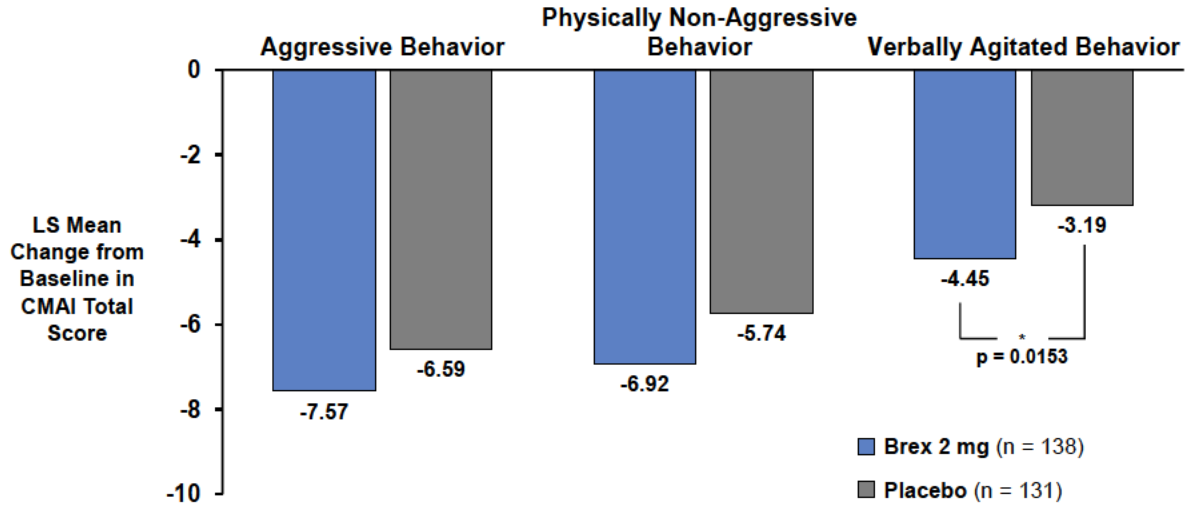
	Brexpiprazole 1mg N = 134	Brexpiprazole 2mg N = 138	Placebo N = 131
CMAI Total score at baseline (Mean [SD])	70.5 (16.0)	70.1 (16.6)	72.2 (17.9)
Mean Change in CMAI Total score at Week 12 (LS Mean [SE])	-17.6 (1.33)	-21.6 (1.32)	-17.8 (1.34)
Treatment Difference vs Placebo at Week 12 (95% CI)	0.23 (-3.40, 3.86) p = 0.9015	-3.77 (-7.38, -0.17) p = 0.0404	---

*p < 0.05 vs placebo; MMRM.
Note: Error bars are LS Mean ± standard error.
Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory; MMRM=mixed-effect model repeated measure.

6.1.3.1.1 Change in CMAI by Factor

As a pre-specified secondary efficacy endpoint, mean change in factor scores from baseline for 3 distinct agitation syndromes of aggressive behavior based on the CMAI Factor scores (1=aggressive behavior; 2=physically nonaggressive behavior; 3=verbally agitated behavior) were compared between each brexpiprazole dose group and placebo at Week 12 (Figure 14). There were consistent directional improvements observed across all 3 CMAI subscale domains with brexpiprazole 2 mg/day vs placebo.

Figure 14: Study 283: Subscale Analysis of Change in CMAI Total Score from Baseline to Week 12 (Efficacy Sample)

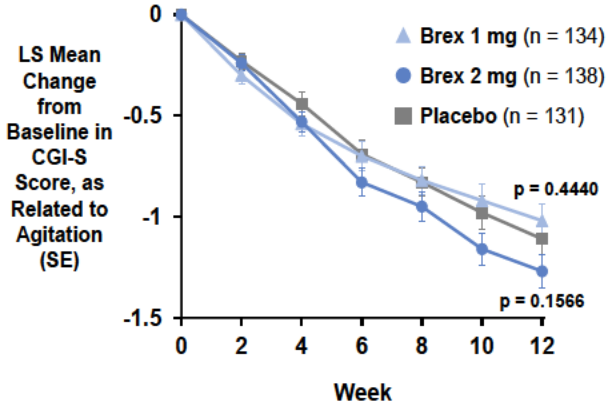


*p < 0.05 vs placebo; nominal p-values presented; MMRM.
*Nominal p-values were not adjusted for multiple comparisons.
Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory; MMRM=mixed-effect model repeated measure.

6.1.3.2 Key Secondary Endpoint Results – Change from Baseline to Week 12 in CGI-S Score as Related to Agitation

The brexpiprazole 2 mg/day group showed a numerically greater improvement in the mean change in CGI-S score as related to agitation from baseline to Week 12 compared with placebo that did not meet statistical significance (LSMD=−0.16 [95% CI: −0.39, 0.06], p=0.1566; Figure 15). No treatment difference was observed between brexpiprazole 1 mg/day group and the placebo group (LSMD=0.09 [95% CI: −0.14, 0.32], p=0.4440).

Figure 15: Study 283: Change from Baseline in CGI-S Score as Related to Agitation After 12 Weeks of Treatment (Efficacy Sample)



	Brexpiprazole 1mg N = 134	Brexpiprazole 2mg N = 138	Placebo N = 131
CGI-S Total score at baseline (Mean [SD])	4.53 (0.62)	4.51 (0.70)	4.50 (0.66)
Mean Change in CGI-S score at Week 12 (LS Mean [SE])	-1.02 (0.08)	-1.27 (0.08)	-1.11 (0.08)
Treatment Difference vs Placebo at Week 12 (95% CI)	0.09 (-0.14, 0.32) p = 0.4440	-0.16 (-0.39, 0.06) p = 0.1566	---

Brex=brexpiprazole; CGI-S=Clinical Global Impression-Severity of Illness scale; MMRM=mixed-effect model repeated measure.
Note: Error bars are LS Mean ± standard error.

6.1.3.3 *Secondary Endpoint Results – Change from Baseline to Week 12 in NPI-NH Total Score*

The brexpiprazole 2 mg/day group showed an improvement in the mean change in NPI-NH 12-item total score from baseline to Week 12, compared with the placebo group (LSMD=−1.77 [95% CI: −4.99, 1.45]). There was no meaningful improvement with brexpiprazole 1 mg/day compared with placebo (LSMD=−0.25 [95% CI: −3.48, 2.98]).

6.1.3.4 *Secondary Endpoint Results – Change from Baseline to Week 12 in NPI-NH AA Score*

The brexpiprazole 2 mg/day group showed an improvement in the secondary efficacy endpoint, the mean change in the NPI-NH AA score from baseline to Week 12, compared with the placebo group (LSMD=−0.55 [95% CI: −1.25, 0.15]). No appreciable treatment difference was shown between brexpiprazole 1 mg/day and placebo (LSMD=−0.10 [95% CI: −0.80, 0.60]).

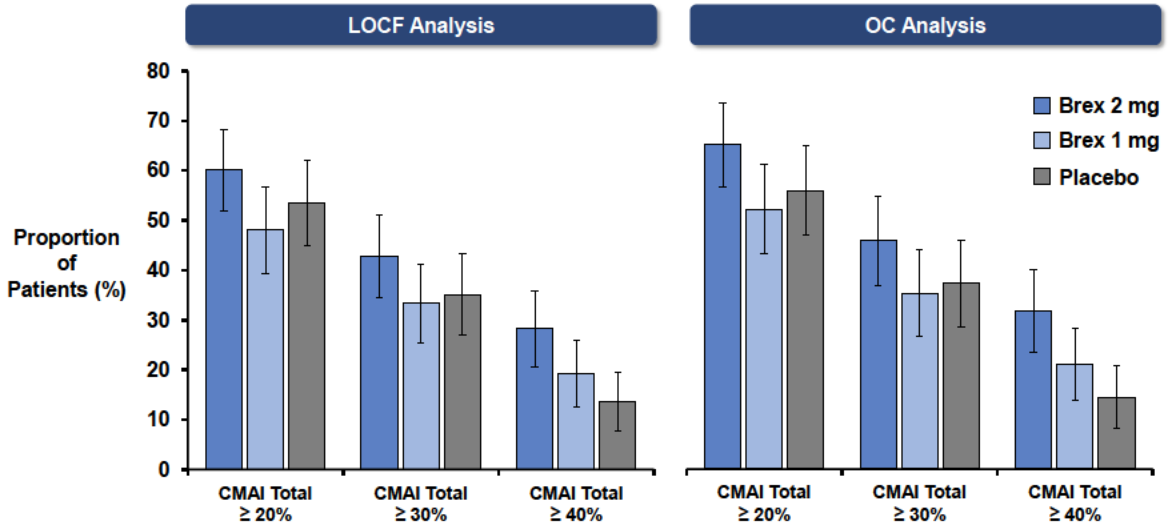
6.1.3.5 *Secondary Endpoint Results – Change from Baseline to Week 12 in CGI-I Score as Related to Agitation*

The brexpiprazole 2 mg/day group showed an improvement in the secondary efficacy endpoint, the mean CGI-I score at Week 12, compared with the placebo group (LSMD=−0.21 [95% CI: −0.49, 0.06]). No appreciable difference was shown between brexpiprazole 1 mg/day and placebo (LSMD=0.05 [95% CI: −0.24, 0.33]).

6.1.3.6 *Exploratory Endpoint Results – CMAI Response Rate After 12 Weeks of Treatment*

The proportion of responders was numerically higher for brexpiprazole 2 mg/day compared to placebo for ≥ 40% reduction in CMAI total score at Week 12 in both the LOCF and OC analyses (Figure 16).

Figure 16: Study 283: Proportion of Patients with CMAI Reductions (Efficacy Sample)



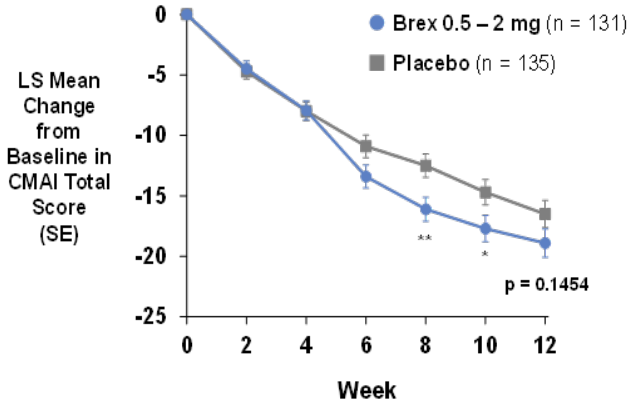
Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory.
Note: Last observation carried forward (LOCF) and observed cases (OC) method was used for missing data imputation.

6.1.4 *Efficacy Results of Flexible-Dose Study 284*

6.1.4.1 *Primary Endpoint Results – Change from Baseline to Week 12 in CMAI Total Score*

The brexpiprazole 0.5–2 mg/day group did not achieve statistical superiority relative to placebo in the primary efficacy endpoint, the mean change in CMAI total score from baseline to Week 12 (−2.34 [95% CI: −5.49, 0.82], p=0.1454; Figure 17).

Figure 17: Study 284: Change from Baseline in CMAI Total Score After 12 Weeks of Treatment (Efficacy Sample)



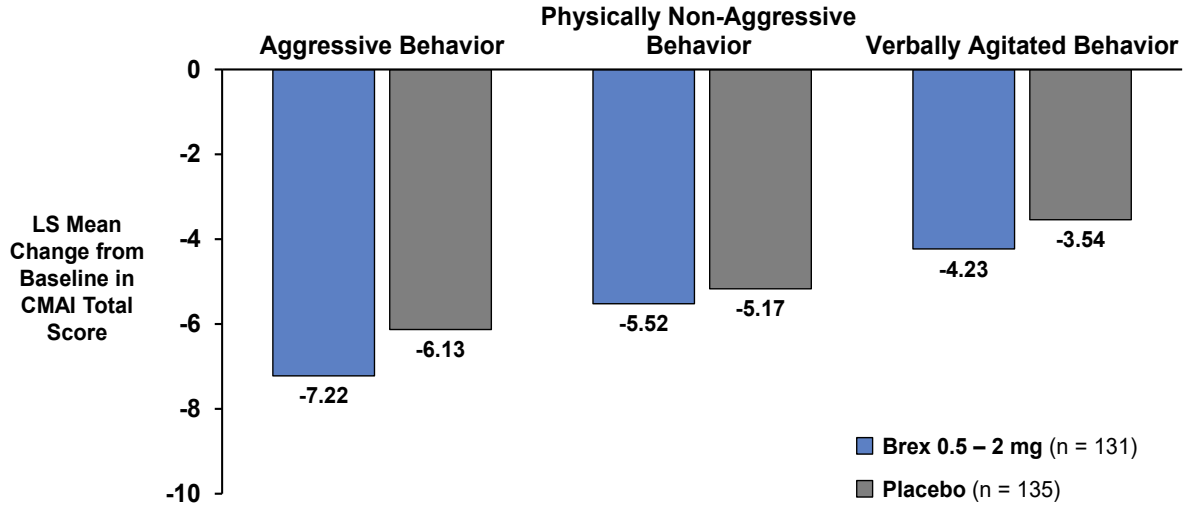
	Brexpiprazole N = 131	Placebo N = 135
CMAI Total score at baseline (Mean [SD])	71.5 (16.8)	68.6 (16.0)
Mean Change in CMAI Total score at Week 12 (LS Mean [SE])	-18.9 (1.17)	-16.5 (1.13)
Treatment Difference at Week 12 (95% CI)	-2.34 (-5.49, 0.82) p = 0.1454	

*p < 0.05 vs placebo, **p<0.001 vs placebo; MMRM.
Note: Error bars are LS Mean ± standard error.
Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory; MMRM=mixed-effect model repeated measure.

6.1.4.1.1 Change in CMAI by Factor

As a pre-specified secondary efficacy endpoint, mean change in factor scores from baseline for 3 distinct agitation syndromes of aggressive behavior based on the CMAI Factor scores (1=aggressive behavior; 2=physically nonaggressive behavior; 3=verbally agitated behavior) were compared between brexpiprazole and placebo at Week 12 (Figure 18). Numerically greater improvements in mean changes from baseline to Week 12 for all 3 CMAI Factor scores were shown in the brexpiprazole group compared with the placebo group.

Figure 18: Study 284: Subscale Analysis of Change in CMAI Total Score from Baseline to Week 12 (Efficacy Sample)

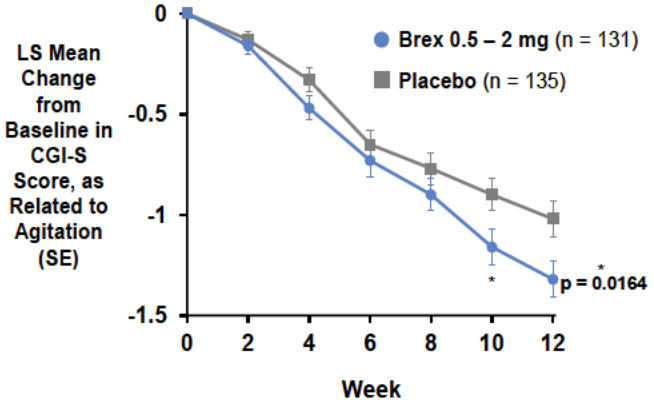


Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory; MMRM=mixed-effect model repeated measure.

6.1.4.2 *Key Secondary Endpoint Results – Change from Baseline to Week 12 in the CGI-S Score as Related to Agitation*

The brexpiprazole 0.5–2 mg/day group showed an improvement in CGI-S as related to symptoms of agitation, with a −0.31-point improvement (95% CI: −0.55, −0.06, nominal p=0.0164) over placebo (Figure 19).

Figure 19: Study 284: Change from Baseline in CGI-S Score as Related to Agitation After 12 Weeks of Treatment (Efficacy Sample)



	Brexpiprazole N = 131	Placebo N = 135
CGI-S score at baseline (Mean [SD])	4.54 (0.77)	4.51 (0.74)
Mean Change in CGI-S score at Week 12 (LS Mean [SE])	-1.32 (0.09)	-1.02 (0.09)
Treatment Difference at Week 12 (95% CI)	-0.31 (-0.55, -0.06) p = 0.0164	

*p < 0.05 vs placebo; MMRM.
*Nominal p-values were not adjusted for multiple comparisons.
Note: Error bars are LS Mean ± standard error.
Brex=brexpiprazole; CGI-S=Clinical Global Impression-Severity of Illness scale; MMRM=mixed-effect model repeated measure.

6.1.4.3 *Post-Hoc Analysis of Study 284: Change from Baseline to Week 12 in CMAI Total Score in Patients Up-Titrated to 2 mg/day*

As the results from the pivotal fixed-dose Study 283 demonstrated the minimum effective dose of brexpiprazole is 2 mg/day, a post-hoc analysis was carried out for patients who were up-titrated to 2 mg/day at Week 4 in Study 284. At the Week 4 visit, Investigators were instructed to evaluate patients based on response and tolerability to the blinded treatment. If the Investigator determined the patient had an inadequate response and was tolerating the treatment, the dose could be increased to 2 mg/day.

At the Week 4 visit, 77 patients in the brexpiprazole group and 74 patients in the placebo group had their dose increased from 1 mg/day to 2 mg/day or corresponding placebo. At Week 12, a greater improvement in mean change in CMAI total score from baseline was demonstrated with brexpiprazole over placebo in the up-titrated subgroup (LSMD=−5.06 [95% CI: −8.99, −1.13], nominal p=0.0121; Table 9). No improvement was observed with brexpiprazole over placebo in the subgroup that did not implement an increase in dose at Week 4 visit (nominal p=0.5506). While post-hoc in nature, these data further support 2 mg/day brexpiprazole as the minimum effective dose.

Table 9: Study 284: Change from Baseline in CMAI Total Score After 12 Weeks of Treatment in Patients Up-Titrated to 2 mg/day (Efficacy Sample)

		Baseline	Week 4		Change from Baseline at Week 12	Treatment Difference Versus Placebo		
Study Treatment Group	N	Mean (SD)	Mean (SD)	Mean Change from Baseline at Week 4	LS Mean (SE)	LS Mean Difference	95% CI	Nominal P-Value*
Dose increase at Week 4								
Brexpiprazole 0.5–2 mg	77	69.19 (15.42)	63.29 (14.97)	-5.91	-17.8 (1.42)	-5.06	(-8.99, -1.13)	0.0121
Placebo	74	68.32 (16.16)	63.51 (15.95)	-4.81	-12.8 (1.42)	-		
No dose increase at Week 4								
Brexpiprazole 0.5–2 mg	50	74.76 (18.12)	64.16 (14.56)	-10.6	-19.3 (1.96)	1.57	(-3.64, 6.78)	0.5506
Placebo	60	69.03 (16.07)	58.62 (14.00)	-10.4	-20.8 (1.78)	-		

*Nominal p-values were not adjusted for multiple comparisons.
Note: Model terms for MMRM method included treatment, pool center, visit, treatment by visit, and baseline by visit interaction.
CMAI=Cohen-Mansfield Agitation Inventory; MMRM=mixed-effect model repeated measure.

6.1.5 Post-Hoc Analyses of Studies 283 and 284 When Applying Enrollment Criteria That Enriched For Agitation

In Studies 283 and 284, defining an agitated patient population based primarily on a NPI agitation/aggression item score of ≥ 4 likely led to enrollment of some patients with insufficient agitation behaviors at baseline to show measurable change over 12 weeks.

Post-hoc analyses from both studies were performed on the primary and key secondary efficacy endpoints for patients who met criteria for being positive for CMAI Factor 1 (Appendix 11.2) at baseline, which included 86% and 84% of all randomized patients for Studies 283 and 284, respectively. Notable differences in the number and frequency of agitation behaviors as assessed by mean CMAI total scores at baseline were observed in patients from Study 283 and Study 284 who met criteria for CMAI Factor 1 (73.4 and 72.3, respectively) vs patients who did not meet this criterion (14% and 16% of all randomized patients, respectively, with baseline mean CMAI total scores of 56.4 and 56.5, respectively), suggesting that patients that meet CMAI Factor 1 criteria had sufficient frequency of baseline agitation symptoms to discern change within the confines of a 12-week clinical study.

6.1.5.1 *Change from Baseline to Week 12 in CMAI Total Score When Applying Enrollment Criteria That Enriched for Agitation*

In both studies, post-hoc analyses were conducted to evaluate the treatment effect of brexpiprazole in patients who met the criteria for CMAI Factor 1 at baseline.

For this subgroup enriched for CMAI Factor 1 in Study 283, the treatment difference with brexpiprazole 2 mg/day was more favorable than placebo (LSMD=−5.35 [95% CI: −9.19, −1.50], nominal p=0.0066) for the pre-specified primary efficacy endpoint, mean change in CMAI total score from baseline at Week 12 (Table 10). The LSMD for brexpiprazole 2 mg/day over placebo in this subgroup was also larger than observed in the full Efficacy Sample (Figure 13), providing further support for the efficacy of brexpiprazole 2 mg/day for the treatment of AAD. In Study 284, these results were numerically improved in the 0.5−2 mg/day subgroup enriched for CMAI Factor 1 (LSMD=−4.04 [95% CI: −7.58, −0.50], nominal p=0.0255; Table 10) and were more pronounced than the results from the full Efficacy Sample (Figure 17), further supporting brexpiprazole for the treatment of AAD.

Table 10: Studies 283 and 284 Post-Hoc Analyses: Change from Baseline in CMAI Total Score After 12 Weeks of Treatment When Applying Enrollment Criteria That Enriched for Agitation

		Baseline	Change from Baseline at Week 12	Treatment Difference Versus Placebo		
Study Treatment Group	**N**	**Mean (SD)**	**LS Mean (SE)**	**LSMD**	**95% CI**	**Nominal P-Value***
Study 283						
Brexpiprazole 1 mg	110	73.00 (15.97)	-19.2 (1.49)	0.22	(-3.76, 4.19)	0.9134
Brexpiprazole 2 mg	125	72.61 (16.11)	-24.8 (1.38)	-5.35	(-9.19, -1.50)	0.0066
Placebo	111	75.16 (17.08)	-19.5 (1.46)			
Study 284						
Brexpiprazole 0.5 – 2 mg	112	74.03 (16.43)	-22.6 (1.32)	-4.04	(-7.58, -0.50)	0.0255
Placebo	114	70.83 (15.62)	-18.6 (1.28)	-		

*Nominal p-values were not adjusted for multiple comparisons.
CMAI=Cohen-Mansfield Agitation Inventory.

6.1.5.2 *Change from Baseline to Week 12 in CGI-S Score as Related to Agitation When Applying Enrollment Criteria That Enriched for Agitation*

In Study 283, the key secondary endpoint of change from baseline at Week 12 in the CGI-S score as related to agitation, brexpiprazole 2 mg/day in the subgroup enriched for CMAI Factor 1 achieved −0.25 points improvement over placebo (95% CI: −0.49,

−0.01; nominal p=0.0445; Table 11). In Study 284, brexpiprazole 0.5–2 mg/day group CGI-S score as related to agitation, were numerically improved compared with placebo in the CMAI Factor 1 subgroup (LSMD=−0.43 [95% CI: −0.69, −0.22], nominal p=0.0017; Table 11). In both studies, this improvement was more pronounced in the enriched subgroup than that seen for the full Efficacy Sample (Figure 15 and Figure 19).

Table 11: Studies 283 and 284 Post-Hoc Analyses: Change from Baseline in CGI-S Score as Related to Agitation After 12 Weeks of Treatment When Applying Enrollment Criteria That Enriched for Agitation

		Baseline	Change from Baseline at Week 12	Treatment Difference Versus Placebo		
Study Treatment Group	N	Mean (SD)	LS Mean (SE)	LSMD	95% CI	Nominal P-Value*
Study 283						
Brexpiprazole 1 mg	110	4.57 (0.61)	-1.07 (0.09)	0.08	(-0.17, 0.33)	0.5326
Brexpiprazole 2 mg	125	4.56 (0.68)	-1.40 (0.09)	-0.25	(-0.49, -0.01)	0.0445
Placebo	111	4.55 (0.67)	-1.15 (0.09)			
Study 284						
Brexpiprazole 0.5–2 mg	112	4.63 (0.75)	-1.46 (0.10)	-0.43	(-0.69, -0.22)	0.0017
Placebo	114	4.56 (0.67)	-1.04 (0.10)	-		

*Nominal p-values were not adjusted for multiple comparisons.
CGI-S=Clinical Global Impression-Improvement Score.

6.1.6 Studies 283 and 284 Efficacy Conclusions and Dose Recommendation for ≥ 2 mg/day

The results from the pivotal fixed-dose Study 283 demonstrated the minimum effective dose of brexpiprazole is 2 mg/day in the treatment of adult patients with AAD. Brexpiprazole 2 mg/day was statistically superior to placebo resulting in improvement in CMAI total score (p=0.0404) and showed numerically greater improvement for the key secondary efficacy endpoint of mean change in CGI-S score as related to agitation, although the difference did not reach statistical significance. No improvements vs placebo were found for the brexpiprazole 1 mg/day group for CMAI total and CGI-S score (p=0.9015 and p=0.4440, respectively).

Study 284 indicated that flexible-dose brexpiprazole 0.5–2 mg/day did not show statistical superiority relative to placebo on the CMAI total score at Week 12. Post-hoc analyses of patients who were titrated to 2 mg/day brexpiprazole (N=77) (or blinded placebo equivalent [N=74]) beginning at Week 4 also supported brexpiprazole 2 mg/day dose (nominal p=0.0121) as the minimal effective dose. A −0.31-point improvement over placebo (nominal p=0.0164) was observed for the key secondary efficacy endpoint of CGI-S in Study 284. These results were consistent with efficacy observations of the

equivalent dose in Study 283. The efficacy and safety results also support a faster titration to the minimum effective dose of 2 mg/day.

Results from the post-hoc analyses suggested to both the Sponsor and FDA (Table 5) that patients with more prominent agitated behaviors should be recruited into future AAD studies to discern change within a 12-week clinical study.

6.2 Pivotal Fixed-Dose Study 213

6.2.1 Design Adaptations Based on Studies 283 and 284

Based on the post-hoc results of applying enrollment criteria that enriched for agitation from Studies 283 and 284, patients in Study 213 must have met 2 additional inclusion criteria. In Study 213, during screening and at baseline, patients must have met the criteria for the provisional IPA consensus definition of agitation in patients with cognitive disorders and the CMAI Factor 1 agitation criteria to ensure enrollment of sufficiently agitated patients. In addition, patients were titrated to the minimum effective dose of 2 mg/day two weeks earlier in Study 213 than in Studies 283 and 284. Also, based on an FDA recommendation (Table 5), 3 mg/day dose of brexpiprazole was added to the fixed-dose design for Study 213.

6.2.2 Study Design

Study 213 was a Phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled, fixed-dose study designed to assess the efficacy, safety, and tolerability of brexpiprazole in the treatment of patients with AAD. The study comprised a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment safety follow-up period (Figure 6). The CMAI Factor 1 inclusion criteria were applied based on the CMAI ratings at screening and baseline and were blinded to the Investigators and patients. Patients were randomized (2:1) to receive either brexpiprazole or placebo during the double-blind treatment period. Within the brexpiprazole arm, patients were further randomized (1:2) to 2 mg/day or 3 mg/day.

6.2.2.1 Key Enrollment Criteria

Patients in Study 213 were enrolled at 103 sites in Bulgaria, Hungary, Serbia, Slovakia, Spain, Ukraine, and the US. Enrollment criteria for Study 213 were similar to Studies 283 and 284, and also included:

- Met the IPA provisional definition of agitation, and
- Met the criteria for CMAI Factor 1:
    - ≥ 1 aggressive behavior(s) occurring several times per week,
    - ≥ 2 aggressive behaviors occurring once or twice per week, or
    - ≥ 3 aggressive behaviors occurring less than once per week.

A full list of eligibility criteria is provided in Appendices 11.1.2 and 11.1.1.

6.2.2.2 Endpoint Definitions

The primary efficacy endpoint was change from baseline to Week 12 in the CMAI total score.

The key secondary endpoint was the change from baseline to Week 12 in the CGI-S score as related to agitation.

Other secondary endpoints included:

- Change from baseline to Week 12 in CMAI subscale scores (aggressive behavior, physically nonaggressive behavior, and verbally agitated behavior),
- Change from baseline in CMAI total score and CGI-S for each study visit during the double-blind treatment period,
- CGI-I for each study visit during the double-blind treatment period, and
- CMAI-based responder analysis.

Exploratory endpoints included change from baseline in NPI-NH total score and NPI-NH AA for each study visit during the double-blind treatment period.

6.2.2.3 Data Sets Analyzed

The following datasets were defined in Study 213:

Sample	Definition
Randomized	The Randomized Sample included all patients who were randomized into the study.
Safety	The Safety Sample included all patients who were administered ≥ 1 dose of brexpiprazole or placebo.
Efficacy	The Efficacy Sample included all patients in the randomized sample who took ≥ 1 dose of brexpiprazole or placebo, had a baseline, and ≥ 1 post-baseline evaluation for the CMAI score. All efficacy analyses were performed on the Efficacy Sample.

CMAI=Cohen-Mansfield Agitation Inventory.

6.2.2.4 Statistical Analyses

6.2.2.4.1 Primary and Key Secondary Analyses

The primary efficacy endpoint was the change from the baseline (i.e., Day 0 visit) to the end of the double-blind treatment period (i.e., Week 12 visit) in CMAI total score. The null hypothesis was defined as no difference in the mean change from baseline to Week 12 in CMAI total score between the brexpiprazole 2 or 3 mg/day treatment arm and the placebo treatment arm. The primary endpoint was analyzed using an MMRM model. The model included fixed-class effect terms for treatment, study site, visit week, and an interaction term of treatment by visit week and include the interaction term of baseline values of CMAI total score by visit week as a covariate. The same statistical analysis method of the primary efficacy endpoints was applied to the key secondary analysis of the change from baseline to Week 12 in the CGI-S score as related to agitation. In order

to control the overall type I error rate for this key secondary efficacy analysis, a hierarchical testing procedure was used so that the overall experiment-wise type I error rate was maintained. Thus, if the primary efficacy analysis for the CMAI total score yields a statistically significant result for the comparison of brexpiprazole vs placebo, then the corresponding comparison for this key secondary efficacy variable (CGI-S score) was to be tested.

6.2.2.4.2 Analyses of Secondary and Exploratory Endpoints

Change from baseline was evaluated using the same MMRM model described in the primary and key secondary analyses. The CGI-I score was evaluated by the CMH row mean score differ test (van Elteren) controlling for trial site in LOCF analysis. Response endpoints were evaluated by the CMH General Association Test controlling for trial site in LOCF analysis.

6.2.2.4.3 Handling of Missing Data

As sensitivity analyses for MAR assumption, analyses for MNAR were carried out. PMM based on MI with mixed missing data mechanisms were used to investigate the response profile of dropout patients by last dropout reason under MNAR mechanism for the following three scenarios:

- Dropout reasons due to AE as MNAR,
- Dropout reasons due to either AE or patient withdrew consent as MNAR, and
- All dropouts as MNAR.

6.2.2.4.4 Interim Analysis

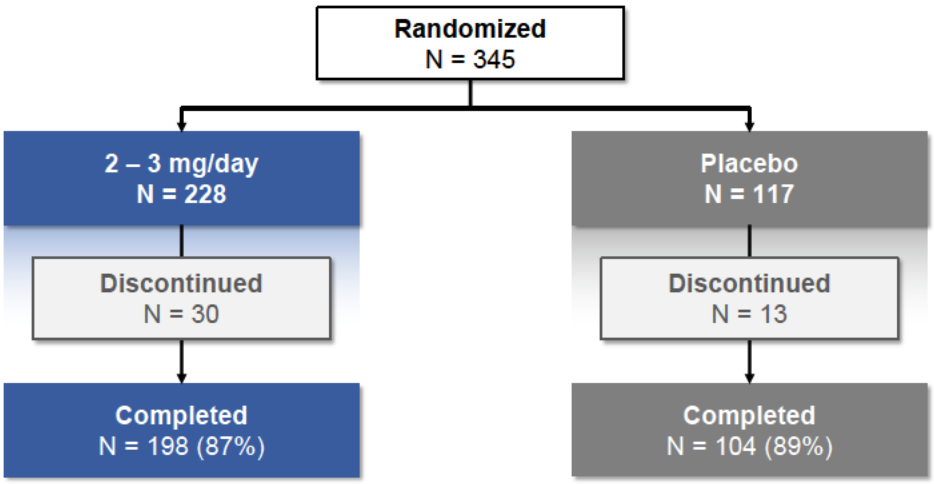
An unblinded interim analysis of efficacy data was performed by an Independent Data Monitoring Committee when the first 255 randomized patients in the study had either completed the Week 12 visit or discontinued from the study. Depending on the result of the interim analysis, the study would either stop at the conclusion of the interim analysis or continue to the final analysis at the planned maximum sample size of approximately N=330. A significance level of 0.015 (2-tailed) was allocated to the interim analysis, and the significance level for the final analysis was 0.035 (two-tailed).

6.2.3 Patient Disposition and Baseline Characteristics

6.2.3.1 Disposition

A total of 345 patients were randomized into the study: 75 patients to brexpiprazole 2 mg/day, 153 patients to brexpiprazole 3 mg/day, and 117 patients to placebo (Figure 20). Of these patients, 198 (86.8%) in the brexpiprazole group and 104 (88.9%) in the placebo group completed treatment through Week 12. The most common reason for early withdrawal was AE and included 12 (5.3%) patients in the brexpiprazole group (2 mg/day, n=1; 3 mg/day, n=11) and 5 (4.4%) patients in the placebo group.

Figure 20: Study 213: Patient Disposition (Randomized Sample)



6.2.3.2 *Baseline Demographics*

Patient demographics were similar across all treatment groups (Table 12). The mean age was 74 years, and the majority of patients were female and white. Approximately 4% of patients were Black or African-American, which represented about 8% of patients randomized in the US.

Table 12: Study 213: Baseline Demographics (Randomized Sample)

Characteristic	Brexpiprazole 2 mg (N=75)	Brexpiprazole 3 mg (N=153)	Brexpiprazole 2 or 3 mg (N=228)	Placebo (N=117)
Age (years), mean (SD)	74.3 (7.3)	74.6 (8.0)	74.5 (7.7)	73.0 (7.0)
Age group, n (%)				
< 65	8 (10.7)	16 (10.5)	24 (10.5)	13 (11.1)
≥ 65 and < 75	29 (38.7)	54 (35.3)	83 (36.4)	54 (46.2)
≥ 75	38 (50.7)	83 (54.2)	121 (53.1)	50 (42.7)
Female, n (%)	43 (57.3)	92 (60.1)	135 (59.2)	60 (51.3)
Race, n (%)				
White	70 (93.3)	144 (94.1)	214 (93.9)	115 (98.3)
Black/African-American	5 (6.7)	6 (3.9)	11 (4.8)	1 (0.9)
Asian	0	3 (2.0)	3 (1.3)	1 (0.9)
Ethnicity, n (%)				
Not Hispanic or Latino	50 (66.7)	107 (69.9)	157 (68.9)	80 (68.4)
Hispanic or Latino	25 (33.3)	46 (30.1)	71 (31.1)	37 (31.6)

6.2.3.3 *Baseline Disease Characteristics*

As shown in Table 13, baseline disease characteristics were similar overall for the brexpiprazole 2 mg/day, brexpiprazole 3 mg/day, and placebo groups. Of note, the baseline mean CMAI total score in this study was approximately 10 points higher across treatment groups than in Studies 283 and 284.

All patients met the criteria for agitation with cognitive disorders (per provisional IPA consensus) and CMAI Factor 1 agitation.

Table 13: Study 213: Baseline Disease Characteristics (Randomized Sample)

Parameter	Brexpiprazole 2 mg (N=75)	Brexpiprazole 3 mg (N=153)	Brexpiprazole 2 or 3 mg (N=228)	Placebo (N=117)
CMAI total score, mean (SD)	78.6 (15.5)	81.2 (17.2)	80.4 (16.7)	79.4 (17.6)
CMAI Factor 1	26.3 (6.4)	26.2 (7.7)	26.2 (7.3)	26.6 (8.7)
CMAI Factor 2	22.7 (7.0)	24.2 (7.4)	23.7 (7.3)	23.3 (7.5)
CMAI Factor 3	17.0 (4.3)	16.9 (4.9)	17.0 (4.7)	16.4 (5.6)
CGI severity score, mean (SD)	4.6 (0.7)	4.7 (0.6)	4.7 (0.7)	4.7 (0.7)
Dementia severity by MMSE score, n (%)				
Mild (> 18)	16 (21.3)	37 (24.2)	53 (23.2)	28 (23.9)
Moderate (13–18)	48 (64)	79 (51.6)	127 (55.7)	66 (56.4)
Severe (≤ 12)	11 (14.7)	37 (24.2)	48 (21.1)	23 (19.7)
Baseline psychosis status, n (%)				
≤ 4 Absent[a]	60 (80.0)	122 (79.7)	182 (79.8)	95 (81.2)
≥ 4 Present	14 (18.7)	30 (19.6)	44 (19.3)	21 (17.9)
Institutionalized, n (%)	32 (42.7)	64 (41.8)	96 (42.1)	54 (46.2)
Times since diagnosis of AD (months), mean (SD)	34.5 (38.9)	37.8 (36)	36.7 (36.9)	34.1 (31.4)
Time since onset of first episode of AAD (months), mean (SD)	22.1 (24.4)	25.2 (23.1)	24.2 (23.5)	21.5 (20.5)
Time since onset of current agitation episode (months), mean (SD)	9.0 (14.4)	10.5 (15.0)	10.0 (14.8)	8.9 (10.7)

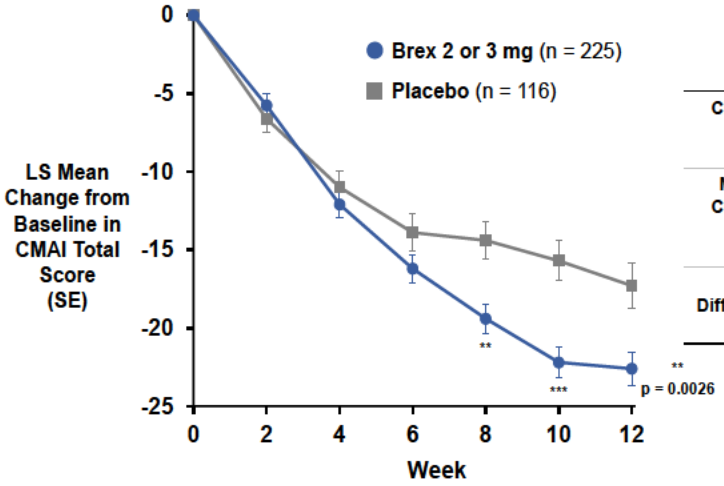
a. Defined as the absence of any ≥ 4 values, as in the absence of psychosis symptoms.
AAD=Agitation associated with Alzheimer's Dementia; AD=Alzheimer's Dementia; CGI=Clinical Global Impression; CMAI=Cohen-Mansfield Agitation Inventory; MMSE=Mini-Mental State Evaluation.

6.2.4 *Primary Endpoint Results – Change from Baseline to Week 12 in CMAI Total Score*

The brexpiprazole 2 or 3 mg/day group met the primary efficacy endpoint, demonstrating statistically significant (p=0.0026) improvement from baseline in CMAI

total score compared with placebo at Week 12 (LSMD=−5.32 [95% CI: −8.77, −1.87]; Figure 21).

Figure 21: Study 213: Change from Baseline in CMAI Total Score After 12 Weeks of Treatment (Efficacy Sample)

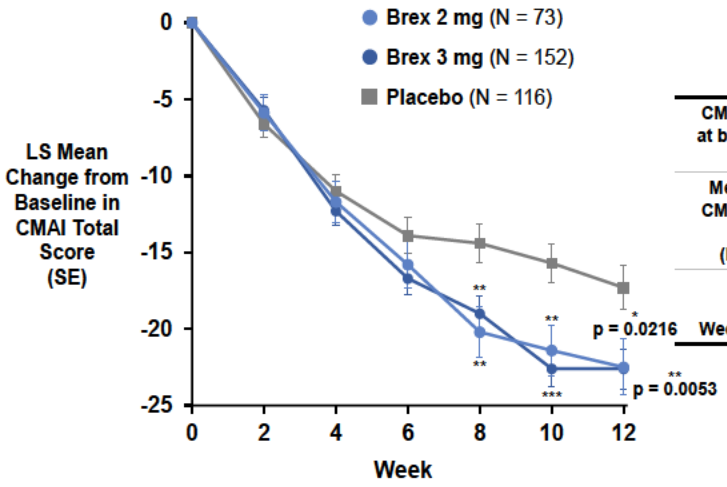


	Brexpiprazole N = 225	Placebo N = 116
CMAI Total score at baseline (Mean [SD])	80.6 (16.6)	79.2 (17.5)
Mean Change in CMAI Total score at Week 12 (LS Mean [SE])	-22.6 (1.08)	-17.3 (1.44)
Treatment Difference at Week 12 (95% CI)	-5.32 (-8.77, -1.87) p = 0.0026	

**p < 0.01, ***p < 0.001 vs placebo; MMRM.
Note: Error bars are LS Mean ± standard error.
Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory; MMRM=mixed-effect model repeated measure.

Both the brexpiprazole 2 mg/day group (LSMD=−5.28 [95% CI: −9.77, −0.78], nominal p=0.0216) and brexpiprazole 3 mg/day group (LSMD=−5.35 [95% CI: −9.09, −1.60], nominal p=0.0053) had a greater mean change from baseline to Week 12 in CMAI total score compared to the placebo group (Figure 22).

Figure 22: Study 213: Change from Baseline in CMAI Total Score After 12 Weeks of Treatment by Dose Group (Efficacy Sample)



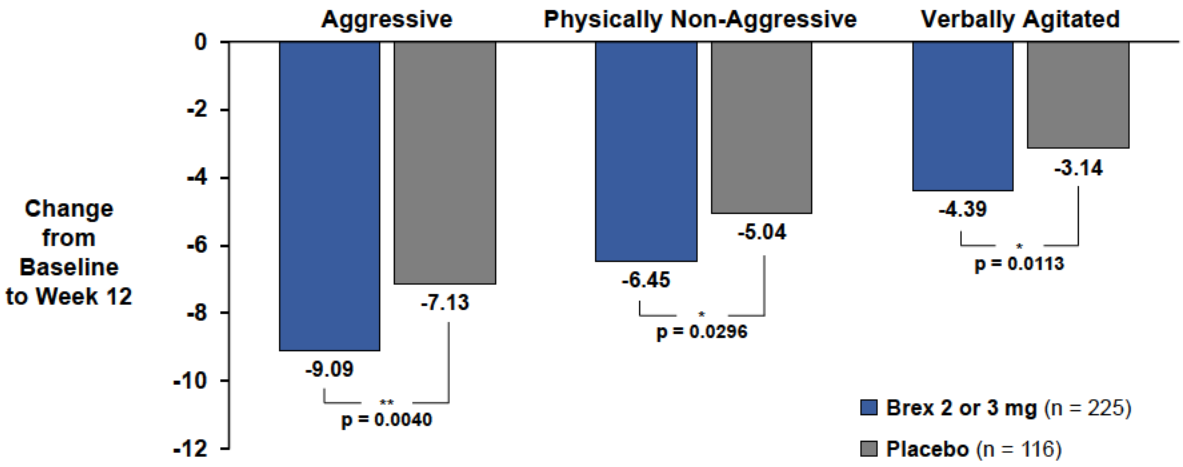
	Brex 2 mg N = 73	Brex 3 mg N = 152	Placebo N = 116
CMAI Total score at baseline (Mean [SD])	79.1 (15.2)	81.3 (17.3)	79.2 (17.5)
Mean Change in CMAI Total score at Week 12 (LS Mean [SE])	-22.5 (1.83)	-22.6 (1.31)	-17.3 (1.45)
Treatment Difference at Week 12 (95% CI)	-5.28 (-9.77, -0.78) p = 0.0216	-5.35 (-9.09, -1.60) p = 0.0053	---

* p <0.05, **p < 0.01, ***p < 0.001 vs placebo; MMRM.
*Nominal p-values were not adjusted for multiple comparisons.
Note: Error bars are LS Mean ± standard error.
Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory; MMRM=mixed-effect model repeated measure.

6.2.4.1 Change in CMAI by Factor

Mean change from baseline in the CMAI Factor scores (1=aggressive behavior; 2=physically nonaggressive behavior; 3=verbally agitated behavior) were compared between brexpiprazole and placebo at Week 12 (Figure 23). Numerically greater improvements in mean changes from baseline to Week 12 for all 3 CMAI Factor scores were shown in the brexpiprazole group compared with placebo group.

Figure 23: Study 213: Subscale Analysis of Change in CMAI Total Score from Baseline to Week 12 (Efficacy Sample)

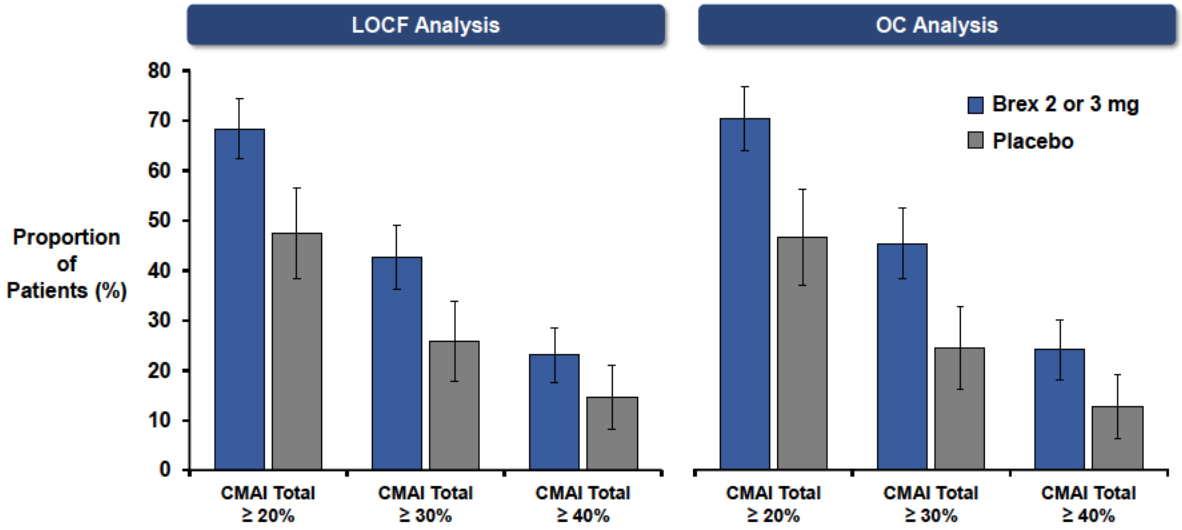


*p < 0.05, **p < 0.01 vs placebo; nominal p-values presented; MMRM.
*Nominal p-values were not adjusted for multiple comparisons.
Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory; MMRM=mixed-effect model repeated measure.

6.2.5 Secondary Endpoint Results – CMAI Response Rate After 12 Weeks of Treatment

The proportion of patients in the brexpiprazole 2 or 3 mg/day group with a ≥ 20%, ≥ 30 %, and ≥ 40% reduction in CMAI total score at Week 12 was larger than in the placebo group in both the LOCF and OC analyses (Figure 24).

Figure 24: Study 213: Proportion of Patients with CMAI Reductions at Week 12 (Efficacy Sample)

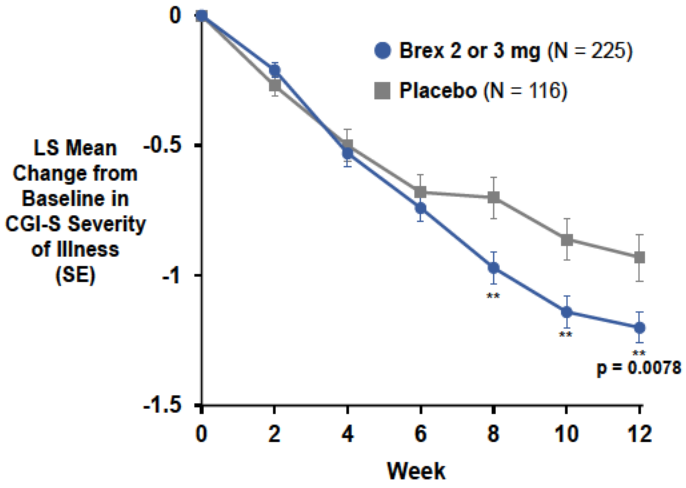


Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory; LOCF=last observation carried forward; OC=observed case.

6.2.6 Key Secondary Endpoint Results – Change from Baseline to Week 12 in CGI-S Score as Related to Agitation

The brexpiprazole 2 or 3 mg/day group met the key secondary efficacy endpoint, demonstrating a statistically significant (p=0.0078) improvement in CGI-S score as related to symptoms of agitation, with a −0.27-point improvement over placebo (95% CI: −0.47, −0.07; Figure 25).

Figure 25: Study 213: Change from Baseline in CGI-S Score as Related to Agitation After 12 Weeks of Treatment (Efficacy Sample)



	Brexpiprazole N = 225	Placebo N = 116
CGI-S score at baseline (Mean [SD])	4.71 (0.66)	4.71 (0.69)
Mean Change in CGI-S score at Week 12 (LS Mean [SE])	-1.20 (0.06)	-0.93 (0.08)
Treatment Difference at Week 12 (95% CI)	-0.27 (-0.47, -0.07) p = 0.0078	

**p-value < 0.01 vs placebo; MMRM.
Note: Error bars are LS Mean ± standard error.
Brex=brexpiprazole; CGI-S=Clinical Global Impression-Severity of Illness scale; MMRM=mixed-effect model repeated measure.

6.2.7 Secondary Endpoint Results – CGI-I Score as Related to Agitation at Week 12

The brexpiprazole 2 or 3 mg/day group showed an improvement compared with the placebo group in the mean CGI-I score (as related to agitation) at Week 12 (LSMD=−0.33 [95% CI: −0.57, −0.09], nominal p=0.0070). Greater improvement in the brexpiprazole 2 or 3 mg/day group was observed at Week 4 (LSMD=−0.25 [95% CI: −0.44, −0.06]) and maintained through Week 12.

6.2.8 Exploratory Endpoint Results – Change from Baseline to Week 12 in NPI-NH Total Score

The brexpiprazole 2 or 3 mg/day group showed a greater improvement in the mean change in NPI-NH 12-item total score from baseline to Week 12 compared with the placebo group (LSMD=−4.60 [95% CI: −7.33, −1.88]).

6.2.9 Exploratory Endpoint Results – Change from Baseline to Week 12 in NPI-NH Score AA Score

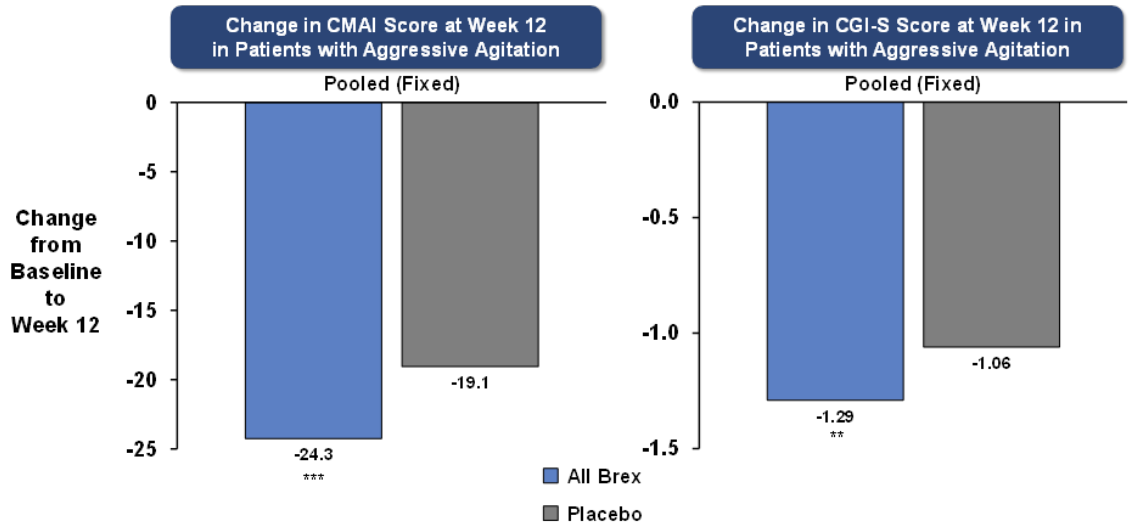
The brexpiprazole 2 or 3 mg/day group showed a numerically greater improvement in mean change in NPI-NH AA score from baseline to Week 12, compared with the placebo group (LSMD=−0.54 [95% CI: −1.13, 0.05]).

6.3 Pooled Fixed-Dose Analyses (Studies 283 and 213)

6.3.1 Primary Efficacy Endpoint: Change from Baseline to Week 12 in CMAI Total Score When Applying Enrollment Criteria That Enriched For Agitation

Post-hoc exploratory analyses were conducted to evaluate the treatment effect of brexpiprazole in patients who met the criteria for CMAI Factor 1 at baseline in both fixed-dose studies (Figure 26). When pooled across both studies, brexpiprazole 2 or 3 mg/day group, demonstrated a statistically significant ($p < 0.0001$) improvement in CMAI total score with a −5.19-point (95% CI: −7.65, −2.73) improvement over placebo and a numerically greater improvement in CGI-S score as related to agitation (LSMD=−0.24, nominal p=0.0026), providing further support for the efficacy of brexpiprazole 2 or 3 mg/day for the treatment of AAD.

Figure 26: Studies 283 and 213: Mean Change in CMAI Total and CGI-S as Related to Agitation at Week 12 When Applying Enrollment Criteria That Enriched for Agitation

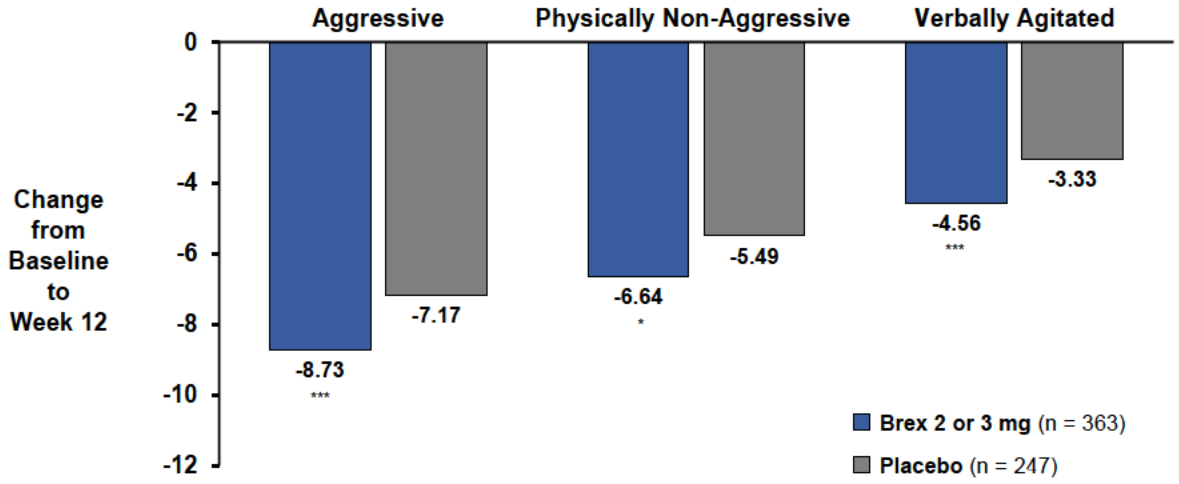


**p < 0.01, ***p < 0.001 vs placebo; MMRM.
*Nominal p-values were not adjusted for multiple comparisons.
Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory; CGI-S=Clinical Global Impression-Severity of Illness Scale; MMRM=mixed-effect model repeated measure.

6.3.2 Change in CMAI by Factor

For fixed-dose Studies 283 and 213, mean change from baseline in the CMAI Factor scores (1=aggressive behavior; 2=physically nonaggressive behavior; 3=verbally agitated behavior) were compared between brexpiprazole and placebo at Week 12 (Figure 27). Numerically greater improvements in mean changes from baseline to Week 12 for all 3 CMAI Factor scores were shown in the brexpiprazole group compared with placebo group.

Figure 27: Studies 283 and 213: Subscale Analysis of Change in CMAI Total Score from Baseline to Week 12 (Efficacy Sample)



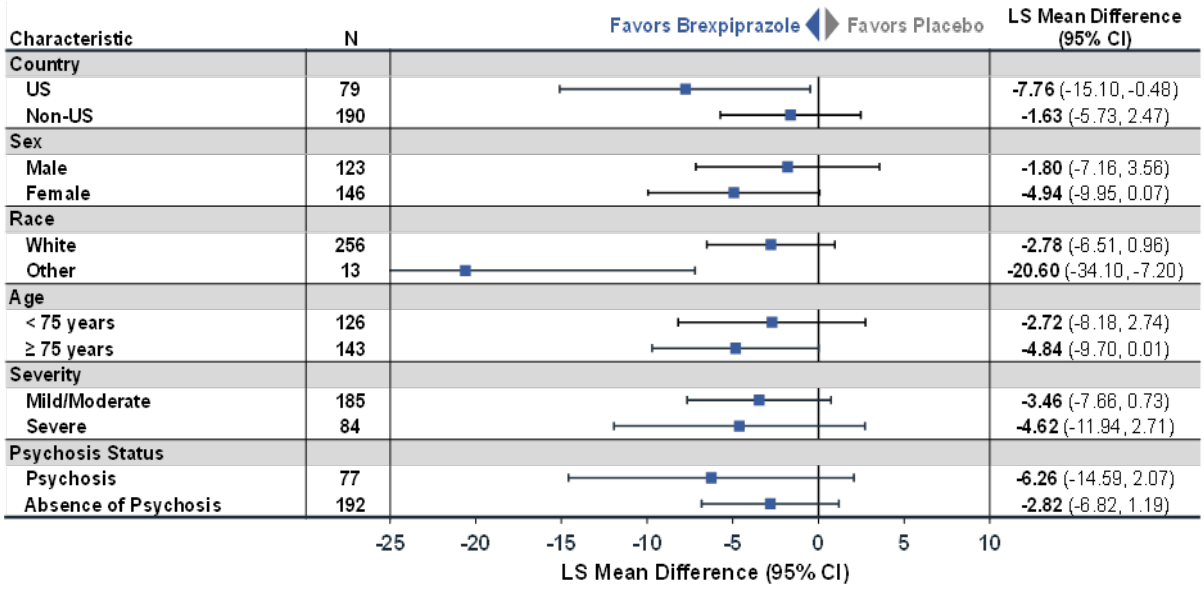
*p < 0.05, ***p < 0.001 vs placebo; nominal p-values presented; MMRM.
*Nominal p-values were not adjusted for multiple comparisons.
Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory; MMRM=mixed-effect model repeated measure.

6.4 Change in CMAI Total Score by Subgroup (Studies 283 and 213)

Analyses of treatment differences in the primary efficacy endpoint (mean change in CMAI total score from baseline at Week 12) were conducted in the pre-specified subgroups of country, gender, race, age, baseline disease severity, and baseline psychosis status in both Studies 283 (Figure 28) and 213 (Figure 29). There was no formal statistical adjustment for multiplicity for any of these subgroups and these analyses are considered exploratory only.

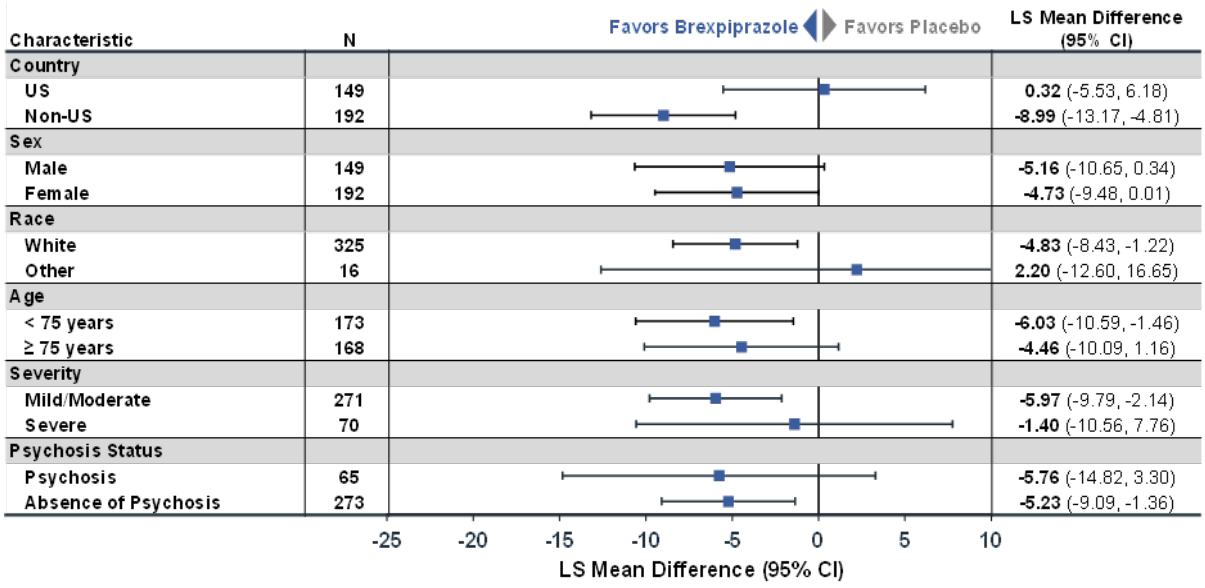
The results from the pre-specified subgroup analyses for the primary endpoint were generally consistent with that of the overall population in both studies with no meaningful differences identified in sub-populations.

Figure 28: Study 283: Change from Baseline in CMAI Total Score After 12 Weeks of Treatment by Subgroup



Note: 'Mild/moderate' and 'severe' refer to baseline dementia severity.
CMAI=Cohen-Mansfield Agitation Inventory.

Figure 29: Study 213: Change from Baseline in CMAI Total Score After 12 Weeks of Treatment by Subgroup



Note: 'Mild/moderate' and 'severe' refer to baseline dementia severity.
CMAI=Cohen-Mansfield Agitation Inventory.

6.5 Meaningful Within-Patient Change Analysis

Exploratory and secondary endpoints in Study 283 and Study 213, respectively, included responder definitions of ≥ 20%, ≥ 30%, and ≥ 40% reduction in CMAI total score (Sections 6.1.3.6 and 6.2.5). As an additional responder definition, an MWPC threshold was defined.

Post-hoc analyses were conducted to generate supportive data for the interpretation of change in the CMAI total score by defining a threshold of MWPC. This analysis explored the relationship between frequency of agitation, as measured by the CMAI total score, and the severity of agitation, as measured by the CGI-S.

An MWPC threshold was derived using a triangulation of methods, including anchor-based and distribution-based approaches, as recommended by the FDA (2019). Post-hoc analyses were conducted initially using separate and pooled data from Studies 283 and 284. These analyses suggested an MWPC threshold for CMAI total score in the range of a 15- to 20-point reduction. The conversative estimate of a 20-point reduction in CMAI total score corresponds to a 2-point improvement (or moderate improvement) based on CGI-S assessment and was deemed as a meaningful threshold for defining clinical benefit in the 283 and 284 study populations. For example, a patient would go from markedly ill to mildly ill.

Triangulation of the analyses using all blinded study data supported that individuals who experienced reductions in CMAI total score of ≥ 20 points can be considered as experiencing a clinically meaningful benefit. As a sensitivity analysis, a range of thresholds (15- to 25-point reduction) were explored as responder definitions for Study 213 and the pooled fixed-dose Studies (283 and 213) to quantify the proportion of individuals achieving a clinically relevant response across study treatment arms (Table 14). The methodologies applied and threshold range identified from the post-hoc analyses were also consistent with the minimal clinically important difference (MCID) of a 17-point reduction in the CMAI total score reported in the literature (De Mauleon et al 2021).

Table 14: Study 283, Study 213, and Pooled Fixed-Dose Studies (283 and 213): Proportion of Patients Achieving MWPC Threshold by Treatment Arm (Efficacy Sample, LOCF)

	Study 283		Study 213		Pooled Fixed-Dose Studies (283 and 213)	
	Brex 2 mg (N=138)	Placebo (N=131)	Brex 2 or 3 mg (N=225)	Placebo (N=116)	Brex 2 or 3 mg (N=363)	Placebo (N=247)
Change in CMAI Total Score, n (%)						
-15 points	77 (55.8)	64 (48.9)	156 (69.3)	59 (50.9)	233 (64.2)	123 (49.8)
-20 points	57 (41.3)	50 (38.2)	125 (55.6)	43 (37.1)	182 (50.1)	93 (37.7)
-25 points	49 (35.5)	34 (26.0)	89 (39.6)	35 (30.2)	138 (38.0)	69 (27.9)

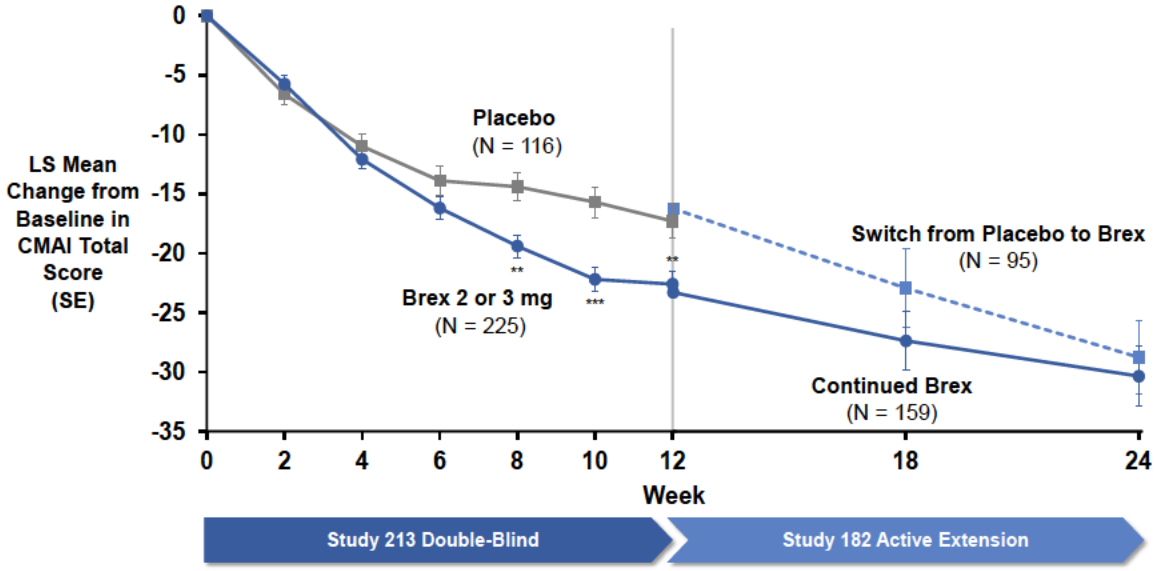
Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory; LOCF=last observation carried forward; MWPC=Meaningful within-patient change.

6.6 Active-Treatment Extension Study 182

Study 182 was a multicenter, active-treatment extension study designed to assess the long-term safety and tolerability of brexpiprazole (2 or 3 mg/day) in adults with AAD. Enrollment into the study consisted of eligible patients who completed 12 weeks of treatment in the double-blind Study 213. Patients randomized to the 2 or 3 mg/day doses of brexpiprazole in Study 213 began treatment on these same doses in the active-treatment extension. Prior treatment was blinded to the study Investigator. Patients who received placebo in Study 213 received 0.5 mg brexpiprazole once a day during Week 1, up-titrated to 1 mg during Week 2, and then up-titrated to 2 mg by Week 3. Efficacy was an exploratory objective and assessed by CMAI total score at 6 and 12 weeks of treatment.

Baseline for Study 182 was the last efficacy visit in the double-blind period of Study 213. As expected, based on prior treatment, mean CMAI total scores at baseline for the prior placebo group were higher than those for the prior brexpiprazole group (62.9 vs 57.3). In Study 182, after 6 weeks of treatment with 2 or 3 mg/day of brexpiprazole, mean CMAI total scores were similar between prior dose groups and mean change from baseline was greater in the 93 patients in the prior placebo group (−6.7) than in the 155 patients in the prior brexpiprazole group (−4.1; Figure 30). After 12 weeks of treatment, mean CMAI total scores remained similar between prior dose groups, with mean change from baseline greater in the prior placebo group (−12.5) than in the prior brexpiprazole group (−7.1).

Figure 30: Studies 213 and 182: Change from Baseline in CMAI Total Score Through 24 Weeks of Treatment (Efficacy Sample)



**p-value < 0.01, ***p < 0.001 vs placebo; MMRM.
Note: 163 patients on brexpiprazole entered Study 182 and continued brexpiprazole.
Brex=brexpiprazole; CMAI=Cohen-Mansfield Agitation Inventory; MMRM=mixed-effect model repeated measure.

6.7 Efficacy Conclusions

The results from the two fixed-dose, Phase 3 studies, Studies 283 and 213, with supporting evidence from Studies 284 and 182, demonstrated that treatment with brexpiprazole 2 or 3 mg/day achieved statistically significant and clinically meaningful improvements in patients with agitation associated with Alzheimer's dementia.

In Study 213, brexpiprazole 2 or 3 mg/day demonstrated a statistically significant difference in comparison to placebo on both the primary endpoint (change in CMAI) and key secondary endpoint (change in CGI-S) at Week 12. Brexpiprazole also demonstrated numerically greater improvements vs placebo across 3 key subdomains of agitation (aggressive, physically non-aggressive, and verbally agitated). These efficacy results were consistent with results from Study 283, in which brexpiprazole 2 mg/day was statistically superior to placebo resulting in improvement in CMAI total score (p=0.0404) and showed numerically greater improvement for the key secondary efficacy endpoint of mean change in CGI-S score as related to agitation, although the difference was not statistically significant. In addition the proportion of patients who met the threshold for clinically meaningful change in CMAI total score (i.e., a 20-point change from baseline) was consistently larger in the brexpiprazole treatment group compared with the placebo group (Study 213: 55.6% vs 37.1%; Studies 283 and 213: 50.1% vs 37.7%). These results were further supported by findings from flexible-dose

Study 284 and continued improvement over the subsequent 12 weeks of brexpiprazole treatment in the active-treatment extension Study 182.

The efficacy of brexpiprazole in Study 213 was demonstrated in an enriched population with higher baseline CMAI scores than patients in Studies 283 and 284. The results of Study 213 were consistent with those of the post-hoc analysis of the same enriched populations in Studies 283 and 284.

When the data from the 3 studies are analyzed in totality, the efficacy findings indicate that brexpiprazole can be an important and novel therapeutic tool for the treatment of adult patients with AAD, a patient population with a high unmet medical need that has no available approved standard of care treatment options.

7 CLINICAL SAFETY

Summary

- Brexpiprazole once daily was generally safe and well tolerated in patients with AAD, consistent with its known safety profile in other approved indications. Most AEs were mild to moderate in severity (94.2%) and non-serious.
    - The incidence of AEs of key safety topics of interest (i.e., falls, cerebrovascular events, cardiovascular events, sedation and somnolence, and EPS) were similar between the brexpiprazole and placebo groups. No difference in the evidence of worsening of cognitive impairment was observed between brexpiprazole and placebo.
- Seven deaths were reported on study: 6 deaths (0.9%) in the all brexpiprazole group and 1 death (0.3%) in the placebo group.
    - While incidence of death was numerically higher in brexpiprazole compared to placebo, the overall incidence was low (< 1%) with no pattern in cause of death and individual cases were confounded by underlying conditions and other factors, including advanced age, comorbidities, and concomitant medications consistent with an AD patient population.
- Extended treatment with brexpiprazole up to 24 weeks was well tolerated and did not reveal any new safety signals. No deaths were reported in the active-treatment extension (Study 182).

7.1 Overall Safety

Consistent with the prior approved indications, brexpiprazole was generally well tolerated with no new safety signals identified in the AAD study population. Cumulatively, 10,291 patients have been treated with brexpiprazole in the Phase 2 and Phase 3 brexpiprazole clinical development program. Of these, 463 patients were in the ≥ 65 to < 75 years of age group and 429 patients were ≥ 75 years of age. In the 12-week controlled AAD studies, a total of 655 patients were treated with brexpiprazole and included in the safety evaluation.

7.2 Safety Presentation

Safety is presented from 3 completed Phase 3,12-week, double-blind, placebo-controlled studies designed to evaluate the safety of brexpiprazole compared to placebo in patients with AAD:

- 2 fixed-dose studies: Study 213 (2 or 3 mg/day) and Study 283 (1 or 2 mg/day), and
- 1 flexible-dose study: Study 284 (dose range: 0.5–2 mg/day).

The results are presented for brexpiprazole ≤ 1 mg, fixed 2 mg or 3 mg, flexible 0.5–2 mg doses, all brexpiprazole dose groups (combined), and placebo groups for the pooled 12-week controlled studies in AAD (Studies 283, 284, and 213), as well as a comparison of the safety data between the 2 mg and 3 mg/day dose separately with placebo from the 2 fixed-dose studies (283 and 213).

In addition, the long-term safety and tolerability data are presented for the completed 12-week, multicenter, active-treatment extension study (Study 182) in patients who completed Study 213.

Study 211 was a 2-month, multicenter, observational, rollover Phase 3 study designed to evaluate the safety of patients with AAD who were previously treated with brexpiprazole (0.5, 1, or 2 mg/day) or placebo during either Study 283 or Study 284. Only patients who completed both the 12-week double-blind treatment period and the 30-day safety follow-up visit of either were eligible for enrollment. No new safety findings were identified in this 2-month follow-up observational study.

7.3 Treatment Exposure

7.3.1 Phase 3 Studies in AAD

In the three 12-week controlled studies in AAD, 655 patients were exposed to ≥ 1 dose of brexpiprazole. Mean treatment duration was similar between the all brexpiprazole (79.4 days) and placebo (80 days) groups and was also similar across the brexpiprazole dose groups (78.4–79.8 days).

A total of 623 patients (95.1%) in the all brexpiprazole group, including 349 patients (95.4%) in the 2 or 3 mg/day dose group, completed at least 6 weeks (≥ 42 days) of treatment compared with 376 patients (96.9%) in the placebo group (Table 15).

Table 15: Studies 283, 284, and 213: Treatment Duration and Overall Exposure (Safety Sample)

	Brexpiprazole				
	≤ 1 mg (N=157)	2 or 3 mg (N=366)	0.5–2 mg (N=132)	All (N=655)	Placebo (N=388)
Mean duration of exposure (days ± SD)	78.4 (15.6)	79.8 (13.9)	79.3 (15.6)	79.4 (14.7)	80 (13.7)
Duration of exposure category, n (%)					
≥ 1 day	157 (100.0)	366 (100.0)	132 (100.0)	655 (100.0)	388 (100.0)
≥ 7 days	156 (99.4)	366 (100.0)	131 (99.2)	653 (99.7)	386 (99.5)
≥ 28 days	154 (98.1)	357 (97.5)	128 (97.0)	639 (97.6)	379 (97.7)
≥ 42 days	149 (94.9)	349 (95.4)	125 (94.7)	623 (95.1)	376 (96.9)
≥ 70 days	136 (86.6)	329 (89.9)	120 (90.9)	585 (89.3)	356 (91.8)
≥ 84 days[a]	114 (72.6)	245 (66.9)	89 (67.4)	448 (68.4)	268 (69.1)

a. The longest duration of exposure was 91 days.
Note: Duration of exposure=(last date – first date of exposure) + 1.
Note: Treatment groups consisted of brexpiprazole ≤ 1 mg consisting of 0.5 mg/day and 1 mg/day arms in Study 283; brexpiprazole 0.5–2 mg arm in Study 284; brexpiprazole 2 or 3 mg/day arms in Studies 283 and 213; and placebo arms in Studies 283, 284, and 213.

7.3.2 Active-Treatment Extension Study 182 in Patients with AAD

In the active-treatment extension study (Study 182), 259 patients from Study 213, were exposed to ≥ 1 dose of brexpiprazole in the double-blind treatment period, of which 163 received brexpiprazole in Study 213 and 96 received placebo. Prior treatment was blinded to the study Investigator. Of the 163 patients in the prior brexpiprazole group, a total of 152 patients (93.3%) were exposed to brexpiprazole treatment for up to 24 weeks (Table 16).

Table 16: Study 182: Treatment Exposure (Safety Sample)

	All Brexpiprazole (N=163)
Mean duration of exposure (days ± SD)	82.6 (48.0)
Duration of exposure category, n (%)	
≥ 85 days	163 (100)
≥ 127 days	152 (93.3)
> 168 days	47 (28.8)

7.4 Summary of Adverse Events from Phase 3 Studies in AAD

Table 17 presents an overall summary of AEs for the Safety Sample of all three 12-week controlled studies in AAD. The overall incidence of AEs in the three 12-week controlled studies was 49.2% with 5.6% SAEs and 5.2% discontinuations due to AEs. Incidences of AEs were similar between the all brexpiprazole group, the 2 or 3 mg/day

group, and the placebo group (51.1%, 48.9%, and 45.9%, respectively). The incidence of SAEs in the 2 or 3 mg/day group was 5.2% vs 4.1% in the placebo group. Discontinuations due to AEs were reported for 4.9% of patients in the 2 or 3 mg/day group compared with 3.4% in the placebo group. Of the 7 deaths that occurred during the treatment phase in the 12-week controlled studies, 6 were reported in the all brexpiprazole group, 1 in the placebo group, with 2 reported in the 2 or 3 mg/day group (0.9%, 0.3 %, and 0.5%, respectively). Of the 4 deaths reported in the ≤ 1 mg/day dose group, 2 were patients treated with 0.5 mg/day and 2 were patients treated with 1 mg/day. One additional death was reported in the flexible-dose Study 284 for a patient in the brexpiprazole group who experienced a SAE of spontaneous subdural hematoma during the study period. The patient died 2 days after the 30-day safety follow-up period (cause of death reported as dyscirculatory encephalopathy and brain oedema) and thus not included in the 7 deaths. Events resulting in death were not considered related to brexpiprazole by the Investigator (additional details on deaths are provided in Section 7.6 and Appendix 11.3.1).

Overall summary of safety for each study by dose is provided in Appendix 11.5.

Table 17: Studies 283, 284, and 213: Overall Summary of Adverse Events (Safety Sample)

	Brexpiprazole					
Patients with any, n (%)	**≤ 1 mg (N=157)**	**2 mg (N=213)**	**3 mg (N=153)**	**0.5–2 mg (N=132)**	**All (N=655)**	**Placebo (N=388)**
AE	77 (49.0)	119 (55.9)	64 (41.8)	75 (56.8)	335 (51.1)	178 (45.9)
AE leading to study drug discontinuation	14 (8.9)	7 (3.3)	11 (7.2)	9 (6.8)	41 (6.3)	13 (3.4)
Severe AE	10 (6.4)	13 (6.1)	6 (3.9)	9 (6.8)	38 (5.8)	16 (4.1)
SAE	16 (10.2)	13 (6.1)	6 (3.9)	7 (5.3)	42 (6.4)	16 (4.1)
Death	4 (2.5)	1 (0.5)	1 (0.7)	0 (0.0)	6 (0.9)	1 (0.3)

Note: Treatment groups consist of brexpiprazole ≤ 1 mg consisting of 0.5 mg/day and 1 mg/day arms in Study 283; brexpiprazole 0.5–2 mg arm in Study 284; brexpiprazole 2 or 3 mg/day arms in Studies 283 and 213; and placebo arms in Studies 283, 284, and 213.
SAE=serious adverse event.

7.4.1 Common Adverse Events

Table 18 presents a summary of AEs (that occurred in ≥ 2% of patients in the all brexpiprazole group and greater than placebo) for the Safety Sample of all three 12-week controlled studies in AAD. Insomnia, somnolence, nasopharyngitis, and urinary tract infection were the only AEs that met these criteria. Overall, rates of somnolence were low and lower compared with other atypical antipsychotic treatments (Muhlbauer et al 2021).

Table 18: Studies 283, 284, and 213: Summary of Adverse Events (≥ 2% of Patients in the All Brexpiprazole Group and Greater Than Placebo) (Safety Sample)

	Brexpiprazole				
Preferred Term, n (%)	≤ 1 mg (N=157)	2 or 3 mg (N=366)	0.5–2 mg (N=132)	All (N=655)	Placebo (N=388)
Patients with any AE	77 (49.0)	183 (50.0)	75 (56.8)	335 (51.1)	178 (45.9)
Insomnia	7 (4.5)	12 (3.3)	5 (3.8)	24 (3.7)	11 (2.8)
Somnolence	2 (1.3)	12 (3.3)	8 (6.1)	22 (3.4)	7 (1.8)
Nasopharyngitis	5 (3.2)	9 (2.5)	4 (3.0)	18 (2.7)	10 (2.6)
Urinary tract infection	3 (1.9)	12 (3.3)	2 (1.5)	17 (2.6)	6 (1.5)

AE=adverse event.

7.4.2 Severe Adverse Events

Overall, 5.8% of patients in the all brexpiprazole group and 4.1% of patients in the placebo group reported ≥ 1 severe AE. The incidence of severe AEs was < 7% in each treatment group. Only 3 severe events were reported by more than 2 patients in any treatment group: seizure in 3 patients (0.5%) and urinary tract infection in 3 patients (0.5%) in the all brexpiprazole group, and agitation in 3 patients (0.8 %) in the placebo group.

7.4.3 Serious Adverse Events

SAEs that occurred in ≥ 2 patients in the all brexpiprazole group and greater than in the placebo group in the three 12-week controlled studies in AAD are provided in Table 19. SAEs reported by ≥ 2 patients in the all brexpiprazole group were urinary tract infection in 6 patients (0.9%); agitation in 3 patients (0.5%); and pneumonia, fall, dementia Alzheimer's type, seizure, and chronic obstructive pulmonary disease in 2 patients (0.3%) each. None of these events were reported in the placebo group except pneumonia in 2 patients (0.5%) and urinary tract infection and seizure in 1 patient (0.3%) each.

In the 2 or 3 mg/day group, 5.2% of patients reported ≥ 1 SAE. Urinary tract infection in 6 patients (1.6%) was the only event reported by ≥ 2 patients in this dose group.

Table 19: Studies 283, 284, and 213: Summary of Serious Adverse Events (≥ 2 Patients in the All Brexpiprazole Group and Greater Than Placebo) (Safety Sample)

	Brexpiprazole				
Preferred Term, n (%)	≤ 1 mg (N=157)	2 or 3 mg (N=366)	0.5–2 mg (N=132)	All (N=655)	Placebo (N=388)
Patients with at least 1 SAE[a]	16 (10.2)	19 (5.2)	7 (5.3)	42 (6.4)	16 (4.1)
Urinary tract infection	0	6 (1.6)	0	6 (0.9)	1 (0.3)
Agitation	2 (1.3)	1 (0.3)	0	3 (0.5)	0
Pneumonia	0	1 (0.3)	1 (0.8)	2 (0.3)	2 (0.5)
Chronic obstructive pulmonary disease	1 (0.6)	1 (0.3)	0	2 (0.3)	0
Dementia Alzheimer's type	1 (0.6)	1 (0.3)	0	2 (0.3)	0
Fall	1 (0.6)	1 (0.3)	0	2 (0.3)	0
Seizure	0	0	2 (1.5)	2 (0.3)	1 (0.3)

a. Patients with AEs in multiple system organ classes were counted only once towards the total.
SAE=serious adverse event.

7.4.4 Adverse Events Leading to Discontinuation

A summary of AEs resulting in discontinuation for the three 12-week controlled studies in AAD is provided in Table 20.

The AEs resulting in discontinuation for ≥ 2 patients in the all brexpiprazole group were agitation (n=4), seizure (n=3), pneumonia (n=3), and asthenia, fall, ALT increased, AST increased, ECG QT prolonged, and insomnia (n=2, each).

In the 2 or 3 mg/day brexpiprazole dose group, 4.9% of patients reported an AE resulting in discontinuation. Asthenia was the only event resulting in discontinuation reported by 2 patients in this dose group.

Table 20: Studies 283, 284, and 213: Summary of Adverse Events Leading to Discontinuation (≥ 2 Patients in the All Brexpiprazole Group) (Safety Sample)

	Brexpiprazole				
Preferred Term, n (%)	≤ 1 mg (N=157)	2 or 3 mg (N=366)	0.5–2 mg (N=132)	All (N=655)	Placebo (N=388)
At least 1 AE leading to discontinuation[a]	14 (8.9)	18 (4.9)	9 (6.8)	41 (6.3)	13 (3.4)
Agitation	3 (1.9)	1 (0.3)	0	4 (0.6)	3 (0.8)
Seizure	0	0	3 (2.3)	3 (0.5)	0
Pneumonia	1 (0.6)	1 (0.3)	1 (0.8)	3 (0.5)	0
Asthenia	0	2 (0.5)	0	2 (0.3)	0
Fall	1 (0.6)	1 (0.3)	0	2 (0.3)	0
AST Increased	0	1 (0.3)	1 (0.8)	2 (0.3)	0
ALT increased	0	1 (0.3)	1 (0.8)	2 (0.3)	0
Electrocardiogram QT prolonged	2 (1.3)	0	0	2 (0.3)	0
Insomnia	1 (0.6)	1 (0.3)	0	2 (0.3)	0

a. Patients with AEs in multiple system organ classes were counted only once towards the total.
AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase.

7.5 Psychosis

Identification of patients as having presence or absence of psychosis symptoms at baseline and the definition of psychosis was pre-specified. AEs were summarized by psychosis status at baseline (presence/absence) in a post-hoc analysis (psychosis defined as having an NPI delusion item score ≥ 4, an NPI hallucination item score ≥ 4, or both). Overall incidence of AEs was similar between patients who had baseline psychosis (81/153 patients; 52.9%) and those who did not (253/500 patients; 50.6%). Distribution of events (by preferred terms) was also similar between the 2 groups. The incidences of serious and severe AEs were comparable between the groups (presence of psychosis vs absence of psychosis: 7.2% vs 6.2% for serious AEs and 5.9% vs 5.8% for severe AEs). The incidence of patients who discontinued study drug due to AEs was numerically lower in patients who had baseline psychosis (4.6%) compared to those who did not (6.8%).

7.6 Deaths

A total of 7 deaths were reported during the double-blind treatment period in the 3 completed, 12-week controlled studies in AAD (Table 21). Six deaths (0.9%) were reported in the all brexpiprazole group and 1 death (0.3%) was reported in the placebo group. One additional death was reported in the flexible-dose Study 284 for a patient in the 0.5–2 mg/day group who experienced a SAE of spontaneous subdural hematoma during the study period. The patient died 2 days after the 30-day safety follow-up period

(cause of death reported as dyscirculatory encephalopathy and brain oedema) and thus not included in Table 21.

Although the incidence of death was numerically higher in brexpiprazole than in the placebo group, the overall incidence was low (< 1%) with no pattern in cause of death (Table 21) and individual cases were confounded by underlying conditions and other factors, including advanced age, comorbidities, and concomitant medications consistent with the AD population. All deaths occurred at least 30 days after beginning administration, with a wide range of when deaths occurred following the last dose (2–67 days). None of the events resulting in death were considered by the Investigator to be related to brexpiprazole.

Baseline psychosis did not have an effect on overall incidence of deaths. Two (1.3%) patients with baseline psychosis died in the 12-week controlled AAD studies. Both fatal events (pneumonia aspiration and hemorrhage intracranial following a fall) were assessed as not related to brexpiprazole by the study Investigators.

Details of the deaths reported are presented in Appendix 11.3.

Table 21: Studies 283, 284, and 213: Summary of Deaths During Study Period (Safety Sample)

Study/ Dose	Age/ Sex	Study Treatment Duration (Days)	Days Since Last Dose	Fatal Event (Verbatim)	Assessment
283/ 0.5 mg	87/F	8	27	Intracranial Hemorrhage	Study treatment discontinued due to an AE of fall. Confounded by prior history of subarachnoid hemorrhage, medical history of hypertension and recent addition of clopidogrel.
283/ 0.5 mg	76/M	50	2	Acute Purulent Meningoencephalitis	Withdrew from the study due to personal reason. Multiple significant medical comorbidities with autopsy findings indicating purulent pneumonia with abscesses, complicated by development of purulent meningoencephalitis.
283/ 1 mg	78/M	65	13	Aspiration Pneumonia	Study treatment discontinued due to this event. Significant medical history included COPD, gastritis, esophagitis, encephalopathy, and small bowel obstruction.
283/ 1 mg	66/F	85	67	Airway Obstruction	Study treatment completed. Event occurred 25 days after completing study treatment. Secondary to mechanical obstruction by choking on an orange.
283/ 2 mg	86/F	86	9	End Stage Alzheimer's Dementia	Study treatment completed. Seven days after completing study treatment, patient went to hospice care as she refused medications, food, and liquids.
213/ 3 mg	78/M	28	23	Heart Failure	Study treatment discontinuation due to acute hallucination. Diagnosed with pneumonia 4 days after treatment discontinuation. Died 23 days after treatment discontinuation. Autopsy findings showed coronary and cerebral atherosclerosis indicating underlying chronic pathology.
284/ Placebo	86/M	74	2	Pneumonia	Study treatment completed. Elderly age and bed ridden nursing home patient could have contributed to the event of pneumonia.

Note: 1 additional death was reported. The patient died 2 days after the 30-day protocol specified safety follow-up period.
AE=adverse event; COPD=chronic obstructive pulmonary disease.

7.7 Active-Treatment Extension Study 182

The overall safety results of Study 182 were consistent with that seen in the placebo-controlled Phase 3 studies. The overall incidence of AEs in the active-treatment extension study was 26.3% (68/259) with 2.3% (6/259) SAEs. The most frequently reported AE was headache, in 6 (3.7%) patients who received brexpiprazole in the previous study and 3 (3.1%) patients who received prior placebo. Fall occurred in 5 (3.1%) patients in the prior brexpiprazole group and 1 (1.0%) patient in the prior placebo group, followed by nasopharyngitis occurring in 5 (5.2%) patients in the prior placebo group. Dizziness and somnolence each occurred in 4 (2.5%) patients in the prior brexpiprazole group and 1 (1.0%) patient in the prior placebo group. The overall incidence of study drug discontinuation due to an AE was 4.6% and was similar between patients who received brexpiprazole in the parent study (7 [4.3%] patients) and patients who received placebo in the parent study (5 [5.2%]). There were no deaths reported in Study 182, no cerebrovascular events, and one cardiovascular event of atrial fibrillation.

7.8 Selected Safety Topics of Special Interest

Safety topics of special interest were identified for enhanced data investigation based on the known pharmacology of the drug class effects, the underlying patient population, and known safety areas of interest for approved atypical antipsychotic agents. Six major topics of interest included falls, cerebrovascular events, cardiovascular events, sedation and somnolence, cognitive worsening, and EPS. Incidence of safety topics of interest were similar between brexpiprazole and placebo groups except somnolence including sedation was higher in the brexpiprazole group (3.7%) compared to the placebo group (1.8%) in the 3 controlled studies and the incidence of EPS related AEs was higher in the brexpiprazole group (5.3%) compared to the placebo group (3.1%; Table 22). However, the overall incidence of these safety topics of interest were lower in the AAD population than that reported in adult populations in approved indications for brexpiprazole. Further details on the safety topics of special interest are provided in Appendix 11.4.

Table 22: Studies 283, 284, and 213: Summary of Safety Topics of Special Interest

System Organ Class/Preferred Term, n (%)	Brexpiprazole 2 or 3 mg (N=366)	Brexpiprazole All (N=655)	Placebo (N=388)
Extrapyramidal symptoms[a]	17 (4.6)	35 (5.3)	12 (3.1)
Somnolence, sedation	13 (3.6)	24 (3.7)	7 (1.8)
Cardiovascular events[a]	10 (2.7)	24 (3.7)	9 (2.3)
Cerebrovascular events[a]	0	3 (0.5)	1 (0.3)
Accidents and Injuries[a]	8 (2.2)	15 (2.3)	16 (4.1)
Fall	7 (1.9)	11 (1.7)	10 (2.6)

a. Grouped terms.
Note: No worsening in cognition as assessed by MMSE change from baseline compared to placebo.
MMSE=Mini-Mental State Examination.

7.9 Vital Signs, Electrocardiograms, and Laboratory Values

In the 12-week controlled studies, mean baseline values were generally similar between the all brexpiprazole and placebo groups for all vital signs (heart rate, systolic blood pressure, diastolic blood pressure, and body temperature), ECG parameters (QTc), and laboratory values (hepatic, metabolic, renal, urinalysis, hematology, and coagulation parameters; electrolytes). The overall percentage of patients with clinically relevant changes in vital signs were low (≤ 0.7%) and were generally similar between the all brexpiprazole and placebo groups. The mean changes from baseline to Week 12 or last visit for each ECG and laboratory value were small in both treatment groups, and none were considered to be clinically meaningful.

7.10 Post-Marketing Information

The estimated cumulative number of patient-years of treatment with marketed brexpiprazole worldwide as of 30 June 2022 was 1,269,877.67 patient-years (based on available sales data).

No patients with underlying Dementia Alzheimer's type reported fatal outcome. A total of 58 fatal events were identified from 41 cases. The estimated fatal case reporting rate was 3.2 per 100,000 patient-years.

The analysis of safety data in patients > 65 years in the brexpiprazole post-marketing experience did not reveal any notable patterns or trends in this population and the characteristics of the events described in the report were consistent with the known safety profile of brexpiprazole.

7.11 Safety Conclusions

Overall, brexpiprazole offers an acceptable safety and tolerability profile based on findings from 751 patients exposed to brexpiprazole throughout the clinical development program for AAD (Studies 283, 284, 213, and 182). Nasopharyngitis, urinary tract infection, somnolence, and insomnia were the only AEs that were reported in ≥ 2% of all brexpiprazole-treated patients and greater than placebo. Most AEs were mild to moderate in severity. The proportion of treatment discontinuations due to AE was low across all 3 studies, providing support for the tolerability of brexpiprazole in patients with AAD. While incidence of death was numerically higher in the brexpiprazole group compared to the placebo group (0.9% vs 0.3%), the overall incidence was low (< 1%) with no pattern in cause of death and individual cases were confounded by underlying conditions and other factors. All of the events resulting in death were considered not related to brexpiprazole.

The clinical development program supports the findings that brexpiprazole treatment with 2 mg/day and 3 mg/day is safe and well tolerated. No notable differences in the incidence of AEs were seen across brexpiprazole treatment groups. Urinary tract infection was the only SAE reported by ≥ 2 patients in the 2 mg/day or 3 mg/day dose group. Tolerability to brexpiprazole 2 mg/day or 3 mg/day is supported by a high overall completion rate (88.4% in 2 mg group and 85% in 3 mg group in AAD short-term studies) and low incidence of discontinuations due to an AE (3.3% in 2 mg group and 7.2% in 3 mg group).

Continued treatment with brexpiprazole up to 24 weeks in the active treatment extension study was well tolerated and did not reveal any new safety signals.

Incidence of safety topics of interest were similar between brexpiprazole and placebo groups except somnolence including sedation and EPS. However, the overall incidence of somnolence including sedation and EPS related events were lower than that observed with adult populations in the approved indications of brexpiprazole. There was no evidence of worsening or more rapid cognitive decline based on MMSE with brexpiprazole compared to placebo.

No clinically meaningful differences were identified in laboratory parameters, ECGs, or vital signs between brexpiprazole and placebo groups. Baseline psychosis did not have an effect on overall incidence of AEs, SAEs, or deaths.

Moreover, safety results in patients with AAD in these studies were consistent with those from the extensive clinical experience with brexpiprazole in other indications and post-market experience. Collectively, the data support an acceptable safety profile for brexpiprazole in patients with AAD.

8 BENEFIT-RISK CONCLUSIONS

There are estimated to be approximately 60 million people living with Alzheimer's dementia and other forms of dementia worldwide. In the US, an estimated 6.5 million Americans aged ≥ 65 years have the condition (Alzheimer's Association 2022). Neuropsychiatric symptoms, including agitation, are serious and common features of dementia associated with Alzheimer's dementia. Agitation has been associated with accelerated disease progression, including rapid cognitive decline and progression to severe dementia, functional decline, loss of independence, decreased quality of life, and increased risk of institutionalization (Banerjee et al 2006; Cloutier et al 2019; Fillit et al 2021; Gaugler et al 2011; Lanctot et al 2017; Peters et al 2015; Rockwood et al 2019; Scarmeas et al 2007; Wilcock et al 2008; Zahodne et al 2015). Currently, no approved therapy is available for AAD, leaving a significant unmet need in a life-limiting disease.

Since there are no approved pharmacological treatments for the management of agitation in patients with Alzheimer's dementia, clinicians rely on off-label pharmacological use of drugs that show mixed results and carry several notable safety considerations such as increased risk of mortality, sedation, falls, and worsening of cognitive status (Hsu et al 2021; Caraci et al 2020; O'Gorman et al 2020; Moretti et al 2006; Schneider et al 2006). Given the serious consequences of AAD and lack of approved, effective, and safe treatment options, there is a significant unmet need for a therapeutic option with a positive benefit-risk profile.

Through 5-HT_{1A} and D_2 receptor partial agonist activity in combination with α_{1B} and α_{2C} receptor antagonism, brexpiprazole may reduce agitation in patients with AAD. Clinically, data from Studies 283 and 213 provide the primary evidence that these effects translate to meaningful improvements in multiple measures of agitation while offering a manageable safety profile. Supportive results come from the flexible-dose Study 284 and the active-treatment extension Study 182.

Efficacy results from two Phase 3 studies, Studies 213 and 283 demonstrated clinically meaningful and statistically significant improvements in agitation for the intended dose, brexpiprazole 2 or 3 mg/day, compared with placebo for the primary efficacy endpoint, mean change in CMAI total score. In addition, in Study 213, treatment with brexpiprazole 2 or 3 mg/day showed statistically significant improvement compared with placebo in the key secondary efficacy endpoint, mean change in CGI-S score as related to agitation. Clinical meaningful change was demonstrated by both pre-specified responder and MWPC analyses.

Safety data from 655 patients exposed to brexpiprazole in the 12-week controlled phase 3 AAD studies and 259 patients exposed to brexpiprazole in the 12-week active-treatment extension AAD study demonstrated that brexpiprazole is well-tolerated in patients with AAD. All AEs observed in the studies were consistent with approved labeling and occurred at incidence rates similar to or lower than previous adult brexpiprazole development programs. The safety profile of brexpiprazole in patients with Alzheimer's dementia has been characterized out to 24 weeks of exposure in the

active-treatment extension study in 152 patients. None of the 6 deaths that occurred in brexpiprazole treated patients during the double-blind treatment period were deemed attributable to brexpiprazole and no deaths occurred during the active-treatment extension. Rates of AEs for safety topics of special interest were generally low and similar between brexpiprazole and placebo. There was no evidence of negative effects on cognition based on MMSE scores with brexpiprazole compared to placebo. Safety and tolerability were comparable between the 2 or 3 mg/day brexpiprazole dose groups.

A total of 153 (of 655) patients in the all brexpiprazole group had baseline psychotic symptoms in the program. There was no meaningful difference in the safety profile observed in patients with or without baseline psychotic symptoms.

The findings from AAD development program were generally consistent with the known safety profile of brexpiprazole. There were no additional safety issues that would preclude use in the intended population. Risks can be adequately described in labeling to allow for safe use of the drug.

Taken together, the overall data indicate that the improvement in agitation behaviors with brexpiprazole addresses several aspects of the disease and supports a positive benefit-risk profile for the treatment of AAD. Importantly, brexpiprazole meets the regulatory criteria for demonstrating the clinical effectiveness in this devastating disease with no approved therapies and significant unmet need. If approved, brexpiprazole would be the first-time clinicians would have data and labeling to make informed choices based on demonstrated benefits and acceptable risks in a high-risk patient population.

9 FDA MANDATED CLASS WARNING FOR ATYPICAL ANTIPSYCHOTICS

In 2005, an FDA analysis of 17 placebo-controlled studies (not including brexpiprazole) resulted in a class (boxed) warning for all antipsychotics in the USPI. FDA concluded that over the course of a typical 10-week controlled study in patients aged ≥ 65 years with dementia-related psychosis, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group. It was also noted that most of the deaths were due to cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) causes. Consequently, all antipsychotic medications carry a boxed warning in the USPI for the increased risk of death in patients aged ≥ 65 years with dementia-related psychosis. In addition, FDA also added a class warning for cerebrovascular AEs in patients aged ≥ 65 years with dementia-related psychosis, noting a higher incidence of stroke and transient ischemic attacks, including fatal stroke with atypical antipsychotics.

The boxed warning in the currently approved brexpiprazole label (REXULTI) indicates an increased risk of death in elderly patients with dementia-related psychosis. The Sponsor proposes that the black box remains. The Sponsor intends to discuss label wording with the FDA to guide healthcare professionals and patients in the safe use of Rexulti in patients with AAD and the exact labeling text will be discussed with FDA to appropriately address risks and to accommodate the AAD indication. As precedence, in 2016, FDA approved pimavanserin (NUPLAZID) for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis and modified the boxed warning language to accommodate this indication.

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11 APPENDICES

11.1 Studies 283, 284, and 213 Inclusion and Exclusion Criteria

11.1.1 Fixed-Dose Study 283 and Flexible-Dose Study 284

Patients were required to fulfill all of the following criteria:

1. For inclusion into Studies 283 and 284, the Investigator was required to assess the capacity of the patient to provide informed consent during the screening period and throughout the course of the study.
2. Male or female between 55 and 90 years of age, inclusive, at the time of informed consent.
3. A diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.
4. A Mini-Mental State Examination (MMSE) score of 5 to 22, inclusive, at screening and baseline visits.
5. Previous magnetic resonance imaging (MRI) or computed tomography (CT) scan of the brain, which was performed after the onset of the symptoms of dementia, with findings consistent with a diagnosis of Alzheimer's disease.
6. Residing at their current location for at least 14 days before screening and were expected to remain at the same location for the duration of the trial.
7. Institutionalized patients with an identified caregiver who had sufficient contact (minimum of 2 hours per day for 4 days per week) to describe the patient's symptoms and had direct observation of the patient's behavior. The identified caregiver could have been a staff member of the institutionalized setting or another individual (e.g., family member, family friend, hired professional caregiver) who met the caregiver requirements.

   Non-institutionalized patients may not have been living alone and must have had an identified caregiver who had sufficient contact (minimum of 2 hours per day for 4 days per week) to describe the patient's symptoms and had direct observation of the patient's behavior.
8. A total score (frequency × severity) of ≥ 4 on the agitation/aggression item of the Neuropsychiatric Inventory–Nursing Home (NPI-NH; for institutionalized patients) or the Neuropsychiatric Assessment for Noninstitutionalized Patients based on the NPI-NH (NPI/NPI-NH; for non-institutionalized patients) at the screening and baseline visits.
9. Onset of symptoms of agitation at least 2 weeks prior to the screening visit.

10. Required pharmacotherapy for the treatment of agitation per the Investigator's judgment, after an evaluation for reversible factors (e.g., pain, infection, polypharmacy) and a trial of nonpharmacological interventions.
11. Capable of self-locomotion or locomotion with an assistive device (e.g., 4-point walker, wheelchair).
12. Willing and able to discontinue all prohibited concomitant medications to meet protocol-required washouts prior to and during the trial period.
13. Able to satisfactorily comply with the protocol requirements.

Any of the following was regarded as criterion for exclusion from the trial. Patients must not have had:

1. Dementia or other memory impairment not due to Alzheimer's disease, such as mixed or vascular dementia, dementia with Lewy bodies, Parkinson's disease dementia, frontotemporal dementia, substance-induced dementia, HIV-dementia, traumatic brain injury, normal pressure hydrocephalus, or any other specific non-Alzheimer's-type dementia; a diagnosis of Down syndrome.
2. Previous MRI or CT scan of the brain, which was performed after the onset of the symptoms of dementia, with findings consistent with a clinically significant central nervous system disease other than Alzheimer's disease, such as vascular changes (e.g., cortical stroke, multiple infarcts), space-occupying lesion (e.g., tumor), or other major structural brain disease.
3. A previous history of stroke, well-documented transient ischemic attack, or pulmonary or cerebral embolism.
4. An insufficient response, based on the Investigator's judgment, to ≥ 2 previous antipsychotic medications for the treatment of agitation associated with Alzheimer's disease.
5. Delirium or history of delirium within 30 days prior to the screening visit.
6. Diagnosed with an Axis I disorder (DSM-IV-TR criteria) including, but not limited to:
    - Schizophrenia, schizoaffective disorder, or other psychotic disorder not related to dementia,
    - Bipolar I or II disorder, bipolar disorder not otherwise specified, or
    - Current major depressive disorder. Patients with major depressive disorder are eligible provided that they have been on a stable dose(s) of antidepressant medication(s) for the 30 days prior to randomization. Please note: antidepressant medications that are CYP2D6 or CYP3A4 inhibitors are prohibited.

7. Evidence of serious risk of suicide based on the Sheehan Suicidality Tracking Scale (Sheehan-STS), i.e., a score of 3 or 4 on any one question 2 through 6 or 11 or a score of 2 or higher on any questions 1a, 7 through 10, or 12, or who, in the opinion of the Investigator, present a serious risk of suicide.
8. Clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, gastrointestinal, or psychiatric disorders. Clinically significant cardiovascular disorders included uncontrolled atrial fibrillation, heart failure, or ischemic heart disease. Surrogates for uncontrolled cardiovascular disease included recent (within the last 6 months) hospitalizations or procedures, such as percutaneous coronary intervention, coronary bypass surgery.

   Medical conditions that were minor or well controlled were considered acceptable if the condition would not expose the patient to an undue risk of a significant adverse event or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor was to be contacted in any instance where the Investigator was uncertain regarding the stability of a patient's medical condition(s) and the potential impact of the condition(s) on trial participation.
9. Uncontrolled hypertension (diastolic blood pressure [DBP] > 95 mmHg) or symptomatic hypotension, or orthostatic hypotension, which was defined as a decrease of ≥ 30 mm Hg in systolic blood pressure (SBP) and/or a decrease of ≥ 20 mmHg in DBP within 3 minutes of standing compared to the previous supine blood pressure, or development of symptoms. Abnormal vital signs results were to be repeated to ensure reproducibility of the abnormality before excluding a patient based on the criteria noted above.
10. Patients with diabetes mellitus were eligible for the trial if their condition was stable and well-controlled as determined by satisfying all of the following criteria at screening and baseline:
    - HbA1c < 8.0%,
    - Screening glucose must be ≤ 125 mg/dL (fasting) or < 200 mg/dL (nonfasting). If the nonfasting screening glucose is ≥ 200 mg/dL, patients must be retested in a fasted state and the retest value must be ≤ 125 mg/dL, and
    - Patient did not have any hospitalizations within the 3 months prior to screening due to diabetes, or Complications related to diabetes.

    Patients with non-insulin-dependent diabetes mellitus (IDDM; i.e., any patients not using insulin) must also have satisfied the below criterion:

    - Patient had to have been maintained on a stable regimen of oral antidiabetic medication(s) for at least 28 days prior to screening or

diabetes had been well-controlled by diet for at least 28 days prior to screening.

Patients with IDDM (i.e., any patients using insulin) must also have to have satisfied the below criterion:

- No current microalbuminuria; i.e., urine albumin-to-creatine ratio (ACR) had to have been < 30 mg/g (calculated).
- Patients with newly diagnosed diabetes during screening were excluded.

11. Hypothyroidism or hyperthyroidism (unless condition had been stabilized with medications for at least the past 90 days) and/or an abnormal result for free T4 at screening.

    Eligibility of patients excluded based on an abnormal free T4 result could be discussed with the medical monitor if, in the Investigator's judgment, the patient was a suitable candidate for the trial.

12. Epilepsy or a history of seizures, except for a single childhood febrile seizure, post traumatic, alcohol withdrawal, etc.
13. Seropositive status for hepatitis B (i.e., HBsAg positive) or hepatitis C (i.e., anti-HCV positive).
14. Considered in poor general health based on the Investigator's judgment. Examples included patients who had a recent clinically significant weight loss, chronic dehydration or hypovolemia, poor fluid or nutritional intake, or a recent clinically significant infection, as per the Investigator's judgment.
15. A body mass index (BMI) < 18.5 kg/m^2.
16. Met DSM-IV-TR criteria for substance abuse or dependence within the past 180 days; including alcohol and benzodiazepines, but excluding caffeine and nicotine.
17. A positive drug screen for cocaine, marijuana (whether medically prescribed or not), or other illicit drugs were excluded and could not be retested or rescreened. Patients with a positive urine drug screen resulting from use of prescription or over the counter (OTC) medications or products that in the Investigator's documented opinion did not signal a clinical condition that would impact the safety of the patient or interpretation of the trial results could continue evaluation for the trial following consultation and approval by the medical monitor.
18. Abnormal laboratory test results, vital sign results, or electrocardiogram (ECG) findings, unless, based on the Investigator's judgment, the findings were not medically significant and would not impact the safety of the patient or the interpretation of the trial results. The medical monitor was to be contacted to discuss individual cases, as needed.

In addition, patients with the following laboratory test and ECG results at screening were excluded from the trial:

- Platelets ≤ 75,000/mm^3,
- Hemoglobin ≤ 9 g/dL,
- Neutrophils, absolute ≤ 1000/mm^3,
- Aspartate aminotransferase (AST) > 2 x the upper limit of normal (ULN),
- Alanine aminotransferase (ALT) > 2 x ULN,
- Creatine phosphokinase (CPK) > 3 x ULN, unless discussed with and approved by the medical monitor,
- Albumin < 3 g/dL,
- HbA_{1c} ≥ 8%,
- Abnormal T4, unless discussed with and approved by the medical monitor. (Note: Free T4 was measured only if the result for thyroid-stimulating hormone [TSH] was abnormal.),
- QTcF ≥ 450 msec in men and ≥ 470 msec in women unless due to ventricular pacing, and
- Tests with exclusionary results were repeated (if ECG, 3 consecutive recordings) to ensure reproducibility of the abnormality before excluding a patient based on the criteria noted above.

19. Sexually active females of childbearing potential and male patients who were not practicing 2 different methods of birth control with their partner during the trial and for 30 days after the last dose of trial medication or who would not remain abstinent during the trial and for 30 days after the last dose. If employing birth control, each couple had to use 2 of the following precautions: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injections, condom with spermicide, or sponge with spermicide.
20. Females who were breast-feeding and/or who had a positive pregnancy test result prior to receiving trial drug.
21. Current medical condition that required treatment with an anticoagulant.
22. Received bapineuzumab, solanezumab, or other immunotherapy, such as vaccines, for the treatment of Alzheimer's disease (through clinical trial or compassionate use program) in the 6 months preceding randomization.
23. Likely required prohibited concomitant therapy during the trial.

24. Received brexpiprazole in any prior clinical trial or commercially available brexpiprazole (Rexulti®).
25. A history of neuroleptic malignant syndrome.
26. A history of true allergic response (i.e., not intolerance) to > 1 class of medications.
27. Participated in a clinical trial within the last 30 days.
28. In the opinion of the Investigator, medical monitor, or Sponsor should not participate in the trial.

11.1.2 Fixed-Dose Study 213

For inclusion into Study 213, patients were required to fulfill the criteria outlined for Studies 283 and 284 (Appendix 11.1.1), with the exception of the following modified or additional criteria:

1. A diagnosis of agitation that meets the International Psychogeriatric Association (IPA) provisional definition of agitation.
2. Residing at their current location for at least 28 days before screening and are expected to remain at the same location for the duration of the trial.
3. Patients who require pharmacotherapy for the treatment of agitation per the Investigator's judgment, after:
    - An evaluation for reversible factors (e.g., pain, infection, or polypharmacy), and
    - A trial of nonpharmacological interventions (e.g., redirecting behavior, group activities, music therapy).

A criterion that site Investigators were blinded to included:

4. Patients must have met the criteria for CMAI Factor 1 agitation at screening and baseline, which include: hitting (including self), kicking, scratching, grabbing, pushing, hurting self or others, throwing things, cursing or verbal aggression, spitting, tearing things or destroying property, screaming and biting.
   In order to meet this criterion, one of the following must be displayed:
    a. ≥ 1 aggressive behaviors occurring several times per week, or
    b. ≥ 2 aggressive behaviors occurring once or twice per week, or
    c. ≥ 3 aggressive behaviors occurring less than once per week.

Any of the following was regarded as criterion for exclusion from the trial. Patients must not have had:

1. Received high-dose antipsychotics exceeding the equivalent of ≥ 3 mg of risperidone (e.g., ≥ 5 mg of haloperidol, ≥ 375 mg quetiapine, ≥ 10 mg olanzapine, or local equivalent) within 90 days prior to screening.

2. Received multiple antipsychotic medications simultaneously for a period of > 7 days within 90 days prior to screening.
3. Patients with diabetes mellitus (IDDM and non-IDDM) were eligible for the trial if their condition was stable and well-controlled as determined by satisfying all of the following criteria at screening and baseline:
    - HbA1c < 8.0%, and
    - Glucose ≤ 125 mg/dL (fasting) or < 200 mg/dL (non-fasting). If the non fasting screening glucose was ≥ 200 mg/dL, patients were retested in a fasted state and the retest value must have been ≤ 125 mg/dL, and
    - Patient did not have any hospitalizations within the 3 months prior to screening due to diabetes or complications related to diabetes.
4. A BMI < 18.5 kg/m^2 at screening and baseline.

11.2 CMAI Factors

Table 23: CMAI Factor Composition, Definition, and Corresponding Scores[a]

	CMAI			
	Factor 1: Aggressive Behavior	**Factor 2: Physically Non-Aggressive Behavior**	**Factor 3: Verbally Agitated Behavior**	**Other Behaviors**
Behaviors	• Hitting • Kicking • Pushing • Scratching • Hurting self or others • Tearing things or destroying property • Throwing things • Screaming • Cursing or verbal agitation • Grabbing • Biting • Spitting	• Pace, aimless wandering • Inappropriate dress or disrobing • Trying to get to a different place • Handing things inappropriately • General restlessness • Performing repetitive mannerisms	• Complaining • Constant requests for attention • Negativism • Repetitious sentences or questions	• Hiding things • Hoarding things • Making strange noises • Eating/drinking inappropriate substances • Intentional falling • Verbal sexual advances • Physical sexual advances
Range of possible scores	≥ 12 and ≤ 84	≥ 6 and ≤ 42	≥ 4 and ≤ 28	≥ 7 and ≤ 49

a. Rabinowitz et al 2005.
CMAI=Cohen-Mansfield Agitation Inventory.

11.3 Details of Deaths Reported in Studies 283, 284, and 213 (Safety Sample)

The causes of death were varied and reflective of the types of events that would be expected in the underlying population including encephalitis, hemorrhage intracranial, Obstructive Airway Disorder, pneumonia aspiration, Dementia Alzheimer's Type, cardiac failure, vascular encephalopathy, brain oedema, and pneumonia (additional details provided in Appendix 11.3.1). All reports were assessed as not related by the Investigator. The majority of the deaths occurred in patients older than 75 years of age (range: 66–87 years of age). There were no patterns in terms of time to onset of the events leading to the fatal reports, ranging from as early as 8 days to 71 days.

11.3.1 Brief Narratives on Deaths

11.3.1.1 Brexpiprazole-Treated Patients

1) Study ID: 331-12-283

   Dose: Brexpiprazole 0.5mg

   Treatment Duration: 50 days

   Event: Acute Purulent Meningoencephalitis (Preferred Term [PT]: Encephalitis)

   A 76-year-old male patient experienced a fatal event of acute purulent meningoencephalitis approximately 52 days after initiating study medication and 2 days after stopping study medication (due to personal reason). Two (2) days prior to stopping study medication, the patient developed generalized weakness; then was diagnosed with bilateral pneumonia (2 days after stopping study medication) along with stagnation and signs of heart failure. The patient was otherwise well without any complaints prior to experiencing symptoms but rapidly deteriorated from his conditions and died.

   Relevant medical history included atherosclerosis of retinal vessels, hypertensive disease, chronic ischemic heart disease, anemia, diabetes type II, and chronic heart failure.

   Concomitant medications included metoprolol and doxazosin.

   Clinical post-mortem summary noted that the patient's condition deteriorated as a result of a combination of bilateral subtotal focal, draining purulent pneumonia with abscesses, complicated by development of purulent meningoencephalitis. The cause of death was provided as acute purulent meningoencephalitis.

   The event of acute purulent meningoencephalitis was considered as not related to brexpiprazole, as this was an incidental infection-related event.

2) Study ID: 331-12-283

   Dose: Brexpiprazole 0.5mg

   Treatment Duration: 8 Days

Event: Intracranial Hemorrhage (PT: Hemorrhage Intracranial)

An 87-year-old female experienced a fall and was hospitalized 8 days after initiation of study medication. Study medication was discontinued due to the fall. Clopidogrel bisulfate was started during the hospitalization because of initial suspicion of acute myocardial infarction which was subsequently ruled out. She was discharged after 6 days. Approximately 10 days after discontinuation from study medication, the patient exhibited worsening of aggressive behavior and was admitted to a psychiatric hospital. Approximately 22 days from discontinuing from study medication, she was found unresponsive with irregular breathing pattern and unstable fluctuating blood pressure and was transferred to a hospital. A CT scan of the brain without contrast revealed a large left-sided intracranial hemorrhage with intraparenchymal, subarachnoid and intraventricular hematoma. The patient died 5 days later (27 days from discontinuing study medication).

Relevant medical history included subarachnoid hemorrhage, hypertension, heart disease, asthma, deep vein thrombosis, hip fracture, spinal stenosis, chronic back pain, and generalized anxiety superimposed up on a suspected personality disorder.

Relevant concomitant medications included escitalopram oxalate, furosemide, lisinopril, alprazolam, metoprolol tartrate, and clopidogrel bisulfate.

Autopsy revealed a massive, subarachnoid, and parenchymal hemorrhage, acute left anterior frontal and parietal lobes.

The event of intracranial hemorrhage with fatal outcome was unrelated to brexpiprazole in view of potential confounders including prior history of subarachnoid hemorrhage and recent initiation of clopidogrel bisulfate.

3) Study ID: 331-12-283

Dose: Brexpiprazole 1mg

Treatment Duration: 85 days

Event: Mechanical obstruction of the airway by a foreign body (orange) (PT: Obstructive Airway Disorder)

A 66-year-old female experienced a cardiopulmonary arrest secondary to a mechanical obstruction of the airway by choking on an orange 25 days after her last dose of study medication. There was no prior complaint of difficulty swallowing or prior history of similar events. She was successfully resuscitated by the medical staff, and transferred to the intensive care unit (ICU). Two days later a tracheostomy was performed. The patient remained comatose on mechanical ventilation and ultimately suffered another cardiac arrest and died 42 days later (152 days after starting study medication and 67 days after her last dose).

Relevant medical history included atherosclerosis of retinal vessels, atherosclerotic cardiosclerosis, chronic ischemic heart disease, and heart failure.

Concomitant medications included akatinol memantine, chlorprothixene, and aspirin.

Post-mortem summary showed extensive ischemic cerebral infarction caused by post-resuscitation illness with brain lesion, in conjunction with post-aspiration bilateral subtotal interstitial pneumonia.

The event of mechanical obstruction by foreign body was not related to brexpiprazole. The event had occurred 25 days after the last dose of brexpiprazole and was due to the patient choking on an orange.

4) Study ID: 331-12-283

Dose: Brexpiprazole 1mg

Treatment Duration: 65 days

Event: Aspiration Pneumonia (PT: Pneumonia Aspiration)

A 78-year-old male developed aspiration pneumonia approximately 65 days after initiation of study medication. The study medication was stopped on the same day. The patient was hospitalized for fever, agitation, confusion, and hypoxic respiratory failure. Chest x-ray showed mild perihilar interstitial prominence suspicious for aspiration pneumonia. He was started on empirical antibiotics. He was found to have dysphagia with an abnormal video swallow evaluation. The family did not want any aggressive management, no tube feeding, and the patient was transferred to hospice for comfort measures of care; active treatment was discontinued. Seventy-eight (78) days after starting study medication and 13 days after the last dose, the patient died.

Relevant medical history included chronic obstructive pulmonary disease (COPD), right carotid artery stenosis, small bowel obstruction, S/P cholecystectomy, S/P small bowel resection for ileus, depression, acute encephalopathy, hypertension, and peripheral vascular disease.

Concomitant medication included propranolol for agitation and latanoprost for glaucoma.

The event of aspiration pneumonia was considered not related to brexpiprazole based on events appearing confounded by the patient’s age, underlying AD, and medical history of COPD and encephalopathy.

5) Study ID: 331-12-283

Dose: Brexpiprazole 2mg

Treatment Duration: 86 days

Event: End stage Alzheimer's Dementia (PT: Dementia Alzheimer’s Type)

An 86-year-old female experienced the event of end-stage Alzheimer's dementia 4 days after completing study treatment. Reportedly, one month prior to stopping study medication, the patient's general condition was starting to decline, and she had started to refuse oral intake and medications about 2 weeks prior to the last dose of study medication. She subsequently experienced weight loss and was diagnosed with urinary tract infection. She was started on ciprofloxacin. Hospice was initiated 5 days after stopping study medication, and the patient was notedly pulling away her IV lines prior to hospice. Subsequently, she experienced uncontrolled dehydration and hypertension due to her refusal of medications and died 9 days after stopping study medication.

Relevant medical history included hypertension, anemia, hypothyroidism, constipation, depression, and gastroesophageal reflux disease.

The event of end-stage Alzheimer's dementia was not related to brexpiprazole but was due to the progression of the patient's underlying Alzheimer's disease.

6) Study ID: 331-14-213

Dose: Brexpiprazole 3mg

Treatment Duration: 28 days

Event: Heart Failure (PT: Cardiac Failure)

A 78-year-old male experienced the serious fatal event of cardiac failure, 51 days from the first dose of study medication and 23 days from the last dose. The patient discontinued the study medication on study Day 28 due to acute hallucination. Approximately 7 days prior to stopping study medication, the patient developed asthenia and subsequently pneumonia and cachexia 4 days and 23 days after stopping study medication, respectively. The patient's general condition continued to decline, with progressively depressed level of consciousness. The patient ultimately experienced a cardiac arrest, with unsuccessful resuscitation attempt and died 23 days after the last dose of study medication. Autopsy revealed cerebral and coronary atherosclerosis.

Relevant medical history included delirium syndrome and acute hallucination.

Concomitant medications included clopixol, donepezil, memantine, and levofloxacin.

The event of cardiac failure was not related to brexpiprazole but was confounded by the patient's elderly age, autopsy finding of coronary atherosclerosis, and multiple concomitant medications including levofloxacin.

7) Death that Occurred After the Reporting Period of the Completed 12-Week Controlled Studies

Study ID: 331-14-284

Dose: Brexpiprazole 2mg

Treatment Duration: 42 days

Event: Dyscirculatory Encephalopathy (PT: Vascular Encephalopathy), Brain Oedema (PT: Brain Oedema)

An 80-year-old male experienced the serious fatal event of dyscirculatory encephalopathy and brain oedema on study Day 74 (32 days after the last dose of study medication) and 2 days after the 30-day safety follow-up period). On study Day 43 patient was found to be irritable, fidgety, and wandering aimlessly. The following morning, he was found unresponsive, unable to be aroused from sleep and noted to be incontinent. Patient was transferred to the hospital and a CT scan confirmed a subdural hematoma of the right hemisphere. Study medication was withdrawn due to the subdural hematoma. It was noted that there was no recent trauma, fall, or head injury. The patient underwent surgery to evacuate the subdural hematoma and was subsequently discharged from the hospital. The event of subdural hematoma was considered resolved with sequelae. Post-operatively the patient complained of a headache, was restless, confused, had no awareness of his illness, and was incontinent. The patient was transferred to a psychiatric hospital 13 days after stopping study medication. Encephalopathy and brain oedema developed secondary to subdural hematoma. Cardiac activity failure developed secondary to ischemic heart disease. Thirty-two (32) days after trial medication was stopped, the patient died. The main cause of death was dyscirculatory encephalopathy complicated by brain oedema, which was secondary to spontaneous subdural hematoma.

Relevant medical history included prostatic adenoma, retinal vascular disorder, aortic arteriosclerosis, myocardial ischemia, and psoriasis.

Concomitant medications included memantine, pramiracetam, pentoxifylline, gidazepam, ceftriaxone, and prednisolone.

The events of dyscirculatory encephalopathy and brain oedema were not related to brexpiprazole, but due to patient's elderly age and status-post spontaneous subdural hematoma.

11.3.1.2 Placebo-Treated Patient

1) Study ID: 331-12-284

Dose: Placebo

Treatment Duration: 74 days

Event: Pneumonia (PT: Pneumonia)

An 86-year-old male experienced the serious fatal event of pneumonia 76 days after initiating study therapy and 2 days after completion of study treatment. Prior to the event, the patient was bed bound, residing in a retirement home, and experienced recurrent urinary infections. Three (3) days prior to stopping study

medication, the patient developed respiratory symptoms with occasional dyspnea and coughing. Pneumonia was diagnosed 2 days prior to stopping study medication, and the patient was prescribed antibiotic therapy and all the supportive measures. The patient's respiratory function was gradually worsening despite the treatment and the patient died due to respiratory insufficiency from the underlying pneumonia.

Relevant medical history included anxiety, permanent urinary catheter, difficulty in urination and urine retention.

Concomitant medications included aspirin, escitalopram, azithromycin pantoprazole, metamizole, paracetamol, ibuprofen, amoxicillin, nitrofurantoin, tamsulosin, and finasteride.

The event of pneumonia was not related to the study medication. The patient had risk factors for developing infections, such as the patient's elderly age (86), bed ridden state, and living in the nursing home.

11.4 Selected Safety Topics of Special Interest

11.4.1 Accident and Injuries Including Falls

Overall, incidences of accidents and injuries including fall were low in all treatment groups in the three 12-week controlled studies (Table 24). The overall incidence of AEs for accidents and injuries including falls was lower in the all brexpiprazole group (2.3%) compared to placebo (4.1%).

Falls were reported by 1.7% of patients in the all brexpiprazole dose groups compared with 2.6% of patients in the placebo group.

Table 24: Studies 283, 284, and 213: Accident and Injuries Including Falls (Safety Sample)

Preferred Term, n (%)	Brexpiprazole ≤ 1 mg (N=157)	Brexpiprazole 2 or 3 mg (N=366)	Brexpiprazole 0.5–2 mg (N=132)	Brexpiprazole All (N=655)	Placebo (N=388)
Patients with any AE[a]	5 (3.2)	8 (2.2)	2 (1.5)	15 (2.3)	16 (4.1)
Buttock injury	0	0	0	0	1 (0.3)
Contusion	1 (0.6)	1 (0.3)	1 (0.8)	3 (0.5)	5 (1.3)
Fall	2 (1.3)	7 (1.9)	2 (1.5)	11 (1.7)	10 (2.6)
Femur fracture	0	0	0	0	1 (0.3)
Head injury	0	0	0	0	2 (0.5)
Hip fracture	0	1 (0.3)	0	1 (0.2)	2 (0.5)
Humerus fracture	1 (0.6)	0	0	1 (0.2)	0
Limb injury	0	0	0	0	1 (0.3)
Patella fracture	0	0	0	0	1 (0.3)
Rib fracture	0	0	0	0	1 (0.3)
Skin laceration	2 (1.3)	0	0	2 (0.3)	1 (0.3)
Thermal burn	0	1 (0.3)	0	1 (0.2)	0

a. Patients with AEs in multiple system organ classes were counted only once towards the total.
AE=adverse event.

11.4.2 Cerebrovascular Events

The incidence of cerebrovascular events was low in all treatment groups, 0.5% in the all brexpiprazole group compared to 0.3% in the placebo group (Table 25). No cerebrovascular events were reported in the 2 or 3 mg/day brexpiprazole dose group.

Table 25: Studies 283, 284, and 213: Cerebrovascular Events (Safety Sample)

Preferred Term, n (%)	Brexpiprazole ≤ 1 mg (N=157)	Brexpiprazole 2 or 3 mg (N=366)	Brexpiprazole 0.5–2 mg (N=132)	Brexpiprazole All (N=655)	Placebo (N=388)
Patients with any AE[a]	2 (1.3)	0	1 (0.8)	3 (0.5)	1 (0.3)
Cerebrovascular accident	1 (0.6)	0	0	1 (0.2)	0
Hemorrhage intracranial	1 (0.6)	0	0	1 (0.2)	0
Lacunar infarction	1 (0.6)	0	0	1 (0.2)	0
Subdural hematoma	0	0	1 (0.8)	1 (0.2)	0
Transient ischemic attack	0	0	0	0	1 (0.3)

a. Patients with AEs in multiple system organ classes were counted only once towards the total.
AE=adverse event.

11.4.3 Cardiovascular Events

The overall incidence of cardiovascular events, which included categories of cardiac arrhythmias, ischemic heart disease, and cardiac failure, was low in all treatment groups in the 12-week controlled studies (Table 26). The incidence of AEs for cardiovascular events was 3.7% (24 patients) in the brexpiprazole group compared to 2.3% (9 patients) in the placebo group. The incidence was similar between brexpiprazole 2 or 3 mg/day dose group (2.7%) and placebo group (2.3%). In the fixed-dose AAD studies (Studies 283 and 213), the incidence for cardiovascular events was higher in the brexpiprazole 2 mg group (4.2%) compared to the 3 mg group (0.7%).

The most common events were in the category of cardiac arrhythmias. Other than ECG QT prolonged, no individual event occurred in > 1% of patients in any of the brexpiprazole dose groups. The incidence of QT prolongation was 1.2% in the brexpiprazole group compared to 0.5% in the placebo group. No trend in the incidences was observed in the different brexpiprazole dosing groups. No brexpiprazole-treated patient had a QT interval corrected for heart rate (QTc) value > 500 msec by any correction method in either study; 4 placebo-treated patients had a QTcB value > 500 msec in all the 12-week controlled studies. No signal related to administration of brexpiprazole has been observed in the AAD clinical program with regard to QT prolongation.

Of the 24 patients in the brexpiprazole group, 2 patients reported serious adverse events (SAEs) for cardiovascular events including pulmonary oedema and cardiac failure.

Table 26: Studies 283, 284, and 213: Cardiovascular Events (Safety Sample)

System Organ Class Preferred Term, n (%)	Brexpiprazole				Placebo
	≤ 1 mg (N=157)	2 or 3 mg (N=366)	0.5–2 mg (N=132)	All (N=655)	(N=388)
Patients with any AE[a]	7 (4.5)	10 (2.7)	7 (5.3)	24 (3.7)	9 (2.3)
Cardiac arrhythmias	7 (4.5)	7 (1.9)	5 (3.8)	19 (2.9)	9 (2.3)
Electrocardiogram QT prolonged	4 (2.5)	3 (0.8)	1 (0.8)	8 (1.2)	2 (0.5)
Atrioventricular block first degree	1 (0.6)	3 (0.8)	0	4 (0.6)	2 (0.5)
Bundle branch block left	1 (0.6)	1 (0.3)	1 (0.8)	3 (0.5)	2 (0.5)
Sinus bradycardia	1 (0.6)	0	1 (0.8)	2 (0.3)	3 (0.8)
Supraventricular extrasystoles	1 (0.6)	0	1 (0.8)	2 (0.3)	1 (0.3)
Atrial fibrillation	0	0	1 (0.8)	1 (0.2)	0
Bundle branch block right	0	1 (0.3)	0	1 (0.2)	0
Ventricular extrasystoles	1 (0.6)	0	0	1 (0.2)	0
Ischemic heart disease	0	1 (0.3)	2 (1.5)	3 (0.5)	0
Angina pectoris	0	0	2 (1.5)	2 (0.3)	0
Myocardial ischemia	0	1 (0.3)	0	1 (0.2)	0
Cardiac failure	0	2 (0.5)	0	2 (0.3)	0
Cardiac failure	0	1 (0.3)	0	1 (0.2)	0
Pulmonary oedema	0	1 (0.3)	0	1 (0.2)	0

a. Patients with AEs in multiple system organ classes were counted only once towards the total.
AE=adverse event.

11.4.4 Sedation and Somnolence

Somnolence/sedation was reported by 3.7% of patients in the all brexpiprazole group compared with 1.8% of patients in the placebo group for the three 12-week controlled studies (Table 27).

Table 27: Studies 283, 284, and 213: Somnolence and Sedation (Safety Sample)

Preferred Term, n (%)	Brexpiprazole ≤ 1 mg (N=157)	Brexpiprazole 2 or 3 mg (N=366)	Brexpiprazole 0.5–2 mg (N=132)	Brexpiprazole All (N=655)	Placebo (N=388)
Patients with any AE[a]	2 (1.3)	13 (3.6)	9 (6.8)	24 (3.7)	7 (1.8)
Somnolence	2 (1.3)	12 (3.3)	8 (6.1)	22 (3.4)	7 (1.8)
Sedation	0	1 (0.3)	1 (0.8)	2 (0.3)	0

a. Patients with AEs in multiple system organ classes were counted only once towards the total.
AE=adverse event.

11.4.5 Cognitive Worsening

The MMSE is a brief practical test for assessing cognitive dysfunction (Folstein et al, 1975). The test consists of 5 sections (orientation, registration, attention and calculation, recall, and language) and has a total possible score of 30. Mean baseline MMSE total score values were similar among the all brexpiprazole and placebo groups (Table 28). Mean changes from baseline to Week 12 or last visit in MMSE total score values were small across both treatment groups, and none were considered clinically meaningful.

Table 28: Studies 283, 284, and 213: Cognitive Worsening (Safety Sample)

	Brexpiprazole ≤ 1 mg (N=157)	Brexpiprazole 2 or 3 mg (N=366)	Brexpiprazole 0.5–2 mg (N=132)	Brexpiprazole All (N=655)	Placebo (N=388)
Baseline					
n[a]	157	366	132	655	388
Mean (SD)	13.1 (3.8)	15.0 (3.7)	14.7 (4.1)	14.5 (3.9)	14.8 (4.1)
Median (min, max)	14.0 (6.0, 22.0)	15.0 (6.0, 22.0)	15.0 (5.0, 22.0)	15.0 (5.0, 22.0)	15.0 (5.0, 25.0)
Change at Week 12					
n[b]	132	313	116	561	338
Mean (SD)	0.1 (2.0)	0.5 (2.6)	-0.2 (2.0)	0.3 (2.4)	0.1 (2.2)
Median (min, max)	0.0 (-6.0, 8.0)	0.0 (-8.0, 9.0)	0.0 (-7.0, 5.0)	0.0 (-8.0, 9.0)	0.0 (-7.0, 8.0)
Change at last visit					
n[c]	140	345	124	609	367
Mean (SD)	0.1 (2.1)	0.4 (2.6)	-0.2 (2.0)	0.2 (2.4)	0.1 (2.2)
Median (min, max)	0.0 (-8.0, 8.0)	0.0 (-8.0, 9.0)	0.0 (-7.0, 5.0)	0.0 (-8.0, 9.0)	0.0 (-7.0, 9.0)

a. Baseline=last pre-dose evaluation; Last Visit=last available post-baseline evaluation including early term.
b. Total number of treated patients with evaluation of the given parameter at the specific visit.
c. Total number of treated patients with both baseline and evaluation of the given parameter at the specific visit.

11.4.6 Extrapyramidal Symptoms

The incidence of reported extrapyramidal symptoms (EPS)-related AEs in the 12-week controlled studies was 5.3% for the all brexpiprazole group compared with 3.1% for the placebo group. The most frequently reported EPS-related AEs in the 2 or 3 mg/day brexpiprazole group were tremor and extrapyramidal disorder (0.8% for each; Table 29). In the placebo group, the incidence of tremor was 1.5% and no patients experienced extrapyramidal disorder. Akathisia, extrapyramidal disorder, and tremor are the only EPS-related AEs reported in > 2 patients in any of the brexpiprazole dose groups.

Table 29: Studies 283, 284, and 213: Extrapyramidal Symptoms (Safety Sample)

	Brexpiprazole				
Preferred Term, n (%)	≤ 1 mg (N=157)	2 or 3 mg (N=366)	0.5–2 mg (N=132)	All (N=655)	Placebo (N=388)
Patients with any AE[a]	5 (3.2)	17 (4.6)	13 (9.8)	35 (5.3)	12 (3.1)
Tremor	2 (1.3)	3 (0.8)	3 (2.3)	8 (1.2)	6 (1.5)
Akathisia	0	2 (0.5)	3 (2.3)	5 (0.8)	1 (0.3)
Extrapyramidal disorder	1 (0.6)	3 (0.8)	1 (0.8)	5 (0.8)	0
Hypokinesia	1 (0.6)	1 (0.3)	2 (1.5)	4 (0.6)	1 (0.3)
Muscle spasms	1 (0.6)	2 (0.5)	0	3 (0.5)	0
Hypertonia	1 (0.6)	2 (0.5)	0	3 (0.5)	1 (0.3)
Muscle rigidity	0	1 (0.3)	1 (0.8)	2 (0.3)	2 (0.5)
Dyskinesia	0	0	2 (1.5)	2 (0.3)	1 (0.3)
Bradykinesia	0	2 (0.5)	0	2 (0.3)	0
Gait disturbance	1 (0.6)	1 (0.3)	0	2 (0.3)	1 (0.3)
Bradyphrenia	0	1 (0.3)	1 (0.8)	2 (0.3)	0
Parkinsonism	0	1 (0.3)	1 (0.8)	2 (0.3)	0
Psychomotor hyperactivity	0	1 (0.3)	0	1 (0.2)	0
Restlessness	0	0	1 (0.8)	1 (0.2)	0
Gait inability	0	0	0	0	1 (0.3)
Musculoskeletal stiffness	0	0	0	0	1 (0.3)
Akinesia	0	0	0	0	1 (0.3)

a. Patients with AEs in multiple system organ classes were counted only once towards the total.
Note: Patients are counted once per term for the most severe of multiple occurrences of a specific MedDRA Preferred Term.
AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities.

11.5 Overall Summary of Safety by Study and Dose

Table 30: Studies 283, 284, and 213: Summary of Adverse Events (Safety Sample)

Patients with any, n (%)	Study 283			Study 284		Study 213		
	Brex ≤ 1 mg (N=157)	Brex 2 mg (N=140)	Placebo (N=135)	Brex 0.5–2 mg (N=132)	Placebo (N=137)	Brex 2 mg (N=73)	Brex 3 mg (N=153)	Placebo (N=116)
AE	77 (49.0)	91 (65.0)	62 (45.9)	75 (56.8)	80 (58.4)	28 (38.4)	64 (41.8)	36 (31.0)
AE leading to study drug discontinuation[a]	14 (8.9)	6 (4.3)	7 (5.2)	9 (6.8)	1 (0.7)	1 (1.4)	11 (7.2)	5 (4.3)
Severe AE	10 (6.4)	13 (9.3)	5 (3.7)	9 (6.8)	8 (5.8)	0	6 (3.9)	3 (2.6)
SAE	16 (10.2)	13 (9.3)	7 (5.2)	7 (5.3)	6 (4.4)	0	6 (3.9)	3 (2.6)
Death	4 (2.5)	1 (0.7)	0	0	1 (0.7)	0	1 (0.7)	0

a. Patients discontinued due to an adverse event not a treatment-emergent adverse event.
Brex=brexpiprazole; SAE=serious adverse event.