FDA Briefing Document

NDA 205422/S-009

Drug name: brexpiprazole

Applicant: Otsuka Pharmaceutical Company Ltd., and Lundbeck Inc.

Joint Meeting of the

Psychopharmacologic Drugs Advisory Committee

and the

Peripheral and Central Nervous System Drugs Advisory Committee

April 14, 2023

Division of Psychiatry/Office of Neuroscience

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought supplemental New Drug Application 205422/S-009, brexpiprazole for the treatment of agitation associated with Alzheimer's dementia, to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

AC	Advisory Committee
AAD	Agitation associated with Alzheimer's dementia
AD	Alzheimer's dementia
ADWG	Agitation Definition Working Group
APA	American Psychiatric Association
BD	Briefing Document
BPSD	Behavioral and psychological symptoms of dementia
CDER	Center for Drug Evaluation and Research
CGI-S	Clinical Global Impression of Severity Scale
CI	Confidence interval
CMAI	Cohen Mansfield Agitation Inventory
DMC	Data monitoring committee
OC	Observed case
FDA	Food and Drug Administration
IA	Interim analysis
IPA	International Psychogeriatric Association
IND	Investigational New Drug Application
LS	Least square
LSM	Least square mean
LSMD	Least square mean difference
MMRM	Mixed-model for repeated measures
MMSE	Mini Mental Status Exam
NINCDS-ADRDA	National Institute of Neurological and Communicated Diseases and Stroke/Alzheimer's Disease and Related Disorders Association
NPI-NH	Neuropsychiatric Inventory – Nursing Home
ROW	Rest of World
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
sNDA	Supplemental New Drug Application
UN	Unstructured
US	United States

2 Executive Summary/Draft Points for Consideration by the Advisory Committee

2.1 Purpose/Objective of the AC Meeting

The purpose of this Advisory Committee meeting is to discuss the use of brexpiprazole (sNDA 205422/S-009) for the treatment of agitation in patients with Alzheimer's dementia (AD). Considering the increased risk of death among elderly patients with dementia receiving antipsychotic treatment and the risks of other off-label medications without established evidence of efficacy, the Committee will be asked to opine on the relative benefits and risks of brexpiprazole for the proposed indication of the treatment of agitation associated with AD (AAD).

2.2 Context for Issues to Be Discussed at the AC

Agitation is one of the most common and challenging aspects of care among patients with AD. Symptoms typically occur across the continuum of cognitive impairment with increasing prevalence and severity with progressive disease. Over the past decade, the clinical community has made strides in creating a common framework to establish diagnostic criteria and clinical outcome assessments for agitation in patients with cognitive impairment, including AD. Although current standard of care consists of a mixture of non-pharmacological and pharmacological treatments (e.g., antipsychotics, benzodiazepines, antidepressants, antiepileptics), there are no currently FDA-approved treatment options for AAD.

According to the American Psychiatric Association (APA), antipsychotics remain the first line, albeit off-label, treatment choice to manage agitation in patients with dementia (Reus VI, et al., 2016). In general, the majority of studies evaluating antipsychotics as treatment options have demonstrated small improvements in highly heterogenous patient populations. In 2005, the Food and Drug Administration (FDA) issued a Boxed Warning for all atypical antipsychotics based on a systematic meta-analysis that revealed a 70% increased risk of death among elderly patients with dementia receiving antipsychotic treatment. After the implementation of the Boxed Warning, various government and private institutions have taken action to decrease off-label antipsychotic prescribing in this population as well as the inappropriate diagnosis of schizophrenia to justify antipsychotic drug use in elderly patients with dementia. Current drug utilization data suggest a decrease in use of antipsychotics and an increase of other treatments such as, opioids, antiepileptics, and benzodiazepines; however, these also pose important risks.

Brexpiprazole, an atypical antipsychotic, is FDA-approved for the adjunctive treatment of major depressive disorder (MDD) in adult patients (2 to 3 mg/day) and for treatment of schizophrenia in patients ages ≥ 13 years (2 to 4 mg/day). To support the clinical development program for the treatment of AAD, the Applicant conducted three double-blind, placebo-controlled, phase 3 studies (331-12-283, 331-12-284, and 331-14-213), one observational post-treatment study (331-13-211), and one active-treatment open-label extension safety study (331-201-00182). Results from Studies 331-12-283 and 331-14-213 suggest that brexpiprazole exhibited a statistically significant treatment effect in the reduction of agitation over a 12-week treatment period, while also showing a similar safety profile relative to its use in adults with schizophrenia and major depressive disorder. Although there were few

deaths across the clinical development program, brexpiprazole's effect on mortality appears to be consistent with the known risk with other antipsychotics in elderly patients with dementia. Given the lack of available treatment options and restrictions on the improper use of antipsychotics in elderly patients, the Agency aims to engage with the Committee to discuss brexpiprazole's clinical implications as a potential first-in-class product for the treatment of AAD, given the drug's benefit/risk profile.

2.3 Draft Points for Consideration

Based upon the presented information, the Agency request that the Committee address the following:

1. Discuss the overall benefit/risk assessment of brexpiprazole for the treatment of agitation associated with AD. The discussion should take into consideration the following:
    - the increased risk of death among elderly patients with dementia receiving antipsychotic treatment
    - the risks of medications that are often used off-label for the treatment of agitation in dementia (e.g., antiepileptics, benzodiazepines) without established evidence of efficacy.
2. Discuss whether there is a population of patients with AD for whom the benefit/risk of brexpiprazole appears acceptable. Is there a population for whom the benefit/risk does not appear to be favorable?
3. Has the Applicant provided sufficient data to allow identification of a population in whom the benefits of treating agitation associated with AD with brexpiprazole outweigh its risks?
    - If you do not believe the Applicant has provided sufficient data, what additional data is needed to support the use of brexpiprazole for the treatment of agitation associated with AD?

3 Introduction and Background

3.1 Background of the Condition/Standard of Clinical Care

Dementia is a serious and debilitating neurological condition characterized by progressive decline in one or more cognitive domains with associated impairment in function, including potential loss of independence with need for at-home or residential care. Alzheimer's disease (AD) is the most common cause of dementia, with an estimated global prevalence of approximately 60 million and 6.5 million people aged ≥ 65 years affected in the United States. AD accounts for an estimated 60 to 80% of dementia cases worldwide (Alzheimer's Association, 2022).

Patients with dementia often present with behavioral and psychological disturbances. These behavioral and psychological symptoms of dementia (BPSD) commonly include irritability, agitation, aggression, delusions, hallucinations, wandering, depression, anxiety, apathy, disinhibition, and sleep disturbances (Lyketsos et al., 2002; Reus et al., 2016). The presence of disruptive BPSD symptoms, including physical aggression and psychosis, are often the leading cause of assisted living or nursing home placement (Toot S, et al., 2017). These symptoms have also been associated with accelerated disease progression (two- to three-fold increase to time to severe dementia), functional decline, and increased mortality (ranging from 20 to 50%) (Bransvik V, et al., 2021 and Peters ME, et al., 2015). Due to the prolonged disease course, increased caregiver burden has led to physical and mental health deterioration, and ultimately decreased quality of life for both patients and caregivers (Deardorff WJ, et al., 2019, and Peters ME, et al., 2015).

Agitation is among the most persistent, complex, stressful, and costly aspects of care among patients with BPSD. Observational studies indicate the presence of agitation across the continuum of cognitive impairment with increasing prevalence with dementia severity. The estimated pooled prevalence of agitation associated with AD (AAD) is approximately 40% and ranges between 40 to 60% among those living in long-term care facilities and 20 to 40% among those living in the community (Zhao, et al., 2016, Gauthier S, et al. 2010). In a cross-sectional study evaluating community-dwelling patients with AD, approximately 50% of patients had co-morbid symptoms of agitation, depression, and psychosis (Tractenberg RE, et al. 2003).

Prior to 2015, there was no commonly accepted description for agitation; studies often utilized lay definitions that were non-specific and included states of excitement, disturbance, or worry (Laughren et al, 2001). In 2015, the International Psychogeriatric Association (IPA) formed the Agitation Definition Working Group (ADWG) to establish a consensus definition of agitation that would facilitate a wide spectrum of research and provide a common framework for diagnostic nomenclatures (Cummings JL, et al., 2015). Recently, the ADWG finalized the IPA provisional consensus definition (Table 1) of agitation with minimal modifications (Sano M, et al., 2023). The definition includes four criteria (A through D) that must be met. These criteria establish the underlying condition (dementia) and the types of behavior to be considered. They also specify that the symptoms must cause impairment and that they must not be attributable to some other condition.

Table 1: IPA Consensus Definition for Agitation in Cognitive Disorders

Must meet all four criteria	**A**	Meets criteria for a cognitive impairment or dementia syndrome (e.g., AD, Frontotemporal dementia [FTD], Dementia with Lewy bodies [DLB], vascular dementia, other dementias, a pre-dementia cognitive impairment syndrome such as mild cognitive impairment or other cognitive disorder)
	B	Exhibits at least one of the following behaviors that are associated with observed or inferred evidence of emotional distress (e.g., rapid changes in mood, irritability, outbursts). The behavior has been persistent or frequently recurrent for a minimum of 2 weeks or the behavior represents a change from the patient's usual behavior.[1] a) Excessive motor activity (e.g., pacing, rocking, gesturing, pointing fingers, restlessness, performing repetitious mannerisms) b) Verbal aggression (e.g., yelling, speaking in an excessively loud voice, using profanity, screaming, shouting). c) Physical aggression (e.g., grabbing, shoving, pushing, resisting, hitting others, kicking objects or people, scratching, biting, throwing objects, hitting self, slamming doors, tearing things, and destroying property)
	C	Behaviors are severe and associated with excess distress or produce excess disability, which in the clinician's opinion is beyond that due to the cognitive impairment and includes at least one of the following significant impairments in: a) Interpersonal relationships b) Other aspects of social functioning c) Ability to perform or participate in daily living activities
	D	While co-morbid conditions may be present, the agitation is not attributable to another psychiatric disorder; medical condition, including delirium; suboptimal care conditions; or the physiological effects of a substance

Source: Sano et al., 2023 and Cummings J, et al. 2015

[1]In special circumstances, the ability to document the behaviors over 2 weeks may not be possible and other terms of persistence and severity may be needed to capture the syndrome beyond a single episode.

There are currently no FDA-approved pharmacological treatment options for AAD. Non-pharmacological approaches typically aim to address the contextual and psychosocial causes for agitation (Agency for Healthcare Research and Quality, 2019). Interventions such as cognitive stimulation/training, group therapy, verbal communication (e.g., redirection and reassurance), distraction (e.g., environmental changes), physical exercise, bright light therapy, music therapy, and multisensory stimulation have shown promising results in decreasing agitation among older adults with dementia. Although non-pharmacological therapies are recommended as a first-line approach for AAD, pharmacological treatments are initiated approximately 60% of the time among patients in residential care and 40% of the time in community-based settings (Aigbogun M, et al., 2020 and Tractenberg RE, et al., 2002).

Clinical management of agitation remains a challenge for clinicians and caregivers due to the lack of evidence supporting the safe and effective use of pharmacological treatment options. Several classes of pharmacological treatments are commonly used off-label in clinical practice to treat agitation and aggression associated with dementia, including benzodiazepines, antihistamines, antidepressants, antiepileptics, and antipsychotics (O'Gorman, et al., 2020). Studies evaluating off-label pharmacologic treatments have often enrolled subjects with presumed AD and who have a variety of comorbid BPSD symptoms, including a combination of agitation and psychosis. The high degree of heterogeneity within and across studies and the use of various efficacy measures limits findings from meta-analyses and comparative effectiveness research and obscures any interpretation of the benefit/risk profile for an

individual drug (Marcinkowska M, et al., 2020). In general, studies have demonstrated, at best, nominal symptom improvements without providing optimized dosing information (Antonsdottir IM, et al., 2015).

In addition to modest efficacy findings, current off-label treatment options are also associated with serious risks and tolerability concerns. Among elderly patients, benzodiazepines have been shown to increase the risks of cognitive decline and fractures and falls (DeFrancesco M, et al. 2015). Safety findings from studies evaluating antidepressants (e.g., citalopram, escitalopram, sertraline) for BPSD symptoms have reported adverse events (AEs) consistent with their use in elderly patients including worsening cognitive function and anticholinergic effects and an increased incidence of gastrointestinal symptoms and QT prolongation (Porsetinsson AP, et al., 2014 and Seitz DP, et al., 2011). According to studies evaluating antiepileptics (e.g., carbamazepine, oxcarbazepine, valproic acid), higher doses can result in sedation, thrombocytopenia, and hyponatremia (Gallagher D, et al., 2014); due to the increased prevalence of underlying comorbidities (e.g., cardiovascular disease) and drug-drug interactions, these risks are often increased in the elderly population.

Historically, clinicians have prescribed antipsychotics as the first-line treatment choice to manage agitation in patients with dementia. The APA Practice Guidelines recommend the use of "non-emergency antipsychotic medications for the treatment of agitation or psychosis in patients with dementia when symptoms are severe, dangerous, or cause significant distress to the patient" (Reus VI, et al., 2016). However, the guidelines also conclude that the clinical benefits observed in clinical trials of antipsychotic medications are small, whether in placebo-controlled, head-to-head comparison, or randomized withdrawal trials (Kales et al. 2015; Maglione et al, 2011; Yunusa I, et al., 2019). For most patients, clinicians initiated antipsychotic treatment within 3 months of agitation onset and after experiencing multiple episodes of agitation (Aigbogun M, et al., 2020). Although treatment duration on average ranges from 1 to 8 months, maintenance treatment is usually based on observed response and safety profile.

In 2005, after receiving reports of serious cerebrovascular AEs and issuing Warning statements for several antipsychotic product labels, the Agency conducted a meta-analysis to systematically assess the available data to determine the magnitude and consistency of the reported mortality risk. The Agency's 2005 meta-analysis included 17 randomized, short-term, placebo-controlled trials of antipsychotics in elderly patients with dementia (total N=5,377; placebo = 1,766; active drug = 3,611) and estimated the mortality risk across five atypical (aripiprazole, olanzapine, quetiapine, and ziprasidone) and one typical antipsychotic (haloperidol). The average age of subjects in the meta-analysis was 81 years; approximately 95% were between ages of 66 and 96 years. Most studies were either 10 weeks (seven studies) or 12 weeks (four studies) in length. The meta-analysis revealed a risk of death in the drug treated subjects of between 1.6 to 1.7 times that observed in the placebo-treated patients. Over the course of a typical 10-week trial, the rate of death was 4.5% for the drug treated group vs. 2.6% in the placebo treated group. Given that the causes of death varied (most deaths appeared to be either cardiovascular or infectious in nature) and that there were a limited number of well-defined cases, the specific mechanism by which antipsychotics increase the risk of death is unclear. Based on these data, the Agency required a new Boxed Warning for all second-generation antipsychotics; in 2008, the Agency expanded the scope of the Boxed Warning to include all antipsychotics. Due to a higher incidence of stroke and transient ischemic attacks, including fatal stroke, the Agency also added a class warning for cerebrovascular adverse events in elderly patients with dementia.

After the implementation of the Boxed Warning in 2005, drug utilization data suggested a subsequent

decrease in use of antipsychotics. However, in the same period, the use of opioids, antiepileptics, and benzodiazepines among patients aged ≥ 65 years with dementia increased (Dorsey ER, et al, 2010; Rubino A, et al., 2020). Furthermore, various regulatory bodies (Center of Medicare and Medicaid Services) have taken action (e.g., audits of healthcare institutions, issuing citations for severe non-compliance) to decrease long-term and off-label prescribing in nursing homes and assisted-living settings (Gerlach LB, et al., 2022). With limited evidence to support antipsychotics and other alternatives, healthcare providers are left with unclear choices for treatment, resulting in increased caregiver distress and hastened patient institutionalization (Jeste DV, et al., 2007).

Although there are currently no FDA-approved treatments for AAD, antipsychotics are still commonly prescribed off-label, despite the small effect sizes described in the current literature and the Boxed Warning for increased risk of mortality. Therefore, evidence-based treatments with favorable benefit/risk profiles are needed to address a serious unmet need in this patient population.

3.2 Product Under Review

Brexpiprazole is an atypical antipsychotic drug that exerts its pharmacological effect through partial agonism of the serotonin subtype-1a (5-HT_{1a}) and dopamine 2 (D_2) receptors, and antagonism of the serotonin subtype-2a (5-HT_{2a}) receptor. FDA initially approved brexpiprazole (trade name: Rexulti) on July 10, 2015, for the adjunctive treatment of major depressive disorder (2 to 3 mg/day) and for the treatment of schizophrenia (2 to 4 mg/day) in adults. Brexpiprazole's mechanism of action in the treatment of AAD is unclear; however, the Applicant hypothesizes that the partial agonist activity at 5-$H1_{1a}$ and D_2 receptors in combination with noradrenaline (α_{1B}) receptor antagonism may be associated with reduced agitation and aggression. The Applicant's proposed indication for this supplemental New Drug Application (sNDA) is for the treatment of AAD (recommended dosage range: 2 to 3 mg/day).

3.3 Pertinent Drug Development and Regulatory History

During an End-of-Phase 2 Meeting in March 2011 (prior to brexpiprazole's original approval), the Applicant inquired about the possibility of seeking a claim for behavioral symptoms associated with AD even though antipsychotics have a Boxed Warning for an increased risk of mortality in the elderly population. The Agency clarified the Boxed Warning is not a contraindication and obtaining a claim would depend on the benefit/risk analysis. Although the Applicant later shifted their focus specifically to "agitation," the Agency commented that the indication should be a well-defined clinical construct with an established endpoint based on input and support from the community. The following list summarizes key milestone meetings and regulatory activities for the development of brexpiprazole for the treatment of AAD:

- November 6, 2012: Type B Meeting (Pre-IND) to discuss the development plan for brexpiprazole for the treatment of agitation in patients diagnosed with dementia of the Alzheimer's type

    - The Applicant inquired about the feasibility of pursuing an indication for the "treatment of agitation in patient with AD," or an alternative indication for the "treatment of aggressive agitation in patients with AD." The Agency agreed that AAD is an important target for treatment, and the decision to target agitation more broadly, or the subgroup of patients with "aggressive agitation," would be the Applicant's choice.

- The Agency emphasized that the Applicant should collaborate with clinical experts and conduct pilot work to carefully define agitation in AD and develop specific criteria to guide clinicians in identifying the appropriate target population.

- The Applicant proposed a clinical development program of two 12-week, phase 3, multicenter, randomized, double-blind, placebo-controlled trials (Study 331-12-283 and Study 331-12-284) in subjects diagnosed with probable AD according to the National Institute of Neurological and Communicated Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria and symptoms of agitation and aggression as confirmed by a score of ≥ 4 on the agitation/aggression item of the Neuropsychiatric Inventory – Nursing Home (NPI-NH) scale. For both studies, the Applicant proposed to utilize the Cohen Mansfield Agitation Inventory (CMAI) as the primary efficacy measure.

- Because the Applicant had not yet settled on a specific target (agitation vs aggressive agitation), the Agency did not provide more specific advice and indicated that the general study designs appeared reasonable. The Agency also encouraged the Applicant to provide details on who would perform the CMAI ratings and rater training.

- September 27, 2017: Type C Meeting (Guidance) to discuss top-line results from Study 331-12-283 and 331-12-284 and to assess the viability of an sNDA for AAD

  - Given that the Agency did not consider Study 331-12-283 to be "statistically persuasive" and emphasized that post-hoc analyses could not serve as the primary support for an application, the Agency recommended that the Applicant conduct another 12-week, double-blind, placebo-controlled, fixed-dose study that would evaluate a higher dosage than previously studied (e.g., 3 mg/day).

  - The Agency emphasized that subjects do not need to exhibit aggressive behaviors to be suitable for enrollment and recommended that the Applicant utilize the IPA provisional consensus definition for agitation to ensure enrolled subjects exhibited sufficient agitation at baseline.

- January 31, 2018: Type C Meeting (Guidance) to discuss key design elements for Study 331-14-213, a 12-week, double-blind, placebo-controlled, fixed-dose phase 3 trial evaluating brexpiprazole 2 mg and 3 mg/day in subjects with AAD

  - Although the proposed enrichment strategy to include subjects with positive CMAI factor 1 aggressive behavior was reasonable, the Agency noted that limiting enrollment may narrow the product's final indication for use.

  - The Agency was unclear regarding the generalizability of the potential study results to individuals with non-aggressive AAD.

  - To obtain sufficient safety data at higher brexpiprazole dosages, the Applicant agreed to randomize at least 100 subjects to receive brexpiprazole 3 mg/day.

- The Agency agreed that a long-term safety study would not be a preapproval requirement but could be a phase 4 commitment.

- September 23, 2022: Type B Meeting (Pre-sNDA) to discuss whether the components of the sNDA are sufficient to facilitate a full and substantial review for the proposed indication

  - The Agency anticipated that an AC meeting may be needed to discuss the safety of brexpiprazole in the context of the broader Boxed Warning for the antipsychotic drug class.

- January 9, 2023: The Agency filed the sNDA and granted a priority review based on the potential for this product to address an unmet need.

4 Overview of Efficacy and Safety

The Applicant's clinical development program consisted of three phase 3 studies (331-12-283, 331-12-284, and 331-14-213), one observational post-treatment study (331-13-211) in subjects who completed Studies 331-12-283 and 331-12-284, and one open-label extension safety study (331-201-00182) in subjects who completed Study 331-14-213. All three phase 3 studies listed below share the basic trial design elements (e.g., study duration, placebo-controlled); differences in the study population (e.g., diagnostic criteria for probable AD and agitation) can be attributed to the Agency's evolving advice over time (331-12-283 and 331-12-284: 2013; 331-14-213: 2018).

4.1 Summary of Efficacy

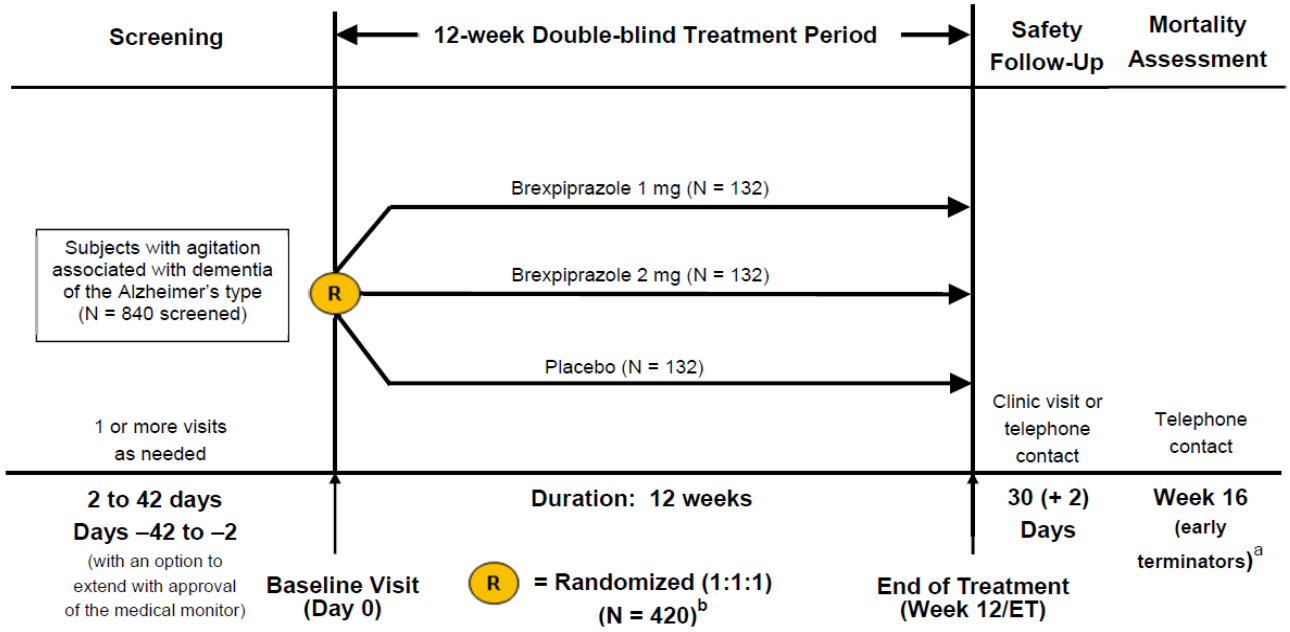
4.1.1 Study 331-12-283

4.1.1.1 Trial Design

Study 331-12-283 was a phase 3 randomized, double-blind, placebo-controlled, multi-center, fixed-dose study intended to evaluate the efficacy, safety, and tolerability of brexpiprazole (1 mg/day and 2 mg/day) in elderly subjects with AAD. A schematic of the trial design is presented in Figure 1. During the screening period (up to 42 days), investigators required subjects to washout prohibited concomitant pharmacotherapy prior to randomization. The Applicant randomized eligible subjects in a 1:1:1 ratio to either brexpiprazole 1 mg/day (BREX 1 mg), brexpiprazole 2 mg/day (BREX 2 mg), or placebo (prior to protocol amendment 3, the Applicant also included a brexpiprazole 0.5 mg/day arm). All subjects randomized to receive brexpiprazole received 0.25 mg/day as a starting dosage. The Applicant increased the brexpiprazole dosage to 0.5 mg/day on Day 4 and to 1 mg/day starting on Day 15. For subjects randomized to BREX 2 mg, the dosage increased to 2 mg/day starting on Day 29. The Applicant withdrew any subjects unable to tolerate their assigned dosage and prohibited any decrease in the dosage at any time during the study. Refer to the Appendix 6.3 for the Applicant's detailed schedule of assessments. Investigators followed each subject for safety evaluation 30 days after receiving the last dose of the study medication. For all subjects who terminated early from the study for any reason, investigators contacted the caregiver at Week 16 to collect mortality status.

The Applicant identified the subject's caregiver as the person who had sufficient contact with the subject to describe the subject's symptoms and could directly observe the subject's behavior during trial assessments. The recommended minimum level of contact between the caregiver and the subject was 2 hours/day for 4 days/week. In the non-institutionalized setting, the subject's caretaker was the person who lived with and cared for the subject on a regular basis. The caregiver role in the non-institutionalized setting may or may not have been the same individual who fulfilled the role of caretaker depending upon the subject's circumstances. In the institutionalized setting, a caregiver could be a staff member of the institutionalized setting or another individual (e.g., family member, family friend, hired professional caregiver).

Figure 1: Study Design Overview for Study 331-12-283



Source: Applicant's 331-12-283 CSR Figure 3.1-1
Abbreviations: ET = early termination

Eligibility Criteria

The target population consisted of elderly subjects aged 55 to 90 years, with a diagnosis of probable AD according to the NINCDS-ADRDA criteria, mild to severe cognitive impairment (Mini Mental Status Exam [MMSE] score between 5 to 22), and living in either an institutionalized or non-institutionalized setting where the subject is not living alone. The Applicant also required subjects to exhibit significant agitation, defined as a total score (frequency x severity) of ≥ 4 on the agitation/aggression item of the Neuropsychiatric Inventory – Nursing Home Scale (NPI-NH) for institutionalized subjects and the Neuropsychiatric Inventory/Neuropsychiatric Inventory – Nursing Home Scale (NPI/NPI-NH) for non-institutionalized subjects and requiring pharmacotherapy after a trial of non-pharmacological interventions, with onset of symptoms at least 2 weeks prior to screening. The Applicant excluded subjects with insufficient response to two or more previous antipsychotic medications for the treatment of agitation, history of cerebrovascular conditions, presence or history of delirium, evidence of serious risk of suicide based on the Sheehan-Suicide Tracking Scale, and clinically significant and uncontrolled medical conditions. The Applicant's listing of prohibited concomitant medications is summarized in Appendix 6.2.

Study Endpoints

Primary Endpoint

The primary efficacy endpoint was mean change from baseline to the end of the double-blind treatment period (Week 12) on the CMAI total score (Long Form).

The purpose of the CMAI is to assess the frequency of agitated behaviors in elderly patients and was originally developed for use in nursing homes. The CMAI-Long Form is a caregiver-rated instrument consisting of 29 items all rated on a 1 to 7 scale with 1 being the "best" rating (no occurrence) and 7 being the "worst" rating (frequency of several times an hour). The CMAI Total Score is the sum of ratings for all 29 items. The distinct agitation syndromes include aggressive behavior, physically non-aggressive behavior, and verbally agitated behavior. The possible total scores range from 29 to 203. Based on the CMAI manual, the rating period is the 2 weeks preceding the administration of the instrument. The developers of the CMAI have conducted several validation studies to support its use in nursing homes and community-dwelling patients (Cohen-Mansfield J, et al., 1989; Cohen-Mansfield J, et al., 1995).

A large-scale factor analysis of the CMAI collected in nursing home patients with dementia and behavior disorders also demonstrated the presence of four domains ("factors" or subscales): aggressive behaviors (CMAI Factor 1), physically non-aggressive behaviors (CMAI Factor 2), verbally agitated behaviors (CMAI Factor 3), and hiding and hoarding (CMAI factor 4). Of note, several items on the CMAI (i.e., making strange noises, intentionally falling, eating, or drinking inappropriate substances, verbal sexual advances, physical sexual advances or exposing) did not load onto a specific factor and were characterized as unloaded or "other" items (Rabinowitz J, et al., 2005). CMAI items loaded onto each of the subscales are described below:

- *Factor 1 (aggressive behaviors):* hitting (including self), kicking, scratching, grabbing onto people, pushing, hurt self or others, throwing things, cursing or verbal aggression, spitting (including at meals), tearing things or destroying property, screaming, and biting
- *Factor 2 (physically non-aggressive behaviors):* pace/aimless wandering, trying to get to a different place, general restlessness, inappropriate dress or disrobing, handling things inappropriately, performing repetitious mannerisms
- *Factor 3 (verbally agitated behaviors):* complaining, constant unwarranted request for attention or help, repetitious sentences or questions, negativism
- *Factor 4 (hiding and hoarding):* hiding things, hoarding things

To explicate the findings from the primary efficacy endpoint, the Applicant evaluated treatment effects for the subscales (Factors 1, 2, and 3) that most closely aligned with the diagnostic criteria for agitation (Table 1). Given that symptoms of hiding and hoarding appear to be non-specific to agitation, are not included in the IPA consensus definition for agitation, and could be closely associated with cognitive impairment, the subsequent exploratory analyses did not evaluate treatment effects for Factor 4. Subscale scores were calculated based on the summation of responses of all items within the subscale. The range of possible scores for Factor 1, 2, and 3 subscales were 12 to 24, 6 to 42, and 4 to 28, respectively. Between-treatment group results for each subscale were provided descriptively (i.e., not in the statistical testing hierarchy).

Key Secondary Endpoint

The key secondary efficacy endpoint was mean change from baseline to end of the double-blind treatment period (Week 12) in the Clinical Global Impression of Severity (CGI-S) scale score, as related to agitation.

Other Secondary or Exploratory Endpoints

Secondary endpoints included change from baseline to Week 12 in the following:

- NPI-NH 12-item total score
- NPI-NH Agitation/aggression (NPI-NH A/A) subscore
- Clinical Global Impression of Improvement (CGI-I) scale score, as related to agitation.

Statistical Considerations

Efficacy Analyses

- *Primary efficacy endpoint* was the mean change from baseline (Day 0) to the end of the double-blind period (Week 12) in the CMAI total score. The Applicant performed the primary analysis on the Efficacy Sample by fitting a Mixed Model for Repeated Measures (MMRM) analysis with an unstructured (UN) variance covariance structure in which the change from the baseline in CMAI total score (Week 2, 4, 6, 8, 10, and 12) was the dependent variable based on the observed case (OC) dataset. The model included fixed class-effect terms for treatment (1 mg/day, 2 mg/day, and placebo), pooled trial center, visit week, an interaction term of treatment by visit week, and an interaction term for baseline values of CMAI total score by visit week as covariates. The Applicant estimated the difference between least squares (LS) means from the interaction term of treatment by visit week for the primary comparison between each brexpiprazole group and the placebo arm at Week 12.

- *Key secondary endpoint* was the change from baseline to Week 12 in the CGI-S score, as related to agitation. The Applicant analyzed the key secondary endpoint using the same statistical methodology specified for the primary efficacy variable.

- *Multiplicity adjustment*: To control the overall type I error at alpha level of 0.05, the primary efficacy endpoint was tested using a hierarchical testing procedure in the order of 1) comparison of BREX 2 mg versus placebo and 2) comparison of BREX 1 mg versus placebo. If the primary efficacy analysis for the CMAI total score yielded statistically significant results for both comparisons, the Applicant repeated the hierarchical testing procedure for the key secondary efficacy variable (CGI-S score).

Sample Size

Subjects were initially randomized to four treatment arms (brexpiprazole 0.5 mg/day, brexpiprazole 1 mg/day, brexpiprazole 2 mg/day, and placebo). In protocol amendment 3, the Applicant decided to remove the brexpiprazole 0.5 mg/day arm. At the time of this amendment, the Applicant already randomized 20 subjects to this arm. The total sample size included these subjects from the brexpiprazole 0.5 mg/day treatment arm, although they were not in the efficacy analysis.

4.1.1.2 Study Results

Disposition

Of the 690 subjects screened, the Applicant randomized 433 subjects into the double-blind treatment period. All subjects except one in the placebo group received at least one dose of the study medication. Of note, only one subject was excluded at screening for reporting insufficient response to least two antipsychotics for AAD. In the Randomized Sample, 56 subjects (13%) discontinued during the trial (11%, 12%, and 13%, discontinued from the study in the placebo, BREX 1-mg, and BREX 2-mg treatment

groups, respectively). The most frequent reason for discontinuation was due to AEs (total N = 28; 6.5%) across all treatment groups (5.9%, 7.3%, and 4.3% in the placebo, BREX 1-mg, and BREX 2-mg treatment groups). The Safety Sample consisted of all randomized subjects who received at least one dose of the double-blind study medication (BREX 1 mg = 137; BREX 2 mg = 140; placebo = 135; total N = 432). The Efficacy Sample consisted of all randomized subjects who received at least one dose of the double-blind study medication and had at least one post-baseline CMAI assessment (BREX 1 mg = 135; BREX 2 mg = 138; placebo = 131).

Demographic and Baseline Disease Characteristics

Table 2 provides a summary of demographic characteristics across treatment groups among subjects included in the Efficacy Sample. In general, demographic and baseline characteristics were similar across treatment arms. Additional baseline disease characteristics and psychiatric history are summarized in Appendix 6.5. Most subjects resided in an institutionalized setting (67%) and exhibited moderate or severe cognitive impairment (91%). Comorbid psychotic symptoms were only present among 26% of subjects.

Table 2: Demographic and Baseline Characteristics for Study 331-12-283 (Efficacy Sample)

Demographic Characteristic	Placebo (N=131)	BREX 1 mg (N=135)	BREX 2mg (N=138)
Age (years)			
Mean (SD)	74.3 (8.0)	73.8 (8.8)	73.7 (8.1)
Median (Range)	76 (58, 90)	76 (51, 89)	75 (55, 89)
Age group (years), n (%)			
< 65	18 (14%)	24 (18%)	22 (16%)
65 to < 75	40 (31%)	34 (25%)	46 (33%)
≥75	73 (56%)	77 (57%)	70 (50%)
Gender, n (%)			
Male	63 (48%)	58 (43%)	60 (44%)
Female	68 (52%)	77 (57%)	78 (56%)
Race, n (%)			
White	125 (95%)	132 (98%)	131 (95%)
Black or African American	5 (3.8%)	2 (1.5%)	5 (3.6%)
Asian	1 (0.8%)	1 (0.7%)	2 (1.4%)
Region, n (%)			
North America	38 (29%)	37 (27%)	41 (30%)
ROW	93 (71%)	98 (73%)	97 (70%)
Ethnicity, n(%)			
Hispanic or Latino[1]	23 (18%)	24 (18%)	23 (17%)
Not Hispanic or Latino	107 (82%)	110 (82%)	115 (83%)
Weight (kg), mean (SD)	68.4 (13.3)	69.4 (14.6)	68.3 (14.0)
Height (cm), mean (SD)	164.4 (10.2)	165.3 (9.2)	164.6 (10.2)
BMI (kg/m^2), mean (SD)	25.3 (4.9)	25.4 (5.0)	25.1 (4.0)

Source: Clinical Reviewer-created using adsl.xpt dataset
Abbreviations: BMI = body mass index; ROW = Rest of World; SD = standard deviation
[1]Ethnicity status was unknown for one subject receiving placebo and one subject receiving BREX 1 mg
Note: Subjects randomized to receive brexpiprazole 0.5 mg/day are not shown

Efficacy Results – Primary Endpoint

A statistically significant treatment effect for BREX 2 mg versus placebo was observed at Week 12 for the CMAI total score. The MMRM least squares mean (LSM) change from baseline at Week 12 was -21.6 for the BREX 2-mg group versus -17.8 for the placebo group for a treatment difference of -3.77 (95% CI: -7.38, -0.17; p-value = 0.0404; Table 3).

Table 3: Study 331-12-283: Primary Endpoint Results Based on Primary Analysis (Efficacy Sample)

	Placebo (N=131)	BREX 1 mg (N=134)[3]	BREX 2 mg (N=138)
Mean CMAI Total Score at Baseline (SD)	72.2 (17.85)	70.5 (15.95)	71.0 (16.56)
Mean CMAI Total Score at Week 12 (SD)	55.0 (16.09)	54.6 (18.59)	50.6 (14.76)
LSM Change from Baseline (SE)	-17.8 (1.34)	-17.6 (1.33)	-21.6 (1.32)
Placebo-subtracted difference (95% CI)[1]		0.23 (-3.40, 3.86)	-3.77 (-7.38, -0.17)
Unadjusted p-value[2]		0.9015	**0.0404**

Source: Applicant's Study 331-12-283 Clinical Study Report, CT-5.2.1, p. 394-395, confirmed by statistical reviewer
Abbreviations: CMAI = Cohen Mansfield Agitation Inventory; LSM = least squares mean; MMRM = mixed-effect model for repeated measures; SD=standard deviation; SE=standard error; 95% CI = unadjusted 95% confidence interval (p-value also unadjusted for multiple dose arms)
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.
[2]All p-values reported in the table are nominal.
[3]One subject in the BREX 1-mg group had only one post-baseline assessment and it was at Week 1, not a planned schedule assessment time. As a result, this subject was not captured in the primary analysis although this subject was in the Efficacy Sample.

The primary efficacy variable was further examined to explore the consistency of the treatment effect across the following subgroups: sex, race, age, region, and ethnicity. Subgroup analyses for the primary endpoint indicated that the observed magnitudes of net treatment effect (Least Squares Mean Difference [LSMD]) were consistently greater with the BREX 2-mg group as compared to placebo for females (LSMD: -4.94 [95% CI: -9.95, 0.07]) vs. males (LMSD: -1.80 [95% CI: -7.16, 3.56]), subjects ≥ 75 years of age (LSMD: -4.84 [95% CI: -9.70, 0.01]) vs. 65 to 74 year of age (LSMD: -1.42 [95% CI: -7.70, 4.86]) , in North America (LSMD: -7.76 [95% CI: -15.1, -0.48]) vs. ROW (LSMD: -1.63 [95% CI: -5.73, 2.47]) and Hispanic (LSMD: -4.67 [95% CI: -13.9, 4.55]) vs. non-Hispanics (LSMD: -3.03 [95% CI: -6.97, 0.91]) compared with their counterparts in all the subgroups.

Efficacy Results – Key Secondary Endpoint

Table 4 provides the results from the key secondary endpoint analysis on the CGI-S scale score, as related to agitation. The treatment differences did not reach statistical significance for either the BREX 1-mg (LSMD = 0.09, p = 0.4440) or BREX 2-mg arm for the key secondary efficacy endpoint, mean change in CGI-S score as related to agitation from baseline to Week 12 (LSMD = -0.16, p = 0.1566).

Table 4: Study 331-12-283 Key Secondary Endpoint Results (Efficacy Sample)

	Placebo (N=131)	BREX 1 mg (N=134)[3]	BREX 2 mg (N=138)
Mean CGI-S Score at Baseline (SD)	4.5 (0.66)	4.5 (0.62)	4.5 (0.70)
Mean CGI-S Score at Week 12 (SD)	3.4 (0.92)	3.5 (0.97)	3.2 (0.91)
LSM Change from Baseline (SE)	-1.1 (0.08)	-1.0 (0.08)	-1.3 (0.08)
Placebo-subtracted difference (95% CI)[1]		0.09 (-0.14, 0.32)	-0.16 (-0.39, 0.06)
Unadjusted p-value[2]		0.4440	0.1566

Source: Applicant's study 331-12-283 Clinical Study Report, Table 11.4.1.2.1.1-1 and CT-5.3.1. p.106, confirmed by Statistical Analyst
Abbreviations: CGI-S = Clinical Global Impression-Severity Scale; LSM = least squares mean; MMRM = mixed-effect model repeated measures; SD=standard deviation, SE=standard error; 95% CI = unadjusted 95% confidence interval (p-value also unadjusted for multiple dose arms)
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.
[2]All p-values reported in the table are nominal.
[3]One subject in the BREX 1-mg group had only one post-baseline assessment and it was at Week 1, not a planned schedule assessment time. As a result, this subject was not captured in the primary analysis although this subject was in the Efficacy Sample.

Additional Analyses

Analyses of other secondary and exploratory endpoints consistently displayed numerical improvements with the BREX 2-mg group vs. placebo. Table 5 displays one of the Applicant's secondary analyses based on the three major factor domains in the CMAI measure and using the same statistical methodology as described for the primary efficacy variable. In this study, the brexpiprazole treatment groups appear to exert a greater effect on the verbally agitated domain (BREX 1 mg: -0.28; BREX 2 mg: -1.26).

Table 5: Study 331-12-283 Change from Baseline to Week 12 in CMAI Factor Scores (Efficacy Sample)

Variable[1,2]	Placebo (N=131)	BREX 1 mg (N=134)	BREX 2 mg (N=138)
Factor 1: Aggressive Behaviors			
Baseline Mean (SD)	23.68 (8.93)	22.53 (8.49)	22.89 (8.38)
LSM Change from Baseline (SE)	-6.59 (0.50)	-6.58 (0.50)	-7.57 (0.49)
Placebo-subtracted difference (95% CI)		0.02 (-1.31, 1.34)	-0.97 (-2.29, 0.35)
Unadjusted p-value[3]		0.98	0.15
Factor 2: Physically Non-aggressive Behaviors			
Baseline Mean (SD)	21.44 (6.55)	21.93 (6.45)	21.33 (6.52)
LSM Change from Baseline (SE)	-5.74 (0.51)	-5.31 (0.51)	-6.92 (0.51)
Placebo-subtracted difference (95% CI)		0.42 (-0.97, 1.81)	-1.18 (-2.57,0.20)
Unadjusted p-value[3]		0.55	0.09
Factor 3: Verbally Agitated Behaviors			
Baseline Mean (SD)	14.76 (5.83)	13.70 (5.30)	14.22 (5.13)
LSM Change from Baseline (SE)	-3.19 (0.38)	-3.46 (0.38)	-4.45 (0.37)
Placebo-subtracted difference (95% CI)		-0.28 (-1.30, 0.75)	-1.26 (-2.29, -0.24)
Unadjusted p-value[3]		0.59	0.015

Source: Clinical Reviewer-adapted using Applicant's Clinical Study Report 331-12-283, Table 11.4.1.2.2.1-1
Abbreviations: CI = unadjusted confidence interval (p-value unadjusted); SD: standard deviation; SE = standard error
[1]The Applicant only included the BREX 1 mg, BREX 2 mg, and placebo in the MMRM model for comparison.
[2]Hiding and hoarding behavior was analyzed with these factors, but this behavior was not one of the three distinct CMAI-defined agitation syndromes and thus was not included in the table.
[3]All p-values reported in the table are nominal.

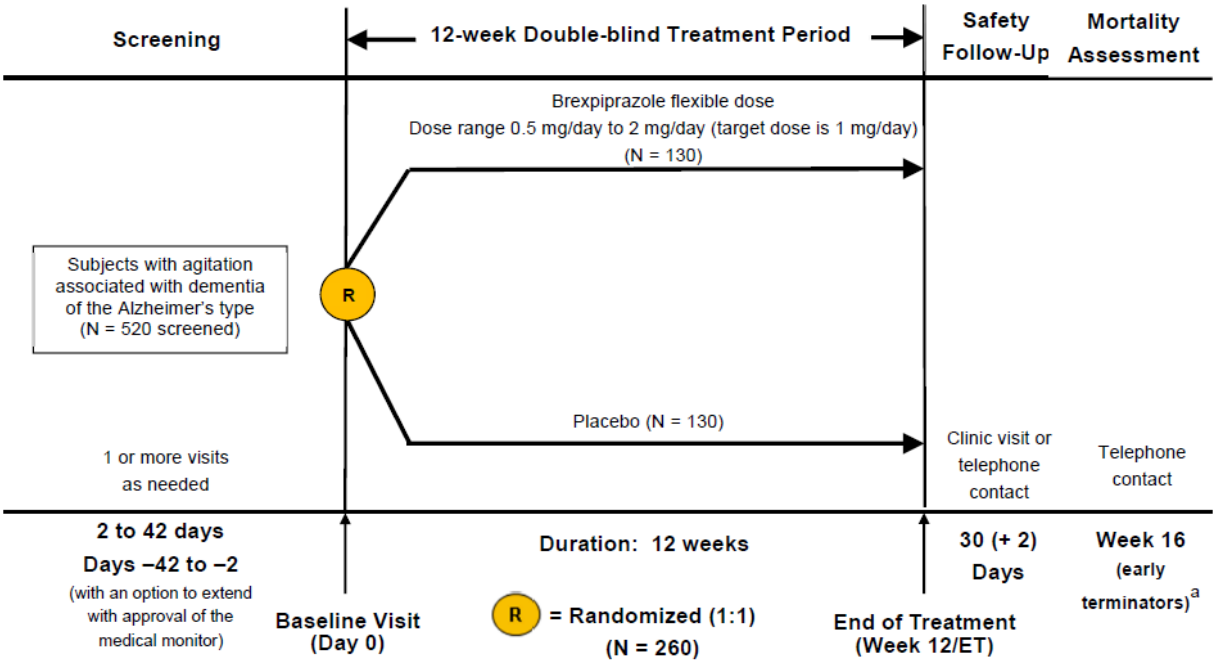
4.1.2 Note: MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.Study 331-12-284

4.1.2.1 Trial Design

Study 331-12-284 was a phase 3 randomized, double-blind, placebo-controlled, multi-center, flexible-dose study intended to evaluate the efficacy, safety, and tolerability of brexpiprazole (dosage range of 0.5 to 2 mg/day) in elderly subjects with AAD. Similar to Study 331-12-283, consisted of a screening period up to 42 days, a 12-week double-blind treatment period, and a 30-day safety follow-up period. Refer to Figure 2 for the Applicant's trial design schematic.

The Applicant randomized eligible subjects in a 1:1 ratio to either flexible-dose brexpiprazole or placebo. All subjects randomized to receive brexpiprazole received 0.25 mg/day as a starting dosage. The dosage increased to 0.5 mg/day on Day 4 and then increased to 1 mg/day starting on Day 15. After achieving the target of 1 mg/day, investigators could decrease the dose to 0.5 mg/day and re-increase to 1 mg/day based on clinical judgement (dose decreases and increases could occur at any time during scheduled or unscheduled visits). After the Week 4 visit (Day 29), the dose could be (not mandatory) further increased from 1 mg/day to 2 mg/day. The investigators exercised clinical judgement based on the subject's response and tolerability to treatment when deciding to increase the dose to 2 mg/day. The Applicant withdrew any subjects unable to tolerate 0.5 mg/day or matching placebo. Investigators evaluated the subject at baseline, Day 3, and at Weeks 2, 4, 6, 8, 10, and 12. Refer to the Appendix 6.3 for the Applicant's detailed schedule of assessments. Caregiver requirements were identical to Study 331-12-283.

Figure 2: Study Design Overview for Study 331-12-284



Source: Applicant's 331-12-284 Clinical Study Report, Figure 9.1-1
Abbreviations: ET = early termination

Eligibility Criteria

The target population was identical to Study 331-12-283 and consisted of elderly subjects aged 55 to 90 years, with a diagnosis of probable AD according to the NINCDS-ADRDA criteria, mild to severe cognitive impairment (MMSE score between 5 to 22), and living in either an institutionalized or non-institutionalized setting where the subject is not living alone. The Applicant also required subjects to exhibit significant agitation, defined as a total score (frequency x severity) of ≥ 4 on the agitation/aggression item of the NPI-NH for institutionalized subjects and the NPI/NPI-NH for non-institutionalized subjects and requiring pharmacotherapy after a trial of non-pharmacological interventions, with onset of symptoms at least 2 weeks prior to screening. The Applicant excluded subjects with insufficient response to two or more previous antipsychotic medications for the treatment of agitation, history of cerebrovascular conditions, presence or history of delirium, evidence of serious risk of suicide based on the Sheehan-Suicide Tracking Scale, and clinically significant and uncontrolled medical conditions. The Applicant's listing of prohibited concomitant medications is summarized in Appendix 6.2.

Study Endpoints

Primary Endpoint

The primary efficacy endpoint was mean change from baseline to the end of the double-blind treatment period (Week 12) in the CMAI (Long-Form) total score.

To evaluate treatment effects in each domain that align with diagnostic criteria for agitation (Table 1), between-treatment group results for each subscale (Factors 1, 2, and 3) were provided descriptively (i.e., not in the statistical testing hierarchy).

Key Secondary Endpoint

The key secondary efficacy endpoint was mean change from baseline to end of the double-blind treatment period (Week 12) in the CGI-S scale score, as related to agitation.

Other Secondary or Exploratory Endpoints

Secondary endpoints included change from baseline to Week 12 in the following:

- NPI-NH 12-item total score
- NPI-NH A/A subscore
- CGI-I scale score, as related to agitation

Statistical Considerations

Efficacy Analyses

- *Primary efficacy endpoint* was the mean change from baseline (Day 0) to the end of the double-blind period (Week 12) in the CMAI total score. The Applicant performed the primary efficacy analysis using MMRM with an UN variance covariance structure in which the change from the baseline in CMAI total score [Week 2, 4, 6, 8, 10, and 12] was the dependent variable based on the OC dataset. The model included fixed class-effect terms for treatment (brexpiprazole and

placebo), trial center, visit week, and an interaction term of treatment by visit week and included the interaction term of baseline values of CMAI total score by visit week as covariates. The primary analysis was identical to Study 331-12-283.

- *Key secondary endpoint* was the change from baseline to Week 12 in the CGI-S score, as related to agitation. The Applicant analyzed the key secondary endpoint using the same statistical methodology specified for the primary efficacy variable.

4.1.2.2 Study Results

Disposition

Of the 394 subjects screened, the Applicant randomized 270 subjects into the double-blind treatment period. All subjects except one in the brexpiprazole group received at least one dose of the study medication. In the Randomized Sample, 32 subjects (12%) discontinued during the trial (12% discontinued from the study in both treatment groups). The most frequent reason for discontinuation was due to AEs (total N = 11; 4.1%) across all treatment groups (BREX = 6.8%; placebo = 1.5%). The Safety Sample (consisting of randomized subjects who received at least one dose of the double-blind study medication) and the Efficacy Sample (consisting of all randomized subjects who received at least one dose of the double-blind study medication and had at least one post-baseline CMAI assessment) were identical (BREX = 132; placebo = 137; total N = 269).

Demographic and Baseline Disease Characteristics

Table 6 provide a summary of demographic and baseline characteristics across treatment groups among subjects included in the Efficacy Sample. In general, demographic and baseline characteristics were similar across treatment arms. Additional baseline disease characteristics and psychiatric history are summarized in Appendix 6.5. Most subjects resided in an institutionalized setting (55%) and exhibited moderate or severe cognitive impairment (76%). Comorbid psychotic symptoms were only present among 22% of subjects.

Table 6: Demographic and Baseline Characteristics for Study 331-12-284 (Efficacy Sample)

Demographic Characteristic	Placebo (N=137)	BREX 0.5 to 2 mg (N=132)
Age (years)		
Mean (SD)	74.0 (7.8)	73.4 (8.5)
Median (Range)	75 (56, 90)	74 (55, 89)
Age group (years), n (%)		
< 65	19 (14%)	24 (18%)
65 to < 75	49 (36%)	46 (35%)
≥75	69 (50%)	62 (47%)
Gender, n (%)		
Male	49 (36%)	51 (39%)
Female	88 (64%)	81 (61%)
Race, n (%)		

Demographic Characteristic	Placebo (N=137)	BREX 0.5 to 2 mg (N=132)
White	129 (94%)	127 (96%)
Black or African American	5 (3.6%)	4 (3.0%)
Asian	3 (2.2%)	-
Other	-	1 (0.8%)
Region, n (%)		
North America	39 (29%)	34 (25%)
ROW	98 (71%)	98 (75%)
Ethnicity, n(%)		
Hispanic or Latino	9 (6.6%)	6 (4.5%)
Not Hispanic or Latino	128 (93%)	124 (94%)
Weight (kg), mean (SD)	69.1 (14.9)	68.6 (14.8)
Height (cm), mean (SD)	163.4 (9.5)	163.9 (9.7)
BMI (kg/m^2), mean (SD)	25.8 (4.7)	25.2 (4.2)

Source: Clinical Reviewer-created using adsl.xpt dataset
Abbreviations: BMI = body mass index; ROW = Rest of World; SD = standard deviation.

Efficacy Results – Primary Endpoint

The result of the primary efficacy endpoint (mean change from baseline in CMAI Total Score at Week 12) for this study was not statistically significant (LSMD= −2.34 [95% CI: −5.49, 0.82]; p = 0.1454; Table 7).

Table 7: Study 331-12-284 Primary Endpoint Results (Efficacy Sample)

	Placebo (N=135)[2]	BREX 0.5 to 2 mg (N=131)[2]
Mean CMAI Total Score at Baseline (SD)	68.6 (16.01)	71.5 (16.84)
Mean CMAI Total Score at Week 12 (SD)	53.2 (14.98)	51.8 (13.88)
LSM Change from Baseline (SE)	-16.5 (1.13)	-18.9 (1.17)
Placebo-subtracted difference (95% CI)[1]		-2.34 (-5.49, 0.82)
P-value		0.1454

Source: Applicant's Study 331-12-284 Clinical Study Report, Table 11.4.1.1.1-1 and CT-5.2.1 p. 101 confirmed by statistical reviewer
Abbreviations: CMAI = Cohen Mansfield Agitation Inventory; LSM = least squares mean; MMRM = mixed-effect model for repeated measures; SD=standard deviation; SE=standard error; 95% CI = 95% confidence interval
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.
[2]Two subjects in the placebo group and one subject in the BREX group had only single post-baseline assessments at Week 1, not a planned schedule assessment time. As a result, those three subjects were not captured in the primary analysis although they were in the Efficacy Sample.

Efficacy Results – Key Secondary Endpoint

The analysis of the key secondary endpoint yielded a −0.31 point numerical improvement for the BREX 0.5 to 2 mg/day group over placebo (95% CI [-0.55, -0.06], p = 0.0164) in CGI-S, as related to agitation, at Week 12 (Table 8). The CGI-S results are considered solely descriptive because the primary endpoint finding was not statistically significant.

Table 8: Study 331-12-284 Key Secondary Endpoint Results (Efficacy Sample)

	Placebo (N=135)[3]	BREX 0.5 to 2 mg (N=131)[3]
Mean CGI-S Score at Baseline (SD)	4.5 (0.74)	4.5 (0.77)
Mean CGI-S Score at Week 12 (SD)	3.4 (1.11)	3.2 (0.92)
LSM Change from Baseline (SE)	-1.0 (0.09)	-1.3 (0.09)
Placebo-subtracted difference (95% CI)[1]		-0.31 (-0.55, -0.06)
Unadjusted p-value[2]		0.0164

Source: Applicant's study 331-12-284 Clinical Study Report, Table 11.4.1.2.1.1-1 and CT-5.3.1, p. 104, confirmed by Statistical Analyst
Abbreviations: CGI-S = Clinical Global Impression-Severity Scale; LSM = least squares mean; MMRM = mixed-effect model repeated measures; SD=standard deviation, SE=standard error, 95% CI = 95% confidence interval
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.
[2]P-value reported in the table is nominal.
[3]Two subjects in the placebo group and one subject in the BREX group had only single post-baseline assessments at Week 1, not a planned schedule assessment time. As a result, those three subjects were not captured in the primary analysis although they were in the Efficacy Sample.

Additional Analyses

Analyses of other secondary and exploratory endpoints consistently resulted in numerical improvements with the brexpiprazole group vs. placebo. Table 9 displays the Applicant's secondary analyses based on the three major factor domains in the CMAI measure and using the same statistical methodology as described for the primary efficacy variable. In this study, the brexpiprazole treatment groups appears to exert its greater effect on the aggressive behavior domain (BREX: -1.09).

Table 9: Study 331-12-284 Change from Baseline to Week 12 in CMAI Factor Scores (Efficacy Sample)

Variable[1]	Placebo (N=135)	BREX 0.5 to 2 mg (N=131)
Factor 1: Aggressive Behaviors		
Baseline Mean (SD)	22.22 (7.69)	23.84 (9.20)
LSM Change from Baseline (SE)	-6.13 (0.42)	-7.22 (0.43)
Placebo-subtracted difference (95% CI)		-1.09 (-2.24, 0.05)
Unadjusted p-value[2]		0.061
Factor 2: Physically Non-aggressive Behaviors		
Baseline Mean (SD)	19.72 (7.15)	20.65 (7.10)
LSM Change from Baseline (SE)	-5.17 (0.42)	-5.52 (0.43)
Placebo-subtracted difference (95% CI)		-0.35 (-1.51, 0.81)
Unadjusted p-value[2]		0.552
Factor 3: Verbally Agitated Behaviors		
Baseline Mean (SD)	14.76 (5.50)	15.40 (4.85)
LSM Change from Baseline (SE)	-3.54 (0.33)	-4.23 (0.34)
Placebo-subtracted difference (95% CI)		-0.69 (-1.59, 0.21)
Unadjusted p-value[2]		0.134

Source: Clinical Reviewer-adapted using Applicant's Clinical Study Report 331-12-284, Table 11.4.1.2.2.1-1 p. 105
Abbreviations: CI = confidence interval; SD: standard deviation; SE = standard error
[1]Hiding and hoarding behavior was analyzed with these factors, but this behavior was not 1 of the three distinct CMAI-defined agitation syndromes and thus was not included in the table.
[2]All p-values reported in the table are nominal.
Note: MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

Although Study 331-12-284 failed to meet its primary endpoint, the Applicant conducted several post-hoc exploratory analyses to further explore treatment response among subjects who received brexpiprazole 2 mg/day. At the Week 4 visit, 77 subjects in the brexpiprazole group and 74 subjects in the placebo group required an increase in dosage from 1 mg/day to 2 mg/day of their respective study medication. The Applicant compared the treatment effect on the primary and key secondary endpoints between the subgroup of subjects who did not have a sufficient response over the first 4 weeks (i.e., those subjects who received a dosage increase after the Week 4 visit) vs. those who exhibited an adequate response to the study medication.

For the primary efficacy endpoint (change in CMAI total score from baseline to Week 12) a numerical improvement was observed with brexpiprazole (LSM change from baseline = -17.8) over placebo (LSM change from baseline = -12.8) in the subgroup whose dosage was titrated to 2 mg/day (LSMD = -5.06 [95% CI: -8.99, -1.13]). For subjects who did not require a dosage increase at Week 4, there was no improvement observed with brexpiprazole (LSM change from baseline = -19.3) over placebo (LSM change from baseline = -20.8) (LSMD = 1.57 [95% CI: -3.64, 6.78]). Similarly, subjects who had a modal dose of ≥ 2 mg showed a greater numerical improvement in the changes from baseline at Week 12 for both CMAI total score (LSMD = -5.25 [95% CI:−9.23, −1.27]) compared with placebo. For subjects who had ≤ 1 mg modal dose, no improvement was shown over placebo for on the primary endpoint (LSMD = 2.26 [95% CI: -2.19, 6.71]).

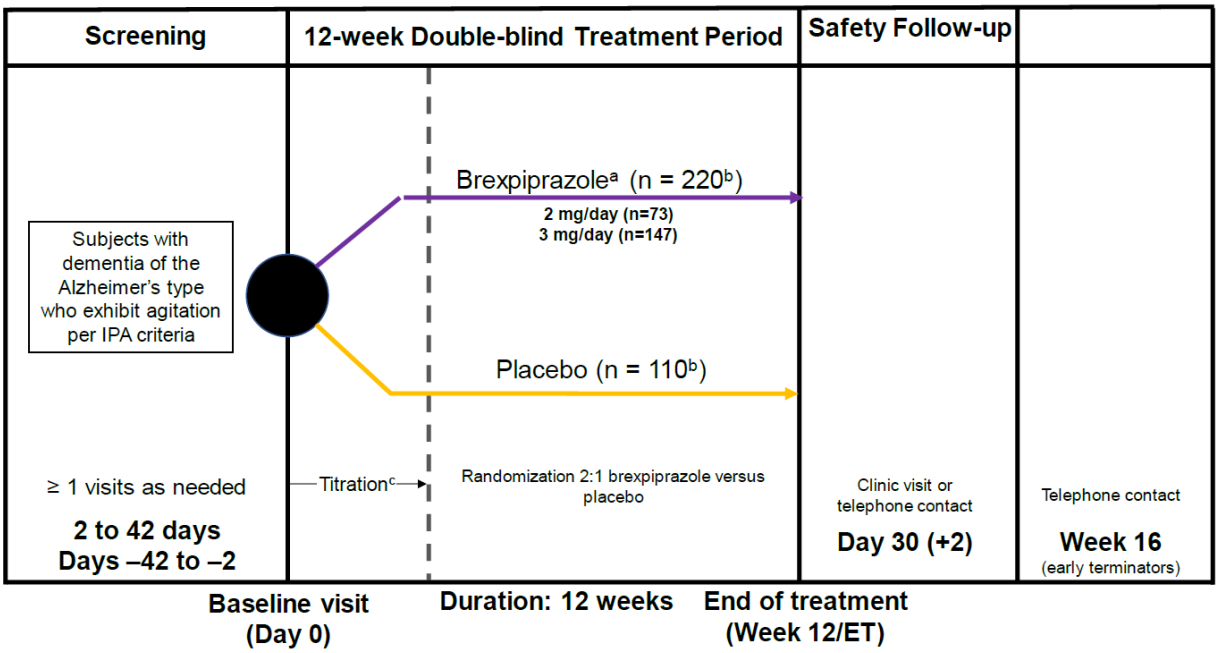
4.1.3 Study 331-14-213

4.1.3.1 Trial Design

Study 331-14-213 was a phase 3 randomized, double-blind, placebo-controlled, multi-center, fixed-dose study intended to evaluate the efficacy, safety, and tolerability of brexpiprazole 2 mg/day and 3 mg/day in elderly subjects with AAD. Similar to Studies 331-12-283 and 331-12-284, this study consisted of a screening period up to 42 days, a 12-week double-blind treatment period, and a 30-day safety follow-up period. See Figure 3 for the Applicant's study design schematic.

The Applicant randomized eligible subjects in a 2:1 ratio to either brexpiprazole (further randomized 1:2 to 2 mg/day [BREX 2 mg] or 3 mg/day [BREX 3 mg]) or placebo. All subjects randomized to receive brexpiprazole received 0.5 mg/day as a starting dosage. The Applicant increased the brexpiprazole dosage 1 mg/day starting on Day 8, and then increased to 2 mg/day starting on Day 15. For subjects randomized to BREX 3 mg, the dosage increased to 3 mg/day starting on Day 29 (after the Week 4 visit). The Applicant withdrew any subjects unable to tolerate their assigned dosage and prohibited any down-titration of the dose at any time during the study. Refer to Appendix 6.4 for the Applicant's detailed schedule of assessments. Caregiver requirements were identical to Studies 331-12-283 and 331-12-284.

Figure 3: Study Design Overview for Study 331-14-213



Source: Applicant's 331-14-213 Clinical Study Report, Figure 3.1-1, p. 33
Abbreviations: ET = early termination

Trial Eligibility

The target population consisted of elderly subjects aged 55 to 90 years, with a diagnosis of probable AD according to the NINCDS-ADRDA criteria, mild to severe cognitive impairment (MMSE score between 5 to 22), and living in either an institutionalized or non-institutionalized setting where the subject is not living alone. The Applicant also required subjects to exhibit significant agitation, defined as a total score (frequency x severity) of ≥ 4 on the agitation/aggression item of the NPI-NH for institutionalized subjects and the NPI/NPI-NH for non-institutionalized subjects and requiring pharmacotherapy after a trial of non-pharmacological interventions, with onset of symptoms at least 2 weeks prior to screening. Unlike the two previous studies, the diagnosis of agitation had to meet the 2015 IPA provisional consensus definition.

A protocol addendum also supplemented the original protocol and provided details of additional eligibility criteria and statistical methods to which the trial site investigators were blinded and which were reviewed only by local Institutional Review Boards and regulatory authorities. The intent of the blinded protocol addendum was to reduce potential subject selection bias (e.g., rater inflation). An Independent Adjudication Panel provided an assessment of each subject's eligibility at the time of enrollment.

In addition to the listed eligibility criteria in the original protocol, the Applicant required all subjects to meet criteria for positive CMAI Factor 1 agitation (i.e., ≥ 1 aggressive behavior occurring several times per week, or ≥ 2 aggressive behaviors occurring once or twice per week, or ≥ 3 aggressive behaviors occurring less than once per week) at screening and baseline. The Applicant excluded subjects with insufficient response to two or more previous antipsychotic medications for the treatment of agitation,

history of cerebrovascular conditions, presence or history of delirium, evidence of serious risk of suicide based on the Sheehan-Suicide Tracking Scale, and clinically significant and uncontrolled medical conditions. The Applicant's listing of prohibited concomitant medications is summarized in Appendix 6.2.

Study Endpoints

Primary Endpoint

The primary efficacy endpoint was mean change from baseline to the end of the double-blind treatment period (Week 12) in the CMAI (Long-Form) total score.

To evaluate treatment effects in each domain that align with diagnostic criteria for agitation (Table 1), between-treatment group results for each subscale (Factors 1, 2, and 3) were provided descriptively (i.e., not in the statistical testing hierarchy).

Key Secondary Endpoint

The key secondary efficacy endpoint was mean change from baseline to end of the double-blind treatment period (Week 12) in the CGI-S scale score, as related to agitation.

Other Secondary or Exploratory Endpoints

Secondary endpoints included the following:

- Change from baseline in CMAI total score for each trial visit during the double-blind treatment period
- Change from baseline in CGI-S scale score for each trial visit during the double-blind treatment period
- CGI-I scale score at each trial visit during the double-blind treatment period.

Statistical Considerations

Efficacy Analyses

- *Primary efficacy endpoint* was the mean change from baseline (Day 0) to the end of the double-blind period (Week 12) in the CMAI total score. The Applicant performed the primary efficacy analysis using MMRM with an unstructured variance covariance structure in which the change from the baseline in CMAI total score [Week 2, 4, 6, 8, 10, and 12] was the dependent variable based on the OC dataset. The model included fixed class-effect terms for treatment (brexpiprazole and placebo), trial center, visit week, and an interaction term of treatment by visit week and included the interaction term of baseline values of CMAI total score by visit week as covariates. The primary analysis was identical to Studies 331-12-283 and 331-12-284.

- *Key secondary endpoint* was the change from baseline to Week 12 in the CGI-S score, as related to agitation. The Applicant analyzed the key secondary endpoint using the same statistical methodology specified for the primary efficacy variable.

- *Interim analysis:* An independent Data Monitoring Committee (DMC) performed an unblinded interim analysis (IA) of efficacy data when the first 255 randomized subjects in the trial had either completed the Week 12 visit or discontinued from the trial. The interim analysis included

a Bonferroni critical boundary for the two-stage group sequential analysis. Specifically, the alpha allocated to the IA was 0.015 and the alpha left for the final analysis was 0.035, both two-sided.

- *Multiplicity adjustment:* The Applicant used a hierarchical testing procedure to maintain the overall experiment-wise type I error rate. After reviewing the unblinded interim analysis results, the DMC recommended that the Applicant should continue the trial to the planned end. At the final analysis, the Applicant tested the primary efficacy endpoint at a two-sided 3.5% significance level and, upon achieving significance on the primary endpoint, tested the key secondary endpoint at the same level.

4.1.3.2 Study Results

Disposition

Of the 900 subjects screened, the Applicant randomized 345 subjects into the double-blind treatment period. Although reasons for screen failures (N=555) varied, the most common reason was withdrawal of consent prior to entering the treatment period. All subjects except three (two in the BREX 2-mg arm and one in the placebo arm) received at least one dose of the study medication. In the Randomized Sample, 43 subjects (13%) discontinued during the trial (9.3%, 15%, and 11% discontinued from the study in the BREX 2-mg, BREX 3-mg, and placebo treatment groups, respectively). The most frequent reason for discontinuation was due to Aes (total N = 17; 4.9%) across all treatment groups (1.3%, 7.2%, and 4.3% in the BREX 2-mg, BREX 3-mg, and placebo treatment groups, respectively). The Safety Sample and the Efficacy Sample were identical (BREX 2 mg = 73; BREX 3 mg = 153; placebo = 116; total N = 342). Of note, the Applicant amended their protocol (protocol amendment 2) to accommodate changes in the conduct of the trial (e.g., remote assessments) due to the COVID-19 pandemic. During the course of the trial, two baseline visits, 10 Week 12 visits, and two end-of-study visits occurred virtually (pre-COVID Efficacy Sample consisted of 195 subjects).

Baseline Demographics and Disease Characteristics

Table 10 provide a summary of demographic and baseline characteristics across treatment groups among subjects included in the Efficacy Sample. In general, demographic and baseline characteristics were similar across treatment arms. Additional baseline disease characteristics and psychiatric history are summarized in Appendix 6.5. Most subjects resided in a non-institutionalized setting (56%) and exhibited moderate or severe cognitive impairment (76%). Comorbid psychotic symptoms were only present among 19% of subjects.

Table 10: Demographic and Baseline Characteristics for Study 331-14-213 (Efficacy Sample)

Demographic Characteristic	Placebo (N=116)	BREX 2 mg (N=73)	BREX 3 mg (N=153)	All BREX (N=226)
Age (years)				
Mean (SD)	73.0 (7.0)	74.2 (7.3)	74.6 (8.0)	74.4 (7.7)
Median (Range)	73 (58, 88)	75 (57, 88)	75 (56, 90)	73 (58, 88)
Age group (years), n (%)				
< 65	13 (11%)	8 (11%)	16 (11%)	24 (11%)
65 to < 75	54 (47%)	29 (40%)	54 (35%)	83 (37%)
≥75	49 (42%)	36 (49%)	83 (54%)	119 (53%)

Demographic Characteristic	Placebo (N=116)	BREX 2 mg (N=73)	BREX 3 mg (N=153)	All BREX (N=226)
Gender, n (%)				
Male	56 (48%)	32 (44%)	61 (40%)	93 (41%)
Female	60 (52%)	41 (56%)	92 (60%)	133 (59%)
Race, n (%)				
White	114 (98%)	68 (93%)	144 (94%)	212 (94%)
Black or African American	1 (0.9%)	5 (6.8%)	6 (3.9%)	11 (4.9%)
Asian	1 (0.9%)	-	3 (2.0%)	3 (1.3%)
Region, n (%)				
North America	49 (42%)	30 (41%)	71 (46%)	101 (45%)
ROW	67 (58%)	43 (59%)	82 (54%)	125 (55%)
Ethnicity, n(%)				
Hispanic or Latino[2]	37 (32%)	23 (32%)	46 (30%)	69 (31%)
Not Hispanic or Latino	79 (68%)	50 (69%)	107 (70%)	157 (70%)
Weight (kg), mean (SD)	71.4 (13.8)	70.9 (15.7)	70.2 (15.5)	70.5 (15.5)
Height (cm), mean (SD)	164.1 (10.1)	163.2 (9.9)	162.5 (10.7)	163.6 (10.4)
BMI (kg/m^2), mean (SD)	25.8 (4.8)	26.6 (4.8)	25.6 (4.7)	26.0 (4.7)

Source: Clinical Reviewer-created using adsl.xpt dataset
Abbreviations: BMI = body mass index; ROW = Rest of World; SD = standard deviation.

Efficacy Results – Primary Endpoint

The combined BREX 2-mg and 3-mg group demonstrated a statistically significant improvement compared to placebo on the primary efficacy endpoint, the mean change in the CMAI Total Score from baseline to Week 12 (LSMD = −5.32 [95% CI: [−8.77, −1.87]; p = 0.0026), shown in Table 11.

Table 11: Study 331-14-213 Primary Endpoint Results (Efficacy Sample)

	Placebo (N=116)	BREX 2 and 3 mg (N=225)[2]
Mean CMAI Total Score at Baseline (SD)	79.2 (17.52)	80.6 (16.64)
Mean CMAI Total Score at Week 12 (SD)	63.2 (18.15)	57.8 (17.08)
LSM Change from Baseline (SE)	-17.3 (1.44)	-22.6 (1.08)
Placebo-subtracted difference (95% CI)[1]		-5.32 (-8.77, -1.87)
P-value		**0.0026**

Source: Applicant's Study 331-14-213 Clinical Study Report, Table 11.4.1.1.1-1 and CT-5.2.1.p. 72 confirmed by statistical reviewer
Abbreviations: CMAI = Cohen Mansfield Agitation Inventory; LSM = least squares mean, MMRM = mixed-effect model for repeated measures; SD=standard deviation, SE=standard error, 95% CI = 95% confidence interval.
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.
[2]One subject in the BREX 2 and 3 mg group had only one post-baseline assessment and it was at Week 7, not a planned schedule assessment time. As a result, this subject was not captured in the primary analysis although this subject was in the Efficacy Sample.
Note: The p-value should be compared with the significance level of 0.035 due to an interim analysis conducted.

The primary efficacy variable was further examined to explore the consistency of the treatment effect across the following subgroups: sex, race, age, region, and ethnicity. For the subgroups by region, numerical differences were notable in the non-US subgroup (LSMD = -8.99 [95% CI: -13.2, -4.81]) vs. the US population (LSMD = 0.32 [95% CI: -5.33, 6.18]), and in the non-Hispanic subgroup (LSMD = -8.3 [95% CI: -12.5, -4.07]) vs. the Hispanic subgroup (LSMD = 1.66 [95% CI: -4.42, 7.74]) . Of note, the placebo

response profile differed for Hispanic (higher) versus non-Hispanic subgroups in the US in this study, although treatment responses appeared similar for both groups.

The Applicant also conducted the post-hoc analyses to investigate the individual treatment effects for the BREX 2-mg and BREX 3-mg group separately. The placebo-adjusted LS mean (95% CI) changes from baseline to Week 12 in CMAI Total Score for BREX 2-mg and BREX 3-mg groups were -5.28 [95% CI: -9.77, -0.78] and -5.35 [95% CI: -9.09, -1.60], respectively. The reductions from baseline to Week 12 in the CMAI Total Score were still nominally statistically significantly greater for both BREX 2 mg (p=0.0216) and BREX 3 mg (p=0.0053) compared to placebo (Table 12).

Table 12: Study 331-14-213 Summary of Mean Change from Baseline to Week 12 in the CMAI total score by Dose Group (Efficacy Sample)

	Placebo (N=116)	BREX 2 mg (N=73)	BREX 3 mg (N=152)
Mean CMAI Total Score at Baseline (SD)	79.2 (17.52)	79.1 (15.24)	81.3 (17.28)
LSM Change from Baseline (SE)	-17.3 (1.45)	-22.5 (1.83)	-22.6 (1.31)
Placebo-subtracted difference (95% CI)[1]		-5.28 (-9.77, -0.78)	-5.35 (-9.09, -1.60)
Unadjusted p-value[2]		0.0216	0.0053

Source: Applicant's Study 331-14-213 Clinical Study Report, Table 11.4.1.1.1-1, p. 83 confirmed by statistical reviewer
Abbreviations: CMAI = Cohen Mansfield Agitation Inventory; LSM = least squares mean, MMRM = mixed-effect model for repeated measures; SD=standard deviation, SE=standard error, 95% CI = unadjusted 95% confidence interval (p-value also unadjusted for multiple groups)
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.
[2]All p-values reported in the table are nominal.

Efficacy Results – Key Secondary Endpoint

The combined BREX 2- and 3-mg group showed a statistically significant improvement compared with the placebo group for the key secondary efficacy endpoint, change from baseline to Week 12 in CGI-S score, as related to agitation (LS mean difference = −0.27 [95% CI: −0.47, −0.07]; p = 0.0078; Table 13). Analyses of the separate effects of the BREX-2 mg and BREX-3 mg treatment groups on the CGI-S indicated that treatment effect was nominally statistically significantly greater for BREX 3 mg (LS mean difference = −0.29 [95% CI: -0.51, -0.08]; p = 0.0084), but not for the BREX 2-mg group (LS mean difference = −0.23 [95% CI: -0.49, 0.03], p = 0.081) relative to placebo.

Table 13: Study 331-14-213 Key Secondary Endpoint Results (Efficacy Sample)

	Placebo (N=116)	BREX 2 and 3 mg (N=225)[3]
Mean CGI-S Score at Baseline (SD)	4.7 (0.69)	4.7 (0.66)
Mean CGI-S Score at Week 12 (SD)	3.8 (0.97)	3.5 (0.91)
LSM[1] Change from Baseline (SE)	-0.9 (0.08)	-1.2 (0.06)
Placebo-subtracted difference (95% CI)[1]		-0.27 (-0.47, -0.07)
Unadjusted p-value[2]		0.0078

Source: Applicant's study 331-14-213 Clinical Study Report, Table 11.4.1.2.1.1-1 and CT-5.3.1, p. 75, confirmed by Statistical Analyst
Abbreviations: CGI-S = Clinical Global Impression-Severity Scale; LSM = least squares mean; MMRM = mixed-effect model repeated measures; SD=standard deviation, SE=standard error; 95% CI = 95% confidence interval
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.
[2]P-value reported in the table is nominal.

[3]One subject in the BREX 2 and 3 mg group had only one post-baseline assessment and it was at Week 7, not a planned schedule assessment time. As a result, this subject was not captured in the primary analysis although this subject was in the Efficacy Sample.
Note: The p-value should be compared with significance level of 0.035.

Additional Analyses

Table 14 displays the Applicant's secondary analyses based on the three factor domains in the CMAI measure and using the same statistical methodology as described for the primary efficacy variable. Although nominally significant improvements are observed with all three major factor domains, the effect on the aggressive behavior domain is the most pronounced (BREX: -1.95).

Table 14: Study 331-14-213 Change from Baseline to Week 12 in CMAI Factor Scores (Efficacy Sample)

Variable[1]	Placebo (N=116)	BREX 2 and 3 mg (N=225)
Factor 1: Aggressive Behaviors		
Baseline Mean (SD)	26.53 (8.69)	26.31 (7.29)
LSM Change from Baseline (SE)	-7.13 (0.56)	-9.09 (0.42)
Placebo-subtracted difference (95% CI)		-1.95 (-3.28, -0.63)
Unadjusted p-value[2]		0.004
Factor 2: Physically Non-aggressive Behaviors		
Baseline Mean (SD)	23.24 (7.42)	23.79 (7.28)
LSM Change from Baseline (SE)	-5.04 (0.53)	-6.45 (0.40)
Placebo-subtracted difference (95% CI)		-1.41 (-2.68, -0.14)
Unadjusted p-value[2]		0.0296
Factor 3: Verbally Agitated Behaviors		
Baseline Mean (SD)	16.34 (5.56)	16.93 (4.67)
LSM Change from Baseline (SE)	-3.14 (0.40)	-4.39 (0.31)
Placebo-subtracted difference (95% CI)		-1.24 (-2.21, -0.28)
Unadjusted p-value[2]		0.0113

Source: Clinical Reviewer-adapted using Applicant's Clinical Study Report 331-14-213, CT-5.1, p. 314
Abbreviations: CI = confidence interval; SD=standard deviation; SE = standard error
[1]Hiding and hoarding behavior was analyzed with these factors, but this behavior was not 1 of the three distinct CMAI-defined agitation syndromes and thus was not included in the table.
[2]All p-values reported in the table are nominal. Note: MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

4.1.4 Overall Conclusion

The Applicant submitted three adequate and well-controlled trials to contribute to substantial evidence of effectiveness for the use of brexpiprazole for the treatment of AAD. Based on the study results, the Applicant demonstrated a statistically significant treatment effect with the BREX 2-mg treatment group in Study 331-12-283 and with the combined BREX 2- and 3-mg treatment group in Study 331-14-213. Although Study 331-12-284 failed to meet its primary endpoint, the treatment effect observed among subjects who received BREX 2 mg (titration after Week 4 or modal dose) was nominally significant relative to placebo and numerically similar to results with the BREX 2-mg group in Studies 331-12-283 and 331-14-213.

Additional analyses on the CMAI factor subscores indicate nominally consistent trends in improvement in aggressive, physically non-aggressive, and verbal agitated behaviors. Although the Applicant enriched

Study 331-14-213 to include a study population that exhibited aggressive behaviors at baseline, subgroup analyses suggest that the treatment effect was also present among subjects who also exhibited significant physically non-aggressive and verbally agitated behavior at baseline.

In summary, the Applicant appears to have provided substantial evidence of effectiveness (via two adequate and well controlled trials meeting their prespecified primary endpoint) for brexpiprazole for the treatment of AAD.

4.2 Summary of Safety

The safety evaluation for this supplemental application is primarily based on three phase 3 studies (331-12-283, 331-12-284, and 331-14-213). In addition, the Applicant conducted two additional safety studies: a 2-month, observational, post-treatment, roll-over phase 3 study (331-12-211) that included subjects who completed Studies 331-12-283 and 331-12-284; and a 12-week, open-label extension study (331-201-00182) that included subjects who completed Study 331-14-213.

4.2.1 Mortality Assessment

4.2.1.1 Estimation of Brexpiprazole's Mortality Risk based on Phase 3 Studies

To better contextualize brexpiprazole's benefit/risk profile for the treatment of AAD, the review team primarily focused on death events observed across all three 12-week, phase 3 studies (331-12-283, 331-12-284, and 331-12-213). The Applicant reported a total of nine death events; eight subjects received brexpiprazole treatment (1.2%, N = 655) and one subject received placebo (0.26%, N = 388). Summary case narratives are provided in Appendix 6.6. Of the nine deaths, six occurred after the last dose of the study drug and prior to 30 days of post-dose follow-up (five events in the brexpiprazole group and one event in the placebo group). A timeline for each death event relative to the last dose of the study medication is provided in Appendix 6.8. Of note, the Applicant also reported one death event (stroke/cardiac arrest; Day 159) in a subject enrolled in Study 331-12-211—the 2-month, observational, roll-over study—who previously received brexpiprazole (Study Day of last dose: 159) in Study 331-12-284. The Applicant did not report any death events in Study 331-201-00182.

In each of the three phase 3 double-blind study protocols, the Applicant indicated that they would make every effort to collect mortality status information by telephone at the Week 16 visit for subjects who terminated early from the trial. In addition, all study completers and subjects who were withdrawn prematurely for any reason underwent a safety evaluation 30 days after receiving their last dose of study medication. The Applicant utilized the sampling time frame of 30 days after the last dose of the study medication (BREX = 6 events; placebo = one event) to calculate the incidence of death for each treatment group. However, the review team believes the sampling time frame introduces a bias for any subject receiving active treatment who drops out because of a drug-related AE (adverse reaction) and dies more than 30 days after the last dose of the study medication. These subjects would have been counted differently and remained in the study had they been assigned to placebo.

In order to juxtapose the findings from this program with the previous Agency meta-analysis and to limit bias, this review utilized a similar methodological approach for assessing various sampling time frames to estimate brexpiprazole's mortality risk in the AAD population. Given the confidence in collecting mortality information at the 30-day safety follow-up period for subject completers and at the Week 16

mortality assessment for subjects who terminated early from the trial, the review team selected a sampling time frame of 114 days (deaths observed in intended period of observation [12 weeks] + 30-days of follow-up) to count the number of death events in the brexpiprazole and placebo treatment groups. The deaths observed sampling time frame assumes the possibility of a significant lag between an adverse reaction and death resulting from the event and limits the aforementioned bias for subject deaths beyond 30 days post-dose.

The statistical model to estimate brexpiprazole's mortality risk (incident rate ratio) included a Poisson mixed-effect model with treatment as a fixed effect, an offset for log (time as person-days), and Study ID as a normally distributed random effect. Further sensitivity analyses included evaluation of all death events that occurred across all three studies (period of observation-all). Subjects who did not die were assigned a censoring time corresponding to the latest occurring death across all three trials (152 days). Refer to Table 15 for a listing of death events occurring by study and treatment arm and for the estimated incident rate ratio (IRR) relative to placebo. Figure 4 displays a comparison of the brexpiprazole's mortality risk in the AAD population relative to the Agency's previous findings based on the deaths observed in the intended period of observation during the study plus follow-up sampling time frame.

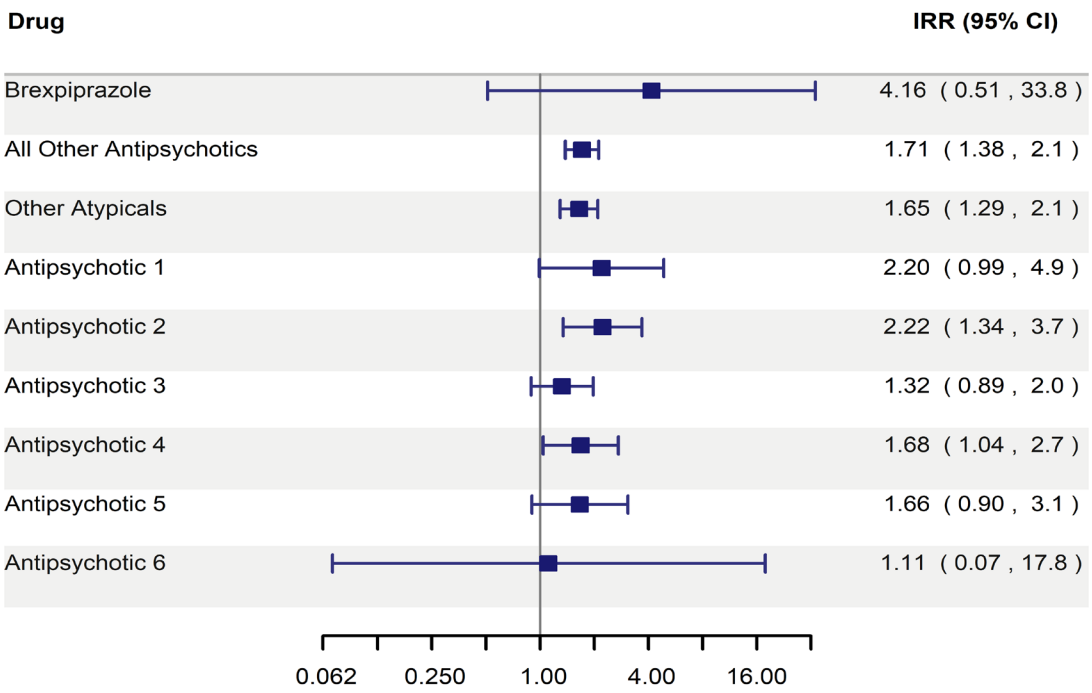
Based on the 114 days sampling time frame, risk of death associated with brexpiprazole (IRR = 4.16 [95% CI: 0.51, 33.83) follows a similar trend with the mortality risk estimated for other antipsychotics. The sensitivity analysis, including all deaths across all phase 3 studies, also estimated a similar mortality risk associated with brexpiprazole over placebo (IRR: 4.75 [95% CI: 0.59, 38.08]). Due to the evidence that the use of antipsychotics to treat dementia-related behavioral disorders (i.e., psychosis and agitation) results in higher mortality, the Boxed Warning should remain to adequately inform health care providers.

Table 15: Mortality Analysis of Deaths Across All 12-Week Phase 3 Studies for AAD

Study ID	Treatment	Number of Subjects	Deaths Observed in the Intended Period of Observation + 30 Days Follow-up) Analysis
			Deaths
331-12-283	BREX	297	4
	PLACEBO	135	0
331-12-284	BREX	132	2
	PLACEBO	137	1
331-14-213	BREX	226	1
	PLACEBO	116	0
Total	BREX	655	7
	PLACEBO	388	1
IRR (95% CI)			4.16 (0.51, 33.83)

Source: Reviewer-created using Applicant's Summary of Clinical Safety and adae.xpt dataset
Abbreviations: BREX = brexpiprazole; CI = confidence interval; IRR = incident rate ratio (also referred to as mortality risk)
Note: IRR calculated using Poisson mixed-effect model with treatment as a fixed effect, an offset for log Person-Year, and a normally distr buted random intercept term for study

Figure 4: Comparison of Brexpiprazole's Mortality Risk versus FDA's Previous Findings (Deaths Observed in the Intended Period of Observation + 30 Days Follow-Up Sampling Time Frame)



Source: Reviewer-created using adae.xpt dataset and the Agency's internal review document authored by Dr. Marc Stone
Abbreviations: CI = confidence interval; IRR = incident rate ratio (referred to as mortality risk)
Note: "All other antipsychotics" and "other atypicals" groups do not include brexpiprazole.

4.2.2 General Safety Findings

Other safety findings (e.g., AEs, laboratory assessments, physical examinations) from the AAD development program were generally consistent with the known safety profile of brexpiprazole. Analyses of the AE data suggested no apparent dose-dependent trends and a similar overall incidence relative to adult subjects enrolled in studies for MDD and schizophrenia. Refer to Appendix 6.10 for a summary analysis of brexpiprazole's observed safety profile across the three phase 3 studies. Continued treatment with brexpiprazole (24 weeks) in Study 331-201-00182 did not reveal any new safety signals and the safety findings were consistent with the drug's known safety profile over 12 weeks of treatment.

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6 Appendix

6.1 CMAI Instrument

THE COHEN-MANSFIELD AGITATION INVENTORY - Long Form

Please read each of the 29 agitated behaviors, and circle how often (from 1-7) each was manifested by the resident during the last 2 weeks:

	Never 1	Less than once a week 2	Once or twice a week 3	Several times a week 4	Once or twice a day 5	Several times a day 6	Several times an hour 7
1. Pace, aimless wandering	1	2	3	4	5	6	7
2. Inappropriate dress or disrobing	1	2	3	4	5	6	7
3. Spitting (include at meals)	1	2	3	4	5	6	7
4. Cursing or verbal aggression	1	2	3	4	5	6	7
5. Constant unwarranted request for attention or help	1	2	3	4	5	6	7
6. Repetitive sentences or questions	1	2	3	4	5	6	7
7. Hitting (including self)	1	2	3	4	5	6	7
8. Kicking	1	2	3	4	5	6	7
9. Grabbing onto people	1	2	3	4	5	6	7
10. Pushing	1	2	3	4	5	6	7
11. Throwing things	1	2	3	4	5	6	7
12. Strange noises (weird laughter or crying)	1	2	3	4	5	6	7
13. Screaming	1	2	3	4	5	6	7
14. Biting	1	2	3	4	5	6	7
15. Scratching	1	2	3	4	5	6	7

	Never 1	Less than once a week 2	Once or twice a week 3	Several times a week 4	Once or twice a day 5	Several times a day 6	Several times an hour 7
16. Trying to get to a different place (e.g., out of the room, building)	1	2	3	4	5	6	7
17. Intentional falling	1	2	3	4	5	6	7
18. Complaining	1	2	3	4	5	6	7
19. Negativism	1	2	3	4	5	6	7
20. Eating/drinking inappropriate substances	1	2	3	4	5	6	7
21. Hurt self or other (cigarette, hot water, etc.)	1	2	3	4	5	6	7
22. Handling things inappropriately	1	2	3	4	5	6	7
23. Hiding things	1	2	3	4	5	6	7
24. Hoarding things	1	2	3	4	5	6	7
25. Tearing things or destroying property	1	2	3	4	5	6	7
26. Performing repetitious mannerisms	1	2	3	4	5	6	7
27. Making verbal sexual advances	1	2	3	4	5	6	7
28. Making physical sexual advances	1	2	3	4	5	6	7
29. General restlessness	1	2	3	4	5	6	7

6.2 Summarized List of Restricted and Prohibited Medications

Medication	Prior to Randomization	During Double-Blind Period
Medications to treat Alzheimer's disease (cholinesterase inhibitors, memantine, and/or other cognitive enhancers)	Allowed provided that the dosage was stable for 90 days prior to randomization, and there is no decrease or discontinuation within 30 days prior to randomization	Subject should remain on the same dosage throughout the duration of the trial, except when medically indicated
Antipsychotics	7-day washout (Clozapine not allowed within 30 days prior to randomization; LAI antipsychotics require washout of 1.5 times the dosing interval)	Prohibited
Antidepressants	Allowed provided that the dosage was stable for 30 days prior to randomization (fluoxetine requires a 28-day washout)	Subject should remain on the same dosage throughout the duration of the trial, except when medically indicated
Mood stabilizers, anticonvulsants, varenicline, nutritional supplements, nonprescription herbal preparations with CNS effects, CYP2D6 inhibitors, or CYP3A4 inhibitors and inducers	7-day washout	Prohibited
Benzodiazepines	Allowed but limited to 4 days/week with a maximum dosage of 2 mg/day of lorazepam (or equivalent) or less depending on dose-limiting side effects.	During the first 4 weeks of the randomized phase: allowed but limited to 4 days/week with a maximum dosage of 2 mg/day of lorazepam (or equivalent) or less depending on dose-limiting side effects. After Week 4 visit: prohibited
Non-benzodiazepine sleep agents	If a bedtime dose of a medication for insomnia was taken prior to screening on a regular basis, a stable pretrial dosage of the sleep agent may be continued as needed during the trial. If a sleep agent was not taken prior to randomization and needs to be initiated, medication should be limited to a maximum dosage of zolpidem 5 mg/day (or equivalent).	Sleep agents must not be administered within 8 hours prior to the efficacy and safety scales. Combined use of benzodiazepines and non-benzodiazepine sleep agents for insomnia is not allowed.
Opioid analgesics	Prohibited unless permission is obtained from the medical monitor.	Prohibited unless permission is obtained from the medical monitor.
Anticholinergics for the treatment of extrapyramidal symptoms (including propranolol)	7-day washout	Prohibited For treatment of akathisia or tremor: maximum propranolol dosage of 20 mg, three times daily (total of 60 mg/day).
Medications to treat other medical conditions (e.g., hypertension)	Allowed provided that the dosage was stable for 30 days prior to randomization	Subject should remain on the same dosage throughout the duration of the trial, except when medically indicated

Source: Reviewer-adapted using Applicant's Protocol 331-12-283, 331-12-284 , and 331-14-213, Table 1

6.3 Abbreviated Schedule of Assessments for Studies 331-12-283 and 331-12-284

Assessment	Visit									
	Screening	Baseline	Day 3	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	WK 12/ ET	Wk 16
Inclusion/exclusion criteria	X	X								
Medical and Psychiatric history	X	X								
Prior medication washout, blood alcohol, and UDS	X									
Hachinski Ischemic Scale (Rosen Modification)	X									
CMAI, CGI-S, NPI-NH, NPI/NPI-NH	X	X		X	X	X	X	X	X	
CGI-I and CGI-E				X	X	X	X	X	X	
M-NCAS (for institutionalized subjects), QoL-AD, NOSGER (for institutionalized subjects), RUD		X							X	
Physical and neurological examinations	X								X	
Vital signs	X	X	X	X	X	X	X	X	X	
Clinical laboratory tests	X	X			X		X		X	
Prolactin, TSH, HbA1c, PT, aPTT, INR, urine pregnancy test	X								X	
ECG	X	X			X		X		X	
MMSE	X	X							X	
Sheehan-STS	X	X		X	X	X	X	X	X	
SAS, AIMS, BARS		X		X	X		X		X	
PK Sampling		X					X		X	
Mortality assessment (for ET)										X

Source: Reviewer created using Applicant's Protocol for Studies 331-12-283 and 331-12-284
Abbreviations: AIMS = Abnormal Involuntary Movement Scale; aPTT = activated partial thromboplastin time; BARS = Barnes Akathisia Rating Scale; CGI-I = Clinical Global Impression – Improvement scale; CGI-E = Clinical Global Impression – Efficacy Index; CGI-S = Clinical Global Impression – Severity scale; CMAI = Cohen Mansfield Agitation Inventory; ECG = electrocardiogram; ET = early termination; HbA1c = glycosylated hemoglobin; INR = International Normalized Ratio; MMSE = Mini-mental State Examination; M-NCAS = Modified Nursing Care Assessment Scale; NPI-NH = Neuropsychiatric Inventory-Nursing Home; NPI/NPI-NH = Neuropsychiatric Inventory for Non-institutionalized Patients based on the NPI-NH; NOSGER = Nurses' Observation Scale for Geriatric Patients; PK = pharmacokinetics; PT = prothrombin time; QoL-AD = Quality of Life in Alzheimer's disease; RUD = Resource Utilization in Dementia; SAS = Simpson Angus Scale, Sheehan-STS = Sheehan Suicidality Tracking Scale

6.4 Abbreviated Schedule of Assessments for Study 331-14-213

Assessment	Visit								
	Screening	Baseline (Day 0)	Wk 2 (± 2 days)	Wk 4 (± 2 days)	Wk 6 (± 2 days)	Wk 8 (± 2 days)	Wk 10 (± 2 days)	WK 12/ ET (± 2 days)	Wk 16
Inclusion/exclusion criteria	X	X							
Medical and psychiatric history	X	X							
Prior medication washout, blood alcohol, and UDS	X								
Hachinski Ischemic Scale (Rosen Modification)	X								
CMAI and CGI-S	X	X	X	X	X	X	X	X	
CGI-I			X	X	X	X	X	X	
NPI-NH (for institutionalized subjects) and NPH/NPI-NH (for non-institutionalized subjects)	X	X			X			X	
Physical and neurological examination	X							X	
Vital signs	X	X	X	X	X	X	X	X	
Clinical laboratory tests	X	X				X		X	
Prolactin, TSH, HbA1c, PT, aPTT, INR, urine pregnancy test	X							X	
ECG	X	X				X		X	
MMSE	X	X						X	
Sheehan-STS	X	X						X	
SAS, AIMS, BARS		X						X	
PK Sampling		X				X		X	
Mortality assessment (for ET)									X

Source: Reviewer created using Applicant's Protocol Amendment 4, Table 3.7.1
Abbreviations: AIMS = Abnormal Involuntary Movement Scale; aPTT = activated partial thromboplastin time; BARS = Barnes Akathisia Rating Scale; CGI-I = Clinical Global Impression – Improvement scale; CGI-E = Clinical Global Impression – Efficacy Index; CGI-S = Clinical Global Impression – Severity scale; CMAI = Cohen Mansfield Agitation Inventory; ECG = electrocardiogram; ET = early termination; HbA1c = glycosylated hemoglobin; INR = International Normalized Ratio; MMSE = Mini-mental State Examination; M-NCAS = Modified Nursing Care Assessment Scale; NPI-NH = Neuropsychiatric Inventory-Nursing Home; NPI/NPI-NH = Neuropsychiatric Inventory for Non-institutionalized Patients based on the NPI-NH; NOSGER = Nurses' Observation Scale for Geriatric Patients; PK = pharmacokinetics; PT = prothrombin time; QoL-AD = Quality of Life in Alzheimer's disease; RUD = Resource Utilization in Dementia; SAS = Simpson Angus Scale, Sheehan-STS = Sheehan Suicidality Tracking Scale

6.5 Baseline Disease Characteristics and Psychiatric History

A. Study 331-12-283 (Efficacy Sample)

Disease Characteristic	Placebo (N=131)	BREX 1 mg (N=135)	BREX 2mg (N=138)
Care Setting, n (%)			
Institutionalized	87 (66%)	89 (66%)	86 (62%)
Non-institutionalized	44 (34%)	46 (34%)	52 (38%)
Time since diagnosis of AD (months), mean (SD)	33.2 (36.1)	36.8 (40.9)	31.5 (30.6)
Time since onset of first episode of agitation (months), mean (SD)	19.3 (20.2)	18.1 (21.5)	21.6 (24.8)
Cognitive Impairment (MMSE), n (%)			
Mild	17 (13%)	7 (5.2%)	11 (8.0%)
Moderate	71 (54%)	74 (55%)	86 (62%)
Severe	43 (33%)	54 (40%)	41 (30%)
Comorbid neuropsychiatric conditions, n (%)			
Irritability/lability	111 (85%)	111 (82%)	106 (77%)
Aberrant motor behavior	100 (76%)	107(79%)	105 (76%)
Anxiety	63 (48%)	67 (50%)	72 (52%)
Sleep disorder	65 (50%)	68 (50%)	64 (46%)
Apathy/indifference	60 (46%)	64 (47%)	67 (49%)
Disinhibition	65 (50%)	58 (43%)	59 (43%)
Delusions	34 (26%)	34 (25%)	42 (30%)
Depression/dysphoria	33 (25%)	31 (23%)	43 (31%)
Appetite changes	21 (16%)	23 (17%)	25 (18%)
Hallucinations	20 (15%)	20 (15%)	17 (12%)
Elation/euphoria	14 (11%)	13 (9.6%)	9 (6.5%)
CMAI Total Score, mean (SD)	72.2 (17.9)	70.5 (16.0)	71.0 (16.6)
Factor 1 sub-score	23.7 (8.9)	22.5 (8.5)	22.9 (8.4)
Factor 2 sub-score	21.4 (6.6)	21.9 (6.5)	21.3 (6.5)
Factor 3 sub-score	14.8 (5.8)	13.7 (5.3)	14.2 (5.1)
CGI-S Score, mean (SD)	4.5 (0.7)	4.5 (0.6)	4.5 (0.7)

Source: Clinical Reviewer-created using adsl.xpt, adeff.xpt, adnpi.xpt, adcmai.xpt, adcgi.xpt, admh.xpt dataset
Abbreviations: CGI-S = Clinical Global Impression of Severity scale; CMAI = Cohen Mansfield Agitation Inventory; MMSE = Mini Mental Status Exam; SD = standard deviation

B. Study 331-12-284 (Efficacy Sample)

Disease Characteristic	Placebo (N=137)	BREX 0.5 to 2 mg (N=132)
Care Setting, n (%)		
Institutionalized	75 (55%)	73 (56.8%)
Non-institutionalized	62 (45%)	59 (44.7%)
Time since diagnosis of AD (months), mean (SD)	32.1 (27.2)	28.0 (28.3)
Time since onset of first episode of agitation (months), mean (SD)	17.5 (19.8)	19.9 (23.5)
Cognitive Impairment (MMSE)[1], n (%)		
Mild	34 (25%)	28 (21%)
Moderate	65 (47%)	64 (49%)
Severe	36 (26%)	40 (30%)
Comorbid BPSD, n (%)		
Irritability/lability	118 (86 %)	114 (86%)
Aberrant motor behavior	94 (69%)	104 (76%)
Anxiety	88 (64%)	92 (70%)
Sleep disorder	65 (47%)	78 (59%)
Apathy/indifference	81 (59%)	76 (58%)
Disinhibition	70 (51%)	54 (41%)
Delusions	38 (28%)	44 (33%)
Depression/dysphoria	32 (23%)	47 (35%)
Appetite changes	33 (24%)	38 (29%)
Hallucinations	13 (9.5%)	18 (14%)
Elation/euphoria	7 (5.1%)	5 (3.8%)
CMAI Total Score, mean (SD)	68.5 (15.9)	71.5 (16.8)
Factor 1 sub-score	22.1 (7.7)	23.8 (9.2)
Factor 2 sub-score	19.6 (7.1)	20.7 (7.1)
Factor 3 sub-score	14.9 (5.5)	15.4 (4.8)
CGI-S Score, mean (SD)	4.5 (0.7)	4.5 (0.8)

Source: Clinical Reviewer-created using adsl.xpt, adeff.xpt, adnpi.xpt, adcmai.xpt, adcgi.xpt, admh.xpt dataset
Abbreviations: CGI-S = Clinical Global Impression of Severity scale; CMAI = Cohen Mansfield Agitation Inventory; MMSE = Mini Mental Status Exam; NPI-NH = Neuropsychiatric Inventory – Nursing Home; SD = standard deviation
[1]Two subjects in the placebo group did not have MMSE information available at baseline

C. Study 331-14-213 (Efficacy Sample)

Disease Characteristic	Placebo (N=116)	BREX 2 mg (N=73)	BREX 3mg (N=153)	All BREX (N=226)
Care Setting, n (%)				
Institutionalized	53 (46%)	32 (44%)	64 (42%)	96 (43%)
Non-institutionalized	63 (54%)	41 (56%)	89 (58%)	130 (57%)
Time since diagnosis of AD (months), mean (SD)	34.4 (31.3)	34.5 (39.2)	37.8 (36.0)	36.7 (37.0)
Time since onset of first episode of agitation (months), mean (SD)	21.5 (20.6)	21.9 (24.3)	25.2 (23.1)	24.1 (23.5)
Cognitive Impairment (MMSE), n (%)				
Mild	28 (24%)	16 (22%)	37 (24%)	53 (24%)
Moderate	66 (57%)	46 (63%)	79 (52%)	125 (55%)
Severe	22 (19%)	11 (15%)	37 (24%)	48 (21%)
Comorbid neuropsychiatric conditions, n (%)				
Irritability/lability	99 (85%)	60 (82%)	131 (86%)	191 (85%)
Aberrant motor behavior	73 (63%)	45 (62%)	95 (62%)	140 (62%)
Anxiety	81 (70%)	53 (73%)	113 (74%)	166 (74%)
Sleep disorder	59 (51%)	43 (59%)	87 (57%)	130 (58%)
Apathy/indifference	44 (38%)	32 (44%)	62 (41%)	94 (42%)
Disinhibition	60 (52%)	32 (44%)	68 (44%)	100 (44%)
Delusions	28 (24%)	16 (22%)	33 (22%)	49 (22%)
Depression/dysphoria	40 (35%)	29 (40%)	54 (35%)	83 (37%)
Appetite changes	18 (16%)	18 (25%)	29 (19%)	47 (21%)
Hallucinations	15 (13%)	8 (11%)	23 (15%)	31 (14%)
Elation/euphoria	12 (10%)	7 (9.6%)	16 (11%)	23 (10%)
CMAI Total Score, mean (SD)	79.2 (17.5)	79.1 (15.2)	81.2 (17.2)	80.5 (16.6)
Factor 1 sub-score	26.5 (8.7)	26.5 (6.3)	26.2 (7.7)	26.3 (7.3)
Factor 2 sub-score	23.2 (7.4)	22.9 (6.9)	24.2 (7.4)	23.8 (7.3)
Factor 3 sub-score	16.3 (5.6)	17.1 (4.3)	16.9 (4.9)	17.0 (4.7)
CGI-S Score, mean (SD)	4.7 (0.7)	4.6 (0.7)	4.7 (0.6)	4.7 (0.7)

Source: Clinical Reviewer-created using adsl.xpt, adeff.xpt, adnpi.xpt, adcmai.xpt, adcgi.xpt, admh.xpt dataset
Abbreviations: CGI-S = Clinical Global Impression of Severity scale; CMAI = Cohen Mansfield Agitation Inventory; MMSE = Mini Mental Status Exam; NPI-NH = Neuropsychiatric Inventory – Nursing Home; NPI-NH A/A = NPI-NH Agitation and Aggression subscale score; SD = standard deviation

6.6 Summary Case Narratives for Death Events

Protocol/ Subject ID	Randomized Treatment (last dose)	Age/ Gender/ Race	Study Day of Last Dose	Study Day of Death	Fatal Adverse Event	Summary Narrative
331-12-283/ (b) (6)	BREX 0.5 mg (0.5 mg/day)	76/ Male/ White	50	52	Acute purulent meningo-encephalitis	Past medical history: benign prostatic hyperplasia, chronic cardiac failure, hypertension, myocardial ischemia, arteriosclerotic retinopathy, cataract, anemia, type 2 diabetes On Day 43, the subject was reportedly active with no impairment in psychological functions. On Day 51, staff observed that the subject was weaker and stayed in bed all the time. The subject received the study medication up to Day 50 and withdrew from the trial for personal reasons. On Day 52, the subject was diagnosed with bilateral pneumonia with developments of stagnation and signs of heart failure and subsequently died. Per the clinical post-mortem epicrisis, the subject's condition deteriorated as a result of acute purulent meningoencephalitis.
331-12-283/ (b) (6)	BREX 0.5 mg (0.5 mg/day)	87/ Female/ White	8	35	Intracranial hemorrhage	Past medical history: spinal column stenosis, rhinitis, arthropathy, gastroesophageal reflux disease, diverticulum, hypertension, hypercholesterolemia, back pain, pyrexia, constipation, subarachnoid hemorrhage, dementia, and congestive heart failure On Day 8, the aide at the assisted living facility reported that she was about to leave the subject's room when the subject blocked her way and verbally quarreled with her. According to the subject, the staff member pushed the subject causing her to fall on the floor, hitting the back of her head. The subject was admitted to the hospital and followed up by a neurologist on Day 9 for neurobehavioral symptoms. The subject discontinued the study medication due to the event, which the investigators considered resolved on Day 14. On Day 30, the subject was admitted to the hospital due to irregular pulse, decreased level of consciousness, irregular breathing, and unstable blood pressure. CT scan revealed a large-left side

Protocol/ Subject ID	Randomized Treatment (last dose)	Age/ Gender/ Race	Study Day of Last Dose	Study Day of Death	Fatal Adverse Event	Summary Narrative
						intracranial hemorrhage with hematoma. The subject later died on Day 35 due to the event. The autopsy confirmed a diagnosis of AD and revelated a massive subarachnoid hemorrhage, with no obvious skin bruises, hematoma, or skull fracture.
331-12-283/ (b) (6)	BREX 1 mg (1 mg/day)	66/ Female/ White	85	152	Airway obstruction	Past medical history: arteriosclerotic retinopathy, arteriosclerosis, chronic heart failure, hypertension, myocardial ischemia On Study Day 110, the subject choked on an orange, after which asphyxia, sudden respiratory arrest, and asystole occurred. The subject was admitted to the intensive care unit after spontaneous breathing was normalized. On Day 112, the subject underwent a tracheostomy and on Day 113, received two plasma blood transfusions. The subject continued to remain on mechanical breathing support. On Day 152, the subject experienced sudden respiratory arrest and asystole and died subsequently. The cause of death was development of extensive ischemic cerebral infarction due to post-resuscitation illness with brain lesion, in conjunction with post-aspiration bilateral interstitial pneumonia.
331-12-283/ (b) (6)	BREX 1 mg (1 mg/day)	78/ Male/ White	65	78	Aspiration pneumonia	Past medical history: cataract, glaucoma, cholecystectomy, depression, encephalopathy, hypertension, peripheral vascular disease, chronic obstructive pulmonary disease, prostate cancer, right carotid artery stenosis, small intestinal obstruction, benign neoplasm of testis, small intestinal resection On Day 60, the subject experienced pyrexia (101 °F) and brought to the ED for agitation. Chest x-ray showed no infiltrates and CT scan of abdomen revealed atelectasis at the lung base. A urine drug screen test was positive for benzodiazepines. On Day 63, pyrexia resolved, and subject was discharged. Upon arrival to a psychiatric facility, the

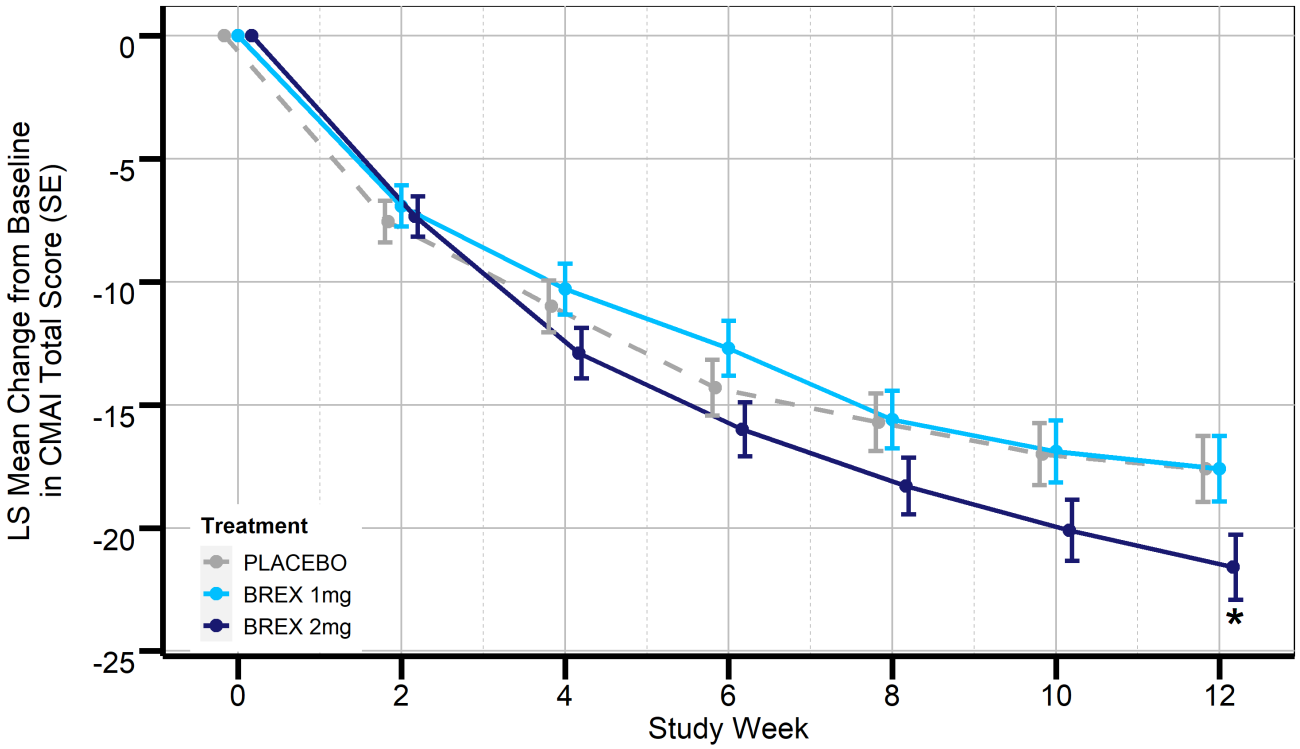
Protocol/ Subject ID	Randomized Treatment (last dose)	Age/ Gender/ Race	Study Day of Last Dose	Study Day of Death	Fatal Adverse Event	Summary Narrative
						subject developed a fever of 102°F and was sent back to the ED due to possible aspiration during initial transport. On Day 65, the subject discontinued the study medication. On Day 73, the subject transferred to hospice care and noted to have aspiration pneumonia, hypoxic respiratory failure, and ventilator-dependent respiratory failure with dysphagia. On Day 78, the subject was pulseless and pronounced deceased.
331-12-283/ (b) (6)	BREX 2 mg (2 mg/day)	86/ Female/ White	86	95	End-stage Alzheimer's dementia	Past medical history: hypertension, anemia, hypothyroidism, constipation, depression, gastroesophageal reflux disease, glaucoma, anxiety The subject completed study product per protocol on Day 86. On Day 90, the subject experience a gradual decline in overall health status. The subject experienced weight loss (decrease of 4.5 kg from baseline) on Day 70 and refused food on Day 78. She further experienced uncontrolled dehydration and hypertension due to refusal of study medication and subsequently died on Day 95. Investigators did not perform an autopsy.
331-12-284/ (b) (6)	PLACEBO	86/ Male/ White	74	76	Pneumonia	Past medical history: anxiety, bladder catheterization, benign prostatic hyperplasia, urine retention The subject was bedbound due to hip pain after a fall in 2016 and experience recurrent urinary infections. On Day 71, nursing staff noticed respiratory symptoms with occasional dyspnea and coughing. On Day 72, the general provider diagnosed respiratory insufficiency due to pneumonia. On Day 74, the subject started wheezing and had difficulties with breathing. On Day 76, the subject died of respiratory insufficiency due to pneumonia.

Protocol/ Subject ID	Randomized Treatment (last dose)	Age/ Gender/ Race	Study Day of Last Dose	Study Day of Death	Fatal Adverse Event	Summary Narrative
331-14-213/ (b) (6)	BREX 3 mg (2 mg/day)	78/ Male/ White	28	51	Heart failure	Past medical history: no medical history records On Day 28, the subject experienced hallucinations and withdrew from the study. On Day 32, the subject was diagnosed with pneumonia. On Day 51, the subject was cachectic and experienced cardiac failure.
331-12-284/ (b) (6) *	BREX 0.5 to 2 mg (2 mg/day)	80/ Male/ White	42	74	Vascular encephalopathy/ Brain edema	Past medical history: prostatic adenoma, retinal vascular disorder, aortic arteriosclerosis, myocardial ischemia, psoriasis, pneymonectasia, hypostatic bilateral pneumonia On Day 43, the subject was transported to a regional hospital and underwent a CT scan that confirmed a subdural hematoma. Based on the Investigator's report, there was no recent trauma, fall, or head injury. The event resolved on Day 54 and the subject was discharged on Day 55. On Day 74 (32 days after treatment discontinuation), the subject experienced vascular encephalopathy and brain edema.
331-12-284/ (b) (6) *	BREX 0.5 to 2 mg (0.5 mg)	77/ Female/ White	13	110	Pancreatic cancer	Past medical history: postmenopause, anxiety, Sjogren's syndrome On Day 7, the subject experienced a non-serious AE of increased hepatic enzymes that led to study drug discontinuation (last dose on Day 13). On Day 22, the Investigator discontinued the subject from the trial due to the AE. During the follow-up mortality assessment, the subject's caregiver indicated that the subject died 3 months after exiting the study (97 days after the last dose of medication).

Source: Clinical Reviewer-adapted using Applicant's summary case narratives of death events
*The subject was included in table listing even though the death event occurred after the 30-day post-dose follow-up period

6.7 Time Course Plots for Change in CMAI Total Score

A. Study 331-12-283

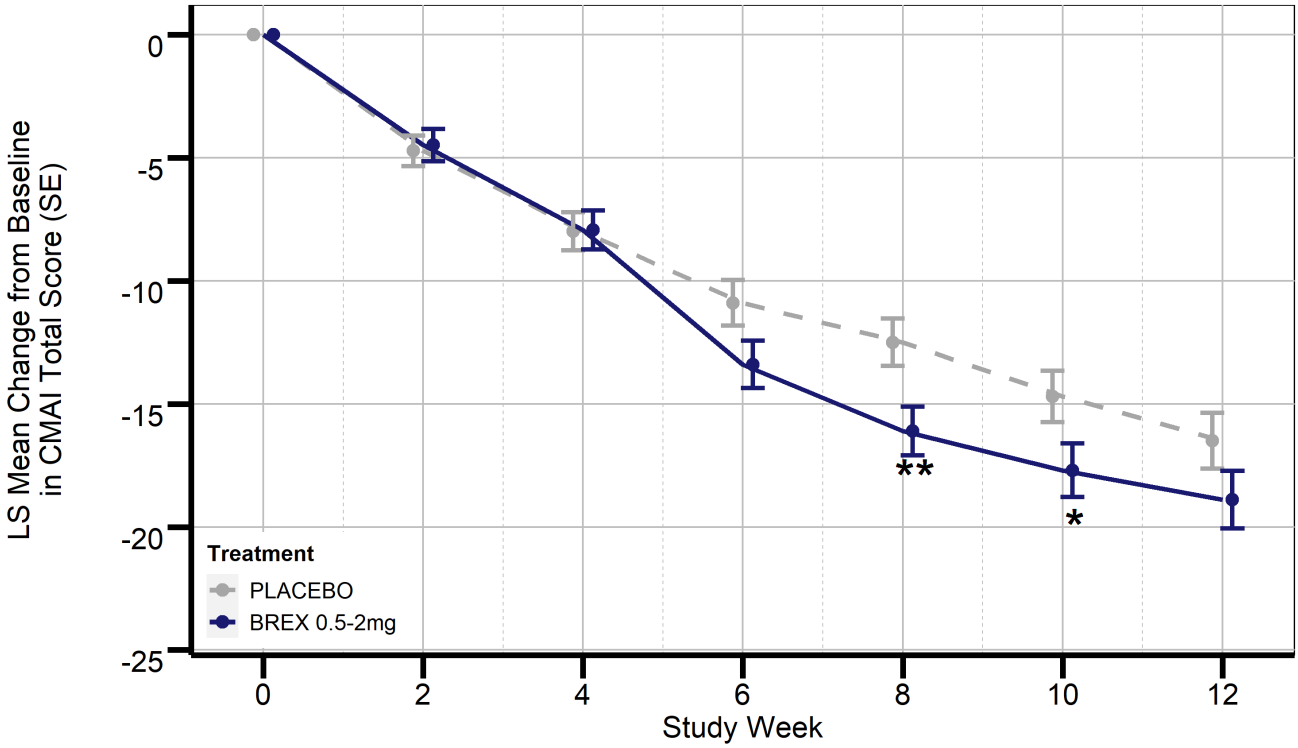


Subjects Observed

PLACEBO	131	131	129	125	122	120	118
BREX 1mg	134	134	130	129	121	120	119
BREX 2mg	138	137	136	129	126	120	120

Source: Clinical Reviewer-adapted figure from Study 331-12-283 Clinical Study Report, Figure 11.4.1.1.2-1, p. 105.
*P-value < 0.05
[1]Dashed line represents the placebo treatment arm. Error bars are LS mean +/- one standard error
Abbreviations: LS = least squares; MMRM = mixed-effect model repeated measures; CMAI = Cohen-Mansfield Agitation Inventory; SE = standard error

B. Study 331-12-284

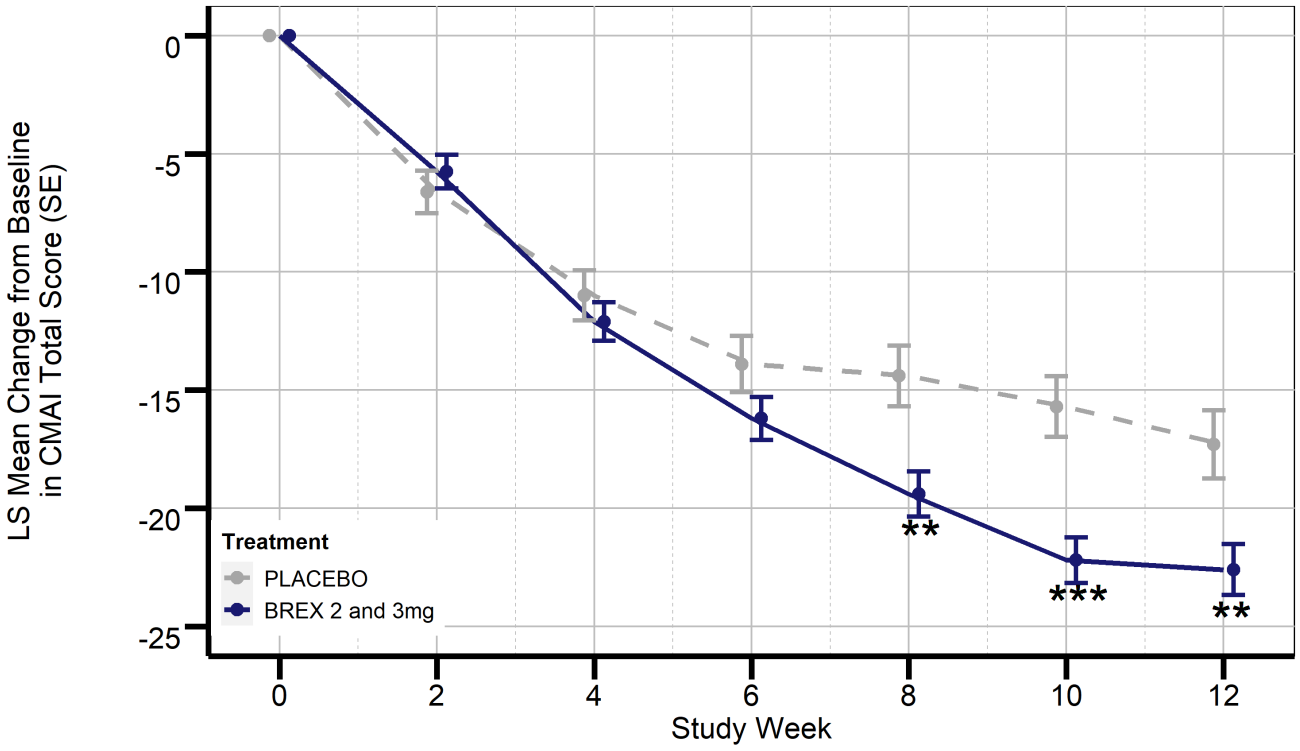


Subjects Observed

PLACEBO	135	134	134	131	128	128	117
BREX 0.5-2mg	131	130	127	126	120	118	116

Source: Clinical Reviewer-adapted figure from Study 331-12-284 Clinical Study Report, Figure 11.4.1.1.2-1, p. 102
*P-value < 0.05, **P-value < 0.01
[1]Dashed line represents the placebo treatment arm. Error bars are LS mean +/- one standard error.
Abbreviations: LS = least squares, MMRM = mixed-effect model repeated measures, CMAI = Cohen-Mansfield Agitation Inventory, SE = standard error

C. Study 331-14-213

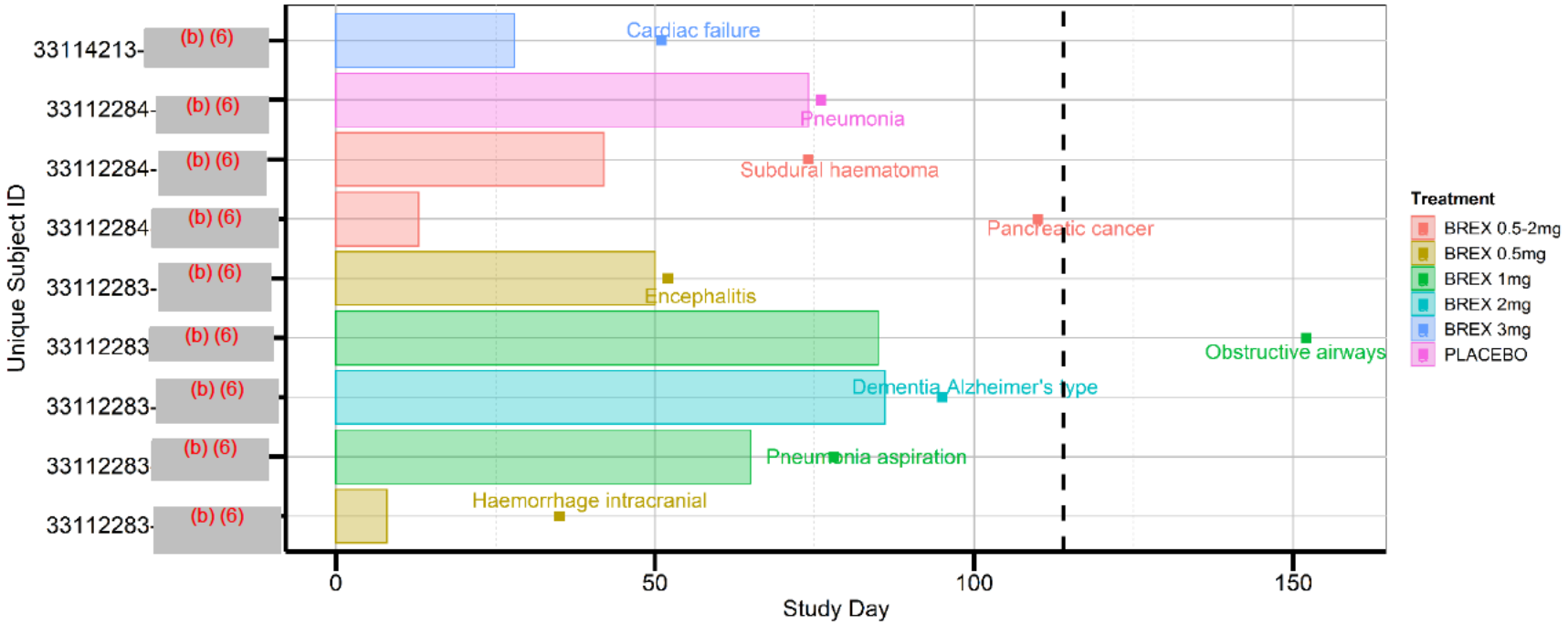


Subjects Observed

PLACEBO	116	114	114	112	105	105	103
BREX 2 and 3mg	225	221	216	213	208	198	192

Source: Clinical Reviewer-adapted figure from Study 331-14-213 Clinical Study Report, Figure 11.4.1.1.2-1, p. 73
**P-value < 0.01; ***P-value < 0.001
[1]Dashed line represents the placebo treatment arm. Error bars are LS mean +/- one standard error.
Abbreviations: LS = least squares, MMRM = mixed-effect model repeated measures, CMAI = Cohen-Mansfield Agitation Inventory, SE = standard error

6.8 Time of Death Events Relative to Study Treatment Duration



Source: Reviewer-created using Summary of Clinical Safety adae.xpt dataset
Note: Shaded region represents duration of study treatment. Points represent time of fatal AE/outcome. Vertical dashed line represents the intended period of observation up to the Week 16 mortality assessment (I.e.,114 days).

6.9 Review of FAERS and Medical Literature

Due to the imbalance of death events across treatment arms in the brexpiprazole AAD development program, the Agency conducted a review of the FDA Adverse Event Reporting System (FAERS) and medical literature reports for serious AEs with brexpiprazole leading to hospitalization or death in patients aged 65 years and older. Using the FAERS database, the Agency identified 22 assessable cases of serious AEs with brexpiprazole leading to hospitalization and death in patients aged 65 years and older. Out of the 22 cases, only three cases reported brexpiprazole use for AAD (all of which were from clinical studies and involved the development of aspiration pneumonia) and five cases indicated an occurrence of death. Although a causal relationship was possible for all 22 cases, the presence of contributors or confounders in each case decreased the likelihood of the AE or death being solely related to brexpiprazole use. Other reported serious AEs were consistent with the known safety profile of brexpiprazole and other atypical antipsychotics. With respect to aspiration pneumonia, brexpiprazole labeling currently notes the association of esophageal dysmotility and aspiration with antipsychotic drug use. There were no reports of patient hospitalizations or deaths reported in the publicly available medical literature.

6.10 Summary of Safety Findings

The most common AE (> 2% in the All BREX group and higher than placebo) included nasopharyngitis, urinary tract infection, dizziness, somnolence, and insomnia. The table below provides the incidence of AEs that are commonly associated with antipsychotic use. Other pertinent safety findings included the following:

- Proportion of subjects with a ≥ 7% increase in body weight was similar across brexpiprazole treatment arms (BREX ≤ 1 mg: 1.9%; BREX 0.5 to 2 mg: 1.5%; BREX 2 mg: 1.9%; BREX 3 mg: 1.3%) relative to placebo (0.8%);
- Incidence of clinically meaningful shifts (normal to high) in fasting glucose (BREX: 11% vs. placebo: 8.2%), fasting total cholesterol (BREX: 6.6% vs. placebo: 9.4%), and fasting triglycerides (8.6% vs. 7.9%) were similar between the brexpiprazole and placebo arms;
- Changes in cognitive function, measured using the MMSE total score, were relatively small across all treatment groups (BREX ≤ 1 mg = 0.11; BREX 2 mg = 0.26; BREX 3 mg = 0.62; BREX 0.5-2 mg = -0.24; All BREX = 0.2; placebo = 0.14);
- Assessment of suicidal ideation and behavior revealed two AE reports of intentional self-injury and suicidal ideation (each observed in one subject and both subjects received placebo).

Incidence of Adverse Events of Special Interest Across all 12-week Phase 3 Studies

AE of Special Interest	BREX ≤ 1 mg (N=157)	BREX 0.5 to 2 mg (N=132)	BREX 2 mg (N=213)	BREX 3 mg (N=153)	Placebo (N=388)
Extrapyramidal Symptom Related Events	5 (3.2%)	9 (6.8%)	10 (4.7%)	4 (2.6%)	12 (3.1%)
Akathisia	-	4 (3.0%)	1 (0.5%)	2 (1.3%)	1 (0.3%)
Dizziness, Syncope, or Orthostatic Hypotension Related Events	4 (2.5%)	9 (6.8%)	12 (5.6%)	5 (3.3%)	9 (3.6%)
QT Prolongation	4 (2.5%)	1 (0.8%)	3 (0.8%)	-	2 (0.5%)
Somnolence	2 (1.3%)	9 (6.8%)	7 (3.3%)	6 (3.9%)	7 (1.8%)
Accidents and Falls	5 (3.2%)	2 (1.5%)	5 (2.3%)	3 (2.0%)	16 (4.1%)
Cardiovascular Events	7 (4.5%)	7 (5.3%)	9 (4.2%)	1 (0.7%)	9 (2.3%)
Cerebrovascular Events	2 (1.3%)	1 (0.8%)	-	-	1 (0.3%)

Source: Reviewer-created using Applicant's Summary of Clinical Safety Report and adae.xpt dataset
Note: *Extrapyramidal symptoms* include: extrapyramidal disorder, dyskinesia, muscle spasms, musculoskeletal stiffness, bradykinesia, bradyphrenia, gait disturbance, hypertonia, hypokinesia, muscle rigidity, parkinsonism, and tremor; *Akathisia* includes: akathisia, psychomotor hyperactivity, and restlessness; *Dizziness* includes: balance disorder, dizziness, hypotension, loss of consciousness, orthostatic hypotension, presyncope, syncope, and vertigo; *Somnolence* includes: sedation and somnolence; Accidents and Falls includes: buttock injury, contusion, fall, femur fracture, head injury, hip fracture, humerus fracture, limb injury, patella fracture, rib fracture; *Cardiovascular events* include: atrial fibrillation, atrioventricular block, bundle branch block, electrocardiogram QT prolonged, sinus bradycardia, supraventricular extrasystoles, ventricular extrasystoles, angina pectoris, myocardial ischemia, cardiac failure, pulmonary edema; *Cerebrovascular events* include: cerebrovascular accident, intracranial hemorrhage, lacunar infarction, subdural hematoma, and transient ischemic attack