CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sNDA; efficacy supplement
Application Number(s)	205422/S-009
Priority or Standard	Priority
Submit Date(s)	November 10, 2022
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PDUFA Goal Date	May 10, 2023
Division/Office	Division of Psychiatry (DP)/ Office of Neuroscience (ON)
Review Completion Date	May 9, 2023
Established/Proper Name	Brexpiprazole
Trade Name	Rexulti
Pharmacologic Class	Atypical antipsychotic
Code name	
Applicant	Otsuka Pharmaceutical Company, Ltd.
Dosage form	Tablet
Applicant proposed Dosing Regimen	Starting: 0.5 mg once daily; Recommended: 2 mg once daily; Maximum: 3 mg once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of agitation associated with Alzheimer's dementia
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Schizophrenia (disorder) SCTID: 58214004
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of agitation associated with Alzheimer's dementia
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Agitation in dementia: 788862002
Recommended Dosing Regimen	Starting Dosage: 0.5 mg/day Recommended Target Dosage: 2 mg/day Maximum Dosage: 3 mg/day

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Abbreviations: OPQ=Office of Pharmaceutical Quality; OPDP=Office of Prescription Drug Promotion; OSI=Office of Scientific Investigations; OSE= Office of Surveillance and Epidemiology; DEPI= Division of Epidemiology; DMEPA=Division of Medication Error Prevention and Analysis; DRISK=Division of Risk Management; DCOA: Division of Clinical Outcome Assessment

Signatures

Please refer to uploaded memos for each discipline in DARRTS.

Glossary

AC	advisory committee
AD	Alzheimer's dementia
AAD	agitation associated with Alzheimer's dementia
ADWG	Agitation Definition Working Group
AE	adverse event
AESI	adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
APA	American Psychiatric Association
AR	adverse reaction
BARS	Barnes Akathisia Rating Scale
BPSD	behavioral and psychological symptoms of dementia
BREX	brexpiprazole
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CI	confidence interval
CMAI	Cohen Mansfield Agitation Inventory
CMC	chemistry, manufacturing, and controls
DBP	diastolic blood pressure
DCOA	Division of Clinical Outcomes Assessment
DRM	Division of Risk Management
DMC	data monitoring committee
ECG	electrocardiogram
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GCP	good clinical practice
HR	heart rate
IA	interim analysis
IND	investigational new drug application
IPA	International Psychogeriatric Association
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LS	least squares
LSM	least square mean
LSMD	least square mean difference
MCMC	Markov chain Monte Carlo

MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed-model for repeated measures
MMSE	Mini Mental State Exam
MNAR	Missing Not at Random
M-NCAS	Modified Nursing Care Assessment
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NDA	new drug application
NOSGER	Nurses' Observation Scale for Geriatric Subjects
NPI-NH	Neuropsychiatric Inventory – Nursing Home
OC	observed case
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMM	pattern mixture model
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PRO	patient reported outcome
QoL-AD	Quality of Life in Alzheimer's Disease
REMS	risk evaluation and mitigation strategy
ROW	rest of world
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson-Angus Scale
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SI/B	suicidal ideation and behavior
sNDA	supplemental new drug application
SOC	standard of care
TEAE	treatment emergent adverse event
UN	unstructured
US	United States

1 Executive Summary

1.1 Product Introduction

Brexpiprazole is an atypical antipsychotic drug, co-developed by Otsuka Pharmaceuticals Co, Ltd and H. Lundbeck A/S (also known together as the Applicant), 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 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.

With this submission, the Applicant's proposed indication is for the treatment of agitation associated with Alzheimer's dementia (AAD). This product is currently available as tablets for oral administration, including dosage strengths of 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg. The proposed starting dosage regimen is 0.5 mg taken orally once daily on Days 1 to 7, followed by titration to 1 mg once daily on Days 8 through 14, and 2 mg on Day 15. The proposed recommend target dosage regimen is 2 mg once daily. After at least 14 days at 2 mg once daily, the dosage regimen can be increased to the maximum recommended daily dosage of 3 mg, based on clinical response and tolerability.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted three adequate and well-controlled trials (Studies 331-12-283, 331-12-283, and 331-14-213) to contribute to substantial evidence of effectiveness for the use of brexpiprazole for the treatment of AAD. The Applicant demonstrated substantial evidence of effectiveness based on two positive adequate and well-controlled trials meeting their prespecified primary endpoint:

- Study 331-12-283: results demonstrated a statistically significant treatment effect with brexpiprazole 2 mg/day placebo
- Study 331-14-213: results demonstrated a statistically significant treatment effect with the combined brexpiprazole 2- and 3-mg/day treatment group over placebo

Findings of a positive dose-response relationship and a numerically similar effect observed in subjects titrated to brexpiprazole 2 mg/day after Week 4 in Study 331-12-284 relative to brexpiprazole 2 mg/day in Studies 331-12-283 and 331-14-213 provided additional supportive evidence of effectiveness. Therefore, the applicant has adequately demonstrated that brexpiprazole is effective for the treatment of AAD.

1.3 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Brexpiprazole (marketed as Rexulti) is an atypical antipsychotic (partial agonist at serotonin subtype 1a and dopamine 2 receptors, and antagonist at serotonin subtype 2A receptors) that was initially FDA-approved in 2015 for the treatment of schizophrenia and for the adjunctive treatment of major depressive disorder in adults. The Applicant's proposed indication for this application is for the treatment of agitation in Alzheimer's disease (AAD) with a recommended dosage range between 2 to 3 mg/day.

Agitation is one of the most persistent and challenging aspects of care among patients with Alzheimer's dementia (AD), resulting in marked morbidity and mortality. Institutionalization is common for afflicted patients and caregivers experience serious burdens. Although the current standard of care for AAD consists of non-pharmacological and pharmacological treatments (e.g., antipsychotics, benzodiazepines, antidepressants, antiepileptics), there are currently no FDA-approved treatment options for AAD. Brexpiprazole, like all antipsychotics, has a Boxed Warning for increased risk of mortality in elderly patients with dementia-related psychosis, based on a meta-analysis our Division conducted in 2005.

To provide substantial evidence of effectiveness for the treatment of AAD, the Applicant conducted three adequate and well-controlled phase 3 studies (331-12-282, 331-12-284, and 331-14-213) evaluating brexpiprazole vs. placebo over a 12-week treatment period. The primary endpoint for all three studies was the mean change from baseline in the Cohen Mansfield Agitation Inventory (CMAI) at Week 12. The Applicant demonstrated substantial evidence of effectiveness based on a statistically significant treatment effect on the primary endpoint with the brexpiprazole 2-mg treatment group in Study 331-12-283 and with the combined brexpiprazole 2- and 3-mg treatment group in Study 331-14-213. Supportive evidence of effectiveness was based on a positive dose-response relationship and post-hoc analyses of data from Study 331-12-284 that suggested a numerically similar improvement among subjects titrated to brexpiprazole 2 mg/day relative to placebo. In addition to the positive findings on the primary endpoint, analyses of the CMAI subscales and individual items indicated nominally consistent and clinically meaningful improvements in aggressive, physically non-aggressive, and verbally agitated behaviors.

The safety evaluation was primarily based on the three phase 3 studies and two additional safety studies: a 2-month open-label observation post-treatment rollover study that included subjects who completed Studies 331-12-283 and 331-12-284; and an open-label active-treatment extension study that included subjects who completed Study 331-14-213. Given the current Boxed Warning, the review team primarily focused on comparing brexpiprazole's mortality risk observed in the target population relative to the Agency's previous findings in elderly patients with dementia. Across the three 12-week, phase 3 studies, the Applicant reported a total of nine deaths; eight subjects (1.2%) received brexpiprazole and one subject (0.26%) received placebo. Although the incidence of death was unbalanced between treatment groups, the

incidence rates in both drug and placebo arms were much lower than what was observed with the 2005 FDA database, with no clear pattern in the causes of death. Cases (per narrative review) were often confounded by underlying comorbidities, advanced age, and concomitant medications that are consistent with an AD patient population (although most did not show any clear drug-related causality). Additional safety findings were generally similar with brexpiprazole's known safety profile for other approved indications in non-geriatric adults and did not reveal any new signals among subjects receiving continued treatment with brexpiprazole for up to 24 weeks.

Given that brexpiprazole appears to exert its effect after at least 4 weeks of continued treatment, healthcare providers should be instructed via a Limitation of Use in labeling that brexpiprazole is not intended to be administered for short-term or "as-needed" use. As our analyses still detected an increased relative risk of mortality on drug versus placebo, the Boxed Warning should remain to adequately inform healthcare providers, caregivers, and patients. Based on the evidence of effectiveness for this serious unmet medical need in the context of risks similar to the use of brexpiprazole for other approved indications and other antipsychotics, the review team recommends approval of brexpiprazole for the treatment of AAD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• AD is one of the most common causes of dementia; the global estimated prevalence is approximately 60 million, with 6.5 million people aged ≥ 65 years affected in the United States (Alzheimer's Association, 2022). The projected US prevalence is expected to double by 2050. • In addition to cognitive decline, patients often experience several behavioral and psychological symptoms of dementia (BPSD). Disruptive BPSD symptoms, including physical aggression and psychosis, are often the leading cause of assisted living or nursing home placement, accelerated disease progression, and increased mortality. Because of the prolonged course of AD, increased caregiver burden has led to decreased quality of life for both patients and caregivers. • Agitation can occur across all severities of cognitive impairment with an estimated pooled prevalence of 40% in patients with AD. • The clinical community recognizes agitation with cognitive impairment	Agitation is a clinically serious aspect of AD and an important target for treatment to decrease mortality, functional disability, and emotional distress worldwide.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	as a unique syndrome and not a response to another disorder. Agitation can be seen in the absence of concomitant psychopathology. • In 2015, the International Psychogeriatric Association established a consensus definition (finalized in 2021) for agitation in patients with cognitive impairment (Table 1).	
Current Treatment Options	• There are no FDA-approved pharmacological treatments for AAD. • Clinical management often consists of a mixture of non-pharmacological treatments (e.g., cognitive stimulation, group therapy, exercise, multisensory therapy) and off-label pharmacological options (e.g., benzodiazepines, antihistamines, antidepressants, antiepileptics, and antipsychotics). • Studies evaluating off-label pharmacological options are highly heterogenous in study design and patient populations leading to study results that suggest, at best, nominal improvements in efficacy with serious risks and tolerability concerns (e.g., benzodiazepines associated with cognitive decline and fractures; antidepressants leading to worsening anticholinergic effects and QT prolongation; and antiepileptic resulting in excess sedation, thrombocytopenia, and hyponatremia) • Although all antipsychotics have a Boxed Warning for the increased risk of mortality (70%) in elderly patients with dementia-related psychosis, antipsychotics are still considered a first-line, “non-emergent” treatment choice for AAD. • Because of the Boxed Warning, various regulatory bodies and healthcare institution have taken action to decrease off-label antipsychotic prescribing. While antipsychotic use has decreased, off-label prescribing	With limited evidence to support safe and effective pharmacological treatments for AAD, healthcare providers are left with unclear choices for treatment. Although there are currently no FDA-approved treatments for AAD, antipsychotics and other medications (benzodiazepines, anticonvulsants, etc.) are commonly prescribed off-label, despite the limited benefit described in the current literature and the increased risk of mortality.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of other options (e.g., opioids, antiepileptics, and benzodiazepines) that are not known to be safe and effective has increased.	
Benefit	• The Applicant submitted data from three adequate and well-controlled studies intended to establish brexpiprazole efficacy for AAD: Studies 331-12-283, 331-12-284, and 331-14-213. All were randomized, double-blind, placebo-controlled studies of 12-weeks in duration and used change from baseline in the CMAI total score at Week 12 as the primary efficacy endpoint. • Although the three phase 3 studies shared similar trial design elements, the Applicant identified the study population based on existing diagnostic criteria at the time. The Applicant initiated Studies 331-12-283 and 331-12-284 in 2013, a few years prior to the creation of the IPA provisional consensus definition for agitation. Study 331-12-213 included an enriched population of subjects with aggressive behaviors that met the current diagnostic criteria for agitation. Analysis of the baseline demographic and disease characteristics across all studies suggest that the study results could be generalizable to the real-world population patients with AAD. • Study 331-12-283 evaluated fixed brexpiprazole dosages of 1 mg/day and 2 mg/day relative to placebo. Study results demonstrated that only the brexpiprazole-2 mg arm was statistically significant vs. placebo. Study 331-14-213 evaluated a combined brexpiprazole treatment group consisting of subjects randomized to fixed dosages of brexpiprazole 2 mg/day and 3 mg/day. Study results also demonstrated that improvement in the combined brexpiprazole group was statistically	The Applicant provided substantial evidence of effectiveness based on two positive adequate and well-controlled studies. Study results suggest that patients often will present with heterogeneous symptoms of agitation that are likely to experience clinically meaningful benefit with brexpiprazole. The characterized dose-response relationship supports brexpiprazole's target recommended dosage of 2 mg/day. Given the observed separation from placebo after at least 4 weeks of treatment, it is important to convey through product labeling (via limitation of use) that brexpiprazole is not intended as an acute or as-needed treatment option and should be administered chronically (once-daily) for at least 4 weeks prior to assessing clinical response. The Applicant's enrichment strategy for Study 331-14-213 allowed for an evaluation of subjects with significant symptoms at baseline. The results suggested that the treatment effect

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	significant vs. placebo. • Study 331-12-284 evaluate subjects receiving flexibly dose brexpiprazole (0.5 to 2 mg/day) relative to placebo. Although the study failed to meet its primary endpoint, post-hoc analyses suggested similar numerical improvements with brexpiprazole among subjects titrated to 2 mg/day after Week 4 relative to placebo. • Analysis of underlying dose/exposure-response relationship using data across all three phase 3 studies revelated that percent change from baseline in the CMAI total score was related to brexpiprazole exposure at steady state. • A visual inspection of the longitudinal response profile across each study suggested that brexpiprazole's onset of efficacy was after 4 weeks of receiving continued once-daily dosing. • Additional analyses of relevant CMAI subscales and items indicated consistent and clinically meaningful improvements in aggressive, physically non-aggressive, and verbally agitated behaviors (i.e., all the major CMAI factor subscales). Results on other secondary and exploratory endpoints (e.g., Clinician's Global Impression of Severity [CGI-S], Neuropsychiatric Inventory – Nursing Home Scale [NPI-NH] 12-item total score, CMAI responder analyses) mirrored the primary endpoint with general numerical improvements with brexpiprazole vs. placebo. • Exploratory subgroup analyses by demographic factors (i.e., age, race, gender) and baseline disease characteristics (i.e., psychosis status, cognitive impairment, care setting) did not identify a population where	was maintained across various frequencies of symptoms. Because different behaviors of agitation occur at different frequencies and levels of disruptiveness, identification of patients with different severities of agitation is difficult. Therefore, the study results support the use of brexpiprazole in the context of a broad population of patients with AAD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the benefits of brexpiprazole were unfavorable.	
Risk and Risk Management	• Safety evaluation was primarily based on the three aforementioned phase 3 studies and two additional safety studies: a 2-month observational, post-treatment rollover phase 3 study (331-13-211) and an active-treatment extension study • Across the three studies, the Applicant reported a total of nine deaths; eight subjects received brexpiprazole (1.2% of N=655) and one received placebo (0.26% of N=388). Although the incidence of death was unbalanced between treatment groups, the overall incidence was relatively lower than what was observed with the Agency's previous findings. There was no clear pattern in the cause of death; cases were often confounded by underlying comorbidities, advanced age, and concomitant medications that are consistent with an AD patient population; and there was no clear evidence of direct drug-related causality. The relatively lower number of deaths (including the low incidence in the placebo arm) also adds uncertainty regarding the true mortality risk estimate and the background risk amongst the real-world population of patients that will be prescribed the drug. • Incidences of adverse events commonly associated with antipsychotics and other safety assessments (i.e., laboratory values, vital signs electrocardiogram measures, and assessment of suicide ideation behavior) observed in this AAD population were generally similar to adult patients with schizophrenia and depression. Mean changes in the Mini Mental State Exam did not suggest worsening cognition or rapid	Over the course of the 12-week treatment period, there was a clear imbalance of deaths, with a higher incidence and relative risk ratio among subjects receiving brexpiprazole vs. placebo. However, the low overall incidence relative to the Agency's previous meta-analysis findings and lack of drug-related causality in the individual death narratives leads to uncertainty regarding the true risk of brexpiprazole use in the intended population. Still, because the use of antipsychotics to treat psychosis and agitation has been associated with higher mortality in elderly patients, including brexpiprazole, the Boxed Warning should remain to adequately inform healthcare providers, patients, and caregivers. Although the increased risk for mortality associated with antipsychotics is well-known and confirmed in additional observational studies in the literature, the risk remains unpredictable, with no clear causal or mitigating factors. Therefore, the Agency concluded that there are no Risk Evaluation

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	cognitive decline among subjects treated with brexpiprazole relative to placebo over the 12-week treatment period. • Results of the active-treatment extension safety study did not reveal any new safety signals with up to 24 weeks of brexpiprazole treatment.	and Mitigation Strategies that could be implemented to reinforce medication use behaviors and action to ensure a favorable benefit/risk profile. In terms of any post-marketing data to consider to further assess the mortality signal, conducting a randomized, placebo-controlled study powered to estimate a difference in mortality between brexpiprazole and placebo would require a very large sample size (> 800 subjects/arm). There are also ethical concerns with randomizing subjects to placebo while brexpiprazole, if marketed, has been demonstrated to be safe and effective. Results from such a study could also be confounded due to various intercurrent events including study dropouts and the use of rescue medications (use of brexpiprazole among subjects randomized to placebo), and natural disease progression over time for worsening agitation. Open-label studies would not provide any interpretable or definitive data. Therefore, we do not feel any post-marketing requirements would be feasible or useful in conclusively characterizing the mortality signal for now.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Section 8.1 and 8.2
		X	Observer reported outcome (ObsRO)	Section 8.1 and 8.2
		X	Clinician reported outcome (ClinRO)	Section 8.1 and 8.2
		□	Performance outcome (PerfO)	
	X	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		Section 8.1 Refer to DCOA review for additional details
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

Clinical Reviewer's Comment: *The Applicant assessed clinician-reported, caregiver-reported, and patient-reported measure of psychiatric symptom severity, caregiver burden/disruptiveness, and quality of life. Refer to Section 8.1 for discussion of results and to the Division of Clinical Outcome Assessments' (DCOA) psychometric review of the measurements.*

2 Therapeutic Context

2.1 Analysis of Condition

Dementia is a serious and debilitating neurological condition characterized by progressive decline in one or more cognitive domains (e.g., complex attention, executive function, learning and memory, language) with associated impairment in function, including potential loss of independence with need for at-home or residential care. The condition affects patients, families, and caregivers; the consequent distress inflicts significant socioeconomic strain. Estimates of the proportion of dementia caused by etiology vary; however, most dementia is caused by a neurodegenerative disease, with the most common being Alzheimer's disease (AD) at an estimated 60 to 80% of dementia cases worldwide (Alzheimer's Association, 2022).

According to a recent report by the Alzheimer's Association, the global estimated prevalence of AD is approximately 60 million, with 6.5 million people aged ≥ 65 years affected in the United States. Current data suggest that almost two-thirds of Americans with AD are women, and older African and Hispanic Americans are disproportionately more likely to have AD than non-Hispanic White Americans. In 2021, AD was recognized as the seventh-leading cause of death in the United States and the fifth-leading cause of death among patients aged ≥ 65 years (commonly noted as late-onset AD). In the absence of interventions to prevent or slow the disease, the estimated global prevalence of AD is expected to grow to 153 million (12.7 million patients age ≥ 65 years affected in the United States) by 2050 (Alzheimer's Association, 2022).

Patients with dementia often present with a plethora of behavioral and psychological disturbances (often collectively noted as behavioral and psychological symptoms of dementia [BPSD]). BPSD commonly includes: 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, is 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). Although the clinical presentation and frequency of BPSD may vary by dementia etiology, most patients experience initial onset of symptoms in later stages of AD and worsening symptoms as AD progresses (Gerlach LB, et al., 2017).

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). A retrospective analysis of the National Alzheimer's Coordinating Center Uniform Data indicated that the annual total incremental cost of institutionalization associated with AAD in the United States was approximately $4.3 billion (Cloutier M, et al., 2019).

Although the underlying pathophysiology is not well understood, neuroimaging studies suggest that agitation is associated with regional volume loss and hypoperfusion across the brain (Rosenberg PB, et al., 2015; Hiorono N, et al., 2000). Neurochemical studies have also suggested that changes in the serotonin, dopamine, noradrenaline, and cholinergic neurotransmitter systems are implicated in various symptoms of BPSD, including agitation (Cummings JL, et al., 1998; Kales HC, et al., 2015). Because of changes in sleep and circadian rhythm, mental and physical exhaustion, and reduced lighting, patients and caregivers commonly report the occurrence of sundown syndrome (often referred to as "sundowning"), which refers to a heightened state of confusion starting in the late afternoon and continuing into the night. However, the temporal relationship is also thought to be confounded due to increased caregiver burden after patients experience significant symptoms during the day (Canevelli M, et al. 2016).

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). The ADWG concluded that agitation with cognitive impairment is a syndrome and not a response to another disorder. Current literature suggests that agitation can be seen in the absence of concomitant psychopathology (e.g., depression and psychosis) and is associated with unique regional dysfunction that is distinct from other disorders. The ADWG also argued that agitation can occur in absence of aggression, and predatory aggression can occur without agitation; however, it is unlikely that aggression occurs without agitation in cognitive impairment syndromes. The ADWG hypothesized that aggression may be a more severe form of agitation or may occur in differing biological or psychological circumstances (Cummings JL, et al., 2015).

In 2021, the ADWG finalized the IPA provisional consensus definition of agitation with minimal modifications (Sano M, et al., 2023). Table 1 provides the IPA consensus definition of agitation applicable to patients with cognitive impairment. Although the ADWG concluded that the current definition's continuity is important for drug development and research, results from surveys and deliberations modified the provisional definition to include supplemental comments on special circumstances (i.e., terminal agitation, acute agitation, agitation presented in the emergency department, and agitation in specific conditions of cognitive impairment) that could hinder the ability to document persistent agitation beyond a single

episode (Criterion B), specify behaviors are severe enough to produce excess distress or disability (Criteria C), and address agitation secondary to delirium (Criterion D).

In summary, agitation is clinically recognized as an important aspect of AD and a potential target for treatment to decrease mortality, emotional distress, and functional disability among patients, families, and caregivers worldwide.

Table 1: IPA Consensus Definition for Agitation in Cognitive Disorders

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., Agitation in cognitive disorders: progress in the International Psychogeriatric Association consensus clinical and research definition. *Int Psychogeriatr.* 2023;doi: 10.1017/S1041610222001041 and Cummings J, et al. Agitation in cognitive disorders: IPA provisional consensus clinical and research definition. *Int Psychogeriatr.* 2015;27:7-17.
[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.

2.2 Analysis of Current Treatment Options

There are currently no FDA-approved pharmacological treatment options for AAD. According to the American Psychiatric Association (APA) Practice Guidelines for the treatment of agitation and psychosis in dementia, initial assessment prior to treatment should include an evaluation for pain and other potentially modifiable factors that may influence choices for treatment (Reus VI, et al., 2016).

In general, well-conducted, evidence-based studies on non-pharmacological interventions are still lacking. 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. While non-pharmacological therapies are recommended as a first-line approach for AAD, use of non-pharmacological therapy before initiating pharmacological treatments is approximately 60% among patients in residential care and 40% in community-based settings (Aigbogun M, et al., 2020 and Tractenberg RE, et al., 2002). The APA Practice guidelines further state that the most consistently effective interventions have focused on caregivers (caregiver training) to develop their skills, improve their general well-being, and reduce their perceived burden (Adelman et al., 2014; Kales et al., 2015). Several studies suggest that improvement in caregiver-related outcomes is predictive of whether a patient is able to remain in the community or is transitioned to institutional care (de Vugt et al, 2005; Miller et al. 2012).

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; Schneider LS, et al., 2006). 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, aggression, and psychosis. The high degree of heterogeneity within and across studies and the use of various efficacy measures limits findings from several 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 improvements in symptom reduction without appropriately 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 concluded that the benefits observed in clinical trials of antipsychotic medications are small, whether in placebo-controlled, head-to-head comparison, or discontinuation trials (Kales et al. 2015; Maglione et al, 2011; Yunusa I, et al., 2019). Current drug utilization data suggest that quetiapine and risperidone are among the top antipsychotics prescribed for the treatment of AAD in residential care and community-based settings (Aigbogun M, et al., 2020). For most patients, clinicians initiated antipsychotic treatment (either as intermittent or chronic therapy) 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 likely based on observed response and safety profiling.

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 and an increase in use of opioids, antiepileptics, and benzodiazepines among patients aged ≥ 65 years with dementia (Dorsey ER, et al, 2010; Rubino A, et al., 2020). Furthermore, various regulatory bodies (Center of Medicare and Medicaid Services) have taken action to decrease inappropriate antipsychotic prescribing in nursing homes and assisted-living settings (Gerlach LB, et al., 2022). Given that there was limited evidence to suggest other treatment options other than antipsychotics, various clinical organizations have expressed that healthcare providers are left with unclear choices for treatment, which has led to increased caregiver distress and hastened institutionalization (Jeste DV, et al., 2007).

Although there currently are no FDA-approved treatments for AAD, antipsychotics are still prescribed off-label, despite the smaller effect size observed 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 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

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. Currently, brexpiprazole is not approved for AAD.

3.2 Summary of Presubmission/Submission Regulatory Activity

During an End-of-Phase 2 (EOP2) Meeting (IND 101871; treatment of schizophrenia) in March 2011, the Applicant inquired (b) (4) even though antipsychotics have a Boxed Warning for an increased risk of mortality in the elderly population. The Agency clarified the Boxed Warning would not be a contraindication, and obtaining a claim would depend on the benefit/risk analysis. Although the Applicant 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 under investigational new drug (IND) application 115960:

- 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 the feasibility of pursuing an indication for the "treatment of agitation in patient with AD", (b) (4) 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," is 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 to identify the target population of interest.
  - The Applicant's proposed clinical development program included two phase 3, 12-week multicenter, randomized, double-blind, placebo-controlled trials (Studies 331-12-283 and 331-12-284) in patients who are hospitalized or residing in a nursing home, assisted living facility, or residential care setting. Both studies would include patients 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. Study 331-12-283

would evaluate three fixed doses of brexpiprazole (0.5 mg, 1mg, and 2 mg/day), while Study 284 would utilize a flexible-dose study design evaluating a brexpiprazole dose range between 0.5 to 2 mg/day. For both studies, the Applicant proposed to utilize the Cohen Mansfield Agitation Inventory (CMAI) as the primary efficacy measure.

- Because the Applicant had not 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.
- The Agency reiterated that an application for AAD would likely be taken to an Advisory Committee (AC).

- February 22, 2013, and June 20, 2013: Applicant submitted protocols 331-12-283 and 331-12-284 to evaluate brexpiprazole for the treatment of AAD

  - The Agency determined both studies were safe to proceed. Given that the minimum effective dose could be lower than 0.5 mg/day, the Agency strongly suggested that randomization be equal across all treatment groups. The Agency also encouraged the Applicant to propose a multiple testing procedure that allowed for testing the primary efficacy endpoint for all doses (Study 283). To assess the impact of missing data, the Agency also sought additional sensitivity analyses that could handle missing not at random data (MNAR).

- February 6, 2015: The Sponsor submitted a Fast Track Designation request for the treatment of AAD. Based on previous results of trials evaluating atypical antipsychotics as treatment for psychosis and/or behavioral disturbances associated with AD and the planned trials 331-12-283 and 331-12-284, the Agency determined that brexpiprazole appeared to have the potential to address this unmet medical need in AAD. The Agency subsequently granted Fast Track Designation on March 16, 2015.

- March 23, 2017: The Agency issued an agreed Pediatric Study Plan (PSP) and granted a full waiver for all pediatric study requirements for this indication in patients birth to 17 years of age because necessary studies are impossible or highly impractical as the disease does not occur in children.

- September 21, 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 a sNDA for AAD

  - The Applicant acknowledged that in Study 331-12-283, brexpiprazole 2 mg/day was superior to placebo in the reduction of CMAI total scores at Week 12, but

brexpiprazole 1 mg/day was not. Study 331-12-284 also demonstrated no significant difference between flexibly-dosed brexpiprazole and placebo.

- The Applicant's post-hoc analyses suggested that subjects titrated to 2 mg/day in Study 331-12-284 and a subgroup of subjects participating in studies 331-12-283 and 331-12-284 who exhibited aggressive behaviors at baseline experienced a more robust treatment effect.
- Given that the Agency did not consider Study 331-12-283 to be "statistically persuasive" (i.e., a single study + supportive evidence approach to substantial evidence was not appropriate) 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 dose 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.

- October 2, 2017: The Applicant submitted a Breakthrough Therapy Designation Request (BTDR) for the treatment of AAD. Although the Agency determined that AAD meets the criteria for a serious or life-threatening disease or condition, the preliminary clinical evidence submitted did not indicate that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Therefore, the Agency denied the BTDR on November 30, 2017. Given that the observed effect size was small, the Agency encouraged the Applicant to provide a more convincing scientific argument by providing responder analyses of the existing data in a future request.

- 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 doses, the Applicant and Agency 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 (possibly because AAD is not always considered a persistent condition).

- August 15, 2022: After demonstrating a positive finding in Study 331-14-213, the Applicant believed that they had requisite preliminary clinical evidence of effectiveness to support a BTDR. In the context of a Preliminary Breakthrough Therapy Advice meeting, and because the Applicant had already scheduled a pre-sNDA meeting for September 2022, the Agency noted that it was not clear how the Applicant would benefit from BTD. The Agency also noted that BTD would not impact the decision to grant priority review and diverting resources to the preparation of a BTDR could delay sNDA filing.

- 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 recommend that the Applicant provide efficacy analyses using individual component scores of the CMAI domains. Regarding Study 331-14-213, the Agency also requested analyses for the intended dose group (2 and 3 mg/day combined) and for the individual dose groups (2 and 3 mg/day separately).
  - The Agency anticipated that an AC meeting would 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 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

The Division consulted the Office of Scientific Investigations (OSI) to request clinical inspections for the following sites:

- Site #118 and #114: Gnyandev Patel, Lakewood, CA (Study 331-12-283: 39 subjects screened, and 24 subjects randomized; Study 331-14-213: 24 subjects screened, and 15 subjects randomized)
- Site #121: Emilio Mantero-Atienza, Miami, FL (Study 331-12-283: 30 subjects screened, and 16 subjects randomized)
- Site #502: Jovanka Petrovic (Study 331-14-213: 17 subjects screened, and 11 subjects randomized)
- Site #192: Manuel Franco Martin, Zamora, Spain (Study 331-12-283: 23 subjects screened, and 13 subjects randomized)
- Site #801: Hristo Kozhuharov, Varna, Bulgaria (Study 331-12-284: 10 subjects screened, and 9 subjects randomized)
- Otsuka Pharmaceutical Development & Commercialization, Inc. (inspection focused on control, oversight, and management of studies)
- [redacted] (b) (4) (inspection focused on site monitoring and Applicant/Clinical Research Organization oversight)

The rationale for selecting these sites was primarily based on the regional distribution of subjects, the number of enrolled subjects, site-specific efficacy results, and results of a subgroup analysis that identified individual sites that drove the overall study results. Foreign sites were included due to insufficient domestic data (i.e., subjects from the US comprised only 32% of the safety population across the three phase 3 efficacy studies combined). Despite several minor protocol deviations and issues with deviation management, the OSI inspection report concludes that the Applicant appears to have conducted the studies adequately, and the data generated at these sites appear acceptable in support of the sNDA. Refer to the OSI review by Dr. Elena Boley for additional details.

4.2 Product Quality

The Applicant did not submit any new product quality information. Refer to the original NDA for information on the drug product.

4.3 Clinical Microbiology

The Applicant did not submit any new clinical microbiology information. Refer to the original NDA for additional information.

4.4 Devices and Companion Diagnostic Issues

The Applicant did not submit any new information regarding companion devices. Refer to the original NDA for additional information.

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

The Applicant did not submit any new nonclinical pharmacology/toxicology information. Refer to the original NDA for additional information.

6 Clinical Pharmacology

6.1 Executive Summary

In this NDA efficacy supplement (NDA/S09), the Applicant is seeking approval for the use of brexpiprazole for the treatment of agitation associated with Alzheimer's dementia (AAD). No new clinical pharmacology studies have been conducted for the treatment of AAD. The applicant conducted an exposure-response (E-R) analysis based on the data from fixed-dose trials (Trials 331-12-283 and 331-14-213). The results of the E-R analysis supports the current dosing recommendations in the AAD patient population.

6.2 Summary of Clinical Pharmacology Assessment

The Office of Clinical Pharmacology (OCP) has reviewed the submission, and determined that changes in CMAI total score are related to brexpiprazole exposure. This information provides supportive evidence of effectiveness of brexpiprazole for the treatment of AAD.

6.2.1 Pharmacology and Clinical Pharmacokinetics

Brexpiprazole is a partial agonist of serotonin 5-HT1A and dopamine D2 receptors, and a antagonist of serotonin 5-HT2A receptor. It is mainly metabolized with major involvement of CYP3A4 and CYP2D6. Steady state was reached after 10 to 12 days of once daily administration of brexpiprazole. The mean terminal half-life was about 91 hours and 86 hours for brexpiprazole and DM-3411, respectively. At steady state, inactive metabolite DM-3411 represents 23-48% of brexpiprazole plasma exposure in adults.

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

The recommended target brexpiprazole dose for the treatment of AAD is 2 mg once daily. The recommended starting dosage of brexpiprazole for the treatment of AAD is 0.5 mg once daily on Days 1 to 7, taken orally with or without food. The dosage should be titrated on Days 8 through 14 to 1 mg and on Day 15 to 2 mg. After at least 14 days at 2 mg once daily, the dose can be increased to the maximum recommended daily dose of 3 mg, if clinically warranted.

Therapeutic Individualization

Same as in currently approved brexpiprazole label.

Outstanding Issues

None

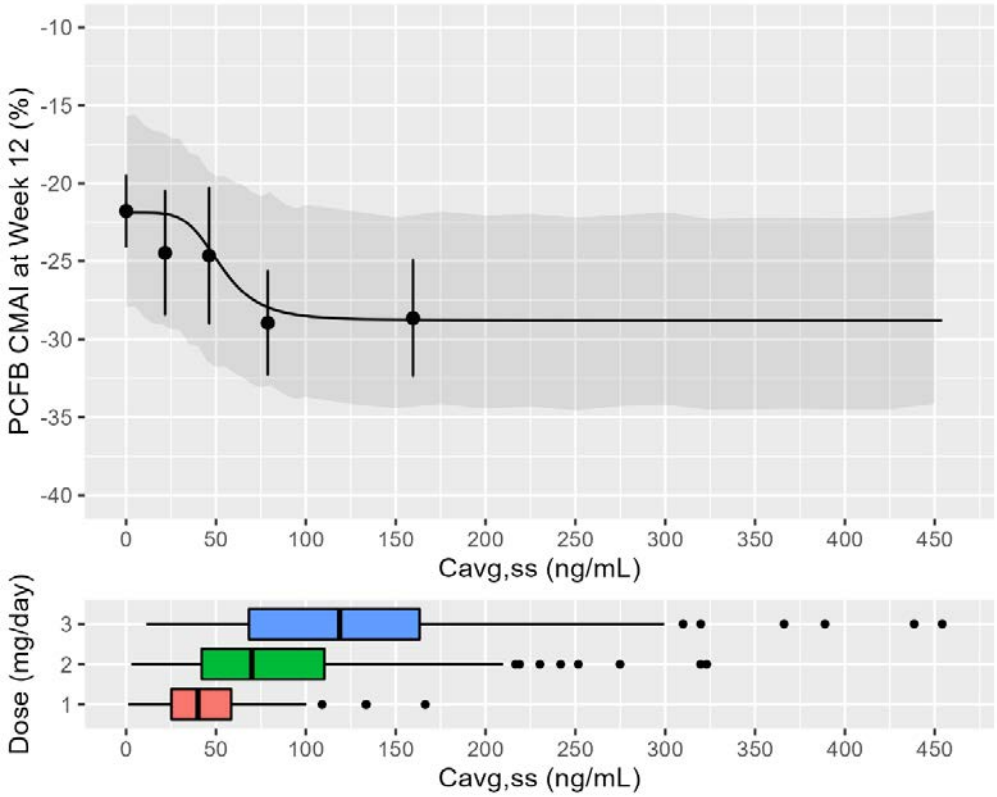
6.3 Comprehensive Clinical Pharmacology Review

6.3.1 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The E-R analysis provides supportive evidence of effectiveness of brexpiprazole for the treatment of AAD. The applicant conducted E-R analysis based on the data from the fixed-dose trials (Trials 331-12-283 and 331-14-213) in patients with AAD. The analysis suggested that percent change from baseline (PCFB) in CMAI Total Score at Week 12 is related to brexpiprazole average concentration at steady state ($Cavg_{SS}$; Figure 1).

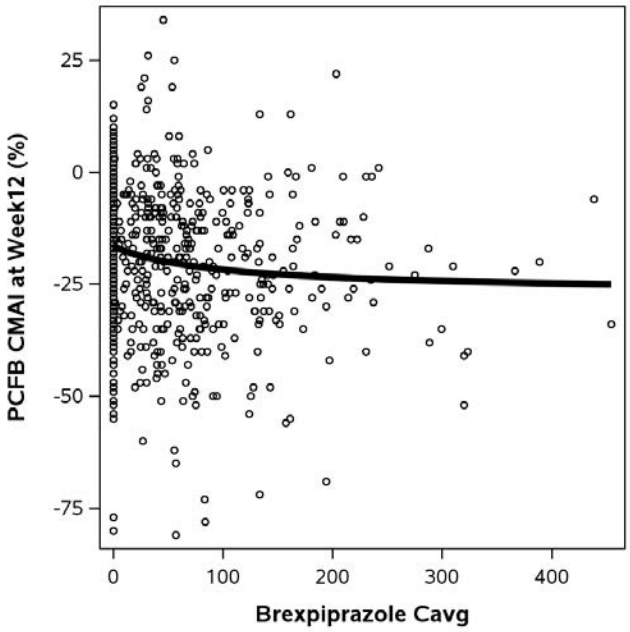
Figure 1: Relationship between Percent Change from Baseline in CMAI Total Score at Week 12 and Brexpiprazole Cavg at Steady-State



Source: Applicant's analysis

The reviewer agrees with the applicant that the reduction in CMAI total score at Week 12 (%) is related to brexpiprazole exposure (Cavg). Figure 2 also shows that the reduction in CMAI total score at Week 12 (%) is related to brexpiprazole exposure (Cavg) based on reviewer's analysis. This finding provides supportive evidence of effectiveness of brexpiprazole for the treatment of AAD. Refer to the clinical review for additional information.

Figure 2: Relationship between Percent Change from Baseline in CMAI Total Score at Week 12 and Brexpiprazole Cavg at Steady-State



Source: Reviewer's analysis

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Same as in currently approved brexpiprazole label

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Same as in currently approved brexpiprazole label

Question on clinically relevant specifications (TBD)?

None

7 Sources of Clinical Data and Review Strategy

7.1 Table of Clinical Studies

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 completing Studies 331-12-283 and 331-12-284, and one ongoing active-treatment extension safety study (331-201-00182) in subjects completing Study 331-14-213. The Applicant is also conducting an additional phase 2/3 randomized, double-blind, placebo-controlled 10-week study (331-101-00088) and an active-treatment extension safety study (331-102-00184) in Japan. For the purpose of this review, only studies intended to support US marketing will be discussed. See Table 2 for a listing of all clinical trial sources of safety and efficacy data to support the development of brexpiprazole for the treatment of AAD.

Table 2: Listing of Clinical Trials Relevant to NDA 205422/S09

Trial Identity	NCT	Trial Design	Regimen/ schedule	Study Endpoints	Treatment Duration/ Follow Up	No. of patients randomized	Study Population[1,2]	No. of Centers and Countries
Completed Efficacy and Safety Studies								
331-12 283	NCT01862640	Randomized, double-blind, placebo-controlled, fixed-dose, 3-arm study	BREX 0.5 mg/day[3] BREX 1 mg/day BREX 2 mg/day Placebo daily	Primary: Change from baseline in the CMAI total score at Week 12	12 weeks	BREX 0.5 mg: 20 BREX 1 mg: 137 BREX 2 mg: 140 Placebo: 136	Institutionalized or non-institutionalized subjects 55 to 90 years of age with probable AD and exhibiting symptoms of agitation (NPI/NPI-NH agitation /aggression score ≥ 4)	USA: 23 Russia: 11 Serbia: 9 Ukraine: 7 Croatia: 5 Germany: 5 Spain: 5
331-12 284	NCT01922258	Randomized, double-blind, placebo-controlled, flexible-dose, 2-arm study	BREX 0.5 to 2 mg/day[4] Placebo daily	Primary: Change from baseline in the CMAI total score at Week 12	12 weeks	BREX: 133 Placebo: 137	Institutionalized or non-institutionalized subjects 55 to 90 years of age with probable AD and exhibiting symptoms of agitation (NPI/NPI-NH agitation /aggression score ≥ 4)	USA: 15 Bulgaria: 9 Russia: 9 Ukraine: 8 France: 4 Slovenia: 3 Canada: 2 UK: 2 Finland: 1
331-14 213	NCT03548584	Randomized, double-blind, placebo-controlled, flexible-dose, 3-arm study	BREX 2 mg/day BREX 3 mg/day Placebo daily	Primary: Change from baseline in the CMAI total score at Week 12	12 weeks	BREX 2 mg: 75 BREX 3 mg: 153 Placebo: 117	Institutionalized or non-institutionalized subjects 55 to 90 years of age with probable AD and exhibiting symptoms of agitation (based on IPA definition) and an NPI-NH or NPI/NPI-NH agitation /aggression score ≥ 4) with CMAI Factor 1 for aggressive behaviors	USA: 39 Ukraine: 9 Bulgaria: 8 France: 4 Spain: 3 Serbia: 3 Hungry: 3 Slovakia: 3

Trial Identity	NCT	Trial Design	Regimen/ schedule	Study Endpoints	Treatment Duration/ Follow Up	No. of patients randomized	Study Population[1,2]	No. of Centers and Countries
331-13-211	NCT02192554	Observational, post-treatment, safety study	No study drug administered	Frequency and severity of AEs	2 months	450	Subjects with AAD previously treated with BREX or placebo in Study 331-12-283 or Study 331-12-284	N/A
331-201-00182	NCT03594123	Blinded, active-treatment, extension study	Prior BREX: same dose as in parent trial Prior Placebo: flexible BREX 1, 2, or 3 mg/day	Exploratory Change from baseline in the CMAI total score	12 weeks	Prior BREX: 163 Prior Placebo: 96	Subjects with AAD who completed 12 weeks of treatment in Study 331-14-213	USA: 33 Ukraine: 9 Bulgaria: 8 Spain: 3 Serbia: 3 Hungry: 3 Slovakia: 3

Source: Reviewer-created
[1]Diagnosis of probable AD was according to the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria
[2]All subjects required to exhibit a Mini Mental State Exam (MMSE) score between 5 to 22 at screening and baseline
[3]At the time of protocol Amendment 3, the Applicant randomized 20 subjects to the brexpiprazole 0.5 mg treatment group. The Applicant did not include subjects from the brexpiprazole 0.5 mg treatment group in the efficacy analyses.
[4]Subjects received 0.25 mg/day on Days 1 to 3, 0.5 mg/day Days 4 to 14, and 1 mg/day during Weeks 3 and 4. Investigators could titrate subjects up to a max dose of 2 mg/day between Weeks 5 to 12. The Applicant allowed for dose increases or decreases at any time based on response and tolerability.
Abbreviations: AD = Alzheimer's disease; AAD = agitation associated with Alzheimer's disease; AE = adverse event BREX = brexpiprazole; CMAI: Cohen Mansfield Agitation Inventory; N/A = Not Available; NPI-NH = Neuropsychiatric Inventory-Nursing Home; NPI/NPI-NH = Neuropsychiatric Inventory for Non-institutionalized Patients based on the NPI-NH

7.2 Review Strategy

The review of efficacy focuses on three phase 3 studies (331-12-283, 331-12-284, and 331-14-213) conducted in subjects with AAD. All three studies were randomized, double-blind, placebo-controlled studies of 12 weeks in duration; however, two studies utilized a fixed-dose study design (331-12-283 and 331-14-213), and one study utilized a flexible-dose study design (331-12-284). Although all three studies showcased characteristics of an adequate and well-controlled trial, the Applicant claimed that Study 331-12-283 and 331-14-213 provided confirmatory evidence, while Study 331-12-284 (a negative study) provided supportive evidence.

We based our efficacy review on analyses the Applicant submitted, supplemented with confirmatory analyses the clinical (Dr. Shamir Kalaria) and biometrics (Dr. Kelly Yang) reviewers conducted. One of the major aims for the efficacy review was to identify a target AAD population that would exhibit sufficient benefit with brexpiprazole to outweigh the known risk of mortality among elderly patients with dementia receiving antipsychotics. Given that the Applicant enriched Study 331-14-213 (one of the two positive adequate and well controlled studies) to include subjects with significant aggressive behaviors, reviewers conducted additional analyses to understand whether the provided evidence would allow for generalizability of clinical benefit to the broad population of AAD. Because of the proposed "first-in-class" indication, the second major aim for this efficacy review was to understand the clinical meaningfulness of the within-patient change in CMAI total scores and the observed treatment effect (with supportive analyses conducted by Dr. Laura Swett [DCOA] and Dr. Kalaria). The clinical pharmacology team also provided additional input that informed the review of efficacy with regards to characterizing the underlying exposure-response relationship to justify the proposed dosing regimen.

The review of safety primarily focuses on the aforementioned trials as well as the completed post-treatment observational study (331-13-211) and Study 331-201-00182, a blinded, 12-week, active-treatment extension study (both open-label). Because all three adequate and well-controlled phase 3 studies were randomized, double-blind, placebo-controlled, 12-week trials, the analyses of safety were based on pooled data from Studies 331-12-283, 331-12-284, and 331-14-213. Due to the current Boxed Warning for antipsychotics, a major aim for the safety review was to juxtapose the mortality risk among AAD subjects receiving brexpiprazole relative to the risk with other antipsychotics used in elderly patients with dementia-related psychosis reported in the Agency's 2005 meta-analysis. Because previous clinical studies evaluating brexpiprazole for treatment of schizophrenia and adjunctive treatment for MDD did not include a sufficient number of subjects aged ≥ 65 years, another aim for the safety review was to evaluate and compare adverse events (AEs), changes in laboratory findings, and other safety assessments in the AAD population to previous safety findings in non-elderly adults reported in the product label.

8 Statistical and Clinical and Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Trial 331-12-283

8.1.1.1 Study Design of Trial 331-12-283

Trial Design

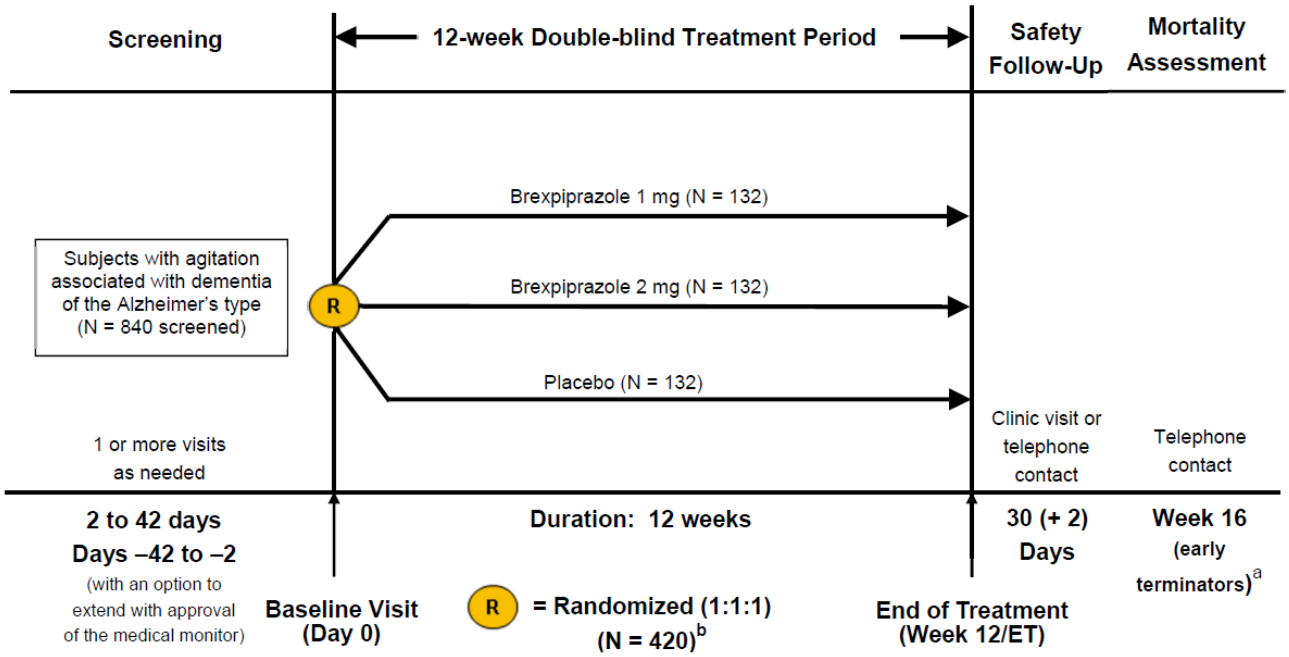
This study was a randomized, double-blind, placebo-controlled, multi-center, fixed-dose study intended to evaluate the efficacy, safety, and tolerability of brexpiprazole (1 mg/day and 2 mg/day) in elderly subjects with AAD. This trial consisted of three periods (a schematic representation of the study design is presented in Figure 3):

- **Screening Period**: The total duration of the screening period was between 2 to 42 days. Investigators determined subject eligibility and required subjects to washout prohibited concomitant pharmacotherapy prior to randomization. Starting at screening and continuing for the rest of the study period, a caregiver or facility staff logged the subject's behavior in a diary along with a collection of progress notes in order to corroborate information recorded on the CMAI. Because the diary data was a tool to assist CMAI rater training, the Applicant did not analyze the data for efficacy purposes.

- **Double-blind Treatment Period:** The Applicant randomized eligible subjects in a 1:1:1 ratio to either brexpiprazole 1 mg/day (abbreviated as BREX 1 mg), brexpiprazole 2 mg/day (abbreviated as 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 dose. The Applicant increased the brexpiprazole dose 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 dose increased to 2 mg/day starting on Day 29. The Applicant withdrew any subjects unable to tolerate their assigned dose and prohibited any down-titration of the dose at any time during the study. Investigators evaluated the subject at baseline, Day 3, and at Weeks 2, 4, 6, 8, 10, and 12. All trial visits occurred at either the investigator's site or residential facility. Investigators also contacted the caregiver by telephone at Weeks 3, 5, and 7 to assess compliance with the study medication and changes to concomitant medications.

- **Safety Follow-up Period:** 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 by telephone at Week 16 to collect follow-up information on mortality status.

Figure 3: Study Design Overview for Study 331-12-283



Source: Applicant's 331-12-283 CSR Figure 9.1-1
Abbreviations: ET = early termination

For purposes of this trial, investigators 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, including completion of the diary. 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). In both settings, the caregiver met the same requirements and assumed the same responsibilities.

Study Eligibility Criteria

The target population consisted of elderly subjects aged 55 to 90 years living in either an institutionalized or non-institutionalized setting where the subject is not living alone. Applicant's comprehensive inclusion and exclusion criteria consisted of appropriate diagnostic and tolerability criteria, a list of prohibited and accepted concomitant medications, and acceptance thresholds for clinically significant abnormal laboratory values and medical history. Pertinent inclusion and exclusion criteria that could impact the evaluation of efficacy and safety are presented below:

Key Inclusion Criteria:

- Diagnosis of probable AD according to the National Institute of Neurological and Communicated Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRA) criteria (McKhann G, et al., 1984)
- MMSE score between 5 to 22, inclusive, at screening and baseline
- Previous magnetic resonance imaging (MRI) or computed tomography (CT) scan of brain (performed after the onset of symptoms of dementia) with findings consistent with a diagnosis of AD
- Residing in current location for at least 14 days before screening and expected to remain at the same location for the duration of the trial
- Total score (frequency x severity) of ≥4 on the agitation/aggression item of the NPI-NH (for institutionalized subjects) or the NPI/NPI-NH (for non-institutionalized subjects) at screening and baseline
- Onset of symptoms of agitation at least 2 weeks prior to screening
- Required pharmacotherapy for agitation, per the investigator's judgement, after an evaluation of reversible factors (e.g., pain, infection, polypharmacy) and a trial of non-pharmacological interventions

Key Exclusion Criteria:

- Diagnosis of dementia or other memory impairment not due to AD (e.g., mixed or vascular dementia, DLB, Parkinson's disease dementia, FTD, etc)
- History of stroke, well-document transient ischemic attack (TIA), or pulmonary or cerebral embolism
- Insufficient response, based on investigator's judgment, to two or more previous antipsychotic medications for the treatment of AAD
- Prescence or history of delirium within 30 days prior to screening
- Diagnosis with an Axis I disorder (e.g., schizophrenia, bipolar I or II disorder, etc) based on the Diagnostic and Statistical Manual for Mental Disorders, 4th Edition Text Revision (DSM-IV-TR)
- Evidence of serious risk of suicide defined as a score of 3 or 4 to any one question 2 through 6 or 11 or a score of 2 or higher on any one question 1a, 7, through 10, or 12 on the Sheehan Suicide Tracking Scale (S-STS), or based on the opinion of the investigator
- Clinically significant and uncontrolled medical conditions including uncontrolled atrial fibrillation, heart failure, or ischemic heart disease (surrogates for uncontrolled cardiovascular disease included hospitalizations or procedures, such as percutaneous coronary intervention or coronary bypass surgery, within the last 6 months)
- Uncontrolled hypertension (diastolic blood pressure [DBP] > 95 mmHg), symptomatic

hypotension, or orthostatic hypotension (decrease of ≥ 30 mmHg in systolic blood pressure [SBP] or decrease of ≥ 20 mmHg in DBP within 3 minutes of standing)

- Diagnosis of epilepsy or history of seizures (except of single childhood febrile seizures, post-traumatic injury, or alcohol withdrawal)
- Newly diagnosed diabetes or unstable diabetes (screening HBA_{1C} ≥ 8%, screening glucose > 125 mg/dl [fasting] or ≥ 200 mg/dl [non-fasting], hospitalization within the 3 months prior to screening due to diabetes or complications related to diabetes)
- Body mass index < 18.5 mg/kg^2
- Diagnosis of substance abuse or dependence within the past 180 days based on DSM-IV-TR criteria (including alcohol, benzodiazepines and excluding caffeine and nicotine)
- Positive urine drug screen for cocaine, marijuana, or other illicit drugs
- Abnormal laboratory tests (i.e., platelets ≤ 75,000/mm^3, hemoglobin ≤ 9g/dL, absolute neutrophils ≤ 1,000/mm^3, aspartate aminotransferase [AST] > 2 x upper limit of normal [ULN], alanine aminotransferase [ALT] > 2 x ULN, glycosylated hemoglobin ≥ 8%) vital signs, or ECG findings (corrected QT interval by Fredericia [QTcF] ≥ 450 msec in men and ≥ 470 msec in women)
- Sexually active females of childbearing potential and male subjects who are not practicing two different methods of birth control with their partner during the trial and for 30 days after the last dose of the study medication
- Received immunotherapy for the treatment of AD (through clinical trial or compassionate use program in the 6 months preceding randomization

Clinical Reviewer's Comment: *Prior to 2015, there was no commonly accepted definition for agitation. In 2015, the IPA established a provisional consensus definition for agitation to provide a common framework for diagnostic nomenclature. Study 331-12-283 was initiated in 2013, a few years before the creation of the IPA provisional definition; therefore, the Applicant did not use the IPA provisional consensus definition to establish the diagnosis of AAD in their study population. However, the proposed inclusion and exclusion criteria (i.e., confirmation of a probable AD diagnosis [IPA Criteria A], symptom duration of at least 2 weeks [IPA Criteria B], symptoms of agitation not attributable to other neurological or psychiatric conditions [IPA Criteria D], and significant severity and frequency of symptoms based on NPI-NH total score ≥ 4 [IPA Criteria B]) closely match the current IPA criteria. Therefore, the results from this study may be generalizable to current practice and could allow for comparisons with other studies utilizing the 2015 IPA consensus definition.*

Similarly, at the time, the Applicant's use of the NINCDS-ADRDA criteria to identify subjects with probable AD was reasonable due to the lack of biomarker-based diagnostic criteria. Since this program was initiated, the science in the field and the Agency's regulatory understanding have evolved. Currently, the Agency recommends sponsors follow the draft guidance for industry Early Alzheimer's Disease: Developing Drugs for Treatment (February 2018) and the National

Institute of Aging – Alzheimer's Association (NIA-AA) criteria to assess eligibility and characterize subjects with probable AD (Jack CR, et al., 2018). Although the current literature suggests that agitation is more prevalent in patients with late-stage AD, the inclusion of subjects with mild to severe probable cognitive impairment (MMSE score between 5 to 22) reflects the full range of subjects likely to have AAD and could also allow for generalizing the study results to a broader population.

Because antipsychotics are commonly prescribed off-label for the treatment of AAD in patients residing in both community-based settings and nursing-homes, the enrollment of both institutionalized and non-institutionalized subjects further broadens the generalizability of the study results. Even though the Applicant defined the role and requirements for caregivers in each setting, biases due to type of caregiver (nurses versus family members), time of direct observation, and caregiver training could influence study results. Given the increased risk of cerebrovascular and cardiovascular events in elderly subjects with dementia receiving antipsychotics, the exclusion of subjects with a history of stroke, uncontrolled hypertension, abnormal ECG parameters, and significant prior cardiovascular history was also reasonable from a safety perspective for clinical trial settings (but could possibly contribute to an overall decreased mortality signal for these trials relative to real-world use).

Procedures and Schedule of Events

Refer to Table 3 below for the Applicant's schedule of procedures and study assessments.

Subject Completion, Discontinuation, or Withdrawal

The Applicant defined the treatment period as the time period during which subjects are evaluated for primary or secondary objectives of the trial irrespective of whether or not the subject was administered all doses of the study medication. The Applicant defined subjects who completed the Week 12 visit as trial completers. Investigators permitted subjects to withdraw from the study at any time for any reason without compromising their medical care. Subject-specific stopping criteria also included: occurrence of any AE, illness, or abnormal laboratory assessment that warrants permanent withdrawal, treatment with prohibited concomitant medications, non-compliance, lack of tolerability with study medication, development of clinically significant agitation that cannot be adequately treated with permitted medications, or transfer from an institutionalized setting to a non-institutionalized setting (or vice versa).

Investigators also contacted the medical monitor if the Sheehan-STS score was 3 or 4 on any one question 3 through 6 or 11 or if the Sheehan-STS score was 2 or higher on any one questions 1a, 7 through 10, 12, or 18. Investigators required subjects who withdrew prior to Week 12 to complete the Week 12/ET evaluation at the time of withdrawal and a follow-up safety evaluation 30 days after the last dose of the study medication. For all subjects who terminate early, investigators made every attempt to collect mortality data at Week 16.

Study Product Information and Compliance

The Applicant supplied the study medication as active brexpiprazole film-coated tablets and matching placebo film-coated tablets and provided weekly blister cards containing sufficient tablets for 7 (+ 2) days. Responsible trial personnel dispensed the study medication and documented accountability and compliance verification in the subject's trial records. Depending on the setting, the caretaker or caregiver was responsible for treatment administration.

Dose Selection

The Applicant selected the doses of brexpiprazole for this trial based on completed phase 1 safety and tolerability studies, including a positron emission tomography study in healthy subjects, phase 2 and 3 studies in subjects with schizophrenia, MDD, or ADHD, and a review of data from other studies of other atypical antipsychotics in subjects with dementia. Because of concerns about tolerability and safety in subjects, the doses of antipsychotics used in clinical trials in subjects with dementia have generally been lower than the doses recommended for subjects with schizophrenia. In the current trial, the selected dose range in subjects with Alzheimer's disease was 1 mg/day to 2 mg/day to maximize tolerability while optimizing potential efficacy. The Applicant also gradually titrated the starting dose (0.5 mg/day) to the target dose to maximize tolerability.

Prior and Concomitant Therapy

Refer to Table 4 for a summarized list of prohibited medications. All subjects must have discontinued all prohibited medications during the screening period to meet the protocol-specified washout periods. Subjects must have discontinued all psychotropics not listed in Table 4 at least 24 hours prior to the first dose of the study medication. The Applicant also prohibited all CYP2D6 inhibitors and CYP3A4 inhibitors and inducers. The Applicant allowed oral benzodiazepine therapy for the first 4 weeks of the double-blind treatment period, but limited administration to 4 days/week with a maximum dose of 2 mg/day of lorazepam (or equivalent) and not within 12 hours prior to efficacy and safety assessments. Subjects receiving non-benzodiazepine sleep aids for insomnia could not receive same day administration of a benzodiazepine. Subjects could receive medications to treat AD (cholinesterase inhibitors, memantine, or other cognitive enhancers), provided that the subject was on a stable dose for 90 days prior to randomization and remained on the same dose throughout the trial period. Although the Applicant did not permit new onset non-pharmacological interventions for the treatment of agitation during the double-blind period, subjects may have continued these therapies if they initiated those interventions prior to trial participation.

Table 3: Schedule of Assessments for Study 331-12-283

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									
Medical and Psychiatric history	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 examination	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	
PK Sampling		X					X		X	
Mortality assessment										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

Clinical Reviewer's Comment: *In general, the basic study design, treatment interventions, and safety monitoring are acceptable to assess the stated objectives. A recent observational study suggested that the discontinuation rate of antipsychotics for the treatment of AAD was < 5% after 90 days (Aigbogun MS, et al., 2020). This result would suggest that durability of effect is important in our understanding of treatment benefit. Because pharmacodynamic effects of antipsychotics may manifest differently in elderly subjects with AD relative to other psychiatric conditions (e.g., schizophrenia, depression), the Applicant's choice of a 12-week treatment period, relative to a shorter trial, allows for a better characterization of the response trajectory and durability of effect. Although the use of concomitant psychotropics and short-acting benzodiazepines could confound the treatment effect, the list of prohibited medications represent "real-world" clinical practice. Because patients are likely to experience breakthrough symptoms of agitation during the early titration phase (up to 4 weeks), the treatment effect at 12 weeks is less likely to be confounded. Therefore, the Applicant's list of prohibited medications is reasonable.*

Because symptoms of agitation not only impact patients but their caregivers, changes in quality of life measures for both the subject and the subject's caregiver are important to contextualize the study results. Therefore, the Applicant's choice for including qualitative measures such as the Modified Nursing Care Assessment (M-NCAS), the Nurses' Observation Scale for Geriatric Subjects (NOSGER), and Quality of Life in Alzheimer's Disease (QoL-AD) appear reasonable. Although the Applicant's hypothesizes that brexpiprazole's effect on agitation is possibly due to neuromodulation rather than directly affecting the underlying disease and on cognition, the use of the MMSE to measure changes in cognition is reasonable from a safety perspective.

Table 4: List of Restricted and Prohibited Medications for Study 331-12-283

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 dose 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 dose 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 dose was stable for 30 days prior to randomization (fluoxetine requires a 28-day washout)	Subject should remain on the same dose 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 dose 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 dose 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 sleep agent for insomnia was taken prior to screening on a regular basis, a stable pretrial dose 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 dose 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 dose of 20 mg, three times daily (total of 60 mg/day).

Medication	Prior to Randomization	During Double-Blind Period
Medications to treat other medical conditions (e.g., hypertension)	Allowed provided that the dose was stable for 30 days prior to randomization	Subject should remain on the same dose throughout the duration of the trial, except when medically indicated

Source: Reviewer-adapted using Protocol 331-12-283 Amendment 4, Table 4.1-1

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.

The purpose of the CMAI is to assess the frequency of agitated behaviors in elderly patients and was originally developed for use in the nursing home. The CMAI-Long Form is a caregivers' rating 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 are from 29 to 203. Based on the CMAI manual, the ratings pertain to 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):* pacing, 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
- *Other (unloaded items):* making strange noises, intentionally falling, eating, or drinking

inappropriate substances, verbal sexual advances, physical sexual advances or exposing

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 84, 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).

***Clinical Reviewer's Comment*:** *Prior to the development program, the Applicant indicated that they convened an advisory board with seven experts in the community to discuss the treatment of behavioral disturbance in patients with AD. The panel concluded that the change in the CMAI total score represents a reasonable outcome to measure in clinical trials for AAD.*

From a clinical perspective, agitation represents a continuum of behaviors with one end of the spectrum representing milder, nonthreatening behaviors, such as complaining and pacing (categorized by the CMAI as verbally agitated and physically non-aggressive behavior factors), to verbally and physically threatening behaviors that may cause harm to self or others, such as hitting or kicking (categorized by Cohen-Mansfield as aggressive behavior factor), on the severe end of the spectrum. In addition to the severity of behaviors, the frequency with which these behaviors play an important role in the intervention and treatment algorithm. For those agitated behaviors that are milder and nonthreatening, there may be a higher frequency threshold (occurring several times a week) before pharmacological intervention is considered, compared to more threatening behaviors, which may have a lower frequency threshold (occurring once or twice per week).

It is also important to note that different agitated behaviors occur under different circumstances and in different people. Because of this heterogeneity, the developers of the CMAI did not recommend the use of the total summed score of all 29 CMAI items and rather indicated that scores should be weighted based upon their level of disruptiveness prior to calculating the total the score. Later in the development program (after Study 331-12-283 was initiated), DP consulted DCOA to opine on the use of the CMAI total score as a primary efficacy measure to measure treatment effect in patients with AAD. DCOA indicated that the CMAI covers agitated behaviors that are included in the IPA consensus definition and allows for the scoring of separate dimensions of agitation. However, DCOA did not agree with the use of the CMAI total score as the primary endpoint and recommended using a composite endpoint formed by the three factor dimensions for future studies. To demonstrate treatment benefit, DCOA also recommended that improvement should be observed across all factor domains. Given that the Applicant planned to proceed with the use of the CMAI total score as the primary efficacy

measure, the Agency discussed the need for the Applicant to show consistent directional improvements in the three major subscales of agitation and to evaluate whether improvements in one subscale were compensated for by worsening in another. Refer to Dr. Laura Swett's COA review for additional information regarding the acceptability of the primary endpoint.

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 and Exploratory Endpoints:

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

- CMAI subscale scores (aggressive behavior [Factor 1], physically non-aggressive behavior [Factor 2], and verbally agitated behavior [Factor 3])
- Neuropsychiatric Inventory – Nursing Home (NPI-NH) 12-item total score
- NPI-NH Agitation/aggression (NPI-NH A/A) subscores
- Clinical Global Impression of Improvement (CGI-I) scale score, as related to agitation

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

- Clinical Global Impression – Efficacy Index (CGI-E) score
- NPI-NH psychosis subscale, occupational disruptiveness (institutionalized subjects only), distress (NPI/NPI-NH in non-institutionalized subjects only), NPI-4A cluster score, NPI-4D cluster score, and individual item scores
- Modified Nursing Care Assessment (M-NCAS) total score (institutionalized subjects only)
- Quality of Life in Alzheimer's disease (QoL-AD) score
- Nurses' Observation Scale for Geriatric Subjects (NOSGER) score (institutionalized subjects only) and NOSER dimension scores (institutionalized subjects only)
- Resource Utilization in Dementia Questionnaire (RUD) score

The Applicant also conducted a CMAI responder analysis at each scheduled visit in the double-blind treatment period, where response was defined as ≥ 40%, ≥ 30%, and ≥ 20% reduction in CMAI total score from baseline.

Statistical Analysis Plan

The primary efficacy outcome measure was the mean change from baseline (Day 0) to the end of the double-blind period (Week 12) in the CMAI total score. The planned sample size was 117

subjects in each of the treatment groups (i.e., brexpiprazole 1 mg/day, brexpiprazole 2 mg/day, and placebo), which was calculated based on the treatment effect of 6.5 points with a standard deviation (SD) of 16.5 in the change from baseline to the end of the double-blind treatment period in the CMAI total score, to achieve 85% power at a two-sided alpha level of 0.05. After allowance of 10% non-evaluable subjects, the total number of subjects to be randomized was 132 per treatment arm. In protocol amendment 3, the Applicant decided to remove the brexpiprazole 0.5 mg/day arm from the efficacy analysis based on data collected from prior studies which suggest that the dose might be ineffective. At the time of protocol amendment 3, the Applicant already randomized 20 subjects to this arm. Therefore, the Applicant proposed to randomize a total of 420, including subjects from the brexpiprazole 0.5 mg/day treatment arm.

The Applicant conducted efficacy analyses on the intent-to-treat (ITT) population (also known as the Efficacy Sample), which consisted of all subjects in the randomized sample, who took at least one dose of the study medication (excluding subjects randomized to brexpiprazole 0.5 mg/day), had a baseline CMAI assessment, and at least one post-baseline evaluation for the CMAI total score. The Applicant identified multiple discrepancies in study conduct at site 181 while the study was ongoing. Thus, the Applicant decided to terminate this site from Study 331-12-283, and the four subjects (b) (6) randomized at this site were excluded from the Efficacy Sample and all efficacy analysis.

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 the interaction term of baseline values of the CMAI total score by visit week as covariates. The Applicant estimated the primary comparison between a brexpiprazole and the placebo arm at Week 12 as the difference between least squares (LS) means from the interaction term of treatment by visit week.

The key secondary efficacy variable 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.

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 following order: 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 would repeat the hierarchical testing procedure for the key secondary efficacy variable (CGI-S score).

The Applicant also performed two sensitivity analyses using Pattern Mixture Models (PMM) based on Multiple Imputation (MI), delta adjustment imputation method, and placebo-based

imputation method on the primary efficacy parameter to assess the impact of the *missing at random* (MAR) assumption made in the MMRM-based primary analysis. For the delta adjustment imputation, the response profile of dropout subjects by last dropout reason under *missing not at random* (MNAR) mechanism was investigated for the following three scenarios:

- dropout reasons due to AEs as MNAR;
- dropout reasons due to either AEs or subject withdrawal consent as MNAR; and
- all dropouts as MNAR.

Under each scenario, for the delta adjustment imputation method, a series of delta values were added respectively as a penalty to the imputed values in the brexpiprazole groups to explore the resulting treatment difference. If a delta value was added for a patient, it would be added for all the values after the dropout time. The Applicant performed imputation of missing values multiple times and the inference of this sensitivity analysis was based on the combined estimates using the standard multiple imputation technique. The delta value would start at 0% of the expected treatment difference of 6.5 points and increase by 10% to 200% or until the conclusion of the primary analysis is overturned. The Applicant also evaluated delta values from 0% to 200% of the observed treatment difference between brexpiprazole and placebo from the primary analysis of MMRM. When delta was equal to 0, the missing data are assumed to be MAR. When delta > 0, the missing data are assumed to be MNAR. For the placebo-based imputation method, missing data for both placebo and drug groups were imputed based on the imputation model derived from placebo data using Markov chain Monte Carlo (MCMC) and Monotone multiple imputation methods, respectively. The Applicant analyzed the imputed datasets with an MMRM model in the primary analysis analogous to that used to estimate departure.

Protocol Amendments

There were four global amendments to the protocol. The Applicant's specified changes to the study protocol are highlighted below:

- Amendment 1 (May 6, 2013)
  - The randomization ratio modified from 1:2:2:2 to 1:1:1:1 (brexpiprazole 0.5 mg/day, brexpiprazole 1 mg/day, brexpiprazole 2 mg/day, placebo, respectively)
  - Changed the number of subjects randomized to each treatment group to 140/arm, from 69, 138, 138, and 138 subjects previously planned for brexpiprazole 0.5 mg/day, brexpiprazole 1 mg/day, brexpiprazole 2 mg/day, placebo, respectively
  - Added actigraphy and eDiary assessments

- Amendment 2 (December 16, 2013)
  - Increased number of participating centers from 46 to 65 and recruitment period from 4 to 5 years
  - Added requirements to screening assessments for an MRI/CT scan of the brain

- Clarified that the detailed neurological examination can be performed by a physician who is not a neurologist
- Added that subjects who complete this study are eligible to enter Study 331-13-211
- Clarified restrictions on antidepressant and psychotropic drug use

- Amendment 3 (July 7, 2014)
  - Added collection of mortality data at Week 16 for subjects who terminate early from the study
  - Removed the 0.5-mg treatment group due to results from a recent PK study in elderly subjects indicating the minimally effective dose was 1 mg/day
  - Allowed the inclusion of non-institutionalized subjects
  - Increased the number of planned centers from 55 to 75
  - Changed the analysis of the primary and key secondary endpoints from the Hochberg procedure to a hierarchical testing procedure
  - Reduced the number of subjects randomized to each treatment group from 140/arm to 132/arm by changing 80% power at a two-sided alpha level of 0.025 to 85% power at a two-sided alpha level of 0.05
  - Added the RUD assessment for both non-institutionalized and institutionalized subjects

- Amendment 4 (September 10, 2015)
  - Broadened the definition of subjects in an institutionalized setting and added overnight passes for these subjects
  - Removed urinalysis, prolactin, and urine pregnancy testing at Weeks 4 and 8
  - Removed the Simpson Angus Scale (SAS) and the Barnes Akathisia Rating Scale (BARS) at Weeks 6 and 10
  - Removed actigraphy from the trial and replaced eDiary with paper diaries
  - Added Bulgaria and Ukraine as participating countries.

Clinical Reviewer's Comment: *The review team previously determined that the proposed protocol changes incorporated in each amendment were reasonable. Refer to the previous clinical reviewer comment regarding the inclusion of non-institutionalized subjects. The majority of revisions appear to assist trial enrollment rates and decrease patient burden. None of the protocol revisions appear to negatively impact the interpretation of study results.*

8.1.1.2 Study Results of Trial 331-12-283

Compliance with Good Clinical Practices

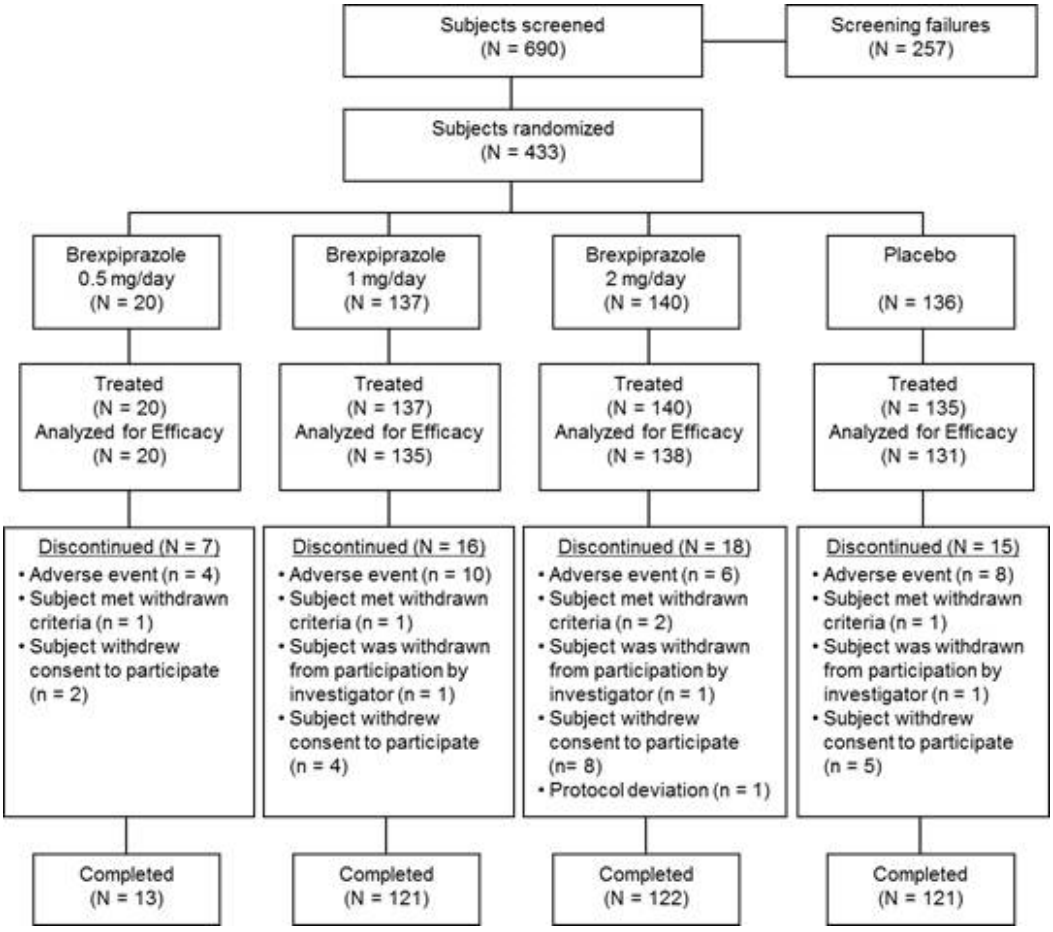
The Applicant conducted this study in accordance with the International Council for Harmonisation Good Clinical Practice Guidelines. The Applicant states that the study protocol, amendments, informed consent form, and other appropriate study related information were reviewed by an independent ethics committee or institutional review board prior to study initiation.

Financial Disclosure

Refer to Section 15.2 of this review for detailed financial disclosure information. There are no disclosed financial interests or arrangements or missing disclosures that raise questions about the integrity of study data.

Patient Disposition

Figure 4: Disposition of Subjects in Study 331-12-283



Source: Applicant's 331-12-283 Clinical Study Report, Figure 10.1-1

The Applicant screened a total of 690 subjects and randomized 433 subjects into the double-blind treatment period. See Figure 4 for an overview of patient disposition. Prior to the third protocol amendment, the Applicant randomized 20 subjects to receive brexpiprazole 0.5 mg/day. The Applicant did not include these subjects in subsequent efficacy analyses. All subjects except one in the placebo group received at least one dose of the study medication (subject was not included in the Safety Sample). In the Randomized Sample, 56 subjects (13%) discontinued during the trial (11%, 12%, 13% discontinued from the study in the placebo, BREX-1 mg, and BREX-2 mg treatment groups, respectively). The most frequent reason for discontinuation across all treatment groups was due to AEs (5.9%, 7.3%, and 4.3% in the placebo, BREX-1 mg, and BREX-2 mg treatment groups). Overall discontinuation percentages were greater across North American trial sites vs. Rest-of-World (ROW) sites (24/121; 20% vs. 32/312; 10%).

Protocol Violations/Deviations

Refer to Table 5 for an overview of the Applicant's listing of major protocol violations during the double-blind period. In general, the percentage of subjects with major protocol deviations was similar across all treatment groups. The Applicant categorized the majority of protocol deviations as related to use of prohibited concomitant medications (e.g., inadequate washout period of prohibited medication prior to randomization, newly initiated treatment for AD, use of benzodiazepines within 12 hours prior to administration, use of benzodiazepines after Week 4) and procedural errors (i.e., date of informed consent after date of study assessment, primary efficacy assessment not done per schedule, missing safety assessment for study eligibility). During the study period, only one subject (0.2%) receiving BREX 2 mg discontinued due to a protocol deviation.

Table 5: Summary of Major Protocol Violations During the Double-Blind Period for Study 331-12-283 (Safety Sample)

Protocol Deviations	Placebo (N=135)	BREX 1 mg (N=137)	BREX 2 mg (N=140)
Number of subjects with major protocol deviations	36 (27%)	40 (29%)	36 (26%)
Entry Criteria	2 (1.5%)	6 (4.4%)	5 (3.6%)
Dosing	8 (5.9%)	9 (6.6%)	7 (5.0%)
Concomitant Medication	22 (16%)	23 (17%)	13 (9.3%)
Procedural	9 (6.7%)	15 (11%)	20 (14%)

Source: Applicant's addv.xpt dataset

Clinical Reviewer's Comment: *For a 12-week study conducted among subjects with AD in various care settings across 65 sites and seven countries, the incidence of major protocol deviations appeared relatively low as compared to other studies evaluating BPSD symptoms in dementia* (b) (4) *Further analyses conducted by region suggest that major protocol deviations were higher in North America vs. ROW for all treatment groups (42% vs. 20%, 49% vs. 22%, and 41% vs. 19% for the placebo, BREX 1 mg, and BREX 2 mg groups respectively). Given the lack of an imbalance of*

protocol deviations between treatment groups, it is unlikely that the study results would be biased towards demonstrating a positive treatment effect. Of note, protocol deviations associated with the use of concomitant medications were numerically higher in the placebo and BREX-1 mg group as compared to the BREX-2 mg group. This could potentially signal a dose-dependent trend in the use of rescue medications.

Table of Demographic Characteristics

Refer to Table 6 through Table 8 below for a summary of demographic, baseline disease characteristics, and prior medication-use history across treatment groups.

Table 6: 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)	Total[1] (N=424)
Age (years)				
Mean (SD)	74.3 (8.0)	73.8 (8.8)	73.7 (8.1)	73.9 (8.3)
Median (Range)	76 (58, 90)	76 (51, 89)	75 (55, 89)	75 (51, 90)
Age group (years), n (%)				
< 65	18 (14%)	24 (18%)	22 (16%)	69 (16%)
65 to < 75	40 (31%)	34 (25%)	46 (33%)	124 (29%)
≥75	73 (56%)	77 (57%)	70 (51%)	231 (55%)
Gender, n (%)				
Male	63 (48%)	58 (43%)	60 (44%)	189 (45%)
Female	68 (52%)	77 (57%)	78 (57%)	235 (55%)
Race, n (%)				
White	125 (95%)	132 (98%)	131 (95%)	408 (96%)
Black or African American	5 (3.8%)	2 (1.5%)	5 (3.6%)	12 (2.8%)
Asian	1 (0.8%)	1 (0.7%)	2 (1.4%)	4 (0.9%)
Country, n (%)				
United States	38 (29%)	37 (27%)	41 (30%)	116 (27%)
Russia	35 (27%)	38 (28%)	38 (28%)	111 (26%)
Ukraine	22 (17%)	21 (16%)	20 (15%)	63 (15%)
Serbia	15 (12%)	16 (12%)	17 (12%)	48 (11%)
Croatia	10 (7.6%)	12 (8.9%)	12 (8.7%)	34 (8.0%)
Spain	8 (6.1%)	5 (3.7%)	6 (4.3%)	19 (4.5%)
Germany	3 (2.3%)	6 (4.4%)	4 (2.9%)	13 (3.1%)
Region, n (%)				
North America	38 (29%)	37 (27%)	41 (30%)	116 (29%)
ROW	93 (71%)	98 (73%)	97 (70%)	228 (71%)
Ethnicity, n(%)				
Hispanic or Latino[2]	23 (18%)	24 (18%)	23 (17%)	71 (17%)
Not Hispanic or Latino	107 (82%)	110 (82%)	115 (83%)	351 (83%)
Weight (kg), mean (SD)	68.4 (13.3)	69.4 (14.6)	68.3 (14.0)	68.6 (13.9)
Height (cm), mean (SD)	164.4 (10.2)	165.3 (9.2)	164.6 (10.2)	164.8 (9.7)
BMI (kg/m^2), mean (SD)	25.3 (4.9)	25.4 (5.0)	25.1 (4.0)	25.2 (4.6)
Weight circumference (cm), mean (SD)	89.0 (12.5)	90.5 (14.4)	88.6 (15.1)	89.2 (14.3)

Source: Clinical Reviewer-created using adsl.xpt dataset
Abbreviations: BMI = body mass index; ROW = Rest of World; SD = standard deviation.
[1]Includes subjects randomized to the brexpiprazole 0.5 mg/day arm (n=20)
[2]Ethnicity status was unknown for one subject receiving placebo and one subject receiving BREX 1 mg

In general, demographic characteristics were similar between males and females, age groups, and race groups across treatment arms. However, there were regional differences in race, ethnicity, and age distribution. The Applicant reported that greater than 50% of ROW subjects were enrolled from clinical trial sites in Ukraine and Russia. Among North American sites, the randomized population (n = 116) was more diverse than ROW sites with 59% Hispanic or Latino subjects. At ROW sites, 100% of randomized subjects (n = 308) were white and < 1% of subjects were Hispanic or Latino. Subjects in North America were also generally older than in other regions with 5% < 65 years and 69% ≥ 75 years compared with 20% < 65 years and 49% ≥ 75 years in other regions.

Other Baseline Characteristics

Across all treatment groups, baseline disease characteristics and psychiatric history were similar based on subjects in the efficacy sample (Table 7). Although the proportion of subjects with different severities in cognitive impairment varied slightly across treatment arms, in general, the majority of subjects exhibited either moderate (57%) or severe cognitive impairment (34%), relative to mild impairment (9%). Approximately 12% of subjects reported a history of anxiety or depression. Most subjects also exhibited various comorbid BPSD symptoms; approximately 80% of subjects reported comorbid irritability or aberrant motor behavior. Analysis of the CMAI factor domains also indicated that 70% of subjects experienced significant symptoms from all three domains of agitation (physically aggressive, physically non-aggressive, and verbally agitated behaviors). Further subgroup analyses indicated the following:

- In North America, the proportion of subjects residing in an institutionalized setting was relatively less than subjects in other countries (46% vs. 73%), while those residing in a non-institutional setting was higher in North American subjects (54% vs. 27%).
- Cognitive impairment severity also varied by gender and age. Severe cognitive impairment (MMSE score ≥ 12) was higher among females compared to males (39% vs. 27%), subjects aged ≥ 75 years compared to < 65 years (38% vs. 25%) and in North Americans compared to other countries (48% vs. 28%).
- More females compared to males (26% vs. 15%), subjects ≥ 75 years compared to < 65 years (23% vs. 15%), and in North Americans compared to other countries (29% vs. 18%) exhibited greater psychotic symptoms (defined by NPI-NH delusions and hallucinations subscores ≥ 6).

Table 7: Baseline Disease and Psychiatry History for Study 331-12-283 (Efficacy Sample)

Disease Characteristic	Placebo (N=131)	BREX 1 mg (N=135)	BREX 2mg (N=138)	Total[1] (N=424)
Care Setting, n (%)				
Institutionalized	87 (66%)	89 (66%)	86 (62%)	282 (67%)
Non-institutionalized	44 (34%)	46 (34%)	52 (38%)	142 (34%)
Time since onset of symptoms of dementia (months), mean (SD)	61.3 (40.3)	64.5 (44.0)	60.3 (33.2)	61.8 (39.1)
Time since diagnosis of AD (months), mean (SD)	33.2 (36.1)	36.8 (40.9)	31.5 (30.6)	33.5 (35.6)
Time since onset of first episode of agitation (months), mean (SD)	19.3 (20.2)	18.1 (21.5)	21.6 (24.8)	19.5 (22.0)
Cognitive Impairment (MMSE), n (%)				
Mild	17 (13%)	7 (5.2%)	11 (8.0%)	38 (9.0%)
Moderate	71 (54%)	74 (55%)	86 (63%)	243 (57%)
Severe	43 (33%)	54 (40%)	41 (30%)	143 (34%)
Comorbid neuropsychiatric conditions, n (%)				
Irritability/lability	111 (85%)	111 (82%)	106 (77%)	342 (81%)
Aberrant motor behavior	100 (76%)	107(79%)	105 (76%)	326 (77%)
Anxiety	63 (48%)	67 (50%)	72 (52%)	215 (51%)
Sleep disorder	65 (50%)	68 (50%)	64 (46%)	207 (49%)
Apathy/indifference	60 (46%)	64 (47%)	67 (49%)	202 (48%)
Disinhibition	65 (50%)	58 (43%)	59 (43%)	191 (45%)
Delusions	34 (26%)	34 (25%)	42 (30%)	117 (28%)
Depression/dysphoria	33 (25%)	31 (23%)	43 (31%)	111 (26%)
Appetite changes	21 (16%)	23 (17%)	25 (18%)	75 (18%)
Hallucinations	20 (15%)	20 (15%)	17 (12%)	57 (13%)
Elation/euphoria	14 (11%)	13 (9.6%)	9 (6.5%)	39 (9.2%)
Agitation features, n (%)				
Aggressive behavior	111 (85%)	111 (82%)	125 (91%)	364 (86%)
Physically non-aggressive behavior	123 (94%)	128 (95%)	129 (94%)	396 (93%)
Verbally agitated behavior	112 (86%)	109 (81%)	118 (86%)	353 (83%)
CMAI Total Score, mean (SD)	72.2 (17.9)	70.5 (16.0)	71.0 (16.6)	70.9 (17.1)
Factor 1 sub-score	23.7 (8.9)	22.5 (8.5)	22.9 (8.4)	22.9 (8.5)
Factor 2 sub-score	21.4 (6.6)	21.9 (6.5)	21.3 (6.5)	21.5 (6.6)
Factor 3 sub-score	14.8 (5.8)	13.7 (5.3)	14.2 (5.1)	14.2 (5.4)
NPI-NH 12 Domain Score[2], mean (SD)	37.6 (16.6)	36.2 (12.7)	36.0 (15.5)	36.3 (15.0)
NPI Agitation/Aggression Score, mean (SD)	7.8 (2.2)	7.3 (1.9)	7.3 (1.9)	7.4 (2.0)
NPI Psychosis Score ≥ 4, n (%)	34 (26%)	31 (23%)	43 (31%)	110 (26%)
CGI-S Score, mean (SD)	4.5 (0.7)	4.5 (0.6)	4.5 (0.7)	4.5 (0.7)

Source: 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]Include subjects randomized to the brexpiprazole 0.5 mg/day treatment arm (n=20)
[2]NPI-NH collected from 130 placebo subjects (total n = 423)

Approximately 66% of subjects received one or more medications for indications other than for the treatment of AD or agitation. The most frequently non-psychotropic drug classes reported were angiotensin converting enzyme (ACE) inhibitors (i.e., enalapril and lisinopril), antithrombotic agents (i.e., aspirin), beta-blockers and calcium channel blockers (i.e., metoprolol, amlodipine), and statins (i.e., simvastatin). Table 8 provides a listing of prior psychotropic medication use by indication. Because most subjects were receiving prior treatments for AD (approximately 85% of subjects) or agitation (approximately 80% of

subjects), psychotropic drug use, including treatment for other indications, was reported in approximately 98% of subjects. Among subjects receiving prior antipsychotic treatment for AAD, most subjects were receiving risperidone (30%) or quetiapine (37%).

Table 8: Psychotropic Medication Use Prior to the Double-Blind Period in Study 331-12-283 (Efficacy Sample)

Indication/Drug, n (%)	Placebo (N=131)	BREX 1 mg (N=135)	BREX 2mg (N=138)	Total[1] (N=424)
Subjects receiving at least one psychotropic	128 (98%)	132 (98%)	135 (98%)	413 (97%)
Agitation[2]	106 (81%)	110 (82%)	107 (78%)	336 (79%)
Antipsychotics	69 (53%)	82 (61%)	69 (50%)	230 (54%)
Benzodiazepines	27 (21%)	21 (16%)	33 (24%)	84 (20%)
SSRI/SNRIs	5 (3.8%)	4 (2.9%)	3 (2.4%)	12 (2.8%)
Alzheimer's disease	128 (98%)	132 (98%)	135 (98%)	413 (97%)
Anticholinesterase inhibitors	73 (56%)	68 (50%)	71 (51%)	218 (51%)
Memantine	66 (50%)	73 (54%)	74 (54%)	223 (53%)
Anxiety	6 (4.6%)	4 (3.0%)	8 (5.8%)	22 (5.2%)
Benzodiazepines	6 (4.6%)	4 (3.0%)	6 (4.3%)	18 (4.2%)
Depression	10 (7.6%)	14 (10%)	16 (12%)	42 (9.9%)
SSRI/SNRIs	7 (5.3%)	12 (8.9%)	14 (10%)	36 (8.5%)
Insomnia/Sleep Disorders	20 (15%)	11 (8.1%)	18 (13%)	50 (12%)
Benzodiazepines	5 (3.8%)	3 (2.2%)	6 (4.3%)	15 (3.5%)
Hypnotics (non-benzodiazepine)	6 (4.6%)	3 (2.2%)	6 (4.3%)	15 (3.5%)
Trazodone	7 (5.3%)	3 (2.2%)	5 (3.6%)	15 (3.5%)

Source: Clinical Reviewer-created using adcm.xpt and adsl.xpt dataset
Abbreviations: SSRI = Selective serotonin reuptake inhibitor; SSNRI = selective serotonin norepinephrine reuptake inhibitor[1]Include subjects randomized to the brexpiprazole 0.5 mg/day treatment arm (n=20)
[2]Agitation includes indications for AAD, pharmacological agitation, agitation prior to washout, agitation secondary to hospitalization, prevention of agitation, increased agitation, and worsening agitation

Clinical Reviewer's Comment: *Overall assessment of baseline demographics, disease characteristics, psychiatric history, and prior psychiatric medication use by treatment group indicates a low potential for confounding efficacy and safety results. Although the Applicant restricted inclusion of subjects with an NPI-NH AA score of at least 4 with the aim to include subjects with significant agitation, the efficacy population consisted of a majority of subjects who exhibited significant symptoms from all three CMAI factor domains (physical aggression, non-physical aggression, and verbal agitation). This further confirms that the study population appears to resemble patients that would meet the IPA consensus definition for agitation. Similar disease characteristics described in the current literature also suggest a high degree of disease heterogeneity across patients with AAD, including the prevalence of other comorbid BPSD (Alzheimer's Association 2022; Deardorff WJ, et al, 2019).*

The overall percentage of subjects with moderate to severe cognitive impairment (91%) and the average time to diagnosis of AD (~2.8 years) suggest that most of studied population are likely in the middle to late stage of AD, which is consistent with the comorbid prevalence of more severe symptoms of agitation. Therefore, it is not surprising to observe that approximately 80% of subjects received pharmacological treatment (mainly antipsychotics and benzodiazepines) for agitation. The inclusion of subjects at various stages of disease progression, presentation of various BPSD, and broad range of agitated features suggest that the results of this study could

be generalizable to real-world clinical patients with AAD. Despite the Boxed Warning for the increased risk of mortality, approximately 50% of subjects also received prior antipsychotic treatment for AAD.

During earlier stages of the IND, the Division previously recommended to utilize a community-based sample for their target population of interest. Given that the Applicant did not provide additional caregiver information (e.g., family vs. professional, qualifications, experience, and training), it is unclear whether those characteristics would impact safety (e.g., biased reporting of AE) and efficacy (e.g., differential item responses on efficacy assessments).

Because the Applicant enrolled significantly less subjects across North American sites (121/424; 28%) vs. ROW sites (312/242; 74%), this review will further examine the applicability of the foreign data to the US population and medical practice. Refer to OSI's review for further information regarding the results foreign on-site inspections and the validity of the foreign data. It is important to note that potential regional differences observed in this study – location of the subject care-setting (greater number of subjects in institutionalized care settings in foreign countries), use of prior medications (greater use of psychotropic medications in the United States), cognitive impairment (more severe subjects in North America), time to diagnosis of AD (on average later in the US population), and comorbid symptoms (higher prevalence of psychotic symptoms) –could be a result of differences in culture, socioeconomics, and medical practice (Rosseli M, et al., 2022).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant measured treatment compliance by dividing the number of study medication tablets taken by the total number of scheduled tablets during the trial period. For lost to follow-up subjects, the last study medication end date was equal to the treatment end date. In the placebo, BREX 1 mg, and BREX 2 mg treatment groups, the Applicant observed ≥80% study compliance in 98.5%, 95.6% and 97.1% of subjects, respectively.

Refer to Table 9 for a listing of concomitant psychotropic medication during the double-blind period. Given that the majority of subjects continued their treatments for AD and other comorbid disorders, the overall percentage of psychotropic use was > 80%. The percentage of subjects receiving treatment for worsening or breakthrough symptoms of agitation was greatest in the placebo group (19%) versus the BREX 1 mg (15%) and BREX 2 (14%) mg treatment arms. Subjects commonly utilized benzodiazepines for the treatment of agitation, anxiety, and for insomnia/sleep-related disorders. The overall percentage of benzodiazepine use was 19% in the placebo arm, 15% in the BREX 1 mg arm, and 13% in the BREX 2 mg arm. During the follow-up period (post-study treatment), approximately 31%, 19%, and 20% of subjects who received placebo, BREX 1 mg, and BREX 2 mg during the treatment period received treatments for agitation.

Table 9: Psychotropic Medication Use During the Double-Blind Period in Study 331-12-283 (Efficacy Sample)

Indication/Drug, n (%)	Placebo (N=131)	BREX 1 mg (N=135)	BREX 2mg (N=138)	Total[1] (N=424)
Subjects receiving at least one psychotropic	112 (86%)	111 (82%)	115 (83%)	351 (83%)
Agitation[2]	26 (20%)	20 (15%)	15 (11%)	62 (15%)
Antipsychotics	2 (15%)	5 (3.7%)	3 (2.2%)	10 (2.4%)
Benzodiazepines	17 (13%)	10 (7.4%)	10 (7.2%)	38 (9.0%)
Alzheimer's disease	99 (76%)	104 (77%)	98 (71%)	311 (73%)
Anticholinesterase inhibitors	57 (44%)	53 (39%)	47 (34%)	159 (38%)
Memantine	42 (32%)	48 (36%)	46 (33%)	144 (34%)
Anxiety	4 (3.1%)	4 (3.0%)	6 (4.3%)	15 (3.5%)
Benzodiazepines	4 (3.1%)	3 (2.2%)	5 (3.6%)	14 (3.3%)
Depression	10 (7.6%)	14 (10%)	14 (10%)	40 (9.4%)
SSRI/SNRIs	7 (5.3%)	10 (7.4%)	10 (7.2%)	30 (7.1%)
Insomnia/Sleep Disorders	18 (14%)	11 (8.1%)	19 (14%)	50 (12%)
Benzodiazepines	3 (2.3%)	3 (2.2%)	4 (2.9%)	12 (2.8%)
Hypnotics (non-benzodiazepine)	8 (6.1%)	3 (2.2%)	8 (5.8%)	20 (4.7%)
Trazodone	7 (5.3%)	5 (3.7%)	7 (5.1%)	19 (4.5%)

Source: Clinical Reviewer-created using adsl.xpt and adcm.xpt dataset
Abbreviations: SSRI = Selective serotonin reuptake inh bitor; SSNRI = selective serotonin norepinephrine reuptake inhibitor
[1]Include subjects randomized to the brexpiprazole 0.5 mg/day treatment arm (n=20)
[2]Agitation includes indications for AAD, pharmacological agitation, agitation prior to washout, agitation secondary to hospitalization, prevention of agitation, increased agitation, and worsening agitation

Clinical Reviewer's Comment: *The use of concomitant psychotropic medications remained high due to continuation of prior treatments for AD and other comorbid disorders. Although prior research suggests some evidence of a treatment effect with anticholinesterase inhibitors on neuropsychiatric symptoms, the dose-dependent trend in decreasing anticholinesterase inhibitor use as a result of improved agitation symptoms is unclear (Wang J, et al. 2015). However, the dose-dependent trend in decreasing treatments for agitation, including benzodiazepine use, is promising and provides additional clinical meaningfulness to the study results. Further analyses suggest that among subjects receiving concomitant treatments for agitation, 27% of subjects in the placebo arm, 35% of subjects in the BREX 1 mg arm, and 20% of subjects in the BREX 2 mg arm received treatment that was not a continuation from prior therapy.*

Efficacy Results – Primary Endpoint

A statistically significant treatment effect for BREX 2 mg versus placebo was observed on Week 12 for the CMAI total score. The MMRM least squares mean (LSM) change from baseline for the BREX 2 mg group was -21.6 versus -17.8 for the placebo group, for a between group treatment difference of -3.77 (95% CI: -7.38, -0.17; p = 0.0404; Table 10).

Table 10: Study 331-12-283: Primary Endpoint Results Based on Primary Analysis (Efficacy Sample)

	Placebo (N=131)	**BREX 1 mg (N=134)[2]**	**BREX 2 mg (N=138)**
Mean CMAI Total Score at Baseline (SD)	72.24 (17.85)	70.49 (15.95)	70.99 (16.56)
Mean CMAI Total Score at Week 12 (SD)	55.03 (16.1)	54.61 (18.59)	50.56 (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)
P-value[1]		0.9015	**0.0404**

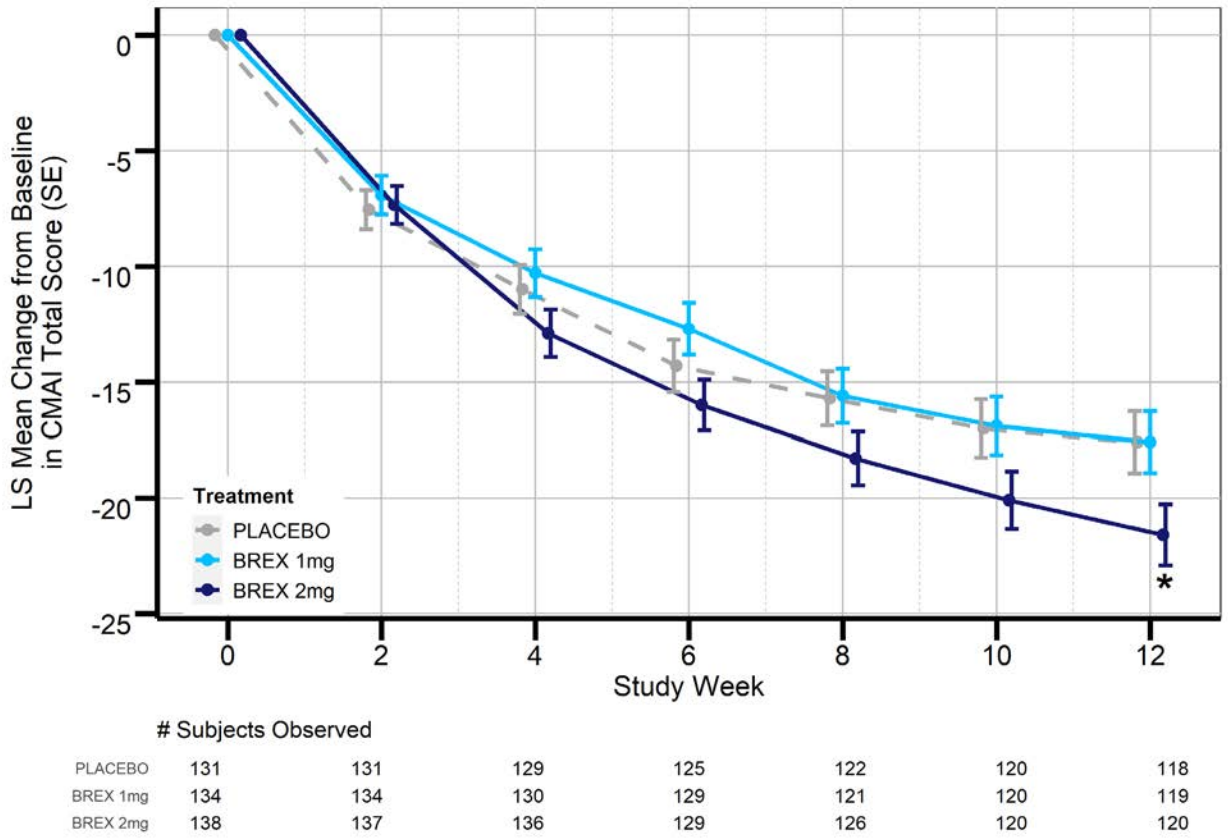
Source: Applicant's Study 331-12-283 Clinical Study Report, CT-5.2.1, p. 394-395, confirmed by statistical reviewer
Abbreviations: CMAI = Cohen Mansfield Agitation Inventory; LSM = least squares mean; MMRM = mixed-effect model for repeated measures; SD=standard deviation; SE=standard error; 95% CI = unadjusted 95% confidence interval (p-value also unadjusted)
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.
[2]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.

Statistical Reviewer's Comment: *Because multiple discrepancies were found in site 181, the four subjects* (b) (6) *from this site were excluded from the efficacy sample. The statistical reviewer re-examined the result after adding site 181 back and concluded that the result is consistent with the primary analysis finding. In addition, the statistical reviewer identified one subject (SUBJID:* (b) (6) *) in the BREX 1 mg group who only had a single post-baseline assessment at Week 1, which was not a scheduled assessment visit for efficacy. Thus, this patient was not included in the primary analysis, although the subject was included in the efficacy sample. The statistical reviewer included this patient in the primary efficacy by mapping its post-baseline assessment to the closest visit (Week 2) in the model; the result is nearly identical with the primary analysis finding.*

Time Course Plot

Figure 5 displays the longitudinal response profile for each treatment group throughout the course of 12 weeks. The LS mean changes in CMAI total score for BREX 2 mg group began to separate from placebo at Week 4 and the treatment differences remained through Week 12. BREX 1 mg did not separate from placebo at each trial week.

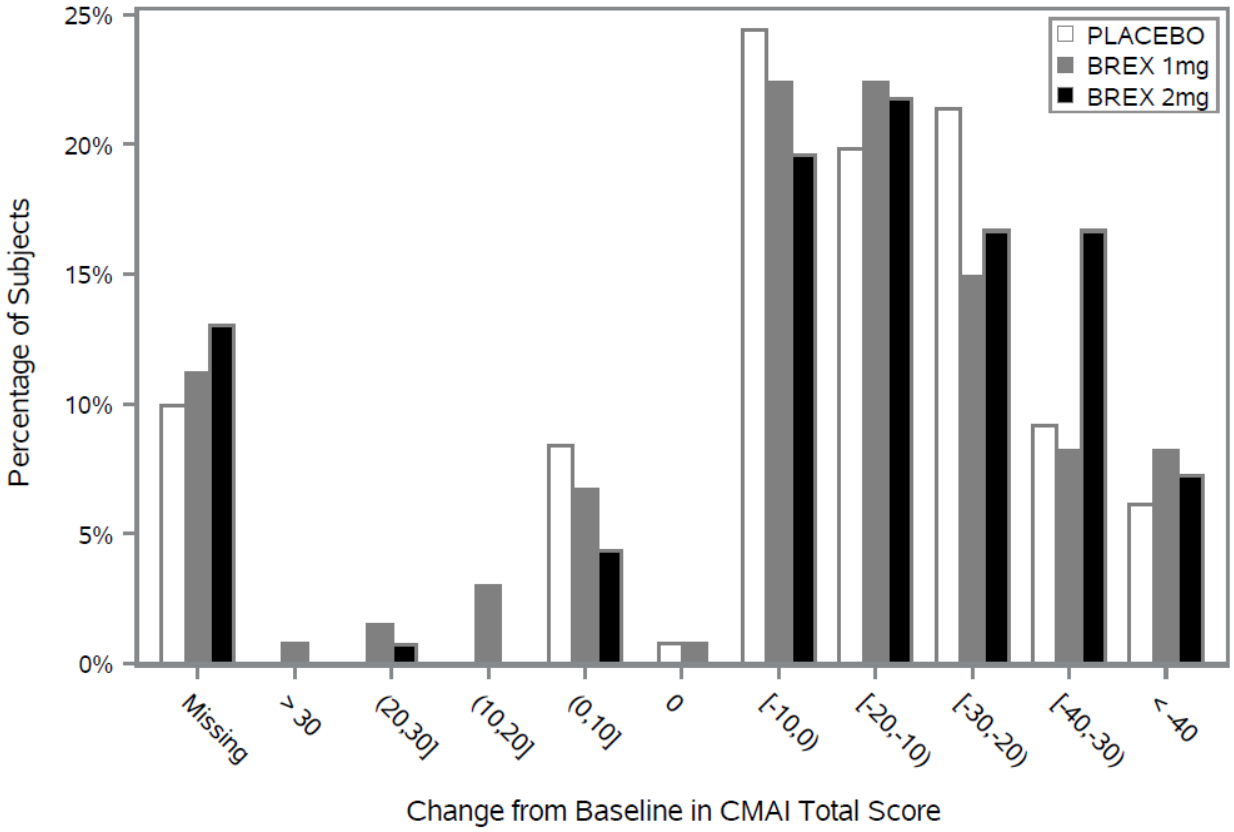
Figure 5: Study 331-12-283 LS Mean Change from Baseline to Week 12 in CMAI Total Score by Week (MMRM; Efficacy Sample)[1]



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

The histogram (Figure 6) displays the proportions of subjects who either improved or worsened on the primary efficacy measure from baseline. The bar on the far left represents the proportion of the subjects with missing data. Negative change scores represent improvement, and positive changes represent worsening. For subjects who had an improvement, the largest difference when comparing the BREX 2 mg group with the other two groups was on the improvement interval of 30 to 40 on the CMAI total score.

Figure 6: Study 331-12-283 Change from Baseline to Week 12 in CMAI Total Score (Efficacy Sample)

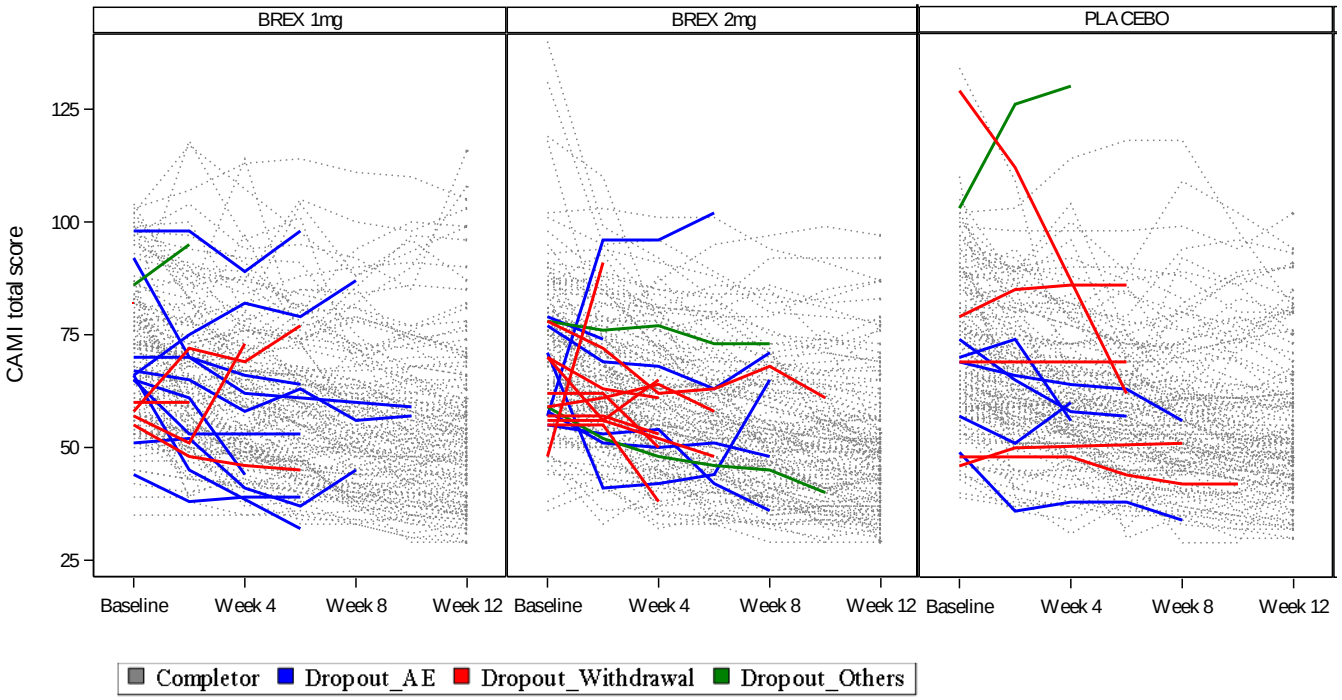


Source: Reviewer-created using the adcmai.xpt dataset, Statistical Analyst Ms. Li's Figure

Individual Patient Response Trajectories Plot

The primary statistical analysis assumes that the missing data mechanism is missing at random (MAR). To explore whether this assumption appears reasonable, the statistical reviewer plotted the individual-patient observed response trajectories in CMAI total score by treatment group (Figure 7). Most of the dropouts had the similar patterns with the completers in each treatment group before they discontinued from the study, which suggests MAR assumption appears reasonable.

Figure 7: Study 331-12-283 Individual-patient Response Trajectories in CMAI total score by Treatment Group (Efficacy Sample)



Source: Statistical Reviewer-created using the adsl.xpt and adcmai.xpt dataset

Sensitivity Analyses for Missing Data

In the delta adjustment imputation sensitivity analysis, there were no statistically significant differences between treatment groups for both Delta 1 (penalty applied based on expected treatment difference) and Delta 2 (penalty applied based on observed treatment difference) methods across all applied scenarios. Only results for shift parameters 0 and 1 are shown in the Table 11. The separation between BREX 2 mg and placebo groups was as high as −3.36, similar to the primary results for this dose when no additional or minimal shift penalty was applied to the missing values. The estimated differences in LS mean for both shift parameters 0 and 1 were smaller than that from the MMRM-based primary analysis. The standard errors were larger due to the multiple imputation implemented in the PMM sensitivity analysis. These two factors led to non-significant p-values. When severity of the penalty increased, the observed separation gradually decreased to as low as −2.6 (results not shown).

Table 11: Study 331-12-283 Sensitivity Analysis of MNAR using Pattern Mixture Model with Multiple Imputation in CMAI Total Score

Sensitivity Analysis	Scenario 1[a]	Scenario 2[b]	Scenario 3[c]
BREX 1 mg vs. Placebo			
Primary Efficacy MMRM	LSMD vs placebo (95% CI): 0.23 (-3.40, 3.86), P value: 0.9015		
Shift parameter: 0			
LSMD vs placebo (95% CI)*	0.208 (-3.31, 3.72)	0.208 (-3.31, 3.72)	0.208 (-3.31, 3.72)
P value*	0.9077	0.9077	0.9077
Delta Method 1[1]			
Shift parameter: 0.65[2]			
LSMD vs placebo (95% CI)*	0.274 (-3.24, 3.79)	0.270 (-3.25, 3.79)	0.251 (-3.26, 3.77)
P value*	0.8787	0.8803	0.8886
Delta Method 2[3]			
Shift parameter: 10%[4]			
LSMD vs placebo (95% CI)*	0.209 (-3.31 3.73)	0.21 (-3.31, 3.73)	0.209 (-3.31, 3.72)
P value*	0.907	0.9069	0.9074
BREX 2 mg vs. Placebo			
Primary Efficacy MMRM	LSMD vs placebo (95% CI): -3.77 (-7.38, -0.17), P value: 0.0404		
Shift parameter: 0			
LSMD vs placebo (95% CI)*	-3.36 (-6.86, 0.14)	-3.36 (-6.86, 0.14)	-3.36 (-6.86, 0.14)
P value*	0.0596	0.0596	0.0596
Delta Method 1[1]			
Shift parameter: 0.65[2]			
LSMD vs placebo (95% CI)*	-3.29 (-6.79, 0.21)	-3.31 (-6.81, 0.191)	-3.34 (-6.84, 0.16)
P value*	0.0657	0.0639	0.0614
Delta Method 2[3]			
Shift parameter: 10%[4]			
LSMD vs placebo (95% CI)*	-3.31 (-6.81,0.18)	-3.33 (-6.83, 0.17)	-3.35 (-6.84, 0.15)
P value*	0.0633	0.0623	0.0608

Source: Study 331-12-283 Clinical Study Report CT-5.11.1 through CT-5.11.6
Abbreviations: LSMD = least squares mean difference; MMRM = mixed-effect model repeated measures; 95% CI = unadjusted 95% confidence interval (nominal p-value also unadjusted)
[a]Dropout reasons due to AE as MNAR
[b]Dropout reasons due to either AE or subject withdrew consent as MNAR
[c]All dropouts as MNAR
[1]Delta Method 1: Delta value would start at 0% of the expected treatment difference of 6.5 points and increase by 10% to 200%.
[2] Shift parameter 0.65 stands for 10% of the expected treatment difference of 6.5 points.
[3]Delta Method 2: Delta value would start from 0% to 200% of the observed treatment difference between brexpiprazole and placebo from the primary analysis of MMRM model.
[4]Shift parameter 10% stands for 10% of the observed treatment difference.
*Derived based on 100 imputations.
Note: Multiple imputation was based on monotone missing data structure of the observed change from baseline using regression option in PROC MI.

For the placebo-based imputation method using both MCMC and Monotone methods, the separations between brexpiprazole groups and placebo were similar to the primary results. The results are shown in Table 12.

Table 12: Study 331-12-283 Sensitivity Analysis of MNAR using Placebo Based Imputation in CMAI Total Score

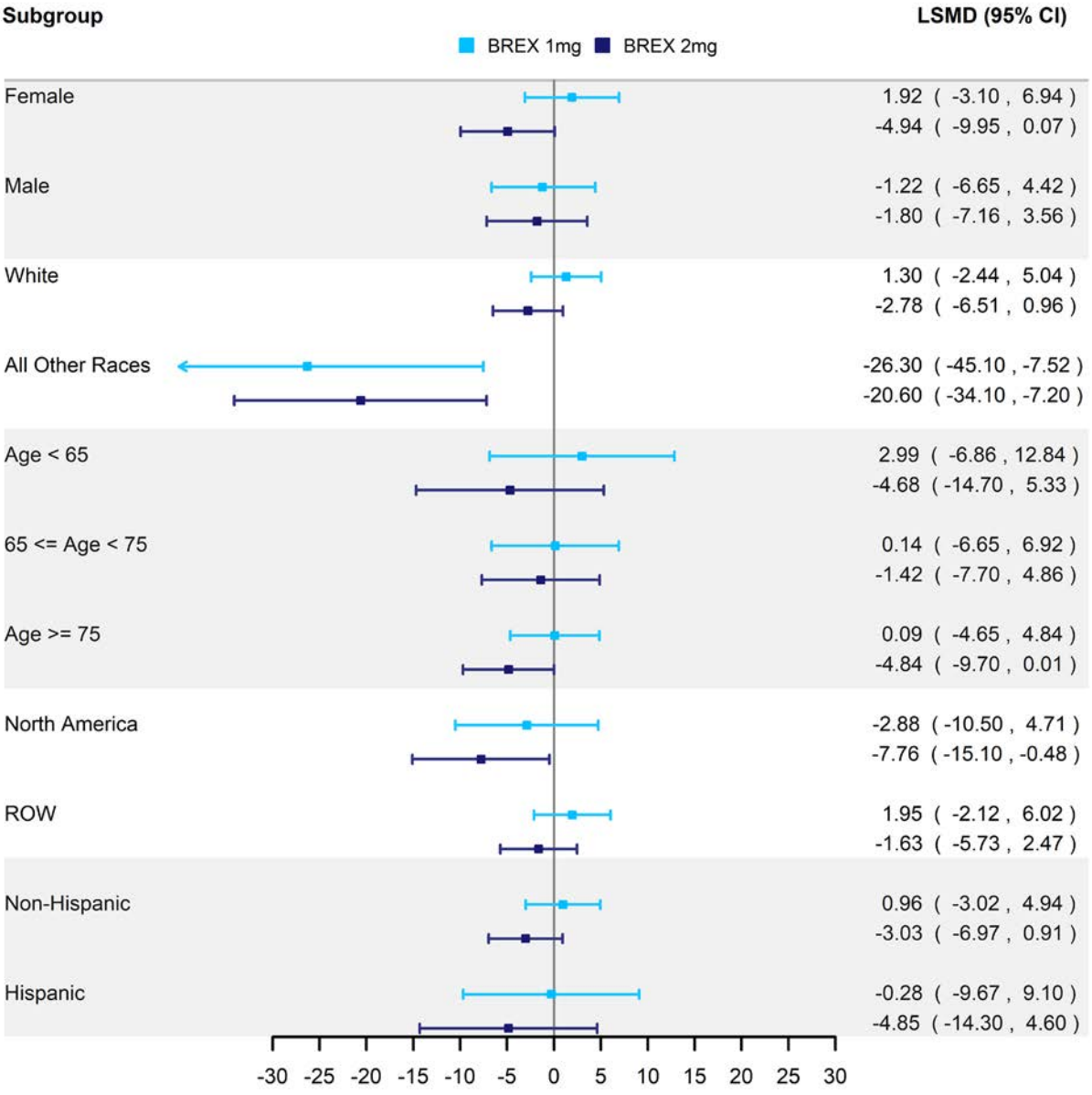
Analysis	LSMD (95% CI)	P value
Primary Efficacy MMRM		
BREX 1 mg vs. Placebo	0.23 (-3.40, 3.86)	0.90
BREX 2 mg vs. Placebo	-3.77 (-7.38, -0.17)	0.04
MNAR-CP MCMC		
BREX 1 mg vs. Placebo	0.19 (-3.24, 3.63)	0.91
BREX 2 mg vs. Placebo	-3.27 (-6.70, 0.16)	0.06
MNAR-CP MONO		
BREX 1 mg vs. Placebo	0.29 (-3.16, 3.75)	0.87
BREX 2 mg vs. Placebo	-3.30 (-6.75, 0.16)	0.06

Source: Study 331-12-283 Clinical Study Report, CT-5.11.7
Abbreviations: LSMD = least squares mean difference; MMRM = mixed-effect model repeated measures; 95% CI = unadjusted 95% confidence interval (nominal p-value also unadjusted); MNAR-CP MCMC = Missing not at random (MNAR) with Copy Placebo for dropout using MCMC Multiple Imputation method; MNAR-CP MONO = Missing not at random (MNAR) with Copy Placebo for dropout using Monotone Multiple Imputation method.
*Derived based on 100 imputations.
Note: Multiple imputation was based on monotone missing data structure of the observed change from baseline using regression option in PROC MI.

Subgroup Analyses

The review examined treatment differences in mean change in CMAI total score from baseline at Week 12 in subgroups of sex, race, age, region, and ethnicity (Figure 8). The subgroup analyses presented in this section are all exploratory. The main objective of the exploratory subgroup analyses is to assess consistency across subgroups with respect to the primary analysis results. Because of the exploratory purpose of these subgroup analyses, p-values are not presented. Treatment differences between subgroups of race were not interpretable due to the imbalance in the number of white subjects (n = 387) and subjects of all other races (n = 16). Subgroup analyses for the primary endpoint indicated that the observed magnitudes of net treatment effect (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: -4.85 [95% CI: -14.30, 4.60]) vs. non-Hispanics (LSMD: -3.03 [95% CI: -6.97, 0.91]) compared with their counterparts in all the subgroups.

Figure 8: Study 331-12-283 Subgroup Analysis for Change from Baseline to Week 12 in CMAI Total Score – Forest Plot (MMRM; Efficacy Sample)



Source: Clinical Reviewer created using Study 331-12-283 Clinical Study Report, CT-6.1.1 (females), CT-6.1.2 (males), CT-6.3.1 (< 65 years), CT-6.3.2 (≥ 65 and < 75 years), and CT-6.3.3 (≥ 75 years), CT-6.2.1 (whites), CT-6.2.2 (all other races), and CT-6.2.3 (whites and all other races at Week 12), CT-6.4.1 (North America) and CT-6.4.2 (other regions) confirmed by statistical reviewer. The subgroup analysis of ethnic status was conducted by statistical reviewer.
Note: In each subgroup stratum, MMRM was conducted with model Terms: treatment, visit, treatment by visit and baseline by visit interaction.

Efficacy Results – Key Secondary Endpoints

The treatment differences did not reach statistical significance for both BREX 1 mg (LS mean difference = 0.09, p = 0.4440) and BREX 2 mg arms for the key secondary efficacy endpoint, mean change in CGI-S score as related to agitation from baseline to Week 12 (LS mean difference = -0.16, p = 0.1566). The results are shown in Table 13.

Table 13: Study 331-12-283 Key Secondary Endpoint Results (Efficacy Sample)

	Placebo (N=131)	BREX 1 mg (N=134)[2]	BREX 2 mg (N=138)
Mean CGI-S Score at Baseline (SD)	4.50 (0.66)	4.53 (0.62)	4.51 (0.70)
Mean CGI-S Score at Week 12 (SD)	3.42 (0.92)	3.49 (0.97)	3.23 (0.91)
LSM[1] Change from Baseline (SE)	-1.11 (0.08)	-1.02 (0.08)	-1.27 (0.08)
Placebo-subtracted difference (95% CI)[1]		0.09 (-0.14, 0.32)	-0.16 (-0.39, 0.06)
P-value[1]		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 Ms. Li.
Abbreviations: CGI-S = Clinical Global Impression-Severity Scale; CI = unadjusted confidence interval (p-value also unadjusted); LSM = least squares mean; MMRM = mixed-effect model repeated measures; SD=standard deviation, SE=standard error
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

[2]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.

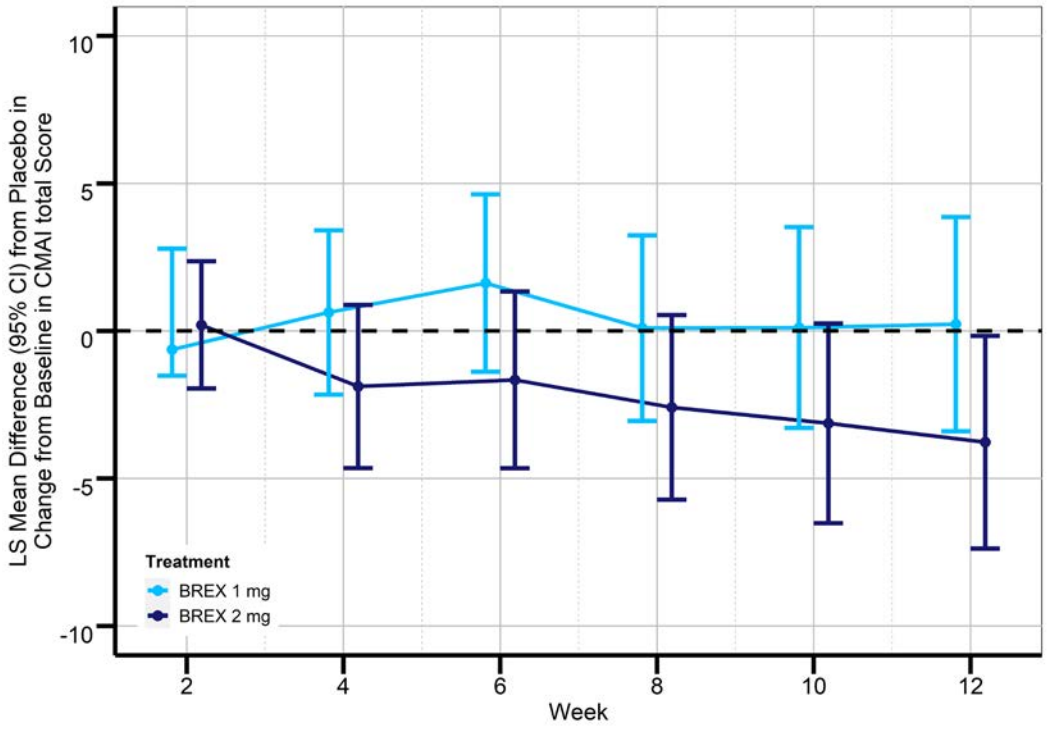
Dose/Dose Response

A positive dose-response relationship was apparent in the change from baseline in total CMAI score and change in the CGI-S score at Week 12. Refer to Dr. Bhattaram's clinical pharmacology/pharmacometrics review (Section 6.2) of the integrated dose-response and exposure-response relationship across all fixed-dose treatment arms from Study 331-12-283 and Study 331-14-213. The positive dose-response relationship was also consistent with subsequent CMAI responder analyses (Table 15) and other exploratory endpoints (Table 16).

Durability of Response

To evaluate durability of response, this review evaluated the change in the net treatment effect over the double-blind period. Figure 9 displays the LSMD from placebo in the change from baseline in the total CMAI score at each visit for both active treatment arms. Although the BREX 1 mg group did not separate from placebo at any time point at nominal significance level of 0.05, the BREX 2 mg group exhibited a nominal treatment effect over placebo starting at Week 4 and maintained its favorable effect through Week 12. Given that the brexpiprazole appears to achieve a pharmacodynamic steady state at approximately 8 to 10 weeks (PK steady state at approximately 3 weeks), the 12-week trial duration may be sufficient to characterize antipsychotic effect in future trials.

Figure 9: Study 331-12-283 Change in Net Treatment Effect over Time



Source: Clinical Reviewer-created using Applicant's Clinical Study Report, Listing CT-5.2.1
Abbreviations: CI = unadjusted confidence interval; CMAI = Cohen Mansfield Agitation Inventory; LS = least-squares

Persistence of Effect

Given that the Applicant did not collect efficacy measures either during the follow-up period for this study or during the post-treatment observational study (Study 331-13-211), the persistence of effect is not discernible. Of note, percentage of subjects who received treatment for agitation during the follow-up period in this study was relatively lower in the brexpiprazole treatment groups versus placebo (approximately 20% vs. 30%, respectively).

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant conducted additional secondary efficacy analyses based on the three factor domains in the CMAI measure (i.e., Factor 1: aggressive behavior; Factor 2: non-physically aggressive behavior, and Factor 3: verbally agitated behavior). The Applicant derived each factor as described in Section 8.1.1.1 and calculated CMAI factors subscores only when all items included in each factor were available (no imputation of missing values). The Applicant applied the same statistical methodology as described for the primary efficacy variable to the factor-based analysis. Table 14: Study 331-12-283 Change from Baseline to Week 12 in CMAI Factor Scores (MMRM; Efficacy Sample)Table 14 provides the summary of the mean change from baseline and the net treatment effect in each of the CMAI factor domains. The results are consistent with the findings from the primary analysis; the BREX 2 mg group showed a nominally greater

improvement across all three factors. However, the brexpiprazole appeared to exert its greatest effect on the verbally agitated domain (BREX 1: −0.28 and BREX 2: −1.26).

Table 14: Study 331-12-283 Change from Baseline to Week 12 in CMAI Factor Scores (MMRM; 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 (0.5)	-6.58 (0.5)	-7.57 (0.49)
Placebo-subtracted difference (95% CI)[1]		0.02 (-1.31, 1.34)	-0.97 (-2.29, 0.35)
P-value		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)[1]		0.42 (-0.97, 1.81)	-1.18 (-2.57,0.20)
P-value		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)[1]		-0.28 (-1.30, 0.75)	-1.26 (-2.29, -0.24)
P-value		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 (nominal p-value also unadjusted); SD = standard deviation; SE = standard error
[1]The Applicant only included the 1 mg, 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 1 of the three distinct CMAI-defined agitation syndromes and thus was not included in the table.
Note: MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

Clinical Reviewer's Comment: *Because the developers of the CMAI did not intend to use the total score, the Applicant evaluated the CMAI subscale scores to further explicate the findings from the primary efficacy endpoint. The Agency emphasized that consistent directional improvements with no compensatory changes should be observed across the CMAI subscales that closely align with the behaviors outline in the IPA consensus definition. Given that the studies were not powered to detect a statistically significant difference on each of the factors, the analyses were considered exploratory.*

Although CMAI Factor 1 (aggressive behaviors) subscale consists of the greatest number of items (12 items), the greatest effect was observed with CMAI Factor 3 (verbal agitation), which only consists of 4 items. Analyses at the item-level suggested that aggressive behaviors were typically reported less frequently than verbally agitated and physically non-aggressive behaviors. From a quantitative perspective, behaviors with a higher frequency could exhibit the greatest change. This variation signifies that not all movement at the item-level has equal importance, and further analyses at the item-level are needed to understand the clinical meaningfulness of these results. Refer to Dr. Swett's DCOA review for additional analyses to evaluate clinically meaningful within-patient change.

The Applicant conducted several responder analyses based on the observed percent change from baseline in total CMAI scores at each scheduled visit. Results from the responder analyses are presented in Table 15. The ratios of response observed at Week 12 provides additional support of a positive dose-response relationship with brexpiprazole by showcasing a consistent nominal benefit with the BREX 2 mg group over placebo across all three responder definitions either using the last observation carried forward (LOCF) or OC methods.

Table 15: Study 331-12-283 CMAI Responder Analyses at Week 12 (LOCF)

Responder Analysis at Week 12[1]	Placebo (N=131)	BREX 1 mg (N=135)	BREX 2 mg (N=138)
CMAI Response Rate (20%)			
Responders at Week 12, n(%)	70 (53.4%)	65 (48.1%)	83 (60.1%)
Ratio of Response (95% CI)		0.92 (0.73, 1.16)	1.12 (0.90,1.39)
CMAI Response Rate (30%)			
Responders at Week 12, n(%)	46 (35.1%)	45 (33.3%)	59 (42.8%)
Ratio of Response (95% CI)		0.97 (0.69, 1.36)	1.21 (0.88, 1.64)
CMAI Response Rate (40%)			
Responders at Week 12, n(%)	18 (13.7%)	26 (19.3%)	39 (28.3%)
Ratio of Response (95% CI)		1.50 (0.88, 2.55)	2.13 (1.27, 3.57)

Source: Clinical Reviewer-adapted using Applicant's Clinical Study Report, Listing CT-5.8.1
Abbreviations: CI = unadjusted confidence interval; CMAI = Cohen Mansfield Agitation Inventory
[1]Responder ratio estimated using the Cochran-Mantel-Haenszel (CMH) General Association Test

Table 16 displays the results based on additional secondary and exploratory efficacy measures. Across all measures, BREX 2 mg consistently demonstrated a numerical improvement over placebo. Analysis of the CGI-I (based on LOCF method) indicated a treatment difference of 0.05 and −0.21 for the BREX 1 mg and 2-mg groups, respectively. A similar proportion of subjects across treatment groups showed much or very much improvement in agitation in response to treatment at Week 12 (BREX 2 mg: 49% of subjects vs. BREX 1 mg: 44% vs. Placebo: 46%). The proportions of subjects in the BREX 1 mg and BREX 2 mg groups who demonstrated a response to treatment based on CGI-E index of 2, 3, or 4 (ratio of current therapeutic effect as related to agitation to severity of side effects) at Week 12 (based on the LOCF method) were 67% and 65%, respectively, compared to 67% in the placebo group. Given the relatively small improvement in on the QoL-AD, it is unclear whether brexpiprazole improved patient and caregiver quality of life.

Clinical Reviewer's Comment: *The Applicant indicated that the quality of life and caregiver burden measures were only included for Studies 331-12-283 and 331-12-284 for exploratory purposes. Because it is unclear whether these scales are capable of detecting change in this patient population, the results may not add additional clinically meaningful context to the primary efficacy results.*

Table 16: Study 331-12-283 Change from Baseline to Week 12 in Secondary and Exploratory Efficacy Measures

Variable[1,2]	Placebo	BREX 1 mg	BREX 2 mg
NPI-NH 12 item Total Score	N=130	N=134	N=138
Baseline Mean (SD)	37.57 (16.57)	36.30 (12.73)	35.99 (15.49)
LSM Change from Baseline (SE)	-16.3 (1.20)	-16.60 (1.19)	-18.10 (1.18)
Placebo-subtracted difference (95% CI)[1]		-0.25 (-3.48, 2.98)	-1.77 (-4.99, 1.45)
NPI-NH Agitation/Aggression Score	N=131	N=134	N=138
Baseline Mean (SD)	7.81 (2.18)	7.31 (1.91)	7.25 (1.94)
LSM Change from Baseline (SE)	-3.68 (0.26)	-3.75 (0.26)	-4.23 (0.25)
Placebo-subtracted difference (95% CI)[1]		-0.10 (-0.80, 0.60)	-0.55 (-1.25, 0.15)
NPI-NH Occupational Disruptiveness Score[2]	N=87	N=88	N=86
Baseline Mean (SD)	13.09 (5.45)	13.64 (5.72)	13.33 (5.93)
LSM Change from Baseline (SE)	-6.06 (0.55)	-6.36 (0.55)	-7.22 (0.57)
Placebo-subtracted difference (95% CI)[1]		-0.30 (-1.75, 1.15)	-1.15 (-2.62, 0.31)
M-CNAS Attitude score[2]	N=84	N=84	N=82
Baseline Mean (SD)	61.83 (13.08)	61.10 (12.26)	60.90 (12.41)
LSM Change from Baseline (SE)	-7.95 (1.25)	-6.90 (1.30)	-9.60 (1.34)
Placebo-subtracted difference (95% CI)[1]		1.06 (-2.06, 4.17)	-1.65 (-4.77, 1.48)
M-CNAS Strain score[2]	N=84	N=84	N=82
Baseline Mean (SD)	75.57 (8.20)	76.03 (9.12)	76.88 (7.65)
LSM Change from Baseline (SE)	2.97 (0.74)	4.55 (0.77)	3.98 (0.78)
Placebo-subtracted difference (95% CI)[1]		1.58 (-0.91, 3.35)	1.01 (-0.77, 2.79)
QoL-AD Patient Score[2]	N=115	N=117	N=119
Baseline Mean (SD)	28.96 (7.29)	28.12 (7.53)	28.96 (7.73)
LSM Change from Baseline (SE)	1.41 (0.43)	0.23(0.43)	1.20 (0.42)
Placebo-subtracted difference (95% CI)[1]		-1.18 (-2.28, -0.08)	-0.21 (-1.31, 0.88)
QoL-AD Caregiver Score[2]	N=126	N=126	N=128
Baseline Mean (SD)	24.05 (5.04)	24.81 (4.58)	24.89 (4.91)
LSM Change from Baseline (SE)	1.78 (0.37)	1.90 (0.37)	1.39 (0.36)
Placebo-subtracted difference (95% CI)[1]		0.12 (-0.85, 1.08)	-0.39 (-1.35, 0.58)

Source: Clinical Reviewer-adapted using Applicant's Clinical Study Report 331-12-283, CT 5.5.1 to 5.14.2
Abbreviations: CI = unadjusted confidence interval (nominal p-value also unadjusted); 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; QoL-AD = Quality of Life in Alzheimer's disease; SD = standard deviation; SE = standard error
[1]The Applicant only included the 1 mg, 2 mg, and placebo in the MMRM model for comparison.
[2]Assessment only collected in institutionalized subjects
Note: MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

Statistical Reviewer's Comment: *These exploratory analysis results based on LOCF approach or OC data should be interpreted with caution. Because of the stronger assumption of missingness behind the LOCF approach, analysis on the LOCF data may not add any value, particularly because single-imputation approaches do not incorporate the variability when imputing missing data. Refer to the publication, "The prevention and treatment of missing data in clinical trials" (https://www.nap.edu/catalog/12955/the-prevention-and-treatment-of-missing-data-in-clinical-trials). Likewise, we do not consider the analysis on OC data (by removing subjects who have missing data at the given visit) a sensible approach either. We further conducted the*

analyses by handling dropouts as non-responders by the composite variable strategy in the estimand framework. Although the results were similar to the findings seen with the LOCF and OC data, we consider this method a more sensible approach.

Additional Analyses Conducted on the Individual Trial Study 331-12-283

Exploratory Post-hoc Significant Agitation Subgroup Analyses

During the pre-IND meeting in 2012, the Applicant discussed the need to target a population of agitated subjects who exhibited aggressive behaviors whose symptoms might be especially troubling. However, the Applicant elected to target a broad AD population with agitated behaviors. The Applicant defined their agitated population primarily based on the NPI-NH Agitation/Aggression item with a threshold score of ≥ 4. After the Applicant presented their topline results during a subsequent Type C meeting in September 2017, the Agency indicated that this threshold score likely led to enrollment of some patients with insufficient behaviors at baseline and unlikely to show a measurable change over 12 weeks.

The Applicant hypothesized that subjects who exhibited significant aggressive behaviors at baseline would likely demonstrate a more robust treatment effect. Therefore, to test this hypothesis, the Applicant identified this subgroup based on observed symptoms in the CMAI Factor 1 for aggressive behavior. According to these criteria, agitation characterized by significant aggressive behavior present when aggressive behaviors occur at least several times a week; for example, at least 1 aggressive behavior occurring with a score of 4 (several times a week), or at least 2 aggressive behaviors occurring with a score of 3 (once or twice a week), or at least 3 aggressive behaviors occurring with a score of 2 (< once a week, but still occurring).

Similarly, the Applicant also identified subgroups of subjects with agitation characterized by significant physically non-aggressive behavior based on symptoms in CMAI Factor 2 and subjects with significant verbally agitated behavior based on symptoms in CMAI Factor 3. According to these criteria, the Applicant classified subjects into the physically non-aggressive and verbally agitated behavior subgroups if the symptoms occur at least once a day; for example, at least 1 physically nonaggressive or verbally agitated behavior occurring with a score of 5 (once or twice a day), or at least 2 physically nonaggressive or verbally agitated behavior occurring with a score of 4 (several times a week), or at least 3 physically nonaggressive or verbally agitated behaviors occurring with a score of 3 (once or twice a week), or at least 4 physically nonaggressive or verbally agitated behaviors occurring with a score of 2 (less than once a week, but still occurring).

The Applicant utilized the same statistical models as used in the aforementioned pre-specified primary analysis to support post-hoc analyses for the evaluation of treatment response versus placebo in subgroups of subjects with agitation manifested by significant aggressive, physically non-aggressive, and verbally agitated behaviors at baseline. The results of the analyses are displayed in Table 17. Although the majority of subjects met the criteria for significant aggressive behaviors (86%), there were notable differences in the mean CMAI total score at

baseline for the aggressive subjects relative to subjects who did not meet the criteria for significant aggressive behaviors (baseline CMAI total score: 73 vs. 56, respectively). This could suggest that the criteria used to identify subjects with significant aggressive behavior could also identify subjects with a higher baseline severity sufficient to discern a change within the 12-week study period.

Similar to the primary analysis, this post-hoc analysis showed consistent numerical improvements with the BREX 2 mg treatment arm relative to placebo across all subgroups of significant agitation. The LS mean difference for BREX 2 mg over placebo was most notable in the aggressive agitation subgroup (LS mean difference = −5.35 [95% CI: −9.19, −1.50]), which was larger than the observed effect in the full efficacy sample (LS mean difference = −3.77 [95% CI: −7.38, −0.17]). The results were also consistent when analyzing change in the CGI-S score.

Table 17: Study 331-12-283 Primary Endpoint Post-hoc Analysis of Change in Total CMAI Scores Across Agitation Behavior Subgroups (MMRM; Efficacy Sample)

Subgroups of Significant Behaviors	Placebo	BREX 1 mg	BREX 2 mg
Significant Aggressive Behaviors	(N=111)	(N=110)	(N=125)
Mean CMAI Total Score at Baseline (SD)	75.16 (17.08)	73.00 (15.97)	72.61 (16.11)
LSM Change from Baseline (SE)	-19.5 (1.46)	-19.2 (1.49)	-24.8 (1.38)
Placebo-subtracted difference (95% CI)[1]		0.22 (-3.76, 4.19)	-5.35 (-9.19, -1.50)
Significant Physically Non-Aggressive Behaviors	(N=123)	(N=128)	(N=129)
Mean CMAI Total Score at Baseline (SD)	73.31 (17.76)	71.28 (15.64)	72.31 (16.07)
LSM Change from Baseline (SE)	-18.6 (1.42)	-18.3 (1.41)	-22.4 (1.4)
Placebo-subtracted difference (95% CI)[1]		0.33 (-3.48, 4.15)	-3.77 (-7.59, 0.04)
Significant Verbally Agitated Behaviors	(N=112)	(N=109)	(N=118)
Mean CMAI Total Score at Baseline (SD)	75.18 (17.19)	74.83 (14.13)	73.30 (15.98)
LSM Change from Baseline (SE)	-19.7 (1.54)	-19.2 (1.57)	-23.9 (1.52)
Placebo-subtracted difference (95% CI)[1]		0.45 (-3.77, 4.67)	-4.17 (-8.33, -0.02)

Source: Study 331-12-283 Clinical Study Report, Table 11.4.1.5.2-1 through 11.4.1.5.3.2-1, p. 116-120
Abbreviations: CI = unadjusted confidence interval; CMAI = Cohen Mansfield Agitation Inventory; LSM = least squares mean, MMRM = mixed-effect model repeated measures; SD = standard deviation; SE = standard error
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

Clinical Reviewer's Comment: *Of note, the Applicant conducted a similar post-hoc analysis for Study 331-12-284 to confirm their hypothesis that subjects with significant aggressive behaviors exhibit a more robust treatment effect on the CMAI total score. However, this finding appears to be consistent with other psychiatric conditions where patients with higher baseline disease severity typically show a greater net treatment effect. Approximately 70% of the population also met the criteria for significant behaviors across all three domains of agitation. In other words, subjects with significant aggressive behaviors also exhibited significant verbally agitated and physically non-aggressive behaviors. Given the limited number of patients without significant symptoms at baseline, it is unclear whether patients with lower frequencies of agitated symptoms (i.e., lower baseline severity) relative to the studied population would benefit from brexpiprazole.*

8.1.2 Trial 331-12-284

8.1.2.1 Study Design of Trial 331-12-284

Trial Design

This study was a randomized, double-blind, placebo-controlled, multi-center, flexible-dose study intended to evaluate the efficacy, safety, and tolerability of brexpiprazole (dose range of 0.5 to 2 mg/day) in elderly subjects with AAD. This trial consisted of three periods identical to Study 331-12-283 (a schematic representation of the study design is presented in Figure 10):

- **Screening Period**: The total duration of the screening period was between 2 to 42 days. Investigators determined subject eligibility and required subjects to washout prohibited concomitant pharmacotherapy prior to randomization. Starting at screening and continuing for the rest of the study period, a caregiver or facility staff logged the subject's behavior in a diary along with a collection of progress notes in order to corroborate information recorded on the CMAI. Because the diary data was a tool to assist CMAI rater training, the diary data, the Applicant did not analyze the data for efficacy purposes.

- **Double-blind Treatment Period:** 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 dose. The dose increased to 0.5 mg/day on Day 4 and then increased to 1 mg/day starting on Day 15. After achieving the target dose of 1 mg/day, investigators may 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. Refer to Table 18 for a visual representation of the flexible-dosing scheme. 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. All trial visits occurred at either the investigator's site or residential facility. Investigators also contacted the caregiver by telephone at Weeks 3, 5, and 7 to assess compliance with the study medication and changes to concomitant medications.

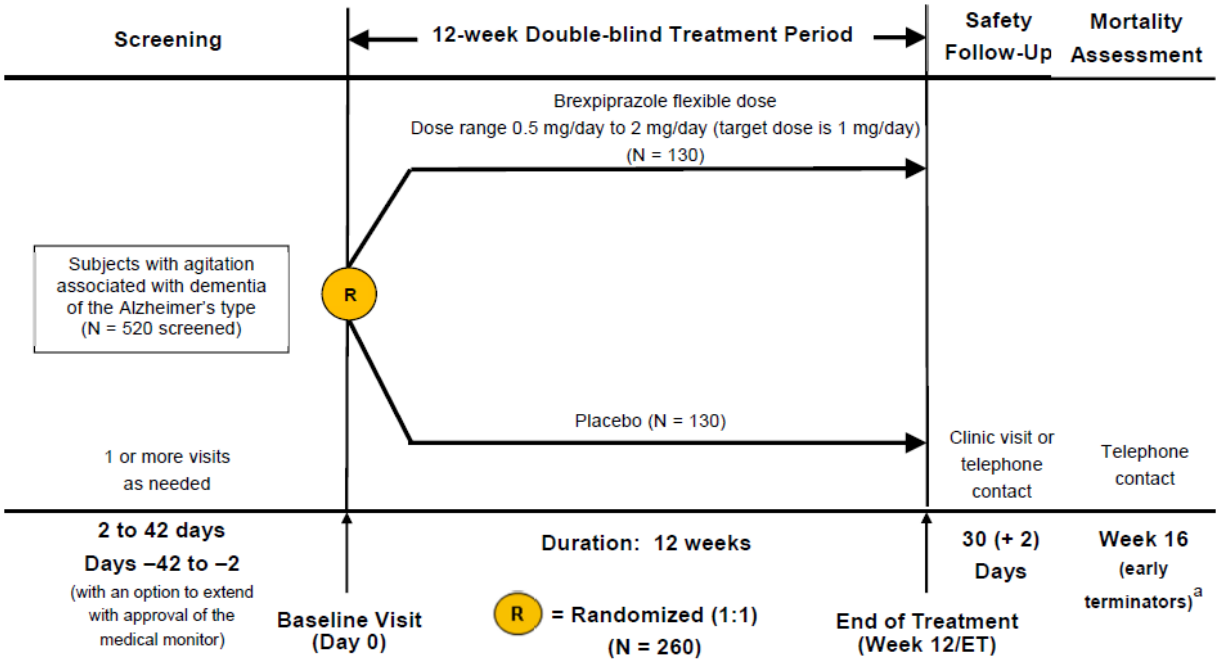
- **Safety Follow-up Period:** Investigators followed each subject for safety evaluation 30 days after receiving the last dose of the study medication. For all subjects who terminated early from the study for any reason, investigators contacted the caregiver by telephone at Week 16 to collect follow-up information on mortality status.

Table 18: Flexible-dosing Scheme for Study 331-12-284

Treatment Group	Recommended Daily Dose Administered			
	Day after the Baseline visit (Day 1)	Day after the Day 3 visit (Day 4[+2 days])	Day after the Week 2 visit (Day 15[±2 days])	Day after the Week 4 visit (Day 29[±2 days])
Brexpiprazole 0.5-2 mg/day	0.25 mg/day	0.5 mg/day	1 mg/day[1]	2 mg/day[2]
Placebo	<----------			---------->

Source: Applicant's 331-12-284 Study Protocol, Table 3.2.1
[1]After achieving the target dose of 1 mg/day, the dose may be decreased to a 0.5 mg/day and re-increased to 1 mg/day based on clinical judgment. Dose decreases and increases can occur at any time (scheduled or unscheduled visits).
[2]The earliest time point that the dose can increase to 2 mg/day is starting on the day after the Week 4 visit (ie, Day 29 [±2 days]); however, it is not mandatory for the dose to be increased to 2 mg/day.

Figure 10: 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

For purposes of this trial, investigators 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, including completion of the diary. 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). In both settings, the caregiver met the same requirements and assumed the same responsibilities.

Study Eligibility Criteria

The target population consisted of elderly subjects aged 55 to 90 years living in either an institutionalized or noninstitutionalized setting where the subject is not living alone. Applicant's comprehensive inclusion and exclusion criteria consisted of appropriate diagnostic and tolerability criteria, a list of prohibited and accepted concomitant medications, and acceptance thresholds for clinically significant abnormal laboratory values and medical history. Pertinent inclusion and exclusion criteria that could impact the evaluation of efficacy and safety are presented below (note that the trial population is identical to Study 331-12-283):

Key Inclusion Criteria:

- Diagnosis of probably AD according to the NINCDS-ADRA criteria (McCann G, et al., 1984)
- MMSE score between 5 to 22, inclusive, at screening and baseline
- Previous MRI or CT scan of brain (performed after the onset of symptoms of dementia) with findings consistent with a diagnosis of AD
- Residing in current location for at least 14 days before screening and expected to remain at the same location for the duration of the trial
- Total score (frequency x severity) of ≥4 on the agitation/aggression item of the NPI-NH (for institutionalized subjects) or the NPI/NPI-NH (for non-institutionalized subjects) at screening and baseline
- Onset of symptoms of agitation at least 2 weeks prior to screening
- Required pharmacotherapy for agitation, per the investigator's judgement, after an evaluation of reversible factors (e.g., pain, infection, polypharmacy) and a trial of non-pharmacological interventions

Key Exclusion Criteria:

- Diagnosis of dementia or other memory impairment not due to AD (e.g., mixed or vascular dementia, DLB, Parkinson's disease dementia, FTD, etc)
- History of stroke, well-document TIA, or pulmonary or cerebral embolism
- Insufficient response, based on investigator's judgment, to two or more previous antipsychotic medications for the treatment of AAD
- Prescence or history of delirium within 30 days prior to screening
- Diagnosis with an Axis I disorder (e.g., schizophrenia, bipolar I or II disorder, etc) based on the DSM-IV-TR

- Evidence of serious risk of suicide defined as a score of 3 or 4 to any one question 2 through 6 or 11 or a score of 2 or higher on any one of questions 1a, 7, through 10, or 12 on the Sheehan-STS, or based on the opinion of the investigator
- Clinically significant and uncontrolled medical conditions including uncontrolled atrial fibrillation, heart failure, or ischemic heart disease (surrogates for uncontrolled cardiovascular disease included hospitalizations or procedures, such as percutaneous coronary intervention or coronary bypass surgery, within the last 6 months)
- Uncontrolled hypertension (DBP > 95 mmHg), symptomatic hypotension, or orthostatic hypotension (decrease of ≥ 30 mmHg in SBP or decrease of ≥ 20 mmHg in DBP within 3 minutes of standing)
- Diagnosis of epilepsy or history of seizures (expect of single childhood febrile seizures, post-traumatic injury, or alcohol withdrawal)
- Body mass index < 18.5 mg/kg^2
- Newly diagnosed diabetes or unstable diabetes (screening HBA_{1C} ≥ 8%, screening glucose > 125 mg/dl [fasting] or ≥ 200 mg/dl [non-fasting], hospitalization within the 3 months prior to screening due to diabetes or complications related to diabetes)
- Diagnosis of substance abuse or dependence within the past 180 days based on DSM-IV-TR criteria (including alcohol, benzodiazepines and excluding caffeine and nicotine)
- Positive urine drug screen for cocaine, marijuana, or other illicit drugs
- Abnormal laboratory tests (i.e., platelets ≤ 75,000/mm^3, hemoglobin ≤ 9g/dL, absolute neutrophils ≤ 1,000/mm^3, AST > 2 x upper limit of normal [ULN], ALT > 2 x ULN, glycosylated hemoglobin ≥ 8%) vital signs, or ECG findings (QTcF ≥ 450 msec in men and ≥ 470 msec in women)
- Sexually active females of childbearing potential and male subject who are not practicing two different methods of birth control with their partner during the trial and for 30 days after the last dose of the study medication
- Received immunotherapy for the treatment of AD (through clinical trial or compassionate use program in the 6 months preceding randomization.

Procedures and Schedule of Events

Refer to Table 19 below for the Applicant's schedule of procedures and study assessments.

Table 19: Schedule of Assessments for Study 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									
Medical and psychiatric history	X									
Prior medication washout, blood alcohol, and UDS	X									
Hachinski Ischemic Scale (Rosen Modification)	X									
CMAI, CGI-S, NPI-NH, and 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 examination	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	
PK Sampling		X					X		X	
Mortality assessment										X

Source: Clinical 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

Subject Completion, Discontinuation, or Withdrawal

The Applicant defined the treatment period as the time period during which subjects are evaluated for primary or secondary objectives of the trial irrespective of whether or not the subject was administered all doses of the study medication. The Applicant defined subjects who completed the Week 12 visit as trial completers. Investigators permitted subjects to withdraw from the study at any time for any reason without compromising their medical care. Subject-specific stopping criteria also included: occurrence of any AE, illness, or abnormal laboratory assessment that warrants permanent withdrawal, treatment with prohibited concomitant medications, non-compliance, lack of tolerability with study medication, development of clinically significant agitation that cannot be adequately treated with permitted medications, or transfer from an institutionalized setting to a non-institutionalized setting (or vice versa).

Investigators also contacted the medical monitor if the Sheehan-STS score was 3 or 4 on any one question 3 through 6 or 11 or if the Sheehan-STS score was 2 or higher on any one questions 1a, 7 through 10, 12, or 18. Investigators required subjects who withdrew prior to Week 12 to complete the Week 12/ET evaluation at the time of withdrawal and a follow-up safety evaluation 30 days after the last dose of the study medication. For all subjects who terminated early, investigators made every attempt to collect mortality data via telephone at Week 16.

Study Product Information and Compliance

The Applicant supplied the study medication as active brexpiprazole film-coated tablets and matching placebo film-coated tablets and provided weekly blister cards containing sufficient tablets for 7 (+ 2) days. Responsible trial personnel dispensed the study medication and documented accountability and compliance verification in the subject's trial records. Depending on the setting, the caretaker or caregiver was responsible for treatment administration.

Dose Selection

The Applicant selected the doses of brexpiprazole for this trial based on completed phase 1 safety and tolerability studies, including a positron emission tomography study in healthy subjects, phase 2 and 3 studies in subjects with schizophrenia, MDD, or ADHD, and a review of data from other studies of other atypical antipsychotics in subjects with dementia. In the current trial, the selected dose range in subjects with Alzheimer's disease was 1 mg/day to 2 mg/day to maximize tolerability while optimizing potential efficacy. The Applicant also gradually titrated the starting dose (0.5 mg/day) to the target dose to maximize tolerability.

Prior and Concomitant Therapy

The Applicant's proposed list of prohibited medications is identical to Study 331-12-283. Refer to Table 4 for a summarized list of prohibited medications and the corresponding protocol-specified washout periods. Subjects must have discontinued all psychotropics not listed in Table

4 at least 24 hours prior to the first dose of the study medication. The Applicant also prohibited all CYP2D6 inhibitors and CYP3A4 inhibitors and inducers. The Applicant allowed oral benzodiazepine therapy for the first 4 weeks of the double-blind treatment period, but limited administration to 4 days/week with a maximum dose of 2 mg/day of lorazepam (or equivalent) and not within 12 hours prior to efficacy and safety assessments. Subjects receiving non-benzodiazepine sleep aids for insomnia could not receive same day administration of a benzodiazepine. Subjects could receive medications to treat AD (cholinesterase inhibitors, memantine, or other cognitive enhancers), provided that the subject was on a stable dose for 90 days prior to randomization and remained on the same dose throughout the trial period. Although the Applicant did not permit new onset non-pharmacological interventions for the treatment of agitation during the double-blind period, subjects may have continued these therapies if they initiated those interventions prior to trial participation.

Clinical Reviewer's Comment: *The proposed basic trial design and eligibility criteria are identical to Study 331-12-283. Refer to the reviewer comments on the inclusion and exclusion criteria in Section 8.1.1.1 of this review. Because the Applicant initiated Study 331-12-284 in parallel with Study 331-12-283, there was no prior knowledge of brexpiprazole's dose-response relationship and safety profile in the target population that could have suggested the Applicant utilize a higher flexible dose range (e.g., 0.5 to 3 mg/day), different target dose (e.g., 2 mg/day) and titration schedule, or treatment paradigm.*

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. Refer to Section 8.1.1.1 for additional information regarding the CMAI instrument.

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

- CMAI subscale scores (aggressive behavior [Factor 1], physically non-aggressive behavior [Factor 2], and verbally agitated behavior [Factor 3])
- NPI-NH 12-item total score and NPI-NH A/A subscores
- CGI-I scale score

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

- CGI-E score
- NPI-NH psychosis subscale, occupational disruptiveness (institutionalized subjects only), distress (NPI/NPI-NH in non-institutionalized subjects only), NPI-4A cluster score, NPI-4D cluster score, and individual item scores
- M-NCAS total score (institutionalized subjects only)
- QoL-AD score
- NOSGER score (institutionalized subjects only) and NOSGER dimension scores (institutionalized subjects only)
- RUD score.

The Applicant also conducted a CMAI responder analysis at each scheduled visit in the double-blind treatment period, where response was defined as ≥ 40%, ≥ 30%, and ≥ 20% reduction in CMAI total score from baseline.

Statistical Analysis Plan

The primary efficacy outcome measure was the mean change from baseline (Day 0) to the end of the double-blind treatment period (Week 12) in the CMAI total score. The Applicant estimated the sample size based on a treatment effect of 6.5 points with a SD of 16.5 in the change from baseline (Day 0 visit) to the end of the double-blind treatment period (Week 12 visit) in the CMAI total score, to achieve 85% power at a 2-sided alpha level of 0.05. This resulted in 117 subjects per treatment arm (i.e., brexpiprazole and placebo). After allowance of 10% non-evaluable subjects, the total number of subjects to be randomized was 130 per treatment arm, which equated to a total sample size is 260 subjects.

The Applicant conducted the efficacy analyses on the ITT population, which consisted of all subjects in the randomized sample who took at least one dose of study medication, underwent baseline evaluation, and at least one post-baseline evaluation for the CMAI total score. The Applicant performed the primary efficacy analysis by fitting a MMRM analysis 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.

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

Protocol Amendments

There were three global amendments to the protocol. The Applicant's specified changes to the study protocol are highlighted below:

- Amendment 1 (December 16, 2013)
  - Increased number of participating centers from 20 to 30 and recruitment period from 3 to 4 years
  - Added requirements to screening assessments for an MRI/CT scan of the brain
  - Clarified that the detailed neurological examination can be performed by a physician who is not a neurologist
  - Added that subjects who complete this study are eligible to enter Study 331-13-211
  - Clarified restrictions on antidepressant and psychotropic drug use

- Amendment 2 (July 7, 2014)
  - Added collection of mortality data at Week 16 for subjects who terminate early from the study
  - Allowed the inclusion of non-institutionalized subjects
  - Increased the number of planned centers from 30 to 46
  - Added the Resource Utilization in Dementia (RUD) assessment for both non-institutionalized and institutionalized subjects

- Amendment 3 (September 10, 2015)
  - Increased the study power from 80% to 85%, which resulted in an increase in the total sample size from 230 to 260 subjects (115 subjects/arm)
  - Broadened the definition of subjects in an institutionalized setting and added overnight passes for these subjects
  - Removed urinalysis, prolactin, and urine pregnancy testing at Weeks 4 and 8
  - Removed the SAS and the BARS at Weeks 6 and 10
  - Removed actigraphy from the trial and replaced electronic diaries with paper diaries
  - Added Bulgaria and Russia as participating countries.

Clinical Reviewer's Comment: *The review team previously determined that the proposed protocol changes incorporated in each amendment were reasonable. Refer to the previous clinical reviewer comment regarding the inclusion of non-institutionalized subjects in Section 8.1.1.1. The majority of revisions appear to assist trial enrollment rates and decrease patient burden. None of the protocol revisions appear to negatively impact the interpretation of study results.*

8.1.2.2 Study Results of Trial 331-12-284

Compliance with Good Clinical Practices

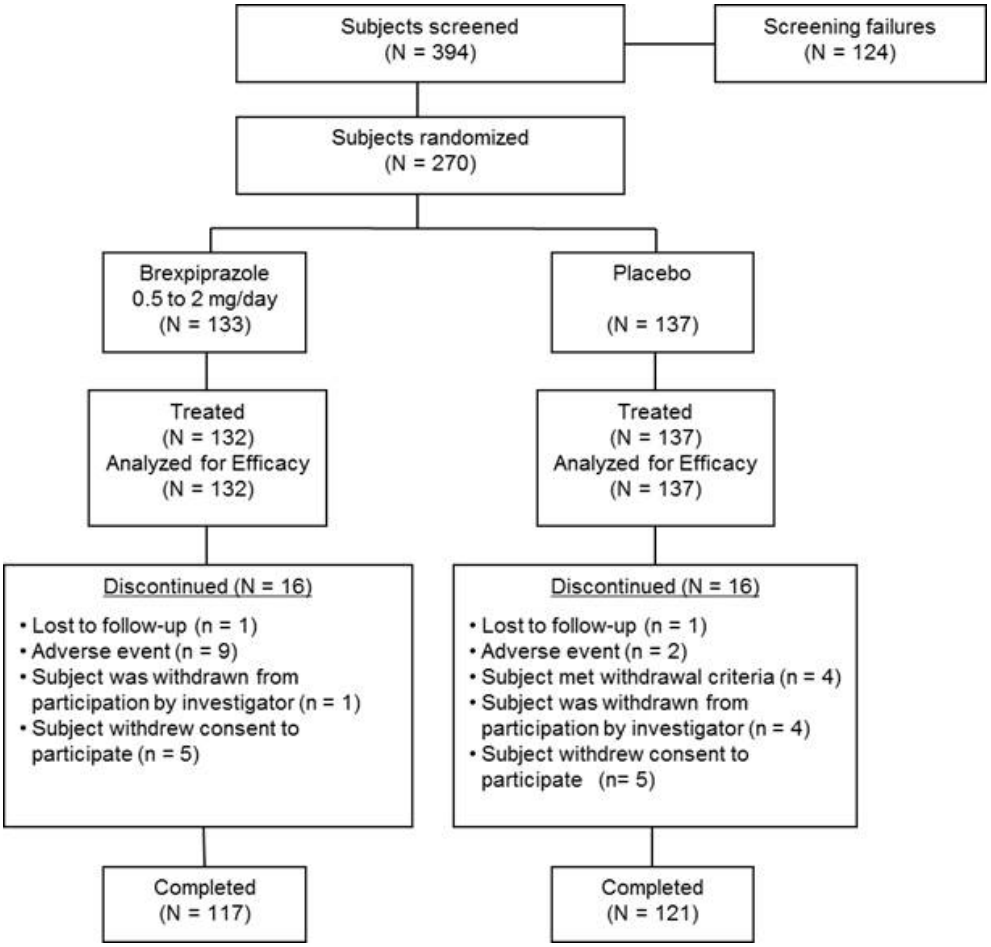
The Applicant conducted this study in accordance with the International Council for Harmonisation Good Clinical Practice Guidelines. The Applicant states that the study protocol, amendments, informed consent form, and other appropriate study related information were reviewed by an independent ethics committee or institutional review board prior to study initiation.

Financial Disclosure

Refer to Section 15.2 of this review for detailed financial disclosure information. There are no disclosed financial interests or arrangements or missing disclosures that raise questions about the integrity of study data.

Patient Disposition

Figure 11: Disposition of Subjects in Study 331-12-284



Source: Applicant's 331-12-284 Clinical Study Report, Figure 10.1-1

The Applicant screened a total of 394 subjects and randomized 270 subjects into the double-blind treatment period (BREX= 133; Placebo = 137). See Figure 11 for an overview of patient disposition. All except one subject in the brexpiprazole group received at least one dose of the study medication; therefore, the Efficacy and Safety Sample Population comprised of 269 subjects. In the Randomized Sample, 32 subjects (12%) discontinued during the trial (BREX= 12%; Placebo = 12%). 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%). Subject withdrawal of consent (total N=10) also contributed to approximately a third of subject dropouts. Overall discontinuation percentages were greater across North American trial sites (includes US and Canada only) vs. ROW sites (15/74; 20% vs. 17/196; 8.7%). There were no observable dropout trends by age, gender, or race.

Protocol Violations/Deviations

Refer to

Table 20 for an overview of the Applicant's listing of major protocol violations during the double-blind period. In general, the percentage of subjects with major protocol deviations was slightly higher in the brexpiprazole (17%) than the placebo group (15%). The Applicant categorized the majority of protocol deviations as related to dosing (overall < 80% complaint, missed > 3 consecutive days of dosing, or received an excess dose of the study medication) and procedural errors (i.e., date of informed consent after date of study assessment, primary efficacy assessment not done per schedule, missing safety assessment for study eligibility). During the study period, no subject discontinued study treatment due to a protocol deviation.

Table 20: Summary of Major Protocol Violations During the Double-Blind Period for Study 331-12-284 (Safety Sample)

Protocol Deviations	Placebo (N=137)	BREX 0.5 to 2 mg (N=132)
Number of subjects with major protocol deviations	21 (15%)	23 (17%)
Entry Criteria	3 (2.2%)	1 (0.8%)
Dosing	8 (5.8%)	10 (7.6%)
Concomitant Medication	4 (2.9%)	6 (4.5%)
Procedural	12 (8.8%)	8 (6.1%)

Source: Applicant's alldev.xpt dataset

Clinical Reviewer's Comment: *Similar to Study 331-12-283, protocol violations appear relatively low for a 12-week study conducted in institutionalized and non-institutionalized care settings across 53 centers. Further analyses conducted by region also indicated that the percent of subjects with major protocol deviations was similar in North America vs. ROW for all treatment groups (17% vs. 17% and 15% vs. 15% for the brexpiprazole and placebo groups respectively). Although dosing errors in the placebo group are less problematic with regards to confounding efficacy, it is unclear whether safety and efficacy is impacted by the 8% of subjects in the brexpiprazole group with dosing-related errors. A closer examination of the description of each*

dosing-related deviation indicated that most subjects had a dosing gap of > 3 days. Although the Applicant did not provide the timing of these deviations and the exact duration of missed study treatment, subjects could still have significant brexpiprazole exposure to elicit an effect (brexpiprazole's estimated half-life of 91 hours) if these events occurred after the first few weeks of trial initiation.

Table of Demographic Characteristics

Table 21: Demographic and Baseline Characteristics for Study 331-12-284 (Efficacy Sample)

Demographic Characteristic	Placebo (N=137)	BREX 0.5 to 2 mg (N=132)	Total (N=269)
Age (years)			
Mean (SD)	74.0 (7.8)	73.4 (8.5)	73.7 (8.1)
Median (Range)	75 (56, 90)	74 (55, 89)	74 (55, 90)
Age group (years), n (%)			
< 65	19 (14%)	24 (18%)	43 (16%)
65 to < 75	49 (36%)	46 (35%)	95 (35%)
≥75	69 (50%)	62 (47%)	131 (49%)
Gender, n (%)			
Male	49 (36%)	51 (39%)	100 (37%)
Female	88 (64%)	81 (61%)	169 (63%)
Race, n (%)			
White	129 (94%)	127 (96%)	256 (95%)
Black or African American	5 (3.6%)	4 (3.0%)	9 (3.3%)
Asian	3 (2.2%)	-	3 (1.1%)
Other	-	1 (0.8%)	1 (0.4%)
Country, n (%)			
United States	33 (24%)	27 (21%)	60 (22%)
Russia	26 (19%)	26 (20%)	52 (19%)
Ukraine	36 (26%)	42 (32%)	78 (29%)
Bulgaria	25 (18%)	23 (17%)	48 (18%)
Canada	6 (4.3%)	7 (5.3%)	13 (4.8%)
France	5 (3.6%)	4 (3.0%)	9 (3.3%)
Slovenia	5 (3.6%)	1 (0.8%)	6 (2.2%)
Great Britain	2 (1.5%)	-	2 (0.7%)
Finland	-	1 (0.8%)	1 (0.3%)
Region, n (%)			
North America	39 (29%)	34 (26%)	73 (27%)
ROW	98 (72%)	98 (74%)	196 (73%)
Ethnicity, n(%)			
Hispanic or Latino	9 (6.6%)	6 (4.5%)	15 (5.6%)
Not Hispanic or Latino	128 (93%)	124 (94%)	252 (94%)
Weight (kg), mean (SD)	69.1 (14.9)	68.6 (14.8)	68.8 (14.8)
Height (cm), mean (SD)	163.4 (9.5)	163.9 (9.7)	163.7 (9.6)
BMI (kg/m^2), mean (SD)	25.8 (4.7)	25.2 (4.2)	24.8 (4.4)
Weight circumference (cm), mean (SD)	89.8 (14.2)	88.8 (12.2)	89.3 (13.3)

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

Note: Ethnicity status was unknown for two subjects in the brexpiprazole group.

Other Baseline Characteristics

Table 22: Baseline Disease and Psychiatry History for Study 331-12-284 (Efficacy Sample)

Disease Characteristic	Placebo (N=137)	BREX 0.5 to 2 mg (N=132)	Total (N=269)
Care Setting, n (%)			
Institutionalized	75 (55%)	73 (55%)	148 (55%)
Non-institutionalized	62 (45%)	59 (45%)	121 (45%)
Time since onset of symptoms of dementia (months), mean (SD)	57.2 (29.7)	53.1 (33.2)	55.2 (31.5)
Time since diagnosis of AD (months), mean (SD)	32.1 (27.2)	28.0 (28.3)	30.1 (27.8)
Time since onset of first episode of agitation (months), mean (SD)	17.5 (19.8)	19.9 (23.5)	18.7 (21.7)
Cognitive Impairment (MMSE)[1], n (%)			
Mild	34 (25%)	28 (21%)	62 (23%)
Moderate	65 (47%)	64 (49%)	129 (48%)
Severe	36 (26%)	40 (30%)	76 (28%)
Comorbid BPSD, n (%)			
Irritability/lability	118 (86%)	114 (86%)	232 (86%)
Aberrant motor behavior	94 (69%)	104 (76%)	198 (74%)
Anxiety	88 (64%)	92 (70%)	180 (67%)
Sleep disorder	65 (47%)	78 (59%)	143 (53%)
Apathy/indifference	81 (59%)	76 (58%)	157 (58%)
Disinhibition	70 (51%)	54 (41%)	124 (46%)
Delusions	38 (28%)	44 (33%)	82 (31%)
Depression/dysphoria	32 (23%)	47 (36%)	79 (29%)
Appetite changes	33 (24%)	38 (29%)	71 (26%)
Hallucinations	13 (9.5%)	18 (14%)	31 (12%)
Elation/euphoria	7 (5.1%)	5 (3.8%)	12 (4.5%)
Agitation features, n (%)			
Aggressive behavior	115 (84%)	113 (86%)	228 (85%)
Physically non-aggressive behavior	115 (84%)	118 (89%)	233 (87%)
Verbally agitated behavior	116 (85%)	118 (89%)	234 (87%)
CMAI Total Score, mean (SD)	68.5 (15.9)	71.5 (16.8)	69.9 (16.4)
Factor 1 sub-score	22.1 (7.7)	23.8 (9.2)	22.9 (8.5)
Factor 2 sub-score	19.6 (7.1)	20.7 (7.1)	20.1 (7.1)
Factor 3 sub-score	14.9 (5.5)	15.4 (4.8)	15.1 (5.2)
NPI-NH 12 Domain Score[2], mean (SD)	34.6 (14.8)	37.2 (14.0)	35.9 (14.5)
NPI Agitation/Aggression Score, mean (SD)	7.4 (1.8)	7.5 (1.9)	7.5 (1.9)
NPI Psychosis Score ≥ 4, n (%)	29 (21%)	31 (24%)	60 (22%)
CGI-S Score, mean (SD)	4.5 (0.7)	4.5 (0.8)	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 State 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.

Baseline demographic characteristics are presented in Table 21. In the efficacy sample, approximately half of the subjects (49%) were aged ≥ 75 years (mean age = 73.7 years). Only

27% of subjects participated in North American clinical trial sites (22% in US sites), while approximately 50% of subjects participated in sites in Ukraine and Russia. Similar to Study 331-12-283, most subjects were female (63%) and white (95%). In general, demographics characteristics were similar between males and females, age groups, and race groups across treatment arm. However, there were regional differences in race, ethnicity, and age distribution. In North America, 60% of subjects were aged ≥ 75 years compared with 44% of subjects in other regions. Among North American sites, the efficacy population (n = 73) was more diverse than ROW sites with 84% white subjects and 15% Hispanic or Latino subjects. In all other regions (n = 196), only one subject reported being Hispanic or Latino. Subjects in North America were also generally older than in other regions with 5% < 65 years and 69% ≥ 75 years compared with 20% < 65 years and 49% ≥ 75 years in other regions.

Across both treatment groups, baseline disease characteristics and psychiatric history was also similar (Table 22). Consistent across treatment arms, the majority of subjects exhibited either moderate (48%) or severe cognitive impairment (28%), rather than mild impairment (23%). Based on past reported medical history, approximately 8% and 6% of subjects reported a history of anxiety and depression, respectively. The most common non-psychiatric conditions reported were those typically associated with age: hypertension (49%), postmenopause (37%), myocardial ischemia (17%), and osteoarthritis (14%). Of the various comorbid BPSD symptoms, most subjects reported histories of irritability (86%), aberrant motor behavior (73%), or anxiety (67%).

Analysis of the CMAI factor domains also indicated that > 80% of subjects experienced significant physically aggressive, physically non-aggressive, or verbally agitated behaviors (approximately 67% of subjects experienced behaviors from all three domains). Further subgroup analyses indicated the following:

- In North America, the proportion of subjects residing in an institutionalized setting was relatively less than subjects in other countries (16% vs. 69%), while the proportion of those residing in a non-institutionalized setting was higher in North American subjects (84% vs. 31%).
- Cognitive impairment severity did not vary by gender or region. Severe cognitive impairment (MMSE score ≤ 12) was higher among subjects aged ≥ 75 years compared to < 65 years (31% vs.19%).
- There were no differences across demographic factors when comparing the percentage of subjects with psychotic symptoms and other efficacy variables.

Approximately 74% of subjects (72% vs. 76% in the brexpiprazole and placebo groups, respectively) received at least one medication for an indication other than for AD or AAD. The most frequent non-psychotropic drug classes reported were angiotensin converting enzyme (ACE) inhibitors (i.e., 23% enalapril and lisinopril), antithrombotic agents (i.e., 23% aspirin), acetaminophen (11%), and statins (i.e., 7% atorvastatin). Table 23 displays the incidence of

psychotropic medication use prior to the double-blind treatment period. All subjects reported use of a psychotropic drug prior to the study period. Across both treatment arms, prior psychotropic medication use was similar for the treatment of AD and AAD.

Table 23: Psychotropic Medication Use Prior to the Double-Blind Period in Study 331-12-284 (Efficacy Sample)

Indication/Drug, n (%)	Placebo (N=137)	BREX 0.5 to 2 mg (N=132)	Total (N=269)
Subjects receiving at least one psychotropic	137 (100%)	132 (100%)	269 (100%)
Agitation[1]	93 (67.9%)	91 (68.9%)	184 (62.2%)
Antipsychotics	73 (53.3%)	69 (52.2%)	142 (48.0%)
Benzodiazepines	16 (11.7%)	14 (10.6%)	30 (10.1%)
SSRI/SNRIs	-	5 (3.8%)	5 (1.7%)
Alzheimer's disease	120 (87.6%)	118 (89.4%)	238 (80.4%)
Anticholinesterase inhibitors	68 (49.6%)	65 (49.2%)	133 (44.9%)
Memantine	76 (55.5%)	73 (55.3%)	149 (55.4%)
Anxiety	6 (4.4%)	4 (3.0%)	10 (3.4%)
Benzodiazepines	4 (2.9%)	-	4 (1.4%)
SSRI/SNRIs	2 (1.5%)	4 (3.0%)	6 (2.0%)
Depression	16 (11.7%)	6 (4.5%)	22 (7.4%)
SSRI/SNRIs	15 (10.9%)	5 (3.8%)	20 (6.8%)
Insomnia/Sleep Disorders	6 (4.4%)	11 (8.3%)	17 (5.7%)
Benzodiazepines	1 (7.3%)	-	1 (0.3%)
Hypnotics (non-benzodiazepine)	4 (2.9%)	6 (4.5%)	10 (3.4%)
Trazodone	-	1 (0.8%)	1 (0.3%)

Source: Clinical Reviewer-created using adcm.xpt and adsl.xpt dataset
Abbreviations: SSRI = Selective serotonin reuptake inhibitor; SSNRI = selective serotonin norepinephrine reuptake inhibitor
[1]Agitation includes indications for AAD, pharmacological agitation, agitation prior to washout, agitation secondary to hospitalization, prevention of agitation, increased agitation, and worsening agitation

Clinical Reviewer's Comment: *Given that the basic trial design and inclusion and exclusion criteria were identical for studies 331-12-283 and 331-12-284, one would expect similar baseline demographic and disease characteristics. However, Study 331-12-284 included more subjects in a non-institutionalized care-setting (45% vs. 34%), shorter history of symptoms associated with dementia (55 months vs. 62 months), and more subjects with mild cognitive impairment (23% vs. 9%). These differences were not reflected in the baseline disease severity; both study populations exhibited similar CMAI total scores, CMAI subscale scores, CGI-S score, and NPI-NH 12-item scores at baseline.*

Similar to Study 331-12-283, the study population exhibited significant agitated behaviors that aligned with the IPA criteria. Overall, the efficacy population for Study 331-12-284 is well-balanced and suggests a low potential for confounding efficacy and safety results. Refer to the reviewer's previous comments on Study 331-12-283 in Section 588.1.1.2 regarding the generalizability of the study population to real-world clinical patients with AAD.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant measured treatment compliance by dividing the number of study medication tablets taken by the total number of scheduled tablets during the trial period. For lost to follow-

up subjects, the last study medication end date was equal to the treatment end date. In the both the brexpiprazole and placebo groups, the Applicant observed ≥80% study compliance in 98% and 99% of subjects, respectively. The Applicant only reported two subjects in the brexpiprazole group (1.5%) and one subject in the placebo group (0.7%) with treatment compliance < 70%.

Refer to Table 24 for a listing of concomitant psychotropic medication during the double-blind period. Given that the majority of subjects continue their treatments for AD and other comorbid disorders, the overall percentage of psychotropic use was > 80%. The percentage of subjects receiving treatment for worsening or breakthrough symptoms of agitation was greater in the brexpiprazole treatment arm vs. placebo (9.1% vs. 3.6%). The overall percentage of benzodiazepine use was 5.8% and 3.8% in the placebo and brexpiprazole treatment arms, respectively. Among the subjects who received brexpiprazole during the double-blind treatment period, approximately 1% of subjects whose dosage was titrated up to 2mg after the Week 4 visit (n=78) received additional treatment for agitation as compared to 20% of subjects who did not have a dose increase after Week 4 (n=54). During the follow-up period (post-study treatment), approximately 14% and 24% of subjects who received placebo and brexpiprazole during the double-blind period received treatments for agitation, respectively. Among the brexpiprazole group, 17% of subjects whose dosages were titrated up to brexpiprazole 2 mg/day after the Week 4 visit required treatment for agitation during the follow-up period as compared to 35% of subjects who did not have a dose increase.

Table 24: Psychotropic Medication Use During the Double-Blind Period in Study 331-12-284 (Efficacy Sample)

Indication/Drug, n (%)	Placebo (N=137)	BREX 0.5 to 2 mg (N=132)	Total (N=269)
Subjects receiving at least one psychotropic	122 (89.1%)	111 (84.1%)	233 (86.6%)
Agitation[1]	5 (3.6%)	12 (9.1%)	17 (6.3%)
Antipsychotics	1 (0.7%)	2 (1.5%)	3 (1.1%)
Benzodiazepines	5 (3.6%)	5 (3.8%)	10 (3.7%)
SSRI/SNRIs	-	4 (3.0%)	4 (1.5%)
Alzheimer's disease	117 (85.4%)	107 (81.1%)	224 (83.3%)
Anticholinesterase inhibitors	61 (44.5%)	52 (39.4%)	113 (42.0%)
Memantine	73 (53.3%)	67 (50.8%)	140 (52.0%)
Anxiety	4 (2.9%)	3 (2.2%)	7 (2.6%)
Benzodiazepines	2 (1.5%)	-	2 (0.7%)
SSRI/SNRIs	3 (2.2%)	2 (1.5%)	5 (1.9%)
Depression	10 (7.3%)	7 (5.3%)	17 (6.3%)
SSRI/SNRIs	10 (7.3%)	4 (3.0%)	14 (5.2%)
Insomnia/Sleep Disorders	10 (7.3%)	13 (9.8%)	23 (8.6%)
Hypnotics (non-benzodiazepine)	4 (2.9%)	8 (6.1%)	12 (4.5%)
Trazodone	-	1 (0.7%)	1 (0.4%)

Source: Clinical Reviewer-created using adcm.xpt and adsl.xpt dataset
Abbreviations: SSRI = Selective serotonin reuptake inhibitor; SSNRI = selective serotonin norepinephrine reuptake inhibitor
[1]Agitation includes indications for AAD, pharmacological agitation, agitation prior to washout, agitation secondary to hospitalization, prevention of agitation, increased agitation, and worsening agitation

***Clinical Reviewer's Comment**: Similar to Study 331-12-283, the use of concomitant psychotropic medications remained high due to continuation of prior treatments for AD and other comorbid disorders. Given that the study designs were similar, it is unclear why the percentage of subjects receiving concomitant treatments for agitation was lower in Study 331-12-284 relative to Study 331-12-283 (6% vs. 15%). However, for Study 331-12-284, the percentage of subjects receiving concomitant treatments for agitation was greater in the brexpiprazole versus placebo group (9.1% vs. 3.6%). Although this difference could be attributed to the lack of overall efficacy for this study as discussed in the subsequent section, the subgroup of subjects whose dosages were titrated to brexpiprazole 2 mg/day received fewer concomitant treatments for agitation. The inverse result in subjects whose dosages were titrated to brexpiprazole 2 mg/day vs. those who were maintained at 1 mg/day after suggests that the use of concomitant medications is confounded by whether subjects' dosages were titrated to a higher dose after the Week 4 visit. Therefore, the lower incidence of concomitant medication use with higher doses of brexpiprazole is promising and consistent with the result from Study 331-12-283.*

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 (LS mean difference = −2.34 [95% CI: −5.49, 0.82]; p = 0.1454; Table 25).

Table 25: Study 331-12-284 Primary Endpoint Results (MMRM; Efficacy Sample)

	Placebo (N=135)[2]	BREX 0.5 to 2 mg (N=131)[2]
Mean CMAI Total Score at Baseline (SD)	68.59 (16.01)	71.52 (16.84)
Mean CMAI Total Score at Week 12 (SD)	53.20 (14.98)	51.81 (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 = unadjusted 95% confidence interval (p-value also unadjusted).
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.
[2]One subject in the BREX group and two subjects in the placebo 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.

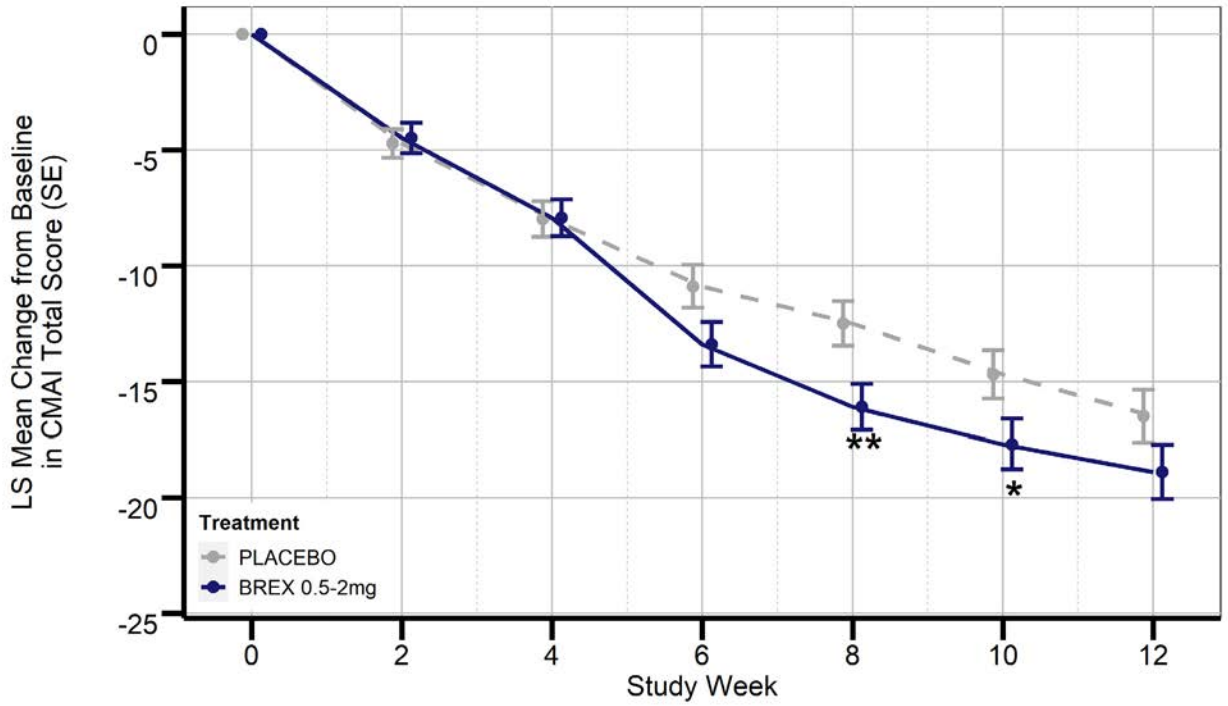
***Statistical Reviewer's Comment*: The statistical reviewer identified three subjects (SUBJIDs: (b) (6)) who only had post-baseline assessments at Week 1, which was not a scheduled assessment visit for efficacy. Thus, those three subjects were not included in the primary analysis, but were included in the efficacy sample. The statistical reviewer included those three patients in the primary efficacy analysis by mapping their post-baseline assessments to the closest visit (Week 2) in the model; the result is nearly identical with the primary analysis finding.**

Clinical Reviewer's Comment: *During a Type C Guidance Meeting (Sept 2017), the Division noted that the treatment effect observed in Study 331-12-284 was likely undercut by including subjects with limited or very mild agitation (based on NPI-NH agitation/aggression scores ≥ 4). However, this reviewer disagrees with this perspective because Study 331-12-283 enrolled subjects with sufficient agitation using identical eligibility criteria and demonstrated a positive treatment effect with the BREX 2 mg dose group. It is likely that the net treatment effect for the flexibly-dosed brexpiprazole was diluted by subjects who may not have experienced an effect while receiving brexpiprazole 1 mg/day.*

Time Course Plot

Figure 12 displays the mean improvement from baseline for each treatment group over 12 weeks. It appears that brexpiprazole group initially started separating from placebo at Week 6, and demonstrated a nominal statistical significance at Weeks 8 (LSMD = -3.55, p=0.009) and 10 (LSMD = -3.01, p=0.0436) without adjusting for multiplicity, but at the endpoint visit (Week 12), the separation diminished and the nominal statistical significance was lost (LSMD = -2.34, p=0.1454).

Figure 12: Study 331-12-284 LS Mean Change from Baseline to Week 12 in CMAI Total Score by Week (MMRM; Efficacy Sample)



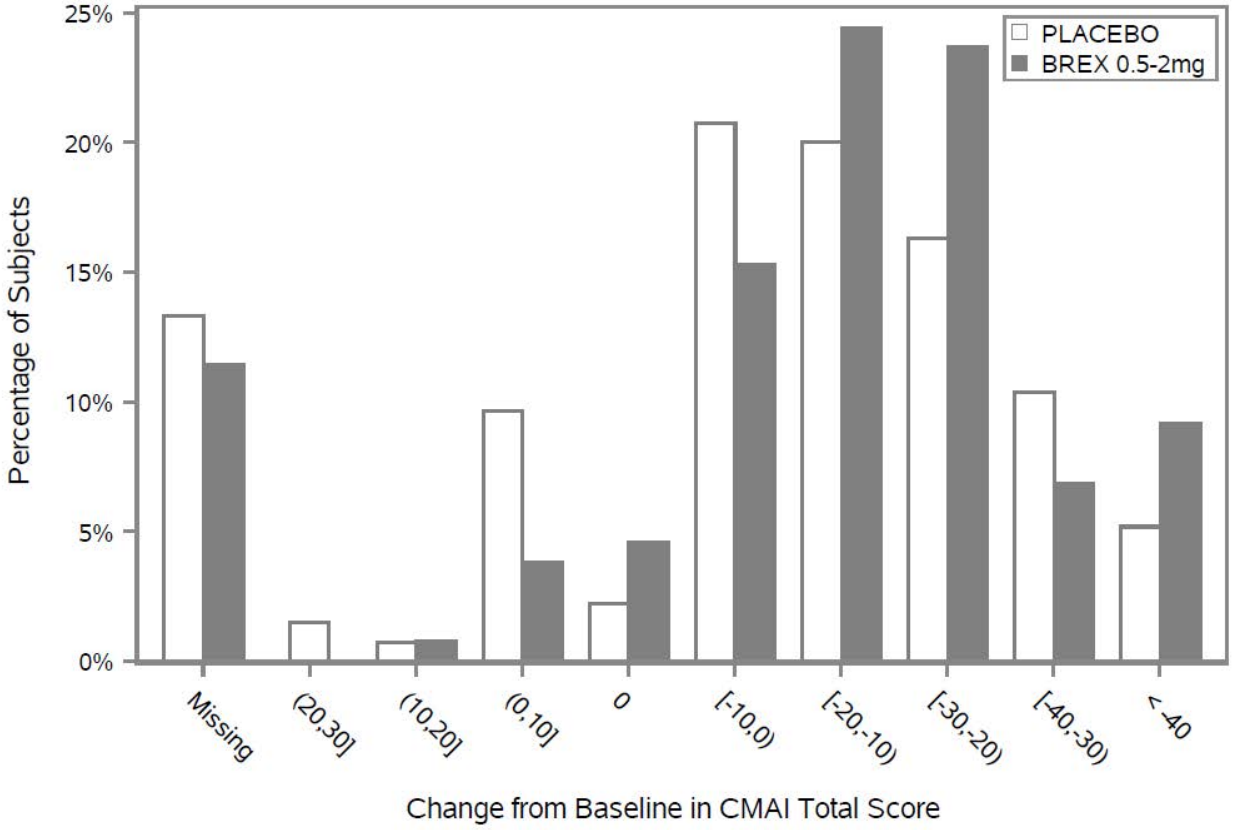
Subjects Observed

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

Figure 13 displays a histogram of the proportions of subjects who either improved or worsened on the primary efficacy measure relative to baseline. The bar on the far left represents the proportion of the subjects with missing data. Negative score represents improvement, and positive represents worsening. For subjects who had an improvement, the largest difference when comparing the brexpiprazole group with placebo was on the improvement interval of 20 to 30 on the CMAI total score.

Figure 13: Study 331-12-284 Change from Baseline to Week 12 in CMAI Total Score (Efficacy Sample)



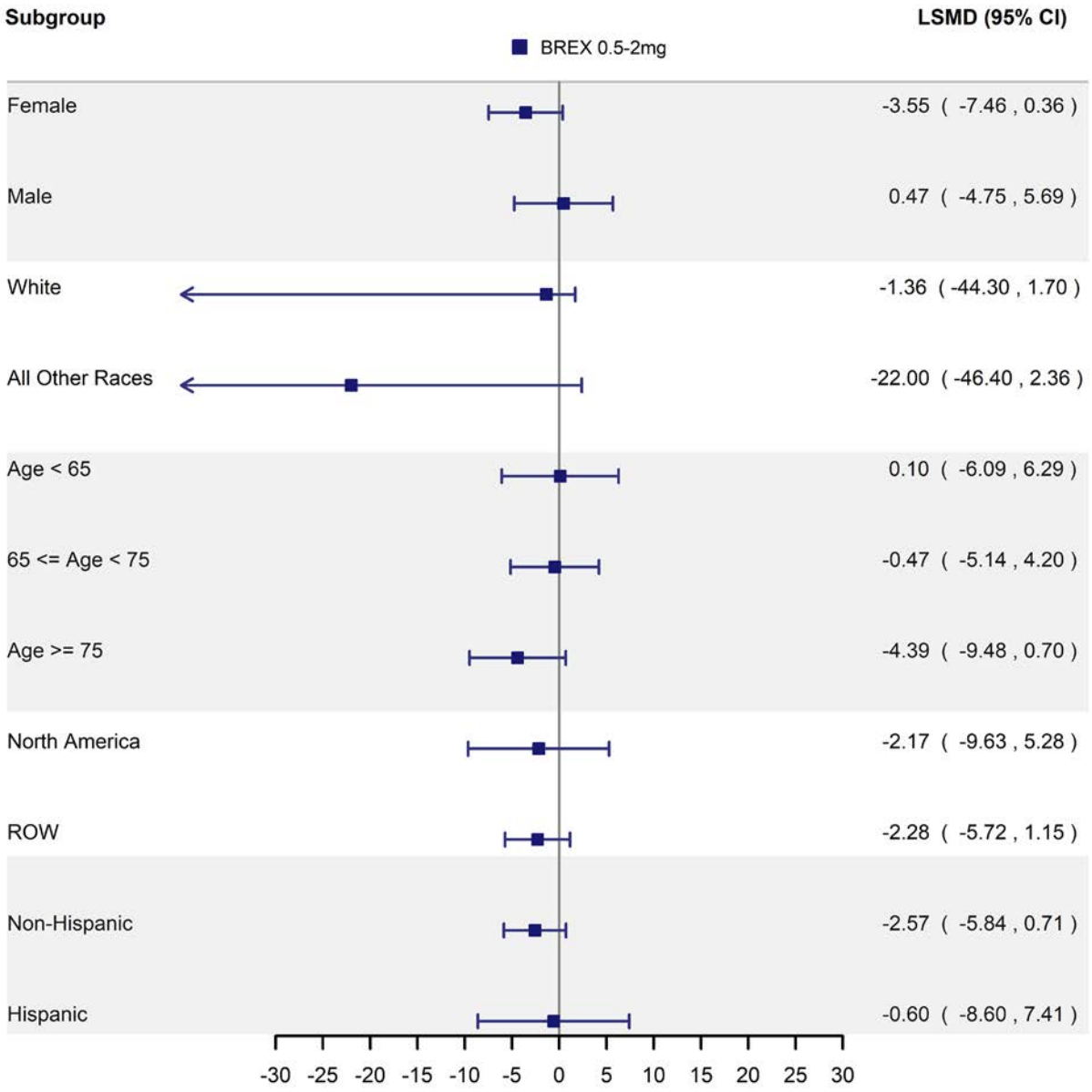
Source: Statistical Analyst-created using adcmai.xpt dataset

Subgroup Analysis

The Applicant conducted exploratory subgroup analyses for brexpiprazole compared to placebo for the change from baseline to Week 12 in the CMAI total score by sex, race, age, region, and ethnicity. The results are shown in Figure 14. The larger magnitudes of treatment effects are observed with brexpiprazole compared with placebo for females (LSMD: -3.55 [95%CI: -4.8, 5.69]) vs. males (LSMD: -3.55 [95%CI: -7.5, 0.36]) and subjects ≥ 75 years of age (LSMD: −4.39

[95%CI: -9.5, 7.0)) vs. 65 to 74 years of age (LSMD: -0.47 [95%CI: -5.1, 4.2]). Similar to the observed findings in Study 331-12-283, treatment differences between subgroups of race were not interpretable because the majority of subjects (95%) were white. The observed magnitude of treatment effects did not suggest regional differences. Regarding ethnicity, non-Hispanic subjects exhibited a higher (LSMD: -2.57 [95%CI: -5.84, 0.71) treatment effect compared to Hispanic or Latino subjects (LSMD: -0.6 [95%CI: -8.60, 7.41]). However, the subgroup for Hispanic or Latino subjects was too small to draw any conclusions regarding this difference.

Figure 14: Study 331-12-284 Subgroup Analysis for Change from Baseline to Week 12 in CMAI Total Score – Forest Plot (MMRM; Efficacy Sample)



Source: Clinical Reviewer created using Study 331-12-284 Clinical Study Report, CT-6.1.1 (females), CT-6.1.2 (males), CT-6.3.1 (< 65 years), CT-6.3.2 (≥ 65 and < 75 years), and CT-6.3.3 (≥ 75 years), CT-6.2.1 (whites), CT-6.2.2 (all other races), and CT-6.2.3 (whites and all other races at Week 12), CT-6.4.1 (North America) and CT-6.4.2 (other regions) confirmed by statistical reviewer. The subgroup analysis of ethnic status was conducted by statistical reviewer.
Note: In each subgroup stratum, MMRM was conducted with model Terms: treatment, visit, treatment by visit and baseline by visit interaction.

Efficacy Results – Key Secondary Endpoint

The primary efficacy 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 26). Although the p-value was nominally significant, the CGI-S results are considered solely descriptive because the primary endpoint finding was not statistically significant.

Table 26: Study 331-12-284 Key Secondary Endpoint Results (MMRM; Efficacy Sample)

	Placebo (N=135)[2]	BREX 0.5 to 2 mg (N=131)[2]
Mean CGI-S Score at Baseline (SD)	4.51 (0.74)	4.54 (0.77)
Mean CGI-S Score at Week 12 (SD)	3.44 (1.11)	3.17 (0.92)
LSM[1] Change from Baseline (SE)	-1.02 (0.09)	-1.32 (0.09)
Placebo-subtracted difference (95% CI)[1]		-0.31 (-0.55, -0.06)
P-value (nominal)		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; CI = confidence interval; LSM = least squares mean; MMRM = mixed-effect model repeated measures; SD = standard deviation, SE = standard error, 95% CI = unadjusted 95% confidence interval (nominal p-value also unadjusted).
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

[2]One subject in the BREX group and two subjects in the placebo 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.

Dose/Dose Response

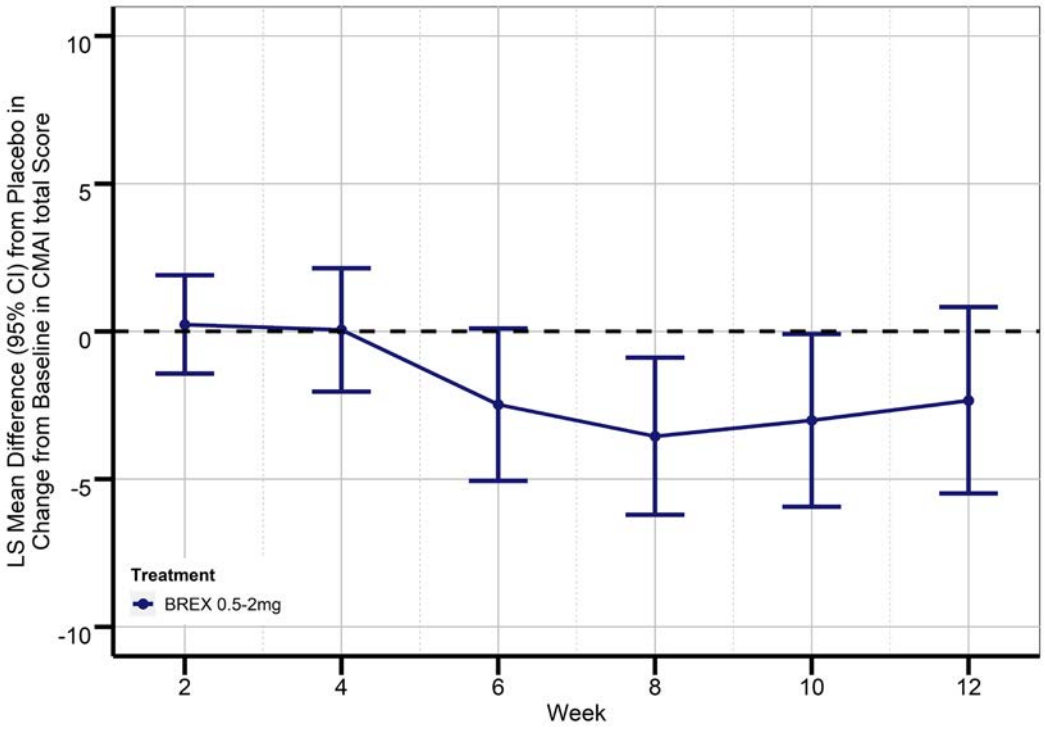
Given that this study did not include fixed-dose treatment arms, the dose-response relationship could not be fully characterized. Refer to the Additional Analyses subsection (analysis of titration status and modal dose) below for a comparison of response between subjects who were titrated up to 2 mg/day after Week 4 and subjects who remained at 1 mg/day. Also refer to Dr. Bhattaram's clinical pharmacology/pharmacometrics review of the integrated dose-response and exposure-response relationship across all fixed-dose treatment arms.

Durability of Response

Figure 15 displays the LSMD from placebo in the change from baseline in the total CMAI score at each visit for the brexpiprazole treatment group relative to placebo. Although the BREX treatment group did not separate from placebo at any time point at nominal significance level of 0.05, there was a numerical treatment effect over placebo starting at Week 6 that was maintained through Week 12. Given that the brexpiprazole appears to achieve a

pharmacodynamic steady state at approximately 8 to 10 weeks (PK steady state at approximately 3 weeks), the 12-week trial duration may be sufficient to characterize antipsychotic effect in future trials.

Figure 15: Study 331-12-284 Change in Net Treatment Effect over Time



Source: Clinical Reviewer-created using Applicant's 331-12-284 Clinical Study Report, Listing CT-5.2.1
Abbreviations: CI = confidence interval; CMAI = Cohen Mansfield Agitation Inventory; LS = least-squares

Persistence of Effect

Given that the Applicant did not collect efficacy measures either during the follow-up period for this study or during the post-treatment observational study (Study 331-13-211), the persistence of effect is not discernible. Of note, percentage of subjects who received treatment for agitation during the follow-up period in this study was higher in the brexpiprazole treatment groups versus placebo (approximately 24% vs. 14%, respectively).

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Table 27 provides the summary of the mean change from baseline in the CMAI total score and the net treatment effect for each agitation domain (Factor 1: aggressive behavior; Factor 2: physically non-aggressive behavior; Factor 3: verbally agitated behavior). Although each agitation domain suggested a nominally consistent favorable effect for the brexpiprazole group, the aggressive behavior domain exhibited the greatest magnitude of treatment effect (LSMD: -1.09 [95% CI: -2.24, 0.05]). This result is in contrast to Study 331-12-283 where both

brexpiprazole treatment groups exerted the largest effect instead on the verbally agitated domain (BREX 1mg: -0.28 and BREX 2mg: -1.26).

Table 27: Study 331-12-284 Change from Baseline to Week 12 in CMAI Factor Scores (MMRM; 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]		-1.09 (-2.24, 0.05)
P-value		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)[1]		-0.35 (-1.51, 0.81)
P-value		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)[1]		-0.69 (-1.59, 0.21)
P-value		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 = unadjusted confidence interval (nominal p-value also unadjusted); 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.
Note: MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

Clinical Reviewer's Comment: *Similar to Study 331-12-283, there was consistent numerical improvement on each of the CMAI subscales with brexpiprazole relative to placebo. Even though this study had a slightly higher percentage of subjects with significant verbal agitation relative to Study 331-12-283 (87% vs. 83%, respectively) and higher CMAI Factor 3 subscore at baseline (15.1 vs. 14.2, respectively), it is unclear why the results suggest a greater group mean difference with the CMAI Factor 1 subscale. Refer to Dr. Swett's COA review for further analyses at the item-level.*

Results from the responder analyses (based on LOCF) are presented in Table 28. The ratios of response (brexpiprazole/placebo) observed at Week 12 were greater than 1 for each responder analysis (percentage of subjects with ≥ 20%, ≥ 30%, ≥40% reduction in CMAI total score).

Table 28: Study 331-12-284 CMAI Responder Analyses at Week 12 (LOCF)

Responder Analysis at Week 12[1]	Placebo (N=137)	BREX 0.5 to 2 mg (N=132)
CMAI Response Rate (20%)		
Responders at Week 12, n(%)	72 (52.6%)	81 (61.4%)
Ratio of Response (95% CI)		1.16 (0.95, 1.41)
CMAI Response Rate (30%)		
Responders at Week 12, n(%)	48 (35.0%)	55 (41.7%)
Ratio of Response (95% CI)		1.19 (0.90, 1.58)
CMAI Response Rate (40%)		
Responders at Week 12, n(%)	20 (14.6%)	21 (15.9%)
Ratio of Response (95% CI)		1.03 (0.59, 1.79)

Source: Clinical Reviewer-adapted using Applicant's 331-12-284 Clinical Study Report, Listing CT-5.1
Abbreviations: CI = unadjusted confidence interval; CMAI = Cohen Mansfield Agitation Inventory
[1]Responder ratio estimated using the Cochran-Mantel-Haenszel (CMH) General Association Test

Table 29 displays the results based on additional secondary and exploratory caregiver and patient reported outcome measures. In general, the brexpiprazole group displayed a numerical improvement relative to placebo across all measures. Analysis of the CGI-I (based on observed cases) indicated a treatment difference of -0.43 points for the brexpiprazole group. Based on the LOCF method, a greater proportion of subjects in the brexpiprazole group reported a much improvement (CGI-I = 2) or very much (CGI-I = 1) improvement in agitation in response to treatment at Week 12 (brexpiprazole: 59.8% vs. placebo: 39.4%). The proportions of subjects in the brexpiprazole group who demonstrated a response to treatment based on CGI-E index of 2, 3, or 4 at Week 12 (LOCF method) was 68.9% compared to 59.1% in the placebo group. Similar to Study 331-12-283, changes in patient and caregiver quality of life were not appreciably different between the two treatment groups.

Table 29: Study 331-12-284 Change from Baseline to Week 12 in Secondary and Exploratory Efficacy Measures (MMRM)

Variable[1]	Placebo	BREX 0.5 to 2mg
NPI-NH 12-item Total Score	N= 131	N=135
Baseline Mean (SD)	34.70 (14.82)	37.18 (14.10)
LSM Change from Baseline (SE)	-13.10 (1.14)	-15.30 (1.17)
Placebo-subtracted difference (95% CI		-2.20 (-5.37, 0.98)
NPI-NH Agitation/Aggression Score	N=131	N=135
Baseline Mean (SD)	7.43 (1.82)	7.53 (1.89)
LSM Change from Baseline (SE)	-3.19 (0.23)	-4.07 (0.23)
Placebo-subtracted difference (95% CI)		-0.87 (-1.50, -0.24)
NPI-NH Occupational Disruptiveness Score[1]	N=74	N=72
Baseline Mean (SD)	13.76 (6.35)	13.97 (5.20)
LSM Change from Baseline (SE)	-4.97 (0.53)	-5.74 (0.55)
Placebo-subtracted difference (95% CI)		-0.77 (-2.19, 0.65)
M-CNAS Attitude score[1]	N=68	N=72
Baseline Mean (SD)	61.00 (12.08)	59.99 (11.04)

Variable[1]	Placebo	BREX 0.5 to 2mg
LSM Change from Baseline (SE)	-6.05 (1.21)	-8.25 (1.25)
Placebo-subtracted difference (95% CI)		-2.20 (-5.42, 1.01)
M-CNAS Strain score[1]	N=68	N=72
Baseline Mean (SD)	75.71 (7.94)	75.14 (6.37)
LSM Change from Baseline (SE)	2.53 (0.77)	1.97 (0.81)
Placebo-subtracted difference (95% CI)		-0.56 (-2.56, 1.44)
QoL-AD Patient Score[1]	N=116	N=116
Baseline Mean (SD)	30.36 (7.23)	29.35 (6.48)
LSM Change from Baseline (SE)	1.18 (0.40)	1.64 (0.38)
Placebo-subtracted difference (95% CI)		0.45 (-0.53, 1.44)
QoL-AD Caregiver Score[1]	N=124	N=122
Baseline Mean (SD)	26.65 (5.92)	25.97 (5.21)
LSM Change from Baseline (SE)	1.52 (0.38)	2.21 (0.38)
Placebo-subtracted difference (95% CI)		0.69 (-0.29, 1.67)

Source: Clinical Reviewer-adapted using Applicant's Clinical Study Report 331-12-284, CT 5.5.1 to 5.14.2
Abbreviations: CI = unadjusted confidence interval (nominal p-value also unadjusted); 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; QoL-AD = Quality of Life in Alzheimer's disease; SD = standard deviation; SE = standard error
[1]Assessment only collected in institutionalized subjects
Note: MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction

Clinical Reviewer's Comment: *The Applicant indicated that the quality of life and caregiver burden measures were only included for Studies 331-12-283 and 331-12-284 for exploratory purposes. Because it is unclear whether these scales are capable of detecting change in this patient population, the results may not add additional clinically meaningful context to the primary efficacy results.*

Additional Analyses Conducted on the Individual Trial Study 331-12-284

Although Study 331-12-284 failed to meet its primary endpoint, the Applicant conducted several post-hoc analyses to further explore the efficacy response to brexpiprazole 2 mg/day and to compare subgroups of agitated behaviors to provide supportive evidence of effectiveness.

Exploratory Subgroup Analyses by Titration Status and Modal Dose

At the Week 4 visit, investigators evaluated subjects based on response and tolerability to the blinded study treatment. If the investigator determined the subject experienced an inadequate response (i.e., lack of efficacy) and tolerated treatment, the dosage of the study medication could be increased to 2 mg/day. The Applicant further allowed for optional dose decreases and increases (max dose of 2 mg/day) at any time after the Week 4 study visit through the remainder of the study period. Due to the Applicant's use of a flexible-dosing treatment paradigm, the effects of brexpiprazole 1 mg/day and 2mg/day could not be directly compared relative to placebo; therefore, dosage-based analyses were performed based on:

- Titration status (i.e., whether or not the investigator increased the dosage to 2 mg/day immediately after the Week 4 visit),
- Modal dose (i.e., the most frequently received dosage during the treatment period).

At the Week 4 visit 77 subjects (59%) in the brexpiprazole group and 74 subjects (55%) in the placebo group required an increase in dose 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 dose increase after the Week 4 visit) vs. those who exhibited an adequate response to the study medication (Table 30 and Table 31). For the primary efficacy endpoint (change in CMAI total score from baseline to Week 12) a greater statistically significant improvement was observed with brexpiprazole over placebo in the titrated subgroup (LSMD = -5.06 [95% CI: -8.99, -1.13]; p = 0.0121). For subjects who did not require a dose increase at Week 4, there was no improvement observed with brexpiprazole over placebo (LSMD = 1.57 [95% CI: -3.64, 6.78]; p = 0.5506). For the key secondary endpoint (change in CGI-S score as related to Agitation from baseline to Week 12), the results suggested a nominal improvement with brexpiprazole over placebo in the titrated subgroup (LS mean difference = -0.60 [95% CI: -0.93, -0.27], p = 0.0004). However, brexpiprazole did not show improvement over placebo in the subgroup that did not require an increase in dose at Visit 4 (LSMD = 0.06, [95% CI: -0.32, 0.43]; p = 0.7693).

Table 30: Study 331-12-284 Primary Endpoint Post-hoc Results by Titration Status (MMRM; Efficacy Sample)

	Placebo	BREX 0.5 to 2 mg
Dose increase at Week 4	N=74	N=77
Mean CMAI Total Score at Baseline (SD)	68.32 (16.16)	69.19 (15.42)
Mean CMAI Total Score at Week 4 (SD)	63.51 (15.95)	63.29 (14.97)
LSM Change at Week 12 from Baseline (SE)	−12.8 (1.42)	−17.8 (1.42)
Placebo-subtracted difference (95% CI)[1]		−5.06 (−8.99, −1.13)
P-value		0.0121
No dose increase at Week 4	N=60	N=50
Mean CMAI Total Score at Baseline (SD)	69.03 (16.07)	74.76 (18.12)
Mean CMAI Total Score at Week 4 (SD)	58.62 (14.00)	64.16 (14.56)
LSM Change at Week 12 from Baseline (SE)	−20.8 (1.78)	−19.3 (1.96)
Placebo-subtracted difference (95% CI)[1]		1.57 (−3.64, 6.78)
P-value		0.5506

Source: Applicant's Study 331-12-284 Clinical Study Report, Tables 11.4.1.5.1.1-1, p. 113, confirmed by statistical reviewer.
Abbreviations: CI = unadjusted confidence interval (nominal p-value also unadjusted); CMAI = Cohen Mansfield Agitation Inventory; LSM = least squares mean; MMRM = mixed-effect model for repeated measures; SD = standard deviation, SE = standard error.
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

Table 31: Study 331-12-284 Key Secondary Endpoint Post-hoc Results by Titration Status (MMRM; Efficacy Sample)

	Placebo	BREX 0.5 to 2 mg
Dose increase at Week 4	N=74	N=77
Mean CGI-S Score at Baseline (SD)	4.55 (0.71)	4.57 (0.73)
Mean CGI-S Score at Week 4 (SD)	4.38 (0.79)	4.16 (0.78)
LSM Change at Week 12 from Baseline (SE)	−0.74 (0.12)	−1.34 (0.12)
Placebo-subtracted difference (95% CI)[1]		−0.60 (−0.93, −0.27)
P-value		0.0004
No dose increase at Week 4	N=60	N=50
Mean CGI-S Score at Baseline (SD)	4.43 (0.77)	4.46 (0.81)
Mean CGI-S Score at Week 4 (SD)	3.88 (0.78)	3.90 (0.93)
LSM Change at Week 12 from Baseline (SE)	−0.33 (0.13)	−1.28 (0.14)
Placebo-subtracted difference (95% CI)[1]		0.06 (−0.32, 0.43)
P-value		0.7693

Source: Applicant's Study 331-12-284 Clinical Study Report, Tables 11.4.1.5.1.1-2, p. 113, confirmed by statistical reviewer.
Abbreviations: CI = unadjusted confidence interval (nominal p-value also unadjusted); CMAI = Cohen Mansfield Agitation Inventory; LSM = least squares mean; MMRM = mixed-effect model for repeated measures; SD = standard deviation, SE = standard error.
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

Subjects who had a modal dose of ≥ 2 mg showed a greater numerical improvement in the changes from baseline at Week 12 for CMAI total score (LSMD = -5.25 [95%CI: -9.23, -1.27]; p = 0.0101) and CGI-S score, as related to agitation (LSMD = -0.55 [95%CI: -0.89, -0.21]; p = 0.0017), compared with placebo. For subjects who had ≤ 1 mg modal dose, no improvement was shown over placebo for either endpoint. The results were shown in Table 32 and Table 33.

Table 32: Study 331-12-284 Primary Endpoint Post-hoc Results by Modal Dose (MMRM; Efficacy Sample)

	Placebo	BREX 0.5 to 2 mg
≥ 2 mg dose	N=83	N=71
Mean CMAI Total Score at Baseline (SD)	68.89 (15.93)	69.82 (16.85)
LSM Change at Week 12 from Baseline (SE)	−12.7 (1.39)	−17.9 (1.51)
Placebo-subtracted difference (95% CI)[1]		−5.25 (−9.23, −1.27)
P-value		0.0101
≤ 1 mg dose	N=53	N=60
Mean CMAI Total Score at Baseline (SD)	68.10 (16.29)	73.53 (16.73)
LSM Change at Week 12 from Baseline (SE)	−22.1 (1.66)	−19.9 (1.57)
Placebo-subtracted difference (95% CI)[1]		2.26 (−2.19, 6.71)
P-value		0.3146

Source: Applicant's Study 331-12-284 Clinical Study Report, Tables 11.4.1.5.1.2-1, p. 115, confirmed by statistical reviewer.
Abbreviations: CI = unadjusted confidence interval (nominal p-value also unadjusted); CMAI = Cohen Mansfield Agitation Inventory; LSM = least squares mean; MMRM = mixed-effect model for repeated measures; SD = standard deviation, SE = standard error.
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

Table 33: Study 331-12-284 Key Secondary Endpoint Post-hoc Results by Modal Dose (MMRM; Efficacy Sample)

	Placebo	BREX 0.5 to 2 mg
≥ 2 mg dose	N=83	N=71
Mean CGI-S Score at Baseline (SD)	4.55 (0.69)	4.59 (0.77)
LSM Change at Week 12 from Baseline (SE)	−0.75 (0.12)	−1.30 (0.13)
Placebo-subtracted difference (95% CI)[1]		−0.55 (−0.89, −0.21)
P-value		0.0017
≤ 1 mg dose	N=52	N=60
Mean CGI-S Score at Baseline (SD)	4.44 (0.83)	4.48 (0.77)
LSM Change at Week 12 from Baseline (SE)	-1.35 (0.013)	−1.31 (0.12)
Placebo-subtracted difference (95% CI)[1]		0.04 (−0.29, 0.37)
P-value		0.7693

Source: Applicant's Study 331-12-284 Clinical Study Report, Tables 11.4.1.5.1.2-1, p. 115, confirmed by statistical reviewer.
Abbreviations: CI = unadjusted confidence interval (nominal p-value also unadjusted); CMAI = Cohen Mansfield Agitation Inventory; LSM = least squares mean; MMRM = mixed-effect model for repeated measures; SD = standard deviation; SE = standard error.
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

Clinical Reviewer's Comment: *After the Week 4 visit, the Applicant reported that approximately 60% of subjects in the brexpiprazole group experienced a dose increase from 1 mg/day to 2 mg/day due to a lack of a sufficient response. This result is consistent with the findings from Study 331-12-283 that suggested a greater effect with BREX 2 mg vs. BREX 1 mg. In fact, the treatment effect observed with subjects who received 2 mg/day after Week 4 in Study 331-12-284 was relatively larger than the BREX 2 mg group in Study 331-12-283 (-5.06 vs. -3.77, respectively). The larger treatment effect was also consistent by modal dose and with the secondary endpoint (change in CGI-S). The Applicant's post-hoc subgroup analysis provides supportive evidence of brexpiprazole's effect on agitation among subjects whose dosage was titrated to 2 mg/day (titration starting after Week 4 and modal dose). When examining the results from Study 331-12-283 and Study 331-12-284 together, this reviewer agrees with the Applicant that the minimum effective dose for the treatment of AAD appears to be 2 mg/day. To further characterize brexpiprazole's dose-response relationship, the Agency suggested that the Applicant evaluate the safety and efficacy of brexpiprazole 3 mg/day for the treatment of AAD.*

Statistical Reviewer's Comment: *These subgroups were defined based on efficacy outcomes, so likely represent different patient populations. In addition, in an outcome-dependent subgroup, randomization which is required for a valid statistical analysis may be lost. Thus, the subgroup analysis results should, in general, be interpreted with caution, although in this study there was not much difference in the demographic and disease characteristics for patients whose dosage was titrated vs. those whose dosage remained the same.*

Exploratory Post-hoc Significant Agitation Subgroup Analyses

As mentioned for Study 331-12-283, the Agency indicated that the NPI-NH Agitation and Aggression threshold score of ≥ 4 likely led to enrollment of some patients with insufficient

behaviors at baseline and unlikely to show a measurable change over 12 weeks. Therefore, to test this hypothesis, the Applicant identified subgroups with significant agitated behavior based on frequency of symptoms reported at baseline (described in Section 8.1.1.2) and conducted similar post-hoc analyses to assess treatment response versus placebo in subgroups of subjects with significant agitated behaviors using the same statistical models as described for the pre-specified primary efficacy analyses (Table 34).

In the subgroup of subjects with agitation with significant aggressive behavior (84% of all subjects in the efficacy sample), brexpiprazole exhibited the greatest treatment effect over placebo for both primary and key secondary endpoints. For the primary endpoint, the LS mean difference for brexpiprazole over placebo in the aggressive behavior subgroup (LSMD: -4.04 [95% CI: -7.58, -0.50]) was larger than the observed treatment effect based on the full efficacy sample (LSMD: -2.34 [95% CI: -5.49, 0.82]). For the key secondary endpoint, the improvement of brexpiprazole over placebo in the aggressive behavior subgroup (LSMD: -0.43 [95% CI: -0.69, -0.22]) was also greater than the effect observed with the full efficacy sample (LSMD: -0.31 [95% CI: -0.55, -0.06]).

Table 34: Study 331-12-284 Primary Endpoint Post-hoc Analysis of Change in Total CMAI Scores Across Agitation Behavior Subgroups (MMRM; Efficacy Sample)

Agitation Behavior Subgroup	Placebo	BREX 0.5 to 2 mg
Significant Aggressive Behaviors	(N=114)	(N=112)
Mean CMAI Total Score at Baseline (SD)	70.83 (15.62)	74.03 (16.43)
LSM Change from Baseline (SE)	-18.6 (1.28)	-22.6 (1.32)
Placebo-subtracted difference (95% CI)[1]		-4.04 (-7.58, -0.50)
Significant Physically Non-Aggressive Behaviors	(N=115)	(N=118)
Mean CMAI Total Score at Baseline (SD)	70.86 (15.82)	73.14 (16.50)
LSM Change from Baseline (SE)	-17.8 (1.28)	-19.6 (1.28)
Placebo-subtracted difference (95% CI)[1]		-1.84 (-5.35, 1.66)
Significant Verbally Agitated Behaviors	(N=116)	(N=118)
Mean CMAI Total Score at Baseline (SD)	73.31 (17.76)	73.79 (15.70)
LSM Change from Baseline (SE)	-18.6 (1.42)	-20.0 (1.25)
Placebo-subtracted difference (95% CI)[1]		-1.46 (-4.89, 1.97)

Source: Study 331-12-284 Clinical Study Report, Table 11.4.1.5.2-1 through 11.4.1.5.3.2-3, confirmed by statistical reviewer.
Abbreviations: CI = unadjusted confidence interval (nominal p-value also unadjusted); CMAI = Cohen Mansfield Agitation Inventory; LSM = least squares mean, MMRM = mixed-effect model repeated measures; SD=standard deviation; SE=standard error
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

Clinical Reviewer's Comment: *The Applicant also claims that brexpiprazole's treatment effect was more robust among subjects with significant aggressive behavior at baseline. It is important to note that 80% of the population of subjects meeting criteria for significant aggressive behavior also met criteria for significant physically non-aggressive behavior and verbally agitated behavior. Given the limited number of patients without significant symptoms at baseline, it is unclear whether patients with lower frequencies of agitated symptoms (i.e., lower baseline severity) would experience a similar effect.*

8.1.3 Trial 331-14-213

8.1.3.1 Study Design of Trial 331-14-213

Trial Design

This study was a 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. This trial consisted of three periods identical to Studies 331-12-283 and 331-12-284 (a schematic representation of the study design is presented in Figure 16):

- **Screening Period**: The total duration of the screening period was between 2 to 42 days. Investigators determined subject eligibility and required subjects to washout prohibited concomitant pharmacotherapy prior to randomization. Starting at screening and continuing for the rest of the study period, a caregiver or facility staff logged the subject's behavior in a diary along with a collection of progress notes in order to corroborate information recorded on the CMAI. Because the diary data was a tool to assist CMAI rater training, and diary use for 7 days a week may not have been possible due to the minimum amount of caregiver observation time (4 days/week), the Applicant did not analyze that data for efficacy purposes.

- **Double-blind Treatment Period:** 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 dose. The Applicant increased the brexpiprazole dose 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). Refer to Table 35 for a visual representation of the forced titration to target dose scheme. The Applicant withdrew any subjects unable to tolerate their assigned dose and prohibited dosage reduction at any time during the study. Investigators evaluated the subject at baseline, and at Weeks 2, 4, 6, 8, 10, and 12. All trial visits occurred at either the investigator's site or residential facility.

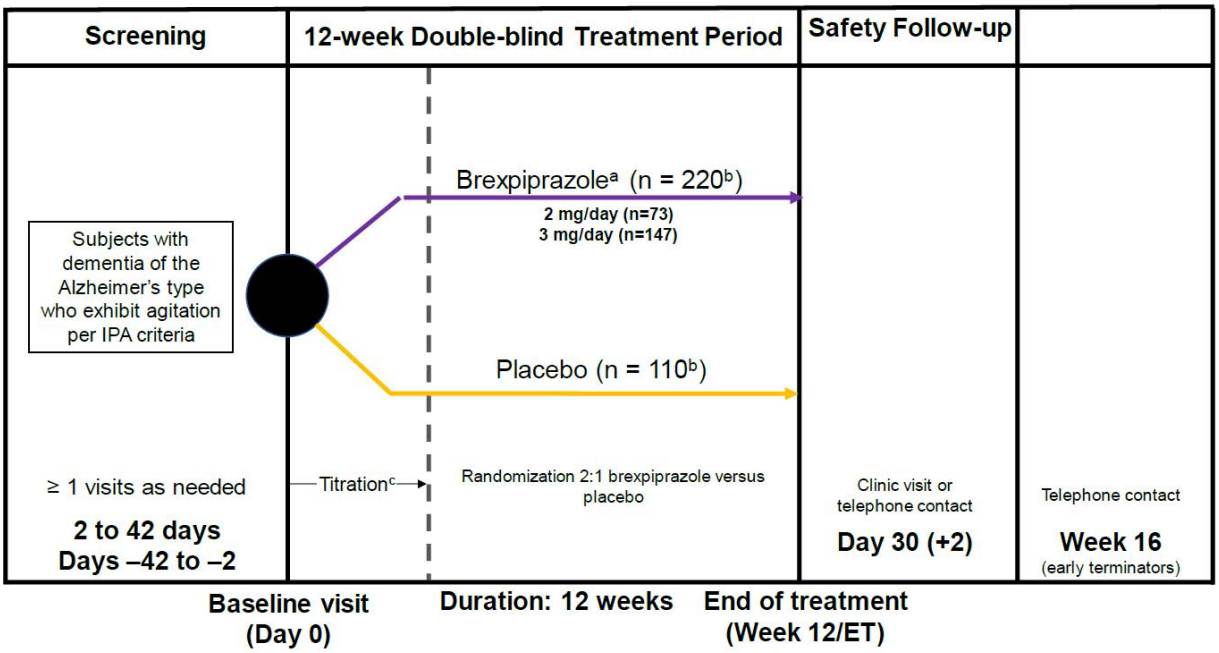
- **Safety Follow-up Period:** Investigators followed each subject, with the exception of those entering the optional active-treatment extension trial (31-201-00182) for safety evaluation 30 days after receiving the last dose of the study medication. For all subjects who terminated early from the study for any reason, investigators contacted the caregiver by telephone at Week 16 to collect follow-up information on mortality status.

Table 35: Dosing Scheme for Study 331-14-213

Treatment Group	Recommended Daily Dose Administered			
	Day after the Baseline visit (Day 1)	Day 8 to 14	Day after the Week 2 visit (Days 15 to 28 [±2 days])	Day after the Week 4 visit (Day 29 through Week 12 [±2 days])
BREX 2 mg	0.5 mg/day	1 mg/day	2 mg/day	2 mg/day
BREX 3 mg	0.5 mg/day	1 mg/day	2 mg/day	3 mg/day
Placebo	<----------			---------->

Source: Applicant's 331-14-213 Study Protocol, Table 3.2-1

Figure 16: Study Design Overview for Study 331-14-213



Source: Applicant's 331-14-213 Clinical Study Report, Figure 9.1-1, p. 33
Abbreviations: ET = early termination

Similar to Studies 331-12-283 and 331-12-284, investigators 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).

Study Eligibility Criteria

The target population consisted of elderly subjects aged 55 to 90 years living in either an institutionalized or non-institutionalized setting where the subject is not living alone. The Applicant's comprehensive inclusion and exclusion criteria consisted of appropriate diagnostic and tolerability criteria, a list of prohibited and accepted concomitant medications, and acceptance thresholds for clinically significant abnormal laboratory values and medical history.

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. Pertinent inclusion and exclusion criteria that could impact the evaluation of efficacy and safety are presented below:

Key Inclusion Criteria:

- Diagnosis of probable AD according to the NINCDS-ADRA criteria (McKhann G, et al., 1984)
- Diagnosis of agitation that meets the IPA provisional definition of agitation
- MMSE score between 5 to 22, inclusive, at screening and baseline
- Previous MRI or CT scan of brain (performed after the onset of symptoms of dementia) with findings consistent with a diagnosis of AD
- Residing in current location for at least 28 days before screening and expected to remain at the same location for the duration of the trial
- Total score (frequency x severity) of ≥4 on the agitation/aggression item of the NPI-NH (for institutionalized subjects) or the NPI/NPI-NH (for non-institutionalized subjects) at screening and baseline
- *Incorporated in Blinded addendum:* Met 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 (aggressive behaviors include: hitting, kicking, scratching, pushing, hurting self or others, throwing things, cursing or verbal aggression, spitting, tearing things or destroying property, screaming, and biting)
- Onset of symptoms of agitation at least 2 weeks prior to screening
- Required pharmacotherapy for agitation, per the investigator's judgement, after an evaluation of reversible factors (e.g., pain, infection, polypharmacy) and a trial of non-pharmacological interventions

Key Exclusion Criteria:

- Diagnosis of dementia or other memory impairment not due to AD (e.g., mixed, or vascular dementia, DLB, Parkinson's disease dementia, FTD, etc.)
- History of stroke, well-document TIA, or pulmonary or cerebral embolism
- Insufficient response, based on investigator's judgment, to two or more previous antipsychotic medications for the treatment of AAD
- Received high-dose antipsychotics exceeding the equivalent of ≥ 3 mg of risperidone (e.g., ≥ 5 mg of haloperidol, ≥ 375 mg quetiapine, ≥ 10 mg olanzapine, or local equivalent) within 90 days prior to screening
- Received multiple antipsychotics simultaneously for a period of > 7 days within 90 days prior to screening
- Prescence or history of delirium within 30 days prior to screening
- Diagnosis with an Axis I disorder (e.g., schizophrenia, bipolar I or II disorder, etc.) based on the Diagnostic and Statistical Manual for Mental Disorders, 5th Edition Text Revision (DSM-5)
- Evidence of serious risk of suicide defined as a score of 3 or 4 to any one question 2 through 6 or 11 or a score of 2 or higher on any one of questions 1a, 7, through 10, or 12 on the Sheehan-STS, or based on the opinion of the investigator
- Clinically significant and uncontrolled medical conditions including uncontrolled atrial fibrillation, heart failure, or ischemic heart disease (surrogates for uncontrolled cardiovascular disease included hospitalizations or procedures, such as percutaneous coronary intervention or coronary bypass surgery, within the last 6 months)
- Uncontrolled hypertension (DBP > 95 mmHg), symptomatic hypotension, or orthostatic hypotension (decrease of ≥ 30 mmHg in SBP or decrease of ≥ 20 mmHg in DBP within 3 minutes of standing)
- Diagnosis of epilepsy or history of seizures (expect of single childhood febrile seizures, post-traumatic seizure, or alcohol withdrawal seizure)
- Newly diagnosed diabetes or unstable diabetes (screening HBA_{1C} ≥ 8%, screening glucose > 125 mg/dl [fasting] or ≥ 200 mg/dl [non-fasting], hospitalization within the 3 months prior to screening due to diabetes or complications related to diabetes)
- Boddy mass index < 18.5 mg/kg^2 at screening and baseline
- Diagnosis of substance abuse or dependence within the past 180 days based on DSM-5 criteria (including alcohol, benzodiazepines and excluding caffeine and nicotine)
- Positive urine drug screen for cocaine, marijuana, or other illicit drugs
- Abnormal laboratory tests (i.e., platelets ≤ 75,000/mm^3, hemoglobin ≤ 9g/dL, absolute neutrophils ≤ 1,000/mm^3, AST > 2 x ULN, ALT > 2 x ULN, HBA_{1C} ≥ 8%), vital signs, or ECG

findings (QTcF ≥ 450 msec in men and ≥ 470 msec in women)

- Sexually active females of childbearing potential and male subject who are not practicing two different methods of birth control with their partner during the trial and for 30 days after the last dose of the study medication
- Received immunotherapy for the treatment of AD (through clinical trial or compassionate use program in the 6 months preceding randomization

Clinical Reviewer's Comment: *One of the biggest differences between the two prior studies (331-12-283 and 331-12-284) and Study 331-14-213 was the use of the IPA provisional consensus definition for agitation as a diagnostic inclusion criterion. As previously discussed in Section 8.1.1.1, the enrolled population for Studies 331-12-283 and 331-12-284 closely resembled subjects who would have met the IPA definition for agitation. Therefore, the results from this study could still allow for comparisons with Studies 331-12-283 and 331-12-284.*

Based on post-hoc analyses from the two previous studies, the Applicant acknowledged that the effect of brexpiprazole was more robust in a subgroup of subjects who exhibited significant aggressive behaviors at baseline. The Applicant included the criteria for meeting CMAI Factor 1 agitation as part of a blinded protocol addendum. The purpose of the blinded addendum was to blind site investigators to the enrichment strategy criteria and prevent raters from inflating baseline symptom frequency and severity to assist with study enrollment. During a Type C Guidance Meeting (September 2018), the Division cautioned the Applicant that limiting enrollment to only subjects exhibiting one or more CMAI Factor 1 agitation behaviors may narrow the product's final indication due to the lack of understanding whether a treatment effect observed in an enriched aggressive population could extrapolate to individuals with non-aggressive AAD. Therefore, the Agency suggested that subjects do not need to exhibit aggressive behavior at baseline to be suitable for enrollment.

Similarly, at the time, the Applicant's use of the NINCDS-ADRDA criteria to identify subjects with probable AD was reasonable. See the previous clinical reviewer comment in Section 8.1.1.1 regarding the Agency's current recommendations for assessing eligibility and characterizing subjects with probably AD.

Procedures and Schedule of Events

Refer to Table 36 below for the Applicant's schedule of procedures and study assessments.

Table 36: 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								
Medical and psychiatric history	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	
TSH, PT, aPTT, and INR	X								
Prolactin, HbA1c, and 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									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

Subject Completion, Discontinuation, or Withdrawal

The Applicant defined subjects who completed the Week 12 visit as trial completers. Investigators permitted subjects to withdraw from the study at any time for any reason without compromising their medical care. Subject-specific stopping criteria also included: occurrence of any AE, illness, or abnormal laboratory assessment that warrants permanent withdrawal, treatment with prohibited concomitant medications, pregnancy, non-compliance, lack of tolerability with study medication, development of clinically significant agitation that cannot be adequately treated with permitted medications, or transfer from an institutionalized setting to a non-institutionalized setting (or vice versa).

Investigators also contacted the medical monitor if the Sheehan-STS score was 3 or 4 on any one question 3 through 6 or 11 or if the Sheehan-STS score was 2 or higher on any one questions 1a, 7 through 10, 12, or 18. Investigators required subjects who withdrew prior to Week 12 to complete the Week 12/ET evaluation at the time of withdrawal and a follow-up safety evaluation 30 days after the last dose of the study medication. For all subjects who terminate early, investigators made every attempt to collect mortality data at Week 16.

Study Product Information and Compliance

The Applicant supplied the study medication as active brexpiprazole film-coated tablets and matching placebo film-coated tablets and provided weekly blister cards containing sufficient tablets for 7 (+ 2) days. Responsible trial personnel dispensed the study medication and documented accountability and compliance verification in the subject's trial records. Depending on the setting, the caretaker or caregiver was responsible for treatment administration.

Dose Selection

The Agency recommended that the Applicant explore the efficacy, safety, and tolerability of a higher dose of brexpiprazole (3 mg/day) for the treatment of AAD, given that the results of Studies 331-12-283 and 331-12-284 suggested that BREX 2 mg was the minimum effective dose. The Applicant included the BREX 2 mg arm to confirm the efficacy findings demonstrated in prior studies. Because this study would be the only source of data for the 3-mg dose in elderly patients with dementia, the Agency also recommend that the Applicant randomize at least 100 subjects to receive BREX 3 mg to adequately evaluate the safety of the higher dose. Therefore, the Applicant selected the treatment allocation of 1:2 (BREX 2 mg: BREX 3 mg) to ensure that at least 100 subjects received BREX 3 mg.

Clinical Reviewer's Comment: *Based on the Applicant's past experience of slow study enrollment into the two completed phase 3 studies (331-12-283 and 331-12-284), the Applicant argued that the completion of a fully powered three-arm study to obtain information on a higher dose of brexpiprazole would significantly increase the trial duration and delay the submission of a potential application. Therefore, the Agency agreed to combine the BREX 2 mg and 3-mg arms for the primary efficacy analysis.*

Prior and Concomitant Therapy

The Applicant's proposed list of prohibited medications was similar to Studies 331-12-283 and 331-12-284. Refer to Table 4 for a summarized list of prohibited medications and the corresponding protocol-specified washout periods. In addition to the prohibited medication list, the Applicant did not allow high-dose antipsychotics exceeding the equivalent of risperidone 3 mg (e.g., ≥ 5 mg haloperidol, ≥ 375 mg quetiapine, ≥ 10 mg olanzapine, or local equivalent) within 90 days prior to screening. Subjects must have discontinued all psychotropics not listed in Table 4 at least 24 hours prior to the first dose of the study medication. The Applicant also prohibited all CYP2D6 inhibitors and CYP3A4 inhibitors and inducers. The Applicant allowed oral benzodiazepine therapy for the first 4 weeks of the double-blind treatment period, but limited administration to 4 days/week with a maximum dose of 2 mg/day of lorazepam (or equivalent) and not within 12 hours prior to efficacy and safety assessments. Subjects receiving non-benzodiazepine sleep aids for insomnia could not receive same day administration of a benzodiazepine. Subjects could receive medications to treat AD (cholinesterase inhibitors, memantine, or other cognitive enhancers), provided that the subject was on a stable dose for 90 days prior to randomization and remained on the same dose throughout the trial period. Although the Applicant did not permit new onset non-pharmacological interventions for the treatment of agitation during the double-blind period, subjects may have continued these therapies if they initiated those interventions prior to trial participation.

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. Refer to Section 8.1.1.1 for additional information regarding the CMAI instrument.

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 and Exploratory Endpoints:

Secondary endpoints included the following:

- Change from baseline to Week 12 in CMAI subscale scores (aggressive behavior [Factor 1], physically non-aggressive [Factor 2], and verbally agitated behavior [Factor 3])
- 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

The Applicant also conducted a CMAI responder analysis at each scheduled visit in the double-blind treatment period, where response was defined as ≥ 40%, ≥ 30%, and ≥ 20% reduction in CMAI total score from baseline.

Statistical Analysis Plan

The primary efficacy endpoint was the change from the baseline (Day 0 visit) to the end of the double-blind treatment period (Week 12 visit) in CMAI Total Score. The null hypothesis was that there was no difference in the mean change from baseline to Week 12 in CMAI total score between the two treatments arms.

The Applicant performed the primary analysis on the efficacy sample (i.e., the ITT population), which included all randomized subjects who took at least one dose of study medication in the double-blind treatment period and who had both a baseline CMAI assessment and at least one post-randomization CMAI total score assessment during the double-blind treatment period.

The primary estimand is described by five attributes as follows**:**

- Target Population: Subjects with AAD who have met protocol eligibility criteria
- Endpoint: Change from baseline to Week 12 in the CMAI total score
- Intercurrent Events: Premature treatment discontinuation (i.e., early dropout) prior to Week 12 attributable to adverse events, lack of efficacy, withdrawal of consent, or any other causes
- Measure of Intervention effect: Difference in endpoint means between the brexpiprazole and placebo treatment arm
- Treatment regimen: 2 or 3 mg daily for 12 weeks

During the course of the trial, the COVID-19 pandemic broke out. The Applicant did not treat virtual visits as an intercurrent event for the primary analysis. The Applicant handled all subjects who dropped out with a reason related to the COVID-19 pandemic as if they would have dropped out for another reason if the pandemic had not happened. An exploratory sensitivity analysis conducted by the Applicant showed no meaningful difference in efficacy trends between pre- and post-pandemic groups.

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 (at Weeks 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 interaction terms of treatment by visit week and 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.

The Applicant also applied two sensitivity analyses (similar to Study 331-12-283): the delta adjustment imputation method and the placebo-based imputation method. The description of the procedure of two sensitivity analyses can be found in 8.1.1.1.

Based on a treatment effect of 6.5 points with a standard deviation of 16.5 points on the change from baseline in CMAI total score, the Applicant estimated an initial sample size of 300 total subjects before the pre-specified unblinded interim analysis to achieve 89% power at a 2-sided alpha level of 0.05. To account for an empirical dropout rate of 12 to 13% and a lack of compliance at one identified clinical site, the Applicant increased the sample size by an additional 30 subjects to maintain the target power. The resulting sample size was 330 subjects randomized in a 2:1 ratio to brexpiprazole or placebo. Within the brexpiprazole arm, subjects were further randomized in a 1:2 ratio to BREX 2 mg or BREX 3 mg.

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. The decision rules for interim analysis are shown in Table 37 below:

Table 37: Decision Rules for Interim Analysis for Study 331-14-213

IA result	DMC Recommendation	Outcome
Two-sided *p*-value ≤ 0.015	Stop the trial for superiority in efficacy	The Applicant will terminate the trial at IA
Observed effect size ≤ 0.10	Stop the trial for futility	The Applicant may terminate the trial at IA (subject to Applicant's final decision)
Otherwise (none of the above)	Continue the trial to the final analysis	The trial will proceed to the planned maximum sample size of approximately N=330

Source: Applicant's Statistical Analysis Plan, Study 331-14-213
Abbreviation: IA = interim analysis

The key secondary efficacy endpoint was the change from baseline to Week 12 in the CGI-S score, as related to agitation. The Applicant used the same statistical methodology specified for the primary analysis to conduct the key secondary efficacy analysis. To control the overall type I error rate for this key secondary efficacy analysis, 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.

Protocol Amendments

The Applicant originally issued the protocol on February 23, 2018. There were three global amendments to the protocol and two amendments to the blinded addendum. The Applicant's specified changes to the study protocol and addendum are highlighted below:

- Protocol Amendment 1 (December 3, 2019) and Blinded Addendum Amendment 1 (December 3, 2019)
  - Increased the sample size from 225 to 255 subjects in order to compensate for noncompliance at one trial site
  - Increased the number of trial sites from 60 to 80 sites to allow for an increase in subject enrollment

- Protocol Amendment 2 (August 6, 2020)
  - Introduced a COVID-19 addendum for any protocol specified activities that are not able to be performed or cannot be performed due to COVID-19 considerations

- Protocol Amendment 3 (September 14, 2020) and Blinded Addendum Amendment 2 (September 11, 2020)
  - Increased the alpha-spending for the interim from 0.001 to 0.015 and decreased the alpha-spending for the final analysis from 0.049 to 0.035 (the Applicant intended to conduct the interim analysis at N=255 instead of N=150)
  - Removed the sample size adaptation that was based on conditional power at the interim analysis
  - Increased the total sample size from 255 to 330 subjects due to an adjustment of the effect size assumption (changing the treatment difference from 7.0 points to 6.5 points and the study power from 85% to 89%) to account for a potential impact of the COVID-19 pandemic on clinical outcomes
  - Increased the trial duration from 2.5 to 4 years due to the COVID-19 pandemic and increased sample size
  - Removed references to German sites due to compliance concerns with the expected enrollment rate
  - Added details of the revised interim analysis plan including if the trial terminated early for overwhelming efficacy, subjects who may not have completed the protocol assessments may enroll into Study 331-20-00182 (active-treatment extension)

Clinical Reviewer's Comment: *The review team previously determined that the proposed protocol changes incorporated in each amendment were reasonable.*

8.1.3.2 Study Results of Trial 331-14-213

Compliance with Good Clinical Practices

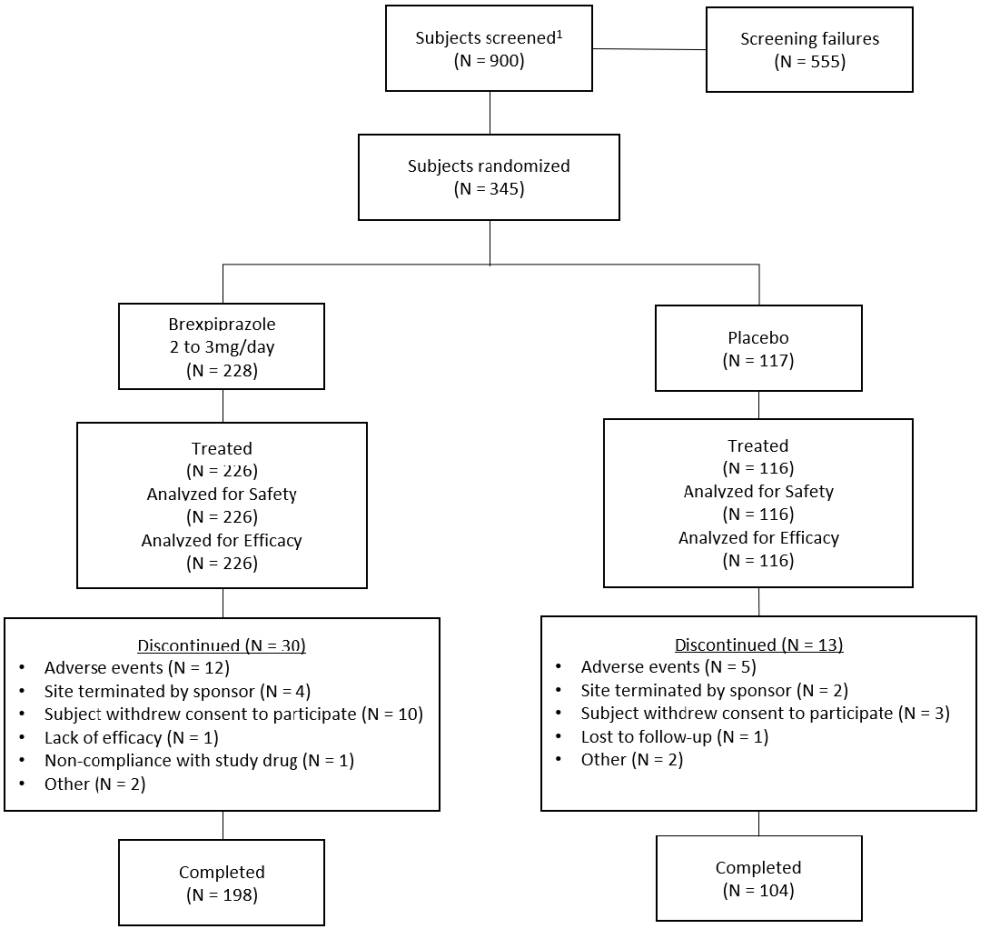
The Applicant conducted this study in accordance with the International Council for Harmonisation Good Clinical Practice Guidelines. The Applicant states that the study protocol, amendments, informed consent form, and other appropriate study related information were reviewed by an independent ethics committee or institutional review board prior to study initiation.

Financial Disclosure

Refer to Section 15.2 of this review for detailed financial disclosure information. There are no disclosed financial interests or arrangements or missing disclosures that raise questions about the integrity of study data.

Patient Disposition

Figure 17: Disposition of Subjects in Study 331-14-213



Source: Applicant's 331-12-283 Clinical Study Report, Figure 10.1-1

The Applicant screened a total of 900 subjects and randomized 345 subjects into the double-blind treatment period (75 to BREX 2 mg, 153 to BREX 3 mg, and 117 to placebo). Although reasons for screen failures (N=555) varied, the most common reason was withdrawal of consent prior to entering the treatment period. See Figure 17: Disposition of Subjects in Study 331-14-213Figure 17 for an overview of patient disposition. All except three subjects (two in the BREX 2 mg arm and one in the placebo arm) received at least one dose of the study medication; therefore, the safety and efficacy sample comprised of 342 subjects. In the Randomized Sample, 43 subjects (13%) discontinued during the trial (9.3%, 15%, 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 across all treatment groups (1.3%, 7.2%, and 4.3% in the BREX 2 mg, BREX 3 mg, and placebo treatment groups, respectively). Overall discontinuation percentages were greater across North American trial sites vs. ROW sites (20/152; 13% vs. 23/193; 12%) and differed by age (< 65 years: 8.1%; ≥ 65 and < 75 years: 11%; ≥ 75 years: 15%).

Protocol Violations/Deviations

Refer to Table 38 below for a summary of the Applicant's listing of major protocol violations during the double-blind treatment period. During the trial, no subjects discontinued due to a protocol deviation. Overall, the percentage of subjects with protocol deviations was slightly higher in the placebo group (21%) relative to the BREX 2 mg (19%) and BREX 3 mg (17%) groups. The Applicant mainly classified protocol deviations as procedural errors (i.e., obtaining pharmacogenomic or future biospecimen research samples without consent, subjects not reconsenting to the latest approved informed consent form, non-certified rater administration of CMAI assessments, subject randomization prior to independent adjudication panel approval, use of another study kit). Procedural errors also included protocol deviations related to the COVID-19 pandemic if the deviation occurred prior to the site receiving regulatory authority and IRB approval of the COVID-19 protocol addendum.

Table 38: Summary of Major Protocol Violations During the Double-Blind Period for Study 331-14-213 (Safety Sample)

Protocol Deviations	Placebo (N=116)	BREX 2 mg (N=73)	BREX 3 mg (N=153)
Number of subjects with major protocol deviations	24 (21%)	14 (19%)	26 (17%)
Entry Criteria	-	2 (2.7%)	-
Dosing	3 (2.6%)	1 (1.4%)	5 (3.3%)
Concomitant Medication	4 (3.4%)	1 (1.4%)	1 (0.7%)
Procedural	18 (16%)	11 (1%)	22 (14%)

Source: Applicant's addv.xpt dataset

Clinical Reviewer's Comment: *The incidence of major protocol deviations was similar to the two previous studies (331-12-283 and 331-12-284). The Applicant reported that investigators administered unscheduled CMAI assessments to four subjects in the BREX 3 mg group (2.6%). Although the Applicant did not state the timing of these deviations, the relatively low percentage is unlikely to impact the study results. One subject in the BREX 2 mg group received*

risperidone during the double-blind period, while one subject in the BREX 3 mg group had an inadequate washout of olanzapine prior to randomization. In addition, relatively low number of deviations related to eligibility criteria, dosing, and concomitant medications appear unlikely to significantly affect the study conclusions. The higher rate of major protocol deviations across North American sites vs. ROW across all treatment groups (placebo: 34% vs. 12%; BREX 2 mg: 40% vs. 4.7%; BREX 3 mg: 25% vs. 9.8%) was consistent with previous studies and likely related to the number of trial sites in each country.

Table of Demographic Characteristics

Refer to Table 39Table 41 below for a summary of demographic, baseline disease characteristics, and prior medication use history across treatment groups.

Table 39: 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)	Total (N=342)
Age (years)					
Mean (SD)	73.0 (7.0)	74.2 (7.3)	74.6 (8.0)	74.4 (7.7)	73.9 (7.5)
Median (Range)	73 (58, 88)	75 (57, 88)	75 (56, 90)	73 (58, 88)	74 (56, 90)
Age group (years), n (%)					
< 65	13 (11%)	8 (11%)	16 (11%)	24 (11%)	37 (11%)
65 to < 75	54 (47%)	29 (40%)	54 (35%)	83 (37%)	137 (40%)
≥75	49 (42%)	36 (49%)	83 (54%)	119 (53%)	168 (49%)
Gender, n (%)					
Male	56 (48%)	32 (44%)	61 (40%)	93 (41%)	149 (44%)
Female	60 (52%)	41 (56%)	92 (60%)	133 (59%)	193 (56%)
Race, n (%)					
White	114 (98%)	68 (93%)	144 (94%)	212 (94%)	326 (95%)
Black or African American	1 (0.9%)	5 (6.8%)	6 (3.9%)	11 (4.9%)	12 (3.5%)
Asian	1 (0.9%)	-	3 (2.0%)	3 (1.3%)	4 (1.2%)
Country, n (%)					
United States	49 (29%)	30 (27%)	71 (30%)	101 (27%)	150 (44%)
Ukraine	35 (30%)	26 (36%)	45 (29%)	71 (31%)	106 (31%)
Bulgaria	13 (11%)	10 (14%)	14 (9.2%)	24 (11%)	37 (11%)
Serbia	8 (6.9%)	2 (2.7%)	9 (5.9%)	11 (4.9%)	19 (5.6%)
Slovakia	4 (3.4%)	2 (2.7%)	7 (4.6%)	9 (4.0%)	13 (3.8%)
Spain	4 (3.4%)	3 (4.1%)	4 (2.6%)	7 (3.1%)	11 (3.2%)
Hungary	3 (2.6%)	-	3 (2.0%)	3 (1.3%)	6 (1.8%)
Region, n (%)					
North America	49 (42%)	30 (41%)	71 (46%)	101 (45%)	150 (44%)
ROW	67 (58%)	43 (59%)	82 (54%)	125 (55%)	192 (56%)
Ethnicity, n(%)					
Hispanic or Latino[2]	37 (32%)	23 (32%)	46 (30%)	69 (31%)	106 (31%)
Not Hispanic or Latino	79 (68%)	50 (69%)	107 (70%)	157 (70%)	236 (69%)
Weight (kg), mean (SD)	71.4 (13.8)	70.9 (15.7)	70.2 (15.5)	70.5 (15.5)	70.8 (15.0)
Height (cm), mean (SD)	164.1 (10.1)	163.2 (9.9)	162.5 (10.7)	163.6 (10.4)	163.8 (10.3)
BMI (kg/m^2), mean (SD)	25.8 (4.8)	26.6 (4.8)	25.6 (4.7)	26.0 (4.7)	26.4 (4.7)
Weight circumference (cm), mean (SD)	92.7 (13.6)	91.0 (14.5)	92.3 (14.8)	91.9 (14.7)	92.2 (14.3)

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

Other Baseline Characteristics

Table 40: Baseline Disease and Psychiatry History for Study 331-14-213 (Efficacy Sample)

Disease Characteristic	Placebo (N=116)	BREX 2 mg (N=73)	BREX 3mg (N=153)	All BREX (N=226)	Total (N=342)
Care Setting, n (%)					
Institutionalized	53 (46%)	32 (44%)	64 (42%)	96 (43%)	149 (44%)
Non-institutionalized	63 (54%)	41 (56%)	89 (58%)	130 (58%)	193 (56%)
Time since onset of symptoms of dementia (months), mean (SD)	56.2 (39.3)	53.9 (37.8)	59.0 (37.6)	57.4 (37.7)	57.0 (38.2)
Time since diagnosis of AD (months), mean (SD)	34.4 (31.3)	34.5 (39.2)	37.8 (36.0)	36.7 (37.0)	35.9 (35.2)
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)	23.2 (22.6)
Cognitive Impairment (MMSE), n (%)					
Mild	28 (24%)	16 (22%)	37 (24%)	53 (24%)	81 (24%)
Moderate	66 (57%)	46 (63%)	79 (52%)	125 (55%)	191 (56%)
Severe	22 (19%)	11 (15%)	37 (24%)	48 (21%)	70 (21%)
Comorbid neuropsychiatric conditions, n (%)					
Irritability/lability	99 (85%)	60 (82%)	131 (86%)	191 (85%)	290 (85%)
Aberrant motor behavior	73 (63%)	45 (62%)	95 (62%)	140 (62%)	213 (62%)
Anxiety	81 (70%)	53 (73%)	113 (74%)	166 (74%)	247 (72%)
Sleep disorder	59 (51%)	43 (59%)	87 (57%)	130 (58%)	189 (55%)
Apathy/indifference	44 (38%)	32 (44%)	62 (41%)	94 (42%)	138 (40%)
Disinhibition	60 (52%)	32 (44%)	68 (44%)	100 (44%)	160 (47%)
Delusions	28 (24%)	16 (22%)	33 (22%)	49 (22%)	77 (23%)
Depression/dysphoria	40 (35%)	29 (40%)	54 (35%)	83 (37%)	123 (36%)
Appetite changes	18 (16%)	18 (25%)	29 (19%)	47 (21%)	65 (19%)
Hallucinations	15 (13%)	8 (11%)	23 (15%)	31 (14%)	46 (14%)
Elation/euphoria	12 (10%)	7 (9.6%)	16 (11%)	23 (10%)	35 (10%)
Agitation features, n (%)					
Aggressive behavior	116 (100%)	73 (100%)	153 (100%)	226 (100%)	342 (100%)
Physically non-aggressive behavior	108 (93%)	69 (95%)	145 (95%)	214 (95%)	322 (94%)
Verbally agitated behavior	104 (90%)	70 (96%)	147 (96%)	217 (96%)	321 (94%)
CMAI Total Score, mean (SD)	79.2 (17.5)	79.1 (15.2)	81.2 (17.2)	80.5 (16.6)	80.1 (16.9)
Factor 1 sub-score	26.5 (8.7)	26.5 (6.3)	26.2 (7.7)	26.3 (7.3)	26.4 (7.8)
Factor 2 sub-score	23.2 (7.4)	22.9 (6.9)	24.2 (7.4)	23.8 (7.3)	23.6 (7.3)
Factor 3 sub-score	16.3 (5.6)	17.1 (4.3)	16.9 (4.9)	17.0 (4.7)	16.7 (5.0)
NPI-NH 12 Score[1], mean (SD)	36.4 (16.9)	38.3 (17.2)	37.3 (18.1)	37.6 (17.8)	37.2 (17.5)
NPI-NH A/A Score, mean (SD)	7.5 (2.1)	8.0 (2.0)	7.6 (2.0)	7.7 (2.2)	7.6 (2.1)
NPI Psychosis Score ≥ 4, n (%)	21 (18%)	14 (19%)	30 (20%)	44 (20%)	65 (19%)
CGI-S Score, mean (SD)	4.7 (0.7)	4.6 (0.7)	4.7 (0.6)	4.7 (0.7)	4.7 (0.7)

Source: Clinical Reviewer-created using adsl.xpt, adeff.xpt, adnpi.xpt, adcmai.xpt, adcgi.xpt, admh.xpt dataset
[1]NPI-NH collected from 339 subjects (placebo: 115; BREX 2mg: 72; BREX 3mg: 152)
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

Overall, the baseline demographics mirrored the studied population in Studies 331-12-283 and 331-12-284. In general, demographics characteristics were similar between males and females, age groups, and race groups across treatment arm. However, there were regional differences in

race, ethnicity, and age distribution. In ROW sites, all subjects were white and there were no Hispanic or Latino subjects in the efficacy sample. In North America, all subjects were from the United States, and 90% of subjects were white, 9% were black or African American, and 3% were Asian. Approximately 71% of subjects in the United States were Hispanic or Latino (30% in the total population). Subjects participating in ROW sites were also generally older than in other regions with 11% < 65 years and 43% ≥ 75 years compared with 10% < 65 years and 55% ≥ 75 years in North America.

Across both treatment groups, baseline disease characteristics and psychiatric history were also similar (Table 40Table 22). Relative to Studies 331-12-283 and 331-12-284, subjects enrolled in this study had a longer mean time since diagnosis of AD (331-12-283: 33.5 months; 331-12-284: 30.1 months; 331-14-213: 35.9 months) and time since first episode of AAD (331-12-283: 19.5 months; 331-12-284: 18.7 months; 331-14-213: 23.2 months). Consistent across treatment arms, the majority of subjects exhibited either moderate (56%) or severe cognitive impairment (21%), relative to mild impairment (24%). Based on past reported medical psychiatric history, approximately 10% of subjects reported a history of depression. The most common non-psychiatric condition reported were those typically associated with age: hypertension (59%), postmenopause (28%), myocardial ischemia (18%), hyperlipidemia (16%), Type 2 diabetes (15%), and osteoarthritis (14%). Of the various comorbid BPSD symptoms, most subjects reported histories of irritability (85%), aberrant motor behavior (62%), or anxiety (72%).

Given that the Applicant enriched this study to include subjects with significant CMAI Factor 1 aggressive behaviors, it is important to note that approximately 94% of subjects also exhibited positive Factor 2 physically non-aggressive and CMAI Factor 3 verbally agitated behaviors (approximately 90% of subjects experienced behaviors from all three domains). Further subgroup analyses of subject care setting indicated that the proportion of subjects residing in an institutionalized setting in North America was relatively less than subjects in other countries (14% vs. 67%), while the proportion residing in a non-institutional setting was higher in North American subjects (86% vs. 33%). This finding is consistent with the two previous studies. There were no differences across demographic factors when comparing the percentage of subjects with psychotic symptoms and other efficacy variables (i.e., CMAI total score, CMAI factor scores, CGI-S, and NPI-NH 12-item domain score).

Clinical Reviewer's Comment: *A cross-study comparison of baseline demographics revealed a larger population of Hispanic and Latino subjects in Study 331-14-213 (31%) vs. Study 331-12-283 (17%) and Study 331-12-284 (6%). Given that the Hispanic and Latino population are mostly located in the United States, it is unclear whether these ethnic differences could lead to differences in treatment effect by region. In addition, the efficacy sample contained more subjects receiving treatment in a non-institutionalized care setting (56%) vs. the two previous studies (43% and 33%, respectively).*

The Applicant's enrichment method of including subjects with significant CMAI Factor 1 aggressive behaviors appeared to increase the baseline severity of the efficacy population.

Subjects enrolled in Studies 331-12-283 and 331-12-284 had a baseline CMAI total score of approximately 70 points (Factor 1 subscore of 23 points), while subjects in this study had a mean baseline CMAI total score of 80 points (Factor 1 subscore of 27 points). Mean baseline scores for other efficacy (i.e., CMAI factor subscores, NPI-NH 12-item score, and NPI-NH A/A score) were higher (10 to 20% depending on the measure) in this study vs. the two previous studies. The presence of psychotic symptoms was also lower in this study (19%) relative to the two previous studies (26% and 22%, respectively). However, it is unclear whether the increased baseline severity and the lower incidence of comorbid psychotic symptoms are inversely related and could translate to an increased treatment effect.

Table 41: Psychotropic Medication Use Prior to the Double-Blind Period in Study 331-14-213 (Efficacy Sample)

Indication/Drug, n (%)	Placebo (N=116)	BREX 2 mg (N=73)	BREX 3 mg (N=153)	ALL BREX (N=226)	Total (N=342)
Subjects receiving at least one psychotropic	110 (95%)	71 (97%)	150 (98%)	221 (98%)	331 (97%)
Agitation	79 (68%)	49 (67%)	92 (60%)	141 (62%)	217 (64%)
Antipsychotics	53 (46%)	34 (47%)	61 (40%)	95 (42%)	148 (43%)
Benzodiazepines	19 (16%)	12 (16%)	17 (11%)	29 (13%)	48 (14%)
SSRI/SNRIs	1 (0.9%)	-	3 (2.0%)	3 (1.3%)	4 (1.2%)
Alzheimer's disease	105 (91%)	64 (88%)	127 (83%)	191 (85%)	296 (87%)
Anticholinesterase inhibitors	54 (47%)	31 (43%)	80 (52%)	111 (49%)	165 (48%)
Memantine	70 (60%)	42 (58%)	89 (58%)	131 (58%)	201 (59%)
Anxiety	11 (9.5%)	4 (5.5%)	27 (18%)	31 (14%)	42 (12%)
Benzodiazepines	8 (6.9%)	2 (2.7%)	18 (12%)	20 (8.8%)	28 (8.2%)
SSRI/SNRIs	1 (0.9%)	2 (2.7%)	4 (2.6%)	6 (2.7%)	7 (2.0%)
Depression	15 (13%)	11 (15%)	24 (16%)	35 (16%)	50 (15%)
SSRI/SNRIs	14 (12%)	9 (12%)	17 (11%)	26 (12%)	40 (12%)
Insomnia/Sleep Disorders	13 (11%)	13 (18%)	14 (9.2%)	27 (12%)	40 (12%)
Hypnotics (non-benzodiazepine)	4 (3.4%)	1 (1.4%)	4 (2.6%)	5 (2.2%)	9 (2.6%)
Benzodiazepine	5 (4.3%)	4 (5.4%)	6 (3.9%)	10 (4.4%)	15 (4.4%)
Trazodone	1 (0.9%)	4 (5.5%)	3 (2.0%)	7 (3.1%)	8 (2.3%)

Source: Clinical Reviewer-created using adcm.xpt and adsl.xpt dataset
Abbreviations: SSRI = Selective serotonin reuptake inhibitor; SSNRI = selective serotonin norepinephrine reuptake inhibitor
[1]Alzhemier's disease included AD, dementia, memory loss

Approximately 82% of subjects (BREX 2 mg: 84%; BREX 3 mg: 80%, and placebo: 83%) received one or more medications for indications other than for the treatment of AD. The most frequent non-psychotropic drug classes reported were angiotensin converting enzyme (ACE) inhibitors (i.e., 17 % enalapril and lisinopril), antithrombotic agents (i.e., 18% aspirin), acid reducing agents (i.e., 9% omeprazole), beta-blockers (i.e., 5% metoprolol), diabetic agents (i.e., 12% metformin), and statins (i.e., 11% atorvastatin). Table 41 provides a listing of prior psychotropic medication use by indication. Given the use of treatments for agitation and AD, the majority of subjects (97%) reported use of a psychotropic drug (i.e., psycholeptic or psychoanaleptic) prior to the study period. Across both treatment arms, prior psychotropic medication use was similar for the treatment of AD and agitation and likely did not affect efficacy results**.**

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant estimated treatment compliance by dividing the number of study medication tablets taken by the total number of scheduled tablets during the trial period. For lost to follow-up subjects, the last study medication end date was equal to the treatment end date. In the placebo, BREX 2 mg, and BREX 3 mg treatment groups, the Applicant observed ≥80% study compliance in 99.1%, 98.6%, and 97.4% of subjects, respectively. The Applicant only reported two subjects in the BREX 3 mg (1.3%) group and one subject in the BREX 2 mg group (1.4%) with treatment compliance < 70%.

Table 42: Psychotropic Medication Use During to the Double-Blind Period in Study 331-14-213 (Efficacy Sample)

Indication/Drug, n (%)	Placebo (N=116)	BREX 2 mg (N=73)	BREX 3 mg (N=153)	ALL BREX (N=226)	Total (N=342)
Subjects receiving at least one psychotropic	102 (88%)	64 (88%)	135 (88%)	199 (88%)	301 (88%)
Agitation	15 (13%)	10 (14%)	20 (13%)	30 (13%)	45 (13%)
Antipsychotics	-	1 (1.4%)	-	1 (0.4%)	1 (0.3%)
Benzodiazepines	11 (9.5%)	7 (9.6%)	12 (7.8%)	19 (8.4%)	30 (8.8%)
SSRI/SNRIs	3 (2.6%)	1 (1.4%)	3 (2.0%)	4 (1.8%)	7 (2.0%)
Alzheimer's disease	102 (88%)	61 (84%)	114 (75%)	175 (77%)	277 (81%)
Anticholinesterase inhibitors	52 (45%)	28 (38%)	78 (51%)	106 (47%)	158 (46%)
Memantine	70 (60%)	41 (56%)	85 (56%)	126 (56%)	196 (57%)
Anxiety	8 (6.9%)	3 (4.1%)	12 (7.8%)	15 (6.6%)	23 (6.7%)
Benzodiazepines	5 (4.3%)	2 (2.7%)	7 (4.6%)	9 (4.0%)	14 (4.1%)
SSRI/SNRIs	2 (1.7%)	1 (1.4%)	4 (2.6%)	5 (3.3%)	7 (2.0%)
Depression	9 (7.8%)	9 (12%)	17 (11%)	26 (12%)	35 (10%)
SSRI/SNRIs	9 (7.8%)	8 (11%)	11 (7.2%)	19 (8.4%)	28 (8.2%)
Insomnia/Sleep Disorders	8 (6.9%)	8 (11%)	13 (8.5%)	21 (9.3%)	29 (8.5%)
Hypnotics (non-benzodiazepine)	5 (4.3%)	2 (2.7%)	9 (5.9%)	11 (4.9%)	16 (4.7%)
Benzodiazepine	2 (1.7%)	-	1 (0.7%)	1 (0.4%)	3 (0.9%)
Trazodone	2 (1.7%)	5 (6.8%)	3 (2.0%)	8 (3.5%)	10 (2.9%)

Source: Clinical Reviewer-created using adcm.xpt and adsl.xpt dataset
Abbreviations: SSRI = Selective serotonin reuptake inhibitor; SSNRI = selective serotonin norepinephrine reuptake inhibitor

Table 42 provides a listing of concomitant psychotropic medication during the double-blind period. Given that the majority of subjects continue their treatments for AD and other comorbid disorders, the overall percentage of psychotropic use was > 85% across all treatment arms. The percentage of subjects receiving treatment for worsening or breakthrough symptoms of agitation was similar between the brexpiprazole treatment arms vs. placebo (ALL BREX: 13% vs. 13%). The overall percentage of benzodiazepine use was 16%, 14%, and 13% in the placebo, BREX 2 mg, and BREX 3 mg treatment arms, respectively. During the follow-up period (post-study treatment), approximately 5.0%, 2.7%, and 4.6% of subjects who received placebo, BREX 2 mg, and BREX 3 mg during the double-blind period received treatments for agitation, respectively.

Efficacy Results – Primary Endpoint

The combined brexpiprazole 2 and 3 mg/day 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 (LS mean difference = -5.32 [95% CI: [-8.77, -1.87], p = 0.0026), shown in Table 43.

Table 43: Study 331-14-213 Primary Endpoint Results (MMRM; Efficacy Sample)

	Placebo (N=116)	BREX 2 and 3 mg (N=225[2])
Mean CMAI Total Score at Baseline (SD)	79.17 (17.52)	80.55 (16.64)
Mean CMAI Total Score at Week 12 (SD)	63.19 (18.15)	57.84 (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 = unadjusted 95% confidence interval (p-value also unadjusted).
[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.

Statistical Reviewer's Comment**:** *The statistical reviewer found that one subject (SUBJID: (b) (6)) in BREX 2 and 3 mg group who only had a single post-baseline assessment at Week 7, which was not a scheduled assessment visit for efficacy. Thus, this patient was not included in the primary analysis although included in the efficacy sample. The statistical reviewer included this patient in the primary efficacy by mapping its post-baseline assessment to the closest visit (Week 8) in the model; the result is nearly identical with the primary analysis finding.*

Subsequently, the Applicant conducted a post-hoc analysis 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 nominally statistically significantly greater for both BREX 2 mg (p=0.0216) and BREX 3 mg (p=0.0053) compared to placebo (Table 44).

Table 44: Study 331-14-213 Summary of Mean Change from Baseline to Week 12 in the CMAI total score by Dose Group (Observed Cases, MMRM; Efficacy Sample)

	Placebo (N=116)	BREX 2 mg (N=73)	BREX 3 mg (N=152)
Mean CMAI Total Score at Baseline (SD)	79.17 (17.52)	79.07 (15.24)	81.26 (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)
P-value		0.0216	0.0053

Source: Applicant's Study 331-14-213 Clinical Study Report, Table 11.4.1.4.1-1, 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 (nominal p-value also unadjusted)
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

Statistical Reviewer's Comment: *The comparison between each individual dose and placebo on the primary endpoint is not pre-specified for statistical testing and therefore it is exploratory. However, in the biometrics team's view, this study provided evidence supporting the efficacy of the 2 mg for the following reasons:*

1) The study succeeded in showing the pooled 2 mg and 3 mg beats placebo on the primary endpoint and key secondary endpoint.

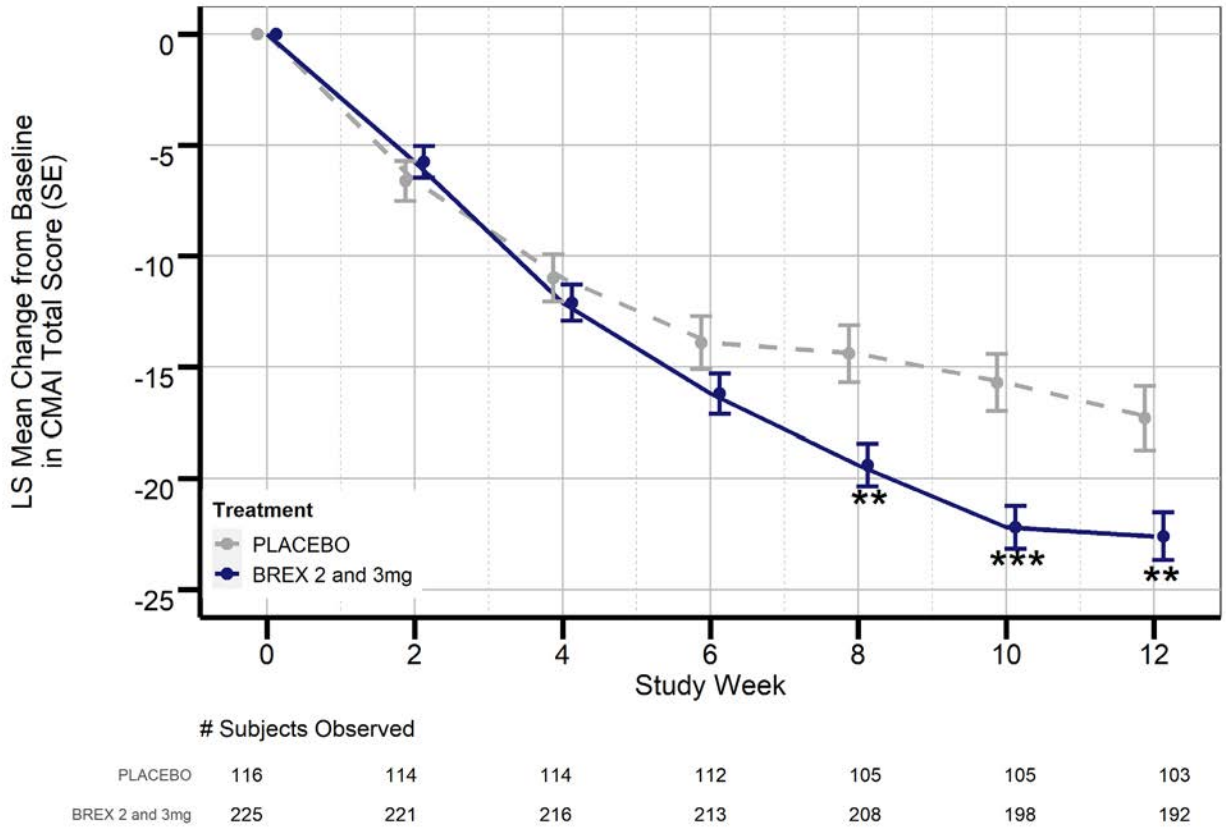
2) The estimated treatment effects of 2 mg alone and 3 mg alone on the primary endpoint are almost identical.

3)The nominal p-values for these estimated treatment effects are less than 0.035, which is the statistical significance threshold used for testing the pooled dose versus placebo.

Time Course Plot

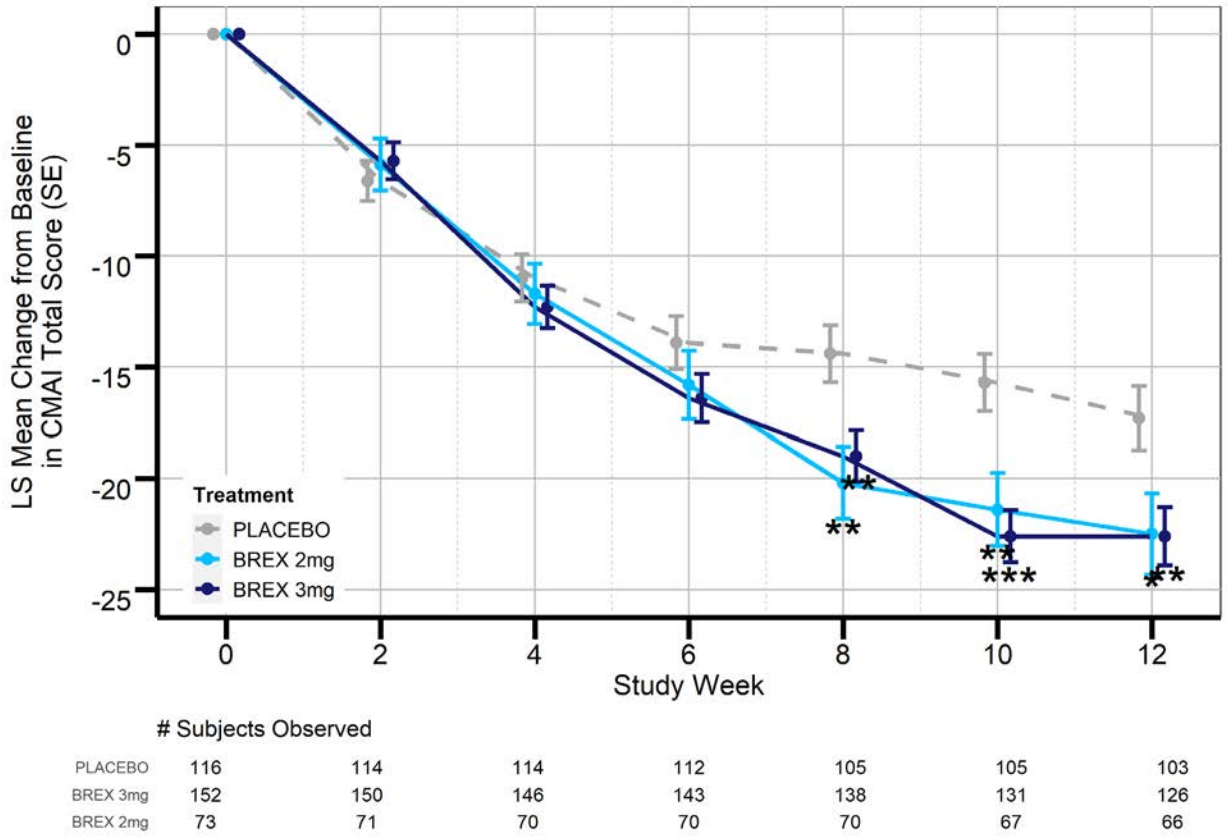
The LSMD in change from baseline in CMAI total score between the combined BREX 2 mg and BREX 3 mg group and the placebo group was numerically greater at Weeks 4, 6, 8, 10 and 12, shown in Figure 18Figure 18. Similarly, the longitudinal response profile for each of the treatment groups is visualized separately in Figure 19. Note that investigators titrated subjects in the BREX 2 mg and BREX 3 mg group to 2 mg/day at starting at Week 2 and subjects in BREX 3 mg group to 3 mg/day starting at Week 4 (refer to Table 35). Similar to the two previous studies, the longitudinal response profiles suggest a separation of the treatment effect starting after 4 weeks of treatment, which is sustained throughout the study period.

Figure 18: Study 331-14-213 LS Mean Change from Baseline to Week 12 in CMAI Total Score by Week - MMRM (Efficacy Sample)



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

Figure 19: Study 331-14-213 LS Mean Change from Baseline to Week 12 in CMAI Total Score by Week and Dose Group - MMRM (Efficacy Sample)

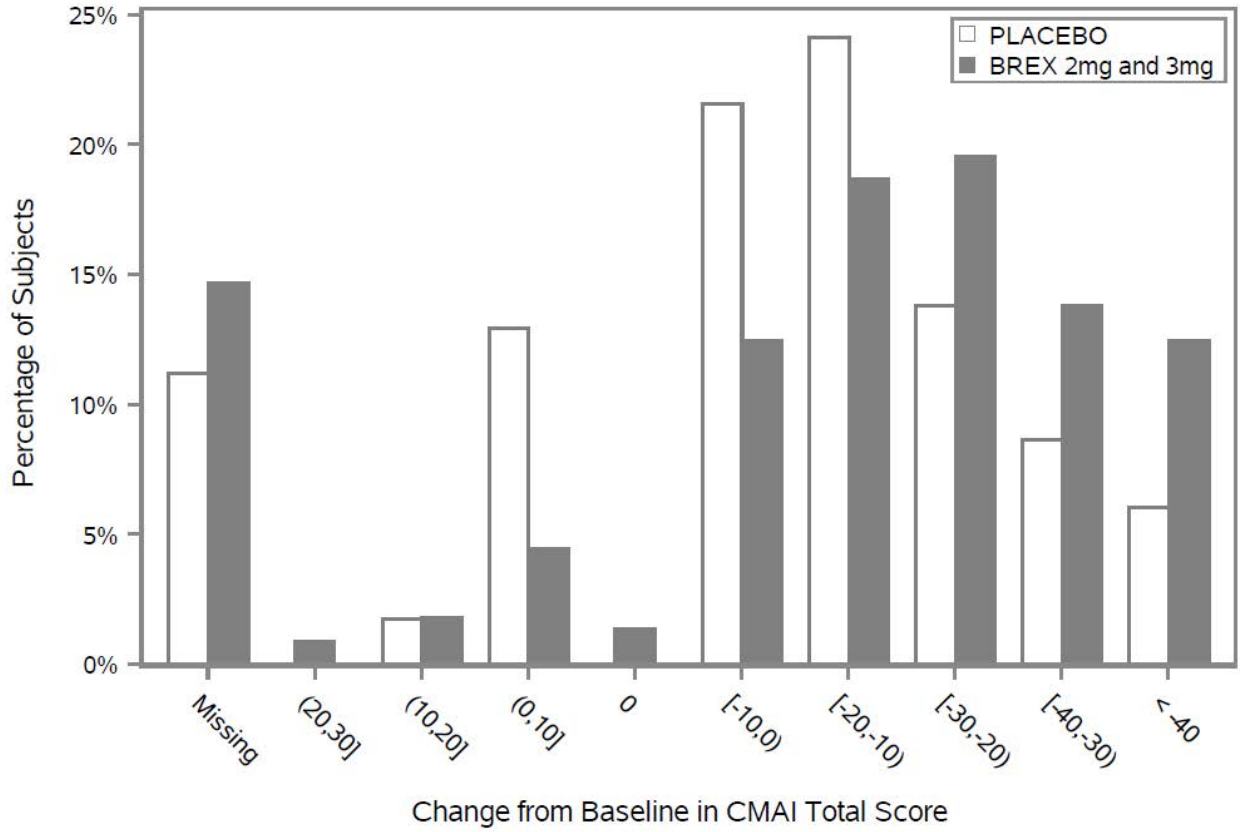


Source: Clinical Reviewer-adapted figure from Study 331-14-213 Clinical Study Report, Figure 11.4.1.4.2-1, p. 84
*P-value < 0.05; **P-value < 0.01; ***P-value < 0.001
[1]Dashed line represents the placebo treatment arm. Error bars are LS mean +/- one standard error.
Abbreviations: LS = least squares, MMRM = mixed-effect model repeated measures, CMAI = Cohen-Mansfield Agitation Inventory, SE = standard error

The histograms (Figure 20 and Figure 21Figure 20: Study 331-14-213 Change from Baseline to Week 12 in CMAI Total Score (Efficacy Sample)

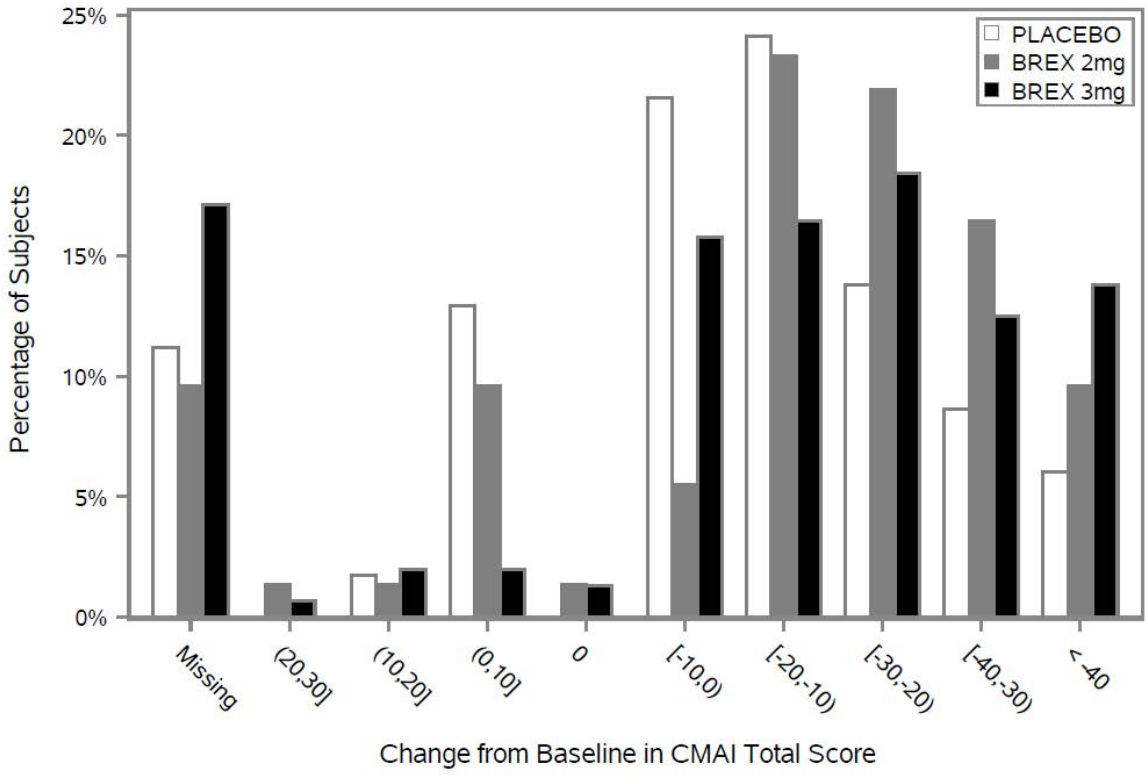
) display the proportions of subjects who either improved or worsened on the primary score from baseline. The far left is the proportion of the subjects with missing data. Negative scores represent improvement, and positive scores represent worsening. The combined BREX 2 mg and 3-mg group had greater proportion of patients demonstrating improvement compared to the placebo group in most of magnitudes of improvement intervals (intervals greater than 20). In addition, the BREX 3 mg group had a greater percentage of dropouts compared to the other two groups.

Figure 20: Study 331-14-213 Change from Baseline to Week 12 in CMAI Total Score (Efficacy Sample)



Source: Created by Statistical Analyst using the adsl.xpt and adcmai.xpt dataset

Figure 21: Study 331-14-213 Change from Baseline to Week 12 in CMAI Total Score by Dose Group (Efficacy Sample)

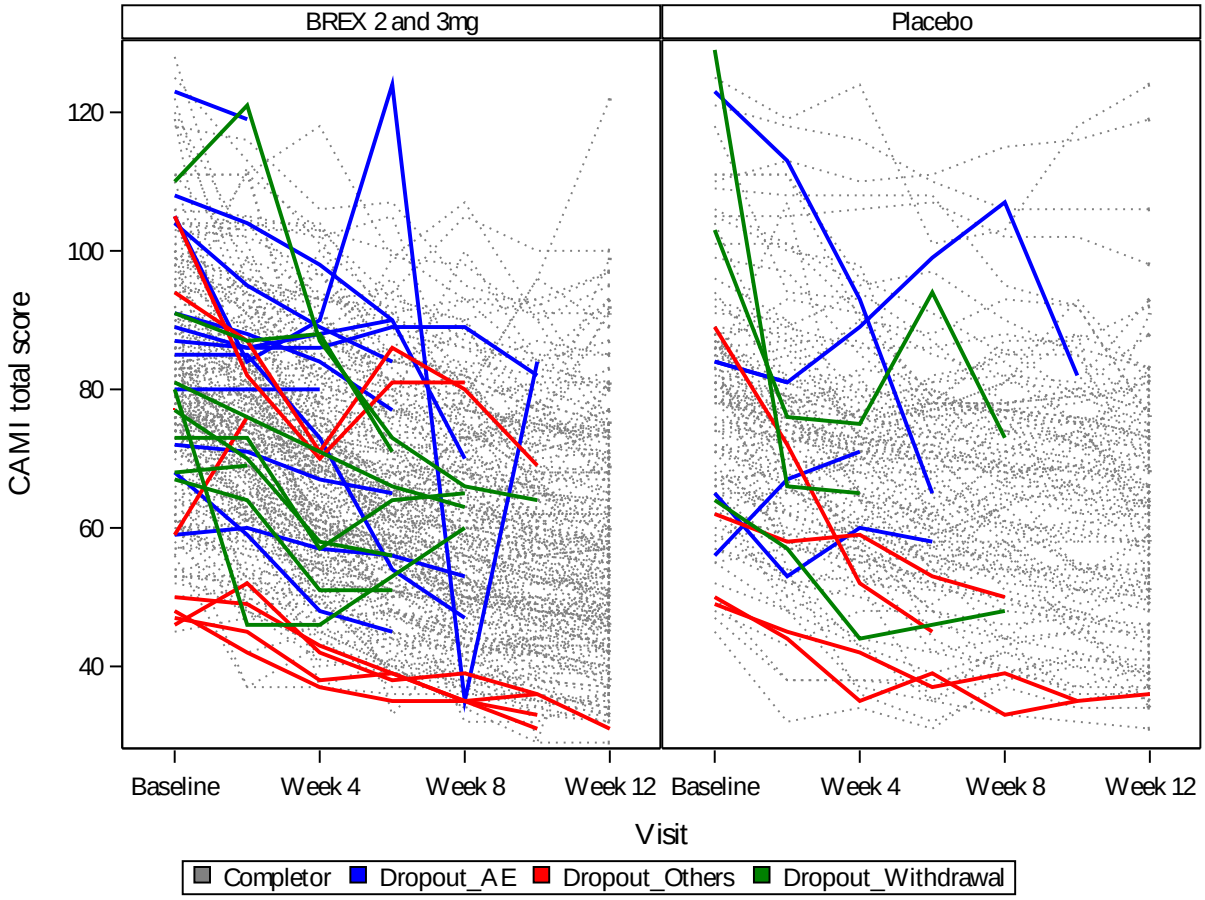


Source: Created by Statistical Analyst using the adsl.xpt and adcmai.xpt dataset

Individual-patient Response Trajectories Plot

The primary statistical analysis assumes that the missing data mechanism is missing at random (MAR). Following the review of the individual-patient observed response trajectories in CMAI total score by treatment group, the results suggest that the missing patient-level responses likely follow the trajectory of the responses of the completers after their last observed response as assumed by MAR in the primary MMRM analysis (Figure 22).

Figure 22: Study 331-14-213 Individual-patient Response Trajectories in CMAI Total Score by Treatment Groups (Efficacy Sample)



Source: Statistical Reviewer-created using the adsl.xpt and adcmai.xpt dataset

Sensitivity Analyses for Missing Data

The Applicant performed sensitivity analyses of the MNAR assumption in the primary efficacy analysis using different imputation methods for missing data for the Efficacy Sample in the MMRM model. The Applicant first analyzed change at Week 12 CMAI total score comparisons with placebo using the pattern mixture model (PMM) with both Delta 1 and Delta 2 methods. The results are shown in Table 45. The Applicant investigated three scenarios based on discontinuation reasons including AEs; AEs and subject withdrew consent as MNAR and other missing data as MAR; and all discontinuations as MNAR. The Applicant defined the tipping point as the value of the factor where statistical significance of the treatment effect is lost. Using the Delta method 1, the tipping points were reached at the penalties of 160% (10.4), 260% (16.9) and 400% (26) of the expected treatment difference for scenarios 1 to 3, respectively. Using the Delta method 2, the tipping points were reached at the penalties of 200%, 310% and 480% of the observed treatment difference for scenarios 1 to 3, respectively. Those inflations are considered sufficiently conservative tests.

Table 45: Study 331-14-213 Sensitivity Analysis of MNAR using Pattern Mixture Model with Multiple Imputation in CMAI Total Score

Sensitivity Analysis	Scenario 1[a]	Scenario 2[b]	Scenario 3[c]
BREX 2 and 3 mg vs. Placebo			
Primary Efficacy MMRM	LSMD vs placebo (95% CI): -5.32 (-8.77, -1.87), P value: 0.0026		
Shift parameter	0	0	0
LSMD vs placebo (95% CI)*	-4.79 (-8.16, -1.41)	-4.79 (-8.16, -1.41)	-4.79 (-8.16, -1.41)
P value*	0.0054	0.0054	0.0054
Delta Method 1[1]			
Shift parameter[2]	10.4	16.9	26
LSMD vs placebo (95% CI)*	-3.42 (-6.88, 0.04)	-3.47 (-6.98, 0.041)	-3.53 (-7.11, 0.04)
P value*	0.0527	0.0527	0.0526
Delta Method 2[3]			
Shift parameter[4]	200%	310%	480%
LSMD vs placebo (95% CI)*	-3.39 (-6.85, 0.076)	-3.50 (-7.01, 0.004)	-3.55 (-7.12, 0.012)
P value*	0.0552	0.0503	0.0508

Source: Statistical Reviewer-adapted based on Study 331-12-283 Clinical Study Report CT-5.9.1 through CT-5.9.6
LSMD= least squares mean difference, CI = confidence interval; MMRM = mixed-effect model repeated measures; 95% CI = unadjusted 95% confidence interval (nominal p-value also unadjusted).
Note: Multiple imputation was based on monotone missing data structure of the observed change from baseline using regression option in PROC MI.
[a]Dropout reasons due to AE as MNAR
[b]Dropout reasons due to either AE or subject withdrew consent as MNAR
[c]All dropouts as MNAR
[1]Delta Method 1: Delta value would start at 0% of the expected treatment difference of 6.5 points and increase by 10% to 200%.
[2]Shift parameters were presented as the tipping points were reached at the penalties of 160% (10.4), 260% (16.9) and 400% (26) of the expected treatment difference for scenarios 1 to 3, respectively.
[3]Delta Method 2: Delta value would start from 0% to 200% of the observed treatment difference between brexpiprazole and placebo from the primary analysis of MMRM model.
[4] Shift parameters were presented as the tipping points were reached at the penalties of 200%, 310% and 480% of the observed treatment difference for scenarios 1 to 3, respectively.
*Derived based on 100 imputations.

The Applicant also performed the sensitivity analysis based on the placebo-based imputation method using both MCMC and Monotone. The results of this analysis, shown in Table 46, were consistent with MMRM results for the primary efficacy variable; therefore, the Applicant concluded that the MMRM results (primary analyses) were robust.

Table 46: Study 331-14-213 Sensitivity Analysis of MNAR using Placebo Based Imputation in CMAI Total Score

Analysis	LSMD (95% CI)	P value
Primary Efficacy MMRM		
BREX 2 and 3 mg vs. Placebo	-5.32 (-8.77, -1.87)	0.0026
MNAR-CP MCMC		
BREX 2 and 3 mg vs. Placebo	-4.25 (-7.64, -0.864)	0.0139
MNAR-CP MONO		
BREX 2 and 3 mg vs. Placebo	-4.31 (-7.76, -0.869)	0.141

Source: Statistical Reviewer-adapted using Study 331-124-213 Clinical Study Report, CT-5.9.7
Abbreviations: LSMD = least squares mean difference; MMRM= mixed-effect model repeated measures; 95% CI = unadjusted 95% confidence interval (nominal p-value also unadjusted).
MNAR-CP MCMC: Missing not at random (MNAR) with Copy Placebo for dropout using MCMC Multiple Imputation method; MNAR-CP MONO: Missing not at random (MNAR) with Copy Placebo for dropout using Monotone Multiple Imputation method.
Note: Multiple imputation was based on monotone missing data structure of the observed change from baseline using regression option in PROC MI.
*Derived based on 100 imputations.

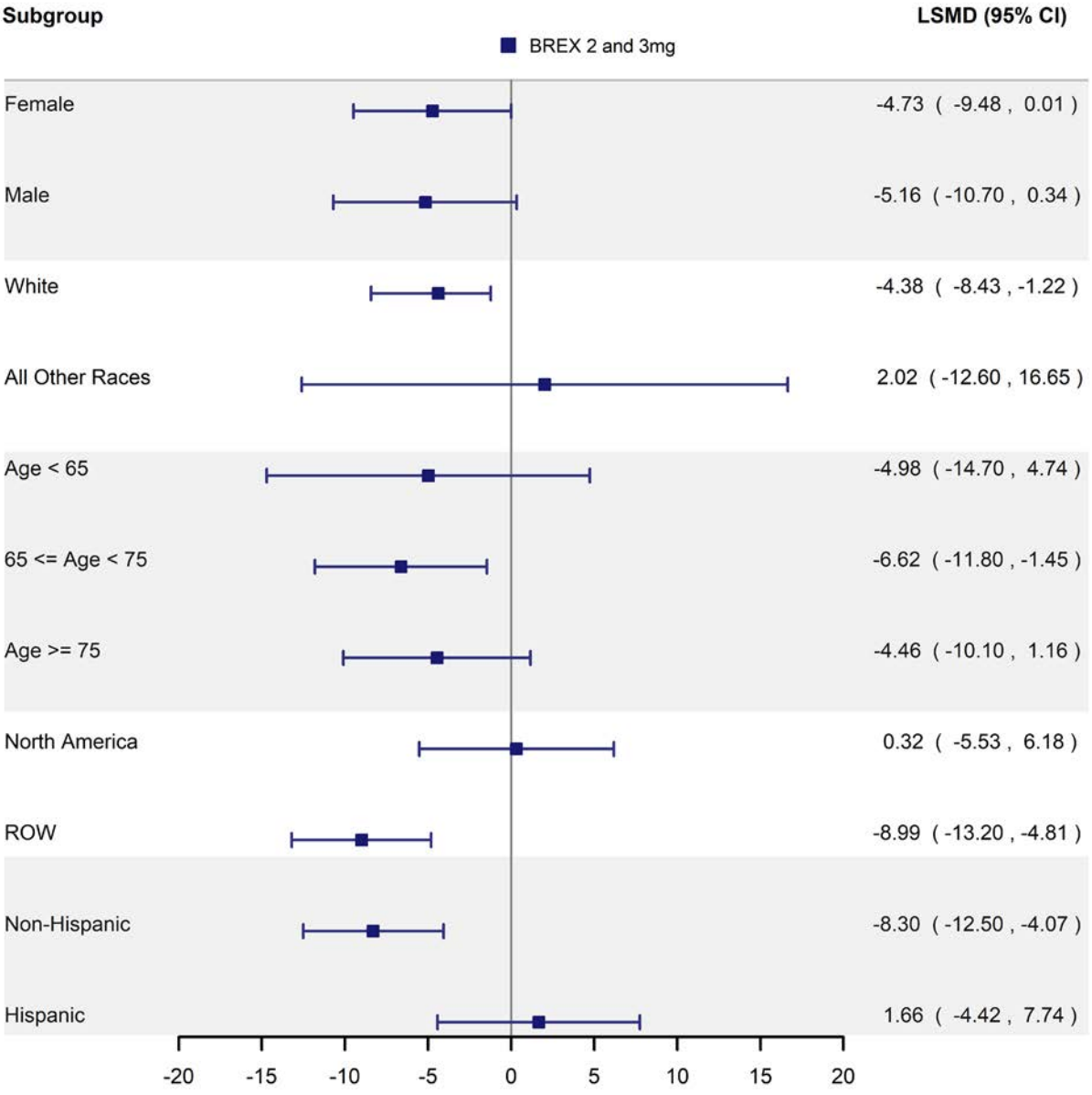
Interim Analysis

An independent DMC performed an interim analysis of the efficacy data after 255 subjects (74% Information time) completed the 12-week trial or discontinued early. The DMC Chair explained to the rest of the DMC that the results seen in IA for the total study population meets the guidelines for the study to stop early for efficacy (LS mean difference = −5.06, p = 0.0125). However, the sub-group analysis performed for North America sites (LS mean difference = -0.21, p = 0.9561) did not meet the guidelines to stop early for efficacy compared to ROW sites (LSMD = -8.27, p = 0.0006). Thus, the Applicant continued the study even though the efficacy was demonstrated in the interim sample.

Subgroup Analysis

The primary efficacy variable was examined to explore the consistency of the treatment effect across the following subgroups: gender, race, age, region, and ethnicity (Figure 23). The trends appeared consistent with the overall results in favor of brexpiprazole for subgroups gender and age. Treatment differences between subgroups of race were not interpretable because the majority of subjects (95%) were white. 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 (refer to Table 48 for additional analyses).

Figure 23: Study 331-14-213 Subgroup Analysis for Change from Baseline to Week 12 in CMAI Total Score – Forest Plot (MRM; Efficacy Sample)



Source: Reviewer created using Study 331-14-213 Clinical Study Report, CT-6.1.1 (females), CT-6.1.2 (males), CT-6.3.1 (< 65 years), CT-6.3.2 (≥ 65 and < 75 years), and CT-6.3.3 (≥ 75 years), CT-6.2.1 (whites), CT-6.2.2 (all other races), and CT-6.2.3 (whites and all other races at Week 12), CT-6.4.1 (North America) and CT-6.4.2 (other regions) confirmed by statistical reviewer. The subgroup analysis of ethnic status was conducted by statistical reviewer.
Note: In each subgroup stratum, MMRM was conducted with model Terms: treatment, visit, treatment by visit and baseline by visit interaction.

Clinical Reviewer's Comment: *Although the results from the subgroup analysis were generally consistent with the overall population, there were notable differences when assessing the treatment effect by region (North America LSMD: 0.32 vs. ROW LSMD: -8.99). As displayed in Table 47, this result was also reversed when comparing by region for the BREX 2 mg group in Study 331-12-283 (North America LSMD: -7.76 vs. ROW LSMD: -1.63). When examining the change from baseline in the combined BREX 2 and 3 mg group, the difference was similar between the two subgroups (North America LS mean change from baseline = -21.8 vs. ROW LS mean change from baseline = -22.5). However, there was a numerically higher placebo response observed in North American vs. ROW subjects (LS mean change from baseline: -22.1 vs. -13.5, respectively). Therefore, the review team conducted further exploratory analyses to evaluate why US subjects in Study 331-14-213 exhibited a numerically higher placebo response relative to ROW subjects. The exploratory analysis of region by ethnicity showed a numerically higher placebo response in the Hispanic or Latino population residing in the US versus non-Hispanic or Latino subjects (Table 48). Re-assessment of the treatment difference after taking into account ethnicity suggested that the treatment effect trended in the right direction for non-Hispanic or Latino US subjects (LSMD: -4.92). It is unclear whether caregivers of Hispanic patients (mostly in the non-institutionalized care-setting) might have responded differently to efficacy measures relative to other subjects.*

Although the current literature suggests that standard-of-care and medical practice may differ in the US vs. ROW countries, there was insufficient data in this application to make any comparisons with regards to caregiver and nursing home responsibilities. However, concomitant medication and AE reporting was generally higher in the US population vs. ROW.

Table 47: Subgroup Analysis to Assess Regional Differences in Change from Baseline to Week 12 in CMAI Total Score

Study/ Treatment	North America			ROW		
	Sample Size	LSM Change at Week 12 (SE)	LSMD[1] (95% CI)	Sample Size	LSM Change at Week 12 (SE)	LSMD[1] (95% CI)
331-12-283						
Placebo	38	-18.51 (2.65)		93	-16.05 (1.48)	
BREX 2 mg	41	-26.27 (2.54)	-7.76 (-15.05, -0.48)	97	-17.68 (1.46)	-1.63 (-5.73, 2.47)
331-14-213						
Placebo	49	-22.14 (2.44)		67	-13.55 (1.70)	
BREX 2 and 3 mg	100	-21.81 (1.68)	0.32 (-5.53, 6.18)	125	-22.54 (1.27)	-8.99 (-13.17, -4.81)

Source: Reviewer's Analysis confirmed by Statistical Reviewer
Abbreviation: 95% CI = unadjusted 95% confidence interval; LSM = least squares mean; LSMD = least squares mean difference; SE= standard error
Note: BREX 1mg group not shown for Study 331-12-283
[1]In each subgroup stratum, MMRM was conducted with model Terms: treatment, visit, treatment by visit and baseline by visit interaction.

Table 48: Subgroup Analysis to Assess Ethnic Differences by Region in Change from Baseline to Week 12 in CMAI Total Score

Study/ Treatment	Hispanic			Non-Hispanic		
	Sample Size	LSM Change at Week 12 (SE)	LSMD[1] (95% CI)	Sample Size	LSM Change at Week 12 (SE)	LSMD[1] (95% CI)
331-12-213 (US)						
Placebo	37	-23.86 (2.47)		12	-16.1 (6.16)	
BREX 2 and 3 mg	69	-22.2 (1.81)	1.66 (-4.42, 7.74)	32	-21.0 (3.61)	-4.92 (-19.39, 9.5)
331-14-213 (ROW)						
Placebo	-	-		67	-13.55 (1.27)	
BREX 2 and 3 mg	-	-	-	125	-22.54 (1.27)	-9.01 (-13.17, -4.81)

Source: Reviewer's Analysis
Abbreviation: 95% CI = unadjusted 95% confidence interval; LSM = least squares mean; LSMD = least squares mean difference; SE= standard error
[1]In each subgroup stratum, MMRM was conducted with model Terms: treatment, visit, treatment by visit and baseline by visit interaction.

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). The results are shown in Table 49.

Table 49: Study 331-14-213 Key Secondary Endpoint Results (MMRM; Efficacy Sample)

	Placebo (N=116)	BREX 2 and 3 mg (N=225)[1]
Mean CGI-S Score at Baseline (SD)	4.71 (0.69)	4.71 (0.66)
Mean CGI-S Score at Week 12 (SD)	3.84 (0.97)	3.51 (0.91)
LSM Change from Baseline (SE)	-0.93 (0.08)	-1.20 (0.06)
Placebo-subtracted difference (95% CI)[2]		-0.27 (-0.47, -0.07)
P-value		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; CI = confidence interval; 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).
[1]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.
[2] MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

Note: The p-value should be compared with nominal significance level of 0.035 because of an unblinded interim look.

Table 50: Study 331-14-213 Summary of Mean Change from Baseline to Week 12 in the CGI-S score by Dose Group (Observed Cases, MMRM; Efficacy Sample)

	Placebo (N=116)	BREX 2 mg (N=73)	BREX 3 mg (N=152)
Mean CGI-S Score at Baseline (SD)	4.71 (0.69)	4.64 (0.69)	4.74 (0.65)
LSM[1] Change from Baseline (SE)	-0.93 (0.08)	-1.16 (0.11)	-1.22 (0.07)
Placebo-subtracted difference (95% CI)[1]		-0.23 (-0.49, 0.03)	-0.29 (-0.51, -0.08)
P-value		0.0810	0.0084

Source: Applicant's Study 331-14-213 Clinical Study Report, Table 11.4.1.1.1-1, p. 86 confirmed by statistical reviewer
Abbreviations: CGI-S = Clinical Global Impression – Severity scale; LSM = least squares mean, MMRM = mixed-effect model for repeated measures; SD = standard deviation, SE = standard error, 95% CI = unadjusted 95% confidence interval (nominal p-value also unadjusted).
[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

For the key secondary efficacy endpoint, change from baseline to Week 12 in CGI-S score, as related to agitation, the reduction from baseline to Week 12 was 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 50).

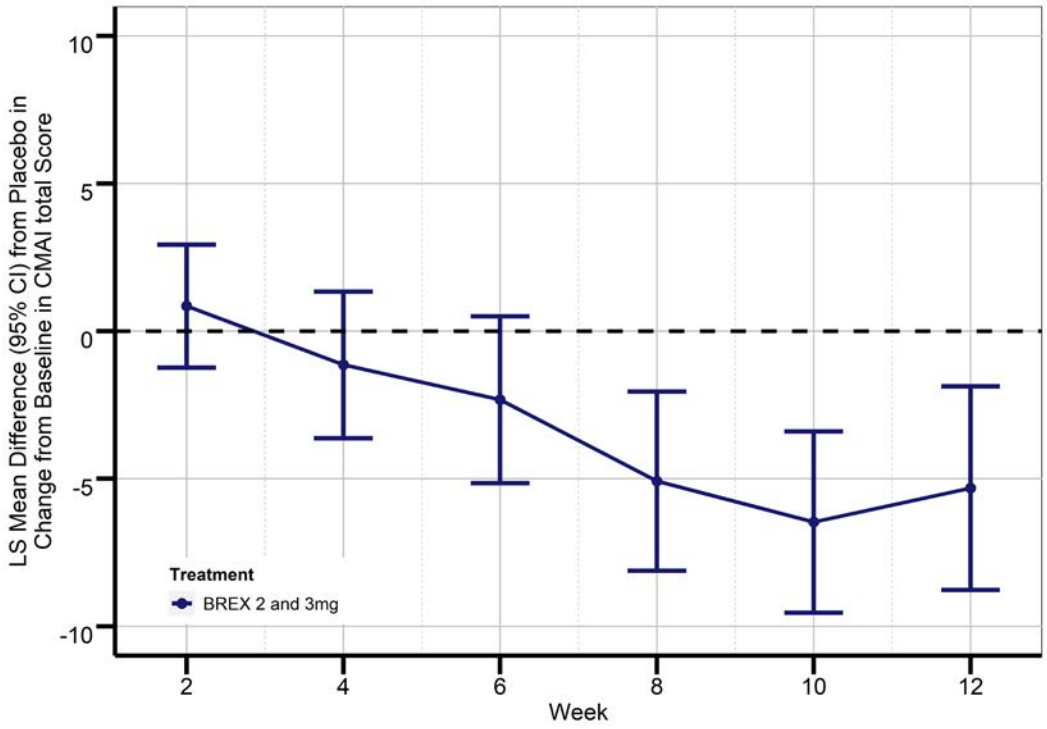
Dose/Dose Response

Refer to Dr. Bhattaram's clinical pharmacology/pharmacometrics review of the integrated dose-response and exposure-response relationship across all fixed dose treatment arms from Studies 331-12-283 and 331-14-213. Refer also to the Additional Analyses subsection below for the Applicant's post-hoc analyses to estimate treatment effects for BREX 2 mg and BREX 3 mg separately. Based on the integrated data, it appears that brexpiprazole exhibits a E_{max} (sigmoidal) dose-response relationship and appears to reach a plateau in response between 2 and 3 mg/day.

Durability of Response

To evaluate durability of response, this review evaluated the change in the net treatment effect over the double-blind period. displays the LSMD from placebo in the change from baseline in the total CMAI score at each visit for the combined BREX 2 and 3 mg group (Figure 24). The combined brexpiprazole group exhibited a nominal treatment effect over placebo starting at Week 4 and maintained its favorable effect through Week 12 (statistically significant separation from placebo starting at Week 8). Given that the brexpiprazole appears to achieve a pharmacodynamic steady state at approximately 8 to 10 weeks, the 12-week trial duration may be sufficient to characterize antipsychotic effect in future trials.

Figure 24: Study 331-14-213 Change in Net Treatment Effect over Time



Source: Reviewer-created using Applicant's Clinical Study Report, Listing CT-5.2.1
Abbreviations: CI = confidence interval; CMAI = Cohen Mansfield Agitation Inventory; LS = least-squares

The Applicant indicated that 259 subjects rolled-over from Study 331-14-213 into Study 331-201-00182, a 12-week, active-treatment, blinded extension study. Based on 163 subjects who continued to receive brexpiprazole and completed Study 331-201-00182, the average change from baseline (at the time of study rollover) in the CMAI total score after 12 weeks of blinded brexpiprazole treatment was -7.1 points. Subjects also experience an average reduction in CGI-S of -0.5 points during the same time frame. This further confirms that subjects continued to experience clinical benefit after a total of 24 weeks of treatment.

Persistence of Effect

Given that the Applicant did not collect efficacy measures during the follow-up period for this study, the persistence of effect is not discernible.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant conducted additional secondary efficacy analyses based on the three factor domains in the CMAI measure (i.e., Factor 1: aggressive behavior; Factor 2: non-physically aggressive behavior, and Factor 3: verbally agitated behavior). The Applicant derived each factor as described in Section 8.1.1.1. The Applicant calculated CMAI factors only when all items included in each factor were available (no imputation of missing values). The Applicant applied

the same statistical methodology as described for the primary efficacy variable. Because the analysis on the CMAI Factor subscales were not included in the statistical testing hierarchy, the between group results for each of the subscales are provided descriptively. Table 51 provides the summary of the mean change from baseline in the CMAI total score and the net treatment effect for each agitation domain. The results demonstrated consistent findings with the primary analysis; the combined BREX 2 and 3 mg group showed a nominally greater improvement across all three factors. However, the brexpiprazole appeared to exert its greatest effect on the CMAI Factor 1 aggressive behavior subscale (LSMD: -1.95 points [95% CI: -3.28, -0.63])

Table 51: Study 331-14-213 Change from Baseline to Week 12 in CMAI Factor Scores (MMRM; 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)
P-value		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)
P-value		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)
P-value		0.0113

Source: Clinical Reviewer-adapted using Applicant's Clinical Study Report 331-14-213, CT-5.1, p. 314
Abbreviations: 95% CI = unadjusted 95% confidence interval (nominal p-value also unadjusted); 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.
Note: MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

Clinical Reviewer's Comment: *Similar to Studies 331-12-283 and 331-12-284, brexpiprazole appears to demonstrate a greater numerical improvement over placebo across the three different CMAI subscales. Given that this study was enriched to include subjects with significant aggressive behaviors at baseline, the higher baseline scores for each of the subscores in this study relative to the two previous studies are expected. Notably, the placebo subtracted treatment differences were also higher relative to the two previous studies (treatment effect for Factor 1 nearly doubled). This finding further suggests that subject with higher baseline severities at the domain level are also expected to experience greater benefit. Refer to Dr. Swett's DCOA review for further domain and item-level analyses to contextualize the study results and evaluate clinically meaningful within-patient change.*

Evaluation of the change from baseline in the CGI-I score at Week 12 (performed using the OC dataset for the Efficacy Sample and using the CMH Row Mean Score Differ Test controlling for trial site) indicated similar improvement favoring the BREX 2 and 3 mg group (mean CGI-I score at Week 12: 2.66) vs. placebo (mean CGI-I score at Week 12: 2.97) with a treatment difference of -0.33 points. The Applicant conducted several responder analyses based on the observed percent change from baseline in total CMAI scores at each scheduled visit. Results from the responder analyses are presented in Table 52 and demonstrates a consistent benefit at nominal significance level of 0.05 with the combined BREX 2 and 3 mg group over placebo across all three responder definitions. Responder analyses on the CGI-I also demonstrated that a larger proportion of subjects in the BREX 2 and 3 mg group compared to placebo exhibited a response (CGI-I score of 1 or 2, very much improved or much improved) to treatment at Week 12 (52.4% vs. 40.5%, respectively).

Table 52: Study 331-14-213 CMAI Responder Analyses at Week 12 (LOCF)

Responder Analysis at Week 12[1]	Placebo (N=116)	BREX 2 and 3 mg (N=225)
CMAI Response Rate, LOCF (20%)		
Responders at Week 12, n(%)	55 (47.4%)	154 (68.4%)
Ratio of Response (95% CI)		1.41 (1.15, 1.72)
CMAI Response Rate, LOCF (30%)		
Responders at Week 12, n(%)	30 (25.9%)	96 (42.7%)
Ratio of Response (95% CI)		1.66 (1.18, 2.23)
CMAI Response Rate, LOCF (40%)		
Responders at Week 12, n(%)	17 (14.7%)	118 (52.4%)
Ratio of Response (95% CI)		1.47 (1.14, 1.89)

Source: Clinical Reviewer-adapted using Applicant's 331-14-213 Clinical Study Report, Listing CT-5.1
Abbreviations: CI = unadjusted confidence interval; CMAI = Cohen Mansfield Agitation Inventory; LOCF = last observation carried forward
[1]Responder ratio estimated using the Cochran-Mantel-Haenszel (CMH) General Association Test

Table 53 provides the results for several additional secondary and exploratory efficacy measures. Across all measures, the combined BREX 2 and 3 mg group consistently demonstrated a numerical improvement over placebo. The Applicant also reported numerical improvements on the NPI-NH anxiety score (LSMD: -0.56 [95% CI: -1.13, -0.05]) and the irritability/lability score (LSMD: -0.94 [95% CI: -1.51, -0.37]).

Table 53: Study 331-14-213 Change from Baseline to Week 12 in Secondary and Exploratory Efficacy Measures

Variable[1]	Placebo	BREX 2 and 3 mg
NPI-NH 12-item Total Score	N=111	N=215
Baseline Mean (SD)	36.63 (17.24)	37.66 (17.83)
LSM Change from Baseline (SE)	-12.7 (1.16)	-17.3 (0.93)
Placebo-subtracted difference (95% CI)		-4.60 (-7.33, -1.88)
NPI-NH Agitation/Aggression Score	N=112	N=217
Baseline Mean (SD)	7.51 (2.15)	7.72 (2.15)
LSM Change from Baseline (SE)	-3.06 (0.25)	-3.60 (0.20)
Placebo-subtracted difference (95% CI)		-0.54 (-1.13, 0.05)
NPI-NH Occupational Disruptiveness Score[1]	N=52	N=94
Baseline Mean (SD)	17.37 (6.82)	16.69 (6.58)
LSM Change from Baseline (SE)	-2.85 (0.76)	-6.44 (0.67)
Placebo-subtracted difference (95% CI)		-3.58 (-5.23, -1.94)

Source: Clinical Reviewer-adapted using Applicant's Clinical Study Report 331-14-213, CT 5.5.1 to 5.14.2
Abbreviations: 95% CI = unadjusted 95% confidence interval; NPI-NH = Neuropsychiatric Inventory-Nursing Home; SD = standard deviation; SE = standard error
[1]Assessment only collected in institutionalized subjects
Note: MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

Clinical Reviewer's Comment: *The Applicant indicated that the quality of life and caregiver burden measures were not included in this study. Given that the treatment effect was larger in this enriched study population, it appears that brexpiprazole's effect was also numerically greater when assessing change in the NPI-NH 12-item total score and occupational disruptiveness subscale score measure relative to the two previous studies. However, it is unclear whether the effect was correlated with changes in quality of life and caregiver burden measures.*

8.1.4 Assessment of Efficacy Across Trials

The Applicant submitted the results of three adequate and well controlled trials (331-12-283, 331-12-284, and 331-14-213) to provide evidence of brexpiprazole's effect for the treatment of AAD. Although the three studies shared the same basic trial design elements (i.e., double-blind, placebo-controlled, randomized study design and trial duration of 12 weeks), differences in the study population (i.e., diagnostic criteria for agitation) can be attributed to the Agency's evolving advice over time. The Applicant conducted Studies 331-12-283 and 331-12-284 in 2013 and used identical inclusion and exclusion criteria to select their trial population. In comparison, the Applicant conducted Study 331-14-213 in 2018 and required subjects to meet the IPA provisional consensus definition for agitation and exhibit significant CMAI Factor 1 aggressive agitation. Given that Study 331-12-284 failed to meet its primary endpoint and Studies 331-12-283 (BREX 1 mg and BREX 2 mg) and 331-14-213 (combined BREX 2 and 3 mg) evaluated different treatment arms for their primary and secondary efficacy analyses, this section intends to only compare the results across studies instead of pooling treatment arms together.

Primary Endpoints

The primary endpoint for all three studies was mean change from baseline in the CMAI total score at Week 12. Table 54 provides a summary of the primary endpoint analysis across the three phase 3 studies. 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. The flexibly dose BREX 0.5 to 2 mg arm in Study 331-12-284 failed to meet its primary endpoint.

Table 54: Primary Endpoint Results Across all 12-week Phase 3 Studies (MMRM; Efficacy Sample)

Study ID	Treatment Arm	Sample Size	Baseline CMAI Total Score	LS Mean Change in CMAI Total Score at Week 12	LSMD (95% CI)
331-12-283	BREX 1 mg	134	70.5	-17.6	0.23 (-3.40, 3.86)
	BREX 2 mg	138	71.0	-21.6	-3.77 (-7.38, -0.17)
	Placebo	131	72.2	-17.8	
331-12-284	BREX 0.5 to 2 mg	131	71.5	-18.9	-2.34 (-5.49, 0.82)
	Placebo	135	68.6	-16.5	
331-14-213	BREX 2 and 3 mg	225	80.6	-22.6	-5.32 (-8.77, -1.87)
	Placebo	116	79.2	-17.3	

Source: Clinical Reviewer-adapted using Applicant's Integrated Summary of Efficacy Clinical Study Report
Abbreviations: 95% CI = unadjusted 95% confidence interval; CMAI = Cohen Mansfield Agitation Inventory; LS = least squares; LSMD = least squares mean difference; NPI-NH = Neuropsychiatric Inventory-Nursing Home; SD = standard deviation; SE = standard error
[1]Assessment only collected in institutionalized subjects
Note: MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

Even though the Applicant enriched Study 331-14-213 to include subjects with significant CMAI Factor 1 aggressive behaviors, the enrichment strategy appeared to have only increased the treatment effect by approximately 1.5 points at the group-mean level. Although enrichment strategy did not influence most of the baseline demographic or disease characteristics, the subjects enrolled in Study 331-14-213 had a mean baseline CMAI total score that was approximately 10 points higher than the subjects enrolled in Studies 331-12-283 and 331-12-284 (70 points vs. 80 points, respectively). The results when comparing across studies suggest that the treatment effect is maintained (and possibly greater) in patients with higher baseline CMAI total score. Further analyses to assess the impact of baseline severity within each individual CMAI domain also suggested that the treatment effect was maintained or greater across the wide range of baseline CMAI subscores observed.

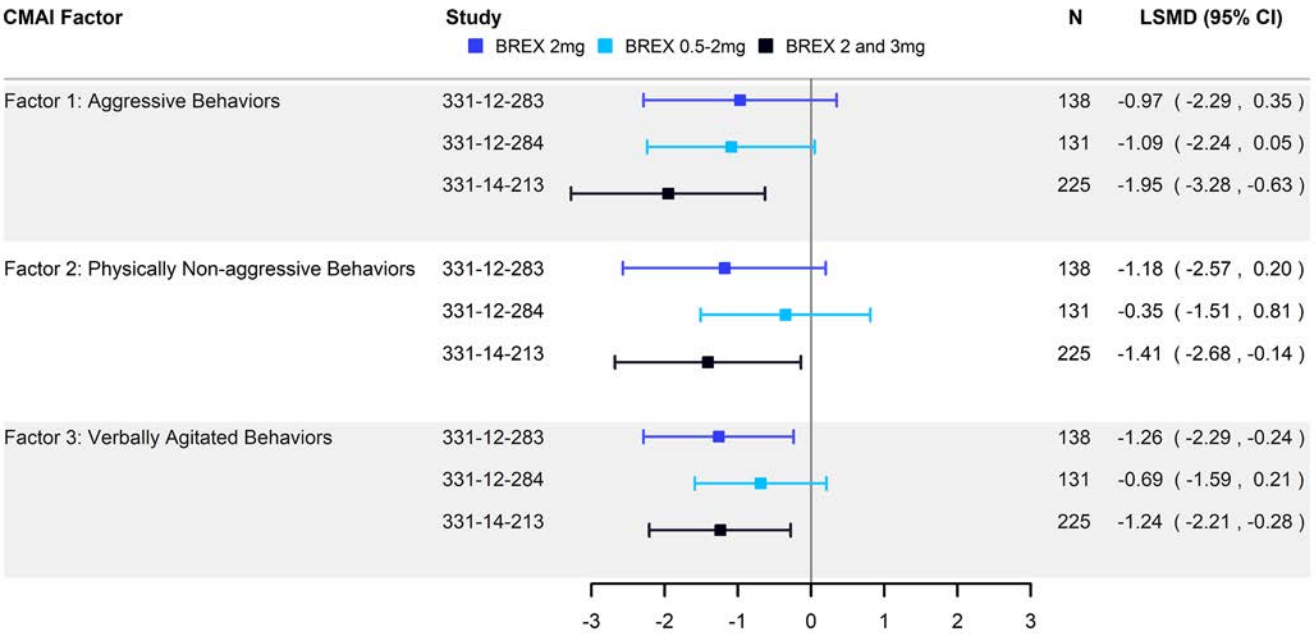
Clinical Reviewer's Comment: *In clinical practice, non-pharmacological treatments are often first-line options for patients with mild AAD. In this development program, the Applicant*

included subjects who previously received non-pharmacological interventions but still exhibited symptoms that were sufficient enough to be eligible for enrollment. Agitation represents a continuum of behaviors with milder, possibly more frequent verbal agitation and physically non-aggressive behaviors, and more severe and less frequent aggressive behaviors. The CMAI is a tool intended to measure symptom frequency; therefore, the use of the CMAI total score to categorize patients into different severity categories is not recommended. Because patients can exhibit a heterogenous range of symptoms, identifying a population with mild, moderate, or severe agitation is difficult. Given the results from these studies, the product indication should not be limited to specific range of baseline agitation severity.

Secondary and Other Endpoints

Because the developers of the CMAI did not intend to use the total score to measure changes in symptoms related to agitation, the Agency and the Applicant discusses the need to show consistent numerical improvements on each of the CMAI subscales that aligned with IPA definition for agitation (Factor 1, 2 and 3). Figure 25 displays a forest plot of the treatment effects observed with each CMAI subscale in each study. The consistent direction improvement observed across all three CMAI subscales suggest no compensatory change in one domain compared with another at the group-mean level. The results were also aligned with the overall change in the CMAI total score

Figure 25: Change from Baseline in CMAI Factor Subscales Across all 12-Week Phase 3 Studies



Source: Clinical Reviewer-created using Applicant's Clinical Summary of Efficacy Report Table 2.7.3.3.2.3.1-1
Abbreviations: 95% CI = unadjusted 95% confidence interval; CMAI = Cohen Mansfield Agitation Inventory; LSMD = least squares mean difference
Note: BREX 1mg group not shown for Study 331-12-283

Clinical Reviewer's Comment: *It is important to note that the Applicant did not conduct a factor analysis with their own data to support the use of a total score; instead, the factors were based on a large-scale factor analysis conducted by Rabinowitz et al. The results suggest that there is movement within each domain and by item, and the correlations between domains by treatment groups appear reasonable. There was also no single factor that overly influenced the CMAI total score. This suggests a broad benefit of brexpiprazole across different behaviors associated with AAD. Refer to Dr. Swett's DCOA review for further interpretation of changes within the CMAI subscales and the correlation with the CMAI total score.*

Subpopulations

See Sections 8.1.1.2, 8.1.2.2, and 8.1.3.2 for results of primary endpoint subgroup analyses for each study. Demographic subgroup analyses were generally similar by age and gender. As the large majority of subjects were white (~95%), subgroup analyses by race would not be informative. Regional differences observed in Study 331-14-213 could be potentially explained by ethnic differences observed on placebo response (Hispanic or Latino subjects resided predominantly in the US and exhibited a higher placebo response compared to non-Hispanic or Latino subjects in the US or ROW; Section 8.1.3.2).

Additional subgroups based on baseline disease characteristics (i.e., presence vs. absence of psychotic symptoms, mild vs. moderate vs. severe cognitive impairment, and institutionalized vs. non-institutionalized care setting) were also evaluated to identify specific subgroups where the benefits of brexpiprazole may not outweigh its risks. The Applicant conducted a pooled analysis of the fixed-dose trials (Studies 331-12-283 and 331-12-213) and evaluated the treatment effect for subjects receiving BREX 2 or 3 mg. The results suggest that there were similar directional improvements based on baseline psychosis status (presence of psychosis: LSMD = -6.02 [95%CI: -11.83, -0.21] vs. absence of psychosis: LSMD = -4.17 [95%CI: 6.62, -1.52]) or cognitive impairment (mild/moderate: LSMD = -4.81 [95%CI: -4.81 [95%CI: -7.56, -2.06] vs. severe: LSMD = -3.18 [-8.37, 2.01]). For Study 331-12-283, the treatment effect by care setting was similar (institutionalized: LSMD = -3.40 [95%CI: -7.76, 0.96] vs. non-institutionalized: LSMD = -4.69 [95%CI: -10.76, 1.36]). However, analysis of the primary endpoint by care-setting for Study 331-14-213 was confounded by ethnicity and region; the proportion of Hispanic and Latino subjects was higher than in the non-institutionalized (52%) vs. the institutionalized (5%) care setting. There were also no Hispanic subjects enrolled in the ROW sites. Therefore, the subgroup analysis by care setting for Study 331-14-213 was not informative.

Clinical Reviewer's Comment: *There were no clinical subgroups identified where the benefits of brexpiprazole did not outweighs its risk. Given the limited number of non-white subjects and subjects < 65 years of age, subgroup analysis by age and race is not informative. It is unclear why Hispanic subjects exhibited a greater placebo response. Given that the CMAI is a caregiver reported outcome measure rated by the clinician, it is unclear whether ethnicity could influence item responses. The studied population was diverse with regards to comorbid BPSD symptoms, other medical comorbidities, and medication use; therefore, the results appear generalizable to a real-world patient population that is likely to receive treatment for AAD.*

Dose Response

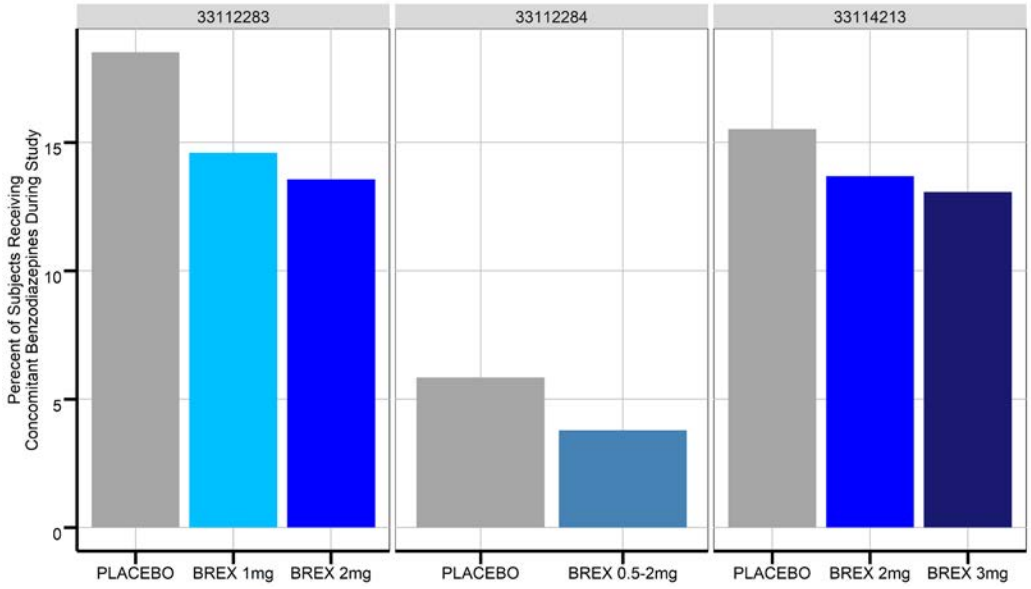
The Applicant only conducted two fixed-dose studies (331-12-283 and 331-14-213) evaluating brexpiprazole dosing regimens of 1, 2, and 3 mg/day. The Applicant exposure-response analysis suggested that percent change from baseline in CMAI total score at Week 12 is related to brexpiprazole average concentration at steady state. The findings of a positive sigmoidal dose-response and exposure-response relationship also provide additional supportive evidence of effectiveness of brexpiprazole use for the treatment of AAD.

Clinical Reviewer's Comment: *Although a positive sigmoidal dose/exposure-response relationship was observed across the dose range studied, the effects of BREX 2 and 3 mg were generally similar across primary, secondary, and exploratory endpoints. It is unclear whether subjects who were randomized to BREX 3 mg would have responded adequately had they continued to receive BREX 2 mg after Week 4. Similarly, it is unclear whether subjects who did not respond adequately to BREX 2 mg would have experienced clinical benefit if their dosage was titrated to BREX 3 mg/day. Although the maximum recommended dosage is 3 mg/day, the Agency agrees with the Applicant that patients' dosage could be titrated from BREX 2 mg to BREX 3 mg after 2 weeks if patients are not responding adequately and report no tolerability concerns.*

Across all three phase 3 studies, the Applicant indicated that concomitant benzodiazepine use was permitted during the first 4 weeks of the randomized phase and limited dosing to 4 days/week with a maximum dose of 2 mg/day of lorazepam (or benzodiazepine equivalent). After the Week 4 visit, benzodiazepine use was prohibited and would be considered a protocol violation. Given that benzodiazepines are commonly used in clinical practice as acute treatment options to manage agitation, a decrease in the percentage of subjects receiving concomitant benzodiazepines among those randomized to brexpiprazole would be clinically meaningful. The review team conducted additional analyses to evaluate the percentage of benzodiazepine use across each treatment arm in each study (Figure 26). Although the differences between treatment groups were small, there was a dose-response trend suggesting decreasing benzodiazepine use with higher doses of brexpiprazole.

Clinical Reviewer's Comment: *Generally, benzodiazepine (lorazepam being the most common) use also varied by region; more subjects enrolled in North American sites received benzodiazepines vs. subjects participating in ROW sites consistently across all treatment groups. Although the results could be confounded based on the use of other off-label treatments for worsening agitation, the results consistently suggested numerically lower percentages of benzodiazepine use in brexpiprazole treated subjects. Given the inherent risks associated with benzodiazepines (e.g., associated with higher risk of falls and fractures, respiratory conditions, cognitive worsening), the results provide additional clinically meaningful context for the use of brexpiprazole in this patient population.*

Figure 26: Percentage of Subjects Receiving Concomitant Benzodiazepines by Treatment Group Across all Phase 3 Studies



Source: Clinical-reviewer created using adcm.xpt datasets from all phase 3 studies
Note: The Applicant allowed benzodiazepine use during the first 4 weeks of the randomized phase and limited administration to 4 days/week with a maximum dosage of 2 mg/day or lorazepam (or equivalent).

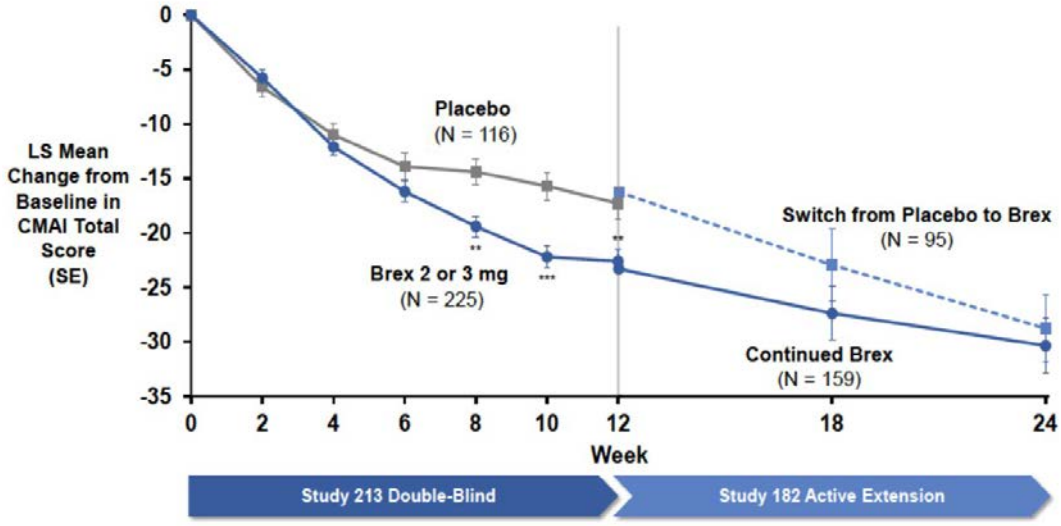
Onset and Durability of Efficacy Effects

See Sections 8.1.1.2, 8.1.2.2, and 8.1.3.2 for information on brexpiprazole's onset of efficacy and durability of effect. Based on the treatment effects observed across the brexpiprazole treatment arms, brexpiprazole appears to begin separating from placebo after approximately 4 to 6 weeks of continuous once-daily treatment.

Study 331-201-00182 was a multi-center, active-treatment extension, 12-week study designed to assess the long-term safety and tolerability of brexpiprazole in subjects who completed 12 weeks of treatment in Study 331-14-213. Refer to Section 8.2.7 for details regarding the study design. After receiving 12 weeks of treatment in Study 331-14-213, mean baseline CMAI total scores for the prior placebo group were higher than those for the prior brexpiprazole group (62.9 vs. 57.3, respectively). After 12 weeks of additional treatment, subjects who received prior brexpiprazole treatment continued to experience a mean change in the CMAI total score of -7.1 points. Subjects who received prior placebo treatment experienced a mean change in the CMAI total score of -12.5 points (Figure 27). However, the mean CMAI total scores at Week 24 (12 weeks after study enrollment) were similar between both treatment groups.

Given that the Applicant did not collect efficacy measures either during the follow-up period for any of the phase 3 efficacy studies or during the post-treatment observational study (Study 331-13-211), the persistence of effect after subjects discontinued brexpiprazole treatment was not discernible.

Figure 27: Change from Baseline in CMAI Total Score Through 24 Weeks of Treatment in Subjects Enrolled in Studies 331-14-213 and 331-201-00182 (MMRM; Efficacy Sample)



Source: Applicant's Advisory Committee Briefing Package, Figure 30; page 79
Abbreviations: CMAI = Cohen Mansfield Agitation Inventory; LS = least squares mean
**P-value < 0.01; ***p < 0.001 vs. placebo
Note: 163 patients on brexpiprazole entered Study 182 and continued brexpiprazole; MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

Clinical Reviewer's Comment: *It is important to note that the results from Study 331-201-00182 are purely exploratory because of the potential expectation bias from subjects receiving unblinded brexpiprazole treatment. The efficacy sample in the extension phase was a convenience sample; only 75% of patients in Study 331-14-213 entered the open-label extension phase. Randomization is likely lost in this convenience sample. In addition, the overall dropout rate over the 24-week duration was very high, 43%. However, subjects who continued to receive unblinded brexpiprazole treatment, on average, did not experience worsening of symptoms.*

In clinical practice, clinicians often use short-term or "as-needed" (PRN) dosing with antipsychotics to treat BPSD symptoms related to AD due to concerns regarding the increased risk of mortality and the preconception that antipsychotics likely have a quicker onset of effect due to their relatively acute sedative effects. In contrast, the results of this development program indicate that brexpiprazole's effect is not discernable from placebo until approximately 4 weeks after chronic once-daily dosing at dosages ≥ 2 mg. Therefore, the product label should clearly communicate to that brexpiprazole is not intended to be used as a PRN treatment for AAD.

Clinically Meaningful Within-Patient Change

The Applicant conducted several post-hoc analyses to derive a clinically meaningful within-patient change threshold for the primary endpoint. The meaningful within-patient change threshold was derived using a triangulation of methods, including anchor-based and

distribution-based methods. The results of the analyses suggested a threshold for the CMAI total score in the range of 15-to-25-point reduction. For a conservative estimate of a 20-point reduction in the CMAI total score, a patient would experience a 2-point improvement on the CGI-S. Table 55 presents the percentage of responders for the CMAI total score using different meaningful change thresholds.

Table 55: Percentage of Responders for the CMAI Total Score Using Different Meaningful Change Thresholds Across all 12-week Phase 3 Studies

Study/Treatment	Sample Size	Clinically Meaningful Within Patient Change Thresholds		
		-15	-20	-25
331-12-283				
Placebo	118	52%	41%	28%
BREX 1 mg	119	51%	39%	29%
BREX 2 mg	120	60%	47%	40%
331-12-284				
Placebo	117	48%	38%	29%
BREX 0.5 to 2 mg	116	60%	49%	33%
331-14-213				
Placebo	103	50%	37%	29%
BREX 2 and 3 mg	194	70%	57%	42%

Source: Reviewer-adapted using Applicant's Interpretation of CMAI Scores Report, Table 3.4-1

The Applicant also collected qualitative data from semi-structured interviews with caregivers of AD patients to better understand their perspectives on the frequency and severity of agitation behaviors and what constitutes a meaningful change in agitation. The data suggests that caregivers understand the severity of agitation as a function of the frequency of the behavior; therefore, most caregivers reported that a change in the frequency of agitated behaviors is considered to be meaningful. Overall, physical behaviors are perceived as more severe than verbal behaviors, although verbal behaviors can escalate into physical behaviors.

Clinical Reviewer's Comment: Refer to Dr. Swett's DCOA review regarding the limitations of conducting anchor-based analysis to interpret within-patient change on the CMAI. The concepts within the primary endpoint (CMAI), which measure symptom frequency, do not align with the anchors (CGI-S and CGI-I), which measure improvement in severity and mental illness. The recall period for the CMAI (over 2 weeks) also does not align with the recall period of the CGI-S (present state). Notably, meaningfulness of the CMAI total scores cannot be interpreted in isolation and should be supplemented with evaluation of change scores by domain and treatment arm. While acknowledging these limitations, the results also generally indicate a higher percentage of patient responders in the brexpiprazole group vs. placebo regardless of the responder threshold/definition. Given that caregivers perceive physical aggressive behaviors as more severe, this reviewer conducted additional analyses to evaluate the degree to which

aggressive behaviors diminished. For example, among subjects who reported aggressive behaviors several times an hour (CMAI score of 7) at baseline, subjects who received brexpiprazole reported an average decrease in frequency to several times a week (CMAI score of 3), while subjects receiving placebo reported a decrease to only one to twice a day (CMAI Score of 5). Overall, the reduction in aggressive behaviors were consistently greater with brexpiprazole relative to placebo regardless of the baseline frequency.

8.1.5 Integrated Assessment of Effectiveness

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. The positive dose/exposure-response relationship characterized across the fixed-dosed groups (BREX 1 mg, 2 mg, and 3 mg) in Studies 331-12-283 and 331-14-213 provides supportive evidence of effectiveness.

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. Therefore, the numerically similar treatment effects may provide additional supportive evidence of effectiveness for brexpiprazole 2 mg/day for the treatment of AAD.

Given interpretability concerns over the use of the CMAI total score as the primary endpoint, the Agency requested analyses on the CMAI Factor subscales to determine whether there was consistent directional improvement on each domain of agitation and whether improvement in one domain was not compensated in another. Analysis of the CMAI subscale scores in each of the three studies indicated nominally consistent trends in improvement in aggressive, physically non-aggressive, and verbal agitated behaviors, which encompass all the major factors measured.

The majority of subjects across all three studies exhibited significant aggressive, physically non-aggressive, and verbally agitated behaviors. The Applicant enrichment strategy to include subjects with significant aggressive behaviors in Study 331-14-213 led a study population that exhibited a higher baseline disease severity relative to Studies 331-12-283 and 331-12-284. Evaluation of the study results from all three studies indicated that the treatment effect was maintained across the wide range of agitated symptoms observed in the population. Subgroup analyses of various demographic and disease characteristics also did not identify a population where the expected benefit was significantly lower than the studied population. Therefore, brexpiprazole appears to be effective for the broader population of patients with AAD.

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

8.2 Review of Safety

8.2.1 Safety Review Approach

The safety evaluation of this supplemental application is based on three phase 3 studies (331-12-283, 331-12-284, and 331-14-213). The integrated assessment of safety also includes data from a post-treatment observational study (331-13-211) and an ongoing blinded, active-treatment extension study (331-201-00182) (both open-label). Details regarding the study design and enrolled patient population for all the aforementioned studies are provided in Section 8.1.1 and 8.2.7 of this review.

Drug utilization data suggest that antipsychotics are frequently used off-label for the treatment of BPSD in elderly patients with dementia (Aigbogun MS, et al., 2020). However, several large-scale meta-analyses of clinical trials, including the Agency's 2005 systematic meta-analysis, have consistently demonstrated a 1.5 to 1.7 times increased risk of mortality and a 2-to-3-fold higher risk for cerebrovascular events among elderly patients with dementia receiving antipsychotics. Given the increased safety concern, various regulatory bodies and healthcare institutions have recommended avoiding antipsychotic therapy. The 2022 American Geriatric Society Beers consensus criteria for safe medication use in elderly patients recommends the use of antipsychotic therapy to treat BPSD if "nonpharmacological options have failed, and the patient is a substantial threat to self or others." Similar to the adult and pediatric population, other AEs of concern include cardiovascular and metabolic effects, EPS, cognitive worsening, infections, and falls. Despite these safety concerns, there are no other alternative psychotropic medications that have shown to be either more effective or safer options to treat BPSD in elderly patients with dementia.

To better contextualize brexpiprazole's benefit-risk profile for the treatment of AAD, this review will primarily focus on the deaths observed across all three 12-week, phase 3 studies (331-12-283, 331-12-284, 331-14-213). In the 2005 meta-analysis, the Agency included 17 randomized placebo-controlled trials of antipsychotics in elderly patients with dementia and estimated the mortality risk across five atypical (aripiprazole, olanzapine, quetiapine, and ziprasidone) and one typical antipsychotic (haloperidol). In order to juxtapose the findings from this program with the previous meta-analysis, this review utilized a similar methodological approach to estimate brexpiprazole's mortality risk in the AAD population. In the Applicant's previous clinical development programs for MDD and schizophrenia, only 248 subjects (3%) aged > 65 years received treatment with brexpiprazole. Because prior clinical studies did not include a sufficient number of elderly subjects, this review also included additional analyses to evaluate brexpiprazole's safety profile in the elderly relative to non-elderly adults.

The pooled dataset for the safety analysis included all subjects who received at least one dose of the study medication in the three phase 3 studies. Due to differences in treatment paradigm (fixed-dose vs. flexible) and dosage strength, the pooled safety analysis was conducted with the following arms: placebo (from all studies), BREX 0.5 to 2 mg (flexible dosing arm from Study 331-12-284), BREX ≤ 1 mg (combines BREX 0.5 [n=20 subjects] and BREX 1 mg from Study 331-

12-283), 2 mg (fixed-dose arms from Studies 331-12-283 and 331-14-213), and 3 mg (fixed-dose arm from Study 331-14-213). The safety analysis reviewed the following data:

- Adverse events (e.g., cerebrovascular, EPS, metabolic changes, orthostatic hypotension, falls, infection)
- Physical examination and vital sign measurements
- ECG parameters
- Laboratory measurements
- MMSE for cognitive impairment
- Sheehan – Suicide Tracking Scale (Sheehan-STS)
- EPS-related scales (i.e., Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], and Simpson-Angus Scale [SAS]).

8.2.2 Review of the Safety Database

Overall Exposure

A summary of the extent of exposure for the three phase 3 studies is shown in Table 56. Across all three trials, 655 subjects were exposed to at least one dose of brexpiprazole. The mean treatment duration (approximately 80 days) was similar between all brexpiprazole groups and placebo. A total of 623 subjects (95%) across all the brexpiprazole groups, including 349 subjects (95%) in the BREX 2- and BREX 3 mg dose group, completed at least 6 weeks (≥ 42 days) of treatment compared with 376 subjects (97%) in the placebo group. There were no differences in mean exposure and dosage by age, gender, region, or race.

Table 56: Treatment Duration and Overall Exposure Across the 12-Week Controlled Trials (Safety Sample)

Variable	BREX ≤ 1 mg (N=157)	BREX 0.5 to 2 mg (N=132)	BREX 2 mg (N=213)	BREX 3 mg (N=153)	ALL BREX (N=655)	Placebo (N=388)
Total duration of exposure (days), mean (SD)	78..4 (15.6)	79.3 (15.6)			79.4 (14.7)	80 (13.7)
Total duration of exposure, cumulative frequency distribution, n (%)						
≥ 7 days	156 (99.4)	131 (99.2)	213 (100.0)	153 (100.0)	653 (99.7)	386 (99.5)
≥ 14 days	155 (98.7)	130 (98.5)	211 (99.1)	153 (100.0)	649 (99.1)	382 (98.5)
≥ 28 days	154 (98.1)	128 (97.0)	207 (97.2)	150 (98.0)	639 (97.6)	379 (97.7)
≥ 42 days	149 (94.9)	125 (94.7)	203 (95.3)	146 (95.4)	623 (95.1)	376 (96.9)
≥ 56 days	139 (88.5)	121 (91.7)	197 (92.5)	142 (92.8)	599 (91.5)	364 (93.8)
≥ 70 days	136 (86.6)	120 (90.9)	193 (90.6)	136 (88.9)	585 (89.3)	356 (91.8)
≥ 84 days	114 (72.6)	89 (67.4)	149 (70.0)	96 (62.7)	448 (68.4)	268 (69.1)

Source: Reviewer-adapted using Applicant's SCS Report, Table 2.7.4.2.1.-1 and 2.7.4.1.2.2-1, p.33-34

Subject demographics for the studied population by study are presented in Section 8.1 of this review. In general, most subjects were white (> 94 %), non-Hispanic or Latino (> 80%), and

female (approximately 60%). The median age in the safety database was approximately 74 years (range: 51 to 90 years). The lack of data available in other racial groups within the United States and ROW is concerning, given that socioeconomic and cultural differences in care for elderly patients could influence reporting of safety information. Overall, demographic characteristics related to height, weight, and BMI were similar within each treatment arm; thus, pharmacokinetic exposures of brexpiprazole are likely similar.

Evaluation of medical and psychiatric history across studies also suggest findings consistent with an elderly population. The average number of months since diagnosis of AD and onset of current episode of AAD was 33.3 months and 20.5 months, respectively. Common medical conditions were similar across treatment arms and included: hypertension (50%), post-menopause (33%), myocardial ischemia (15%), osteoarthritis (13%), gastroesophageal reflux (11%), hyperlipidemia (11%), depression (10%), Type 2 diabetes (10%), and insomnia (8.9%).

The Applicant's list of prohibited medication was similar for all three studies and the incidence of subjects receiving concomitant medications was similar across treatment arms. General medication use mostly included drugs acting on the renal-angiotensin system (39%), antithrombotic agents (23%), beta-blockers (14%), calcium channel blockers (11%), acid reducing agents (13%), anti-diabetic medications (10%), lipid modifying agents (21%), psychoanaleptics (13%), and psycholeptics (11%). Approximately 30% of subjects received at least one EPS-related medication in the pooled safety population, which was also similar across all treatment arms. Given the underlying AD diagnosis, the majority of subjects continued to receive treatment with an anticholinesterase inhibitor (43%) or memantine (51%) during the study period. Benzodiazepine use also appeared to be inversely related to dose and varied across studies (approximately 5 to 15%). Refer to Section 8.1 for additional details regarding concomitant medication use during each study.

Adequacy of the Safety Database

For an efficacy supplement, the size of the safety database (655 subjects) and overall extent of exposure (~ 90% exposed for at least 10 weeks) appears adequate to evaluate the short-term safety profile for brexpiprazole in the AAD population. Treatment duration for managing AAD could vary (e.g., several months to years). Although the Applicant conducted an active-treatment extension study consisting of 162 subjects treated with brexpiprazole for an additional 12 weeks, it is unclear whether 6 months of total treatment is sufficient to characterize the safety profile for patients likely receiving brexpiprazole, sometimes indefinitely, in the real-world.

Clinical Reviewer's Comment: *Although the percentage of subjects with other psychiatric and non-psychiatric comorbid conditions and concomitant medication use was high, the safety population is consistent with an elderly AD patient population. Because the majority of subjects exhibited moderate to severe cognitive impairment, subject-specific AE reporting may not be reliable. Although the Applicant required a specific duration of caregiver oversight (at least 2 hours/day for 4 days/week), obtaining accurate caregiver reporting of AEs may be difficult for*

subjects whose caregiver only meets the minimum reporting requirements.

It is also important to note that brexpiprazole has been approved since 2015 for the treatment of schizophrenia (recommended dose range: 2 to 4 mg/day) and for the adjunctive treatment of MDD (recommended dose range: 2 to 3 mg/day) in adults. In total, the Applicant's brexpiprazole safety database consists of 10,291 subjects exposed at least one dose and approximately half of the subjects completed at least 14 weeks of treatment across 42 completed phase 2 or 3 studies. Although there is sufficient safety experience with brexpiprazole in the general adult population, only 222 subjects were aged > 65 years (~ 2%) in prior studies evaluating brexpiprazole.

Generally, the safety profile observed in long-term open-label studies of other antipsychotics are consistent with findings from short-term studies. Given the lack of a control-arm, concomitant medication use, disease progression, underlying comorbidities, the interpretability of results from a safety study in elderly subjects with AD is limited. Refer to Section 13 for potential post-marketing studies and the feasibility of obtaining long-term safety data in the AAD population.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant provided original Case Report Forms (CRFs) for all deaths, serious AEs (SAEs), and AEs leading to discontinuation. From a safety perspective, there are no issues regarding data integrity and submission quality.

Categorization of Adverse Events

The Applicant assessed for AEs at each study visit throughout the treatment period and categorized AEs by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA; version 19.0 for Studies 331-12-283 and 331-12-384 and version 25.0 for Study 331-14-213). The Applicant collected AEs as per the schedule provided in Section 8.1 of this review. The Applicant defined treatment-emergent adverse events (TEAEs) as AEs that were new in onset or increased in severity following treatment initiation, regardless of causality. The review summarized the number and percentage of patients with any AEs, drug-related AEs, AEs by severity (mild, moderate, and severe), SAEs, AEs leading to discontinuation, and AEs leading to death by treatment group.

Clinical Reviewer's Comment: *The Applicant's AE monitoring, severity determinations, and mapping of verbatim-to-preferred terms are reasonable. The Applicant's categorization of adverse events also align with their previous safety analysis for the original NDA. This reviewer grouped the following preferred terms together:*

- *Cardiac conduction disturbance: atrioventricular block first degree, bundle branch block left, bundle branch block right, electrocardiogram QT prolonged*

- *Decreased appetite: cachexia, decreased appetite, diet refusal, feeding disorder*
- *Dizziness: dizziness, presyncope, vertigo*
- *Insomnia: initial insomnia, insomnia, poor quality sleep, sleep disorder*
- *Psychosis: delusions, hallucinations, psychotic disorder, psychotic symptoms, schizophrenia*
- *Nasopharyngitis: acute sinusitis, nasopharyngitis, pharyngitis, rhinitis, upper respiratory tract infection*
- *Fatigue: fatigue, asthenia, lethargy, malaise*
- *Bone Fracture: bone fracture, hip fracture, patella fracture*
- *Extrapyramidal symptoms: dystonia, dyskinesia, parkinsonism, bradykinesia, hypokinesia, muscle rigidity, musculoskeletal stiffness, reduced facial expression, blepharospasm, muscle spasms, tardive dyskinesia, Parkinsonism, and tremor*
- *Renal and urinary tract infection: cystitis, pyelonephritis, pyelonephritis acute, pyuria, urinary tract infection*

Routine Clinical Tests

The schedule of routine clinical tests for each study was presented in Section 8.1 of this review. The Applicant required all subjects to provide blood sample after fasting for a minimum of 8 hours at the scheduled visit. The scheduling of clinical tests appears similar across studies and adequate to support the review of clinical safety.

8.2.4 Safety Results

Deaths

Across all three phase 3 trials, the Applicant reported a total of nine deaths; eight (1.2%; n = 655) subjects received brexpiprazole treatment and one subject (0.26%, n=388) received placebo. Out of the eight deaths in the brexpiprazole group, four deaths (2.5%; n=157) occurred among subjects receiving BREX ≤ 1 mg, one subject receiving BREX 2 mg (0.5%; n=213), two subject receiving flexible dose BREX 0.5 to 2 mg (1.5%; n=132), and one subject receiving BREX 3 mg (0.7%; n = 153). Of the four deaths reported in the ≤ BREX 1 mg dose group, two subjects received BREX 0.5 mg, and two subjects received BREX 1 mg. Table 57 provides the timing of each death, a summary of each case narrative, and a corresponding direct causality assessment. In general, the cause of death varied and included: heart failure, encephalopathy/encephalitis, aspiration pneumonia, end-stage AD, intracranial hemorrhage, and airway obstruction.

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 visual timeline for each death relative to the last dose of the study medication is

provided in Figure 28. Of note, the Applicant also reported one death (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 deaths in Study 331-201-00182. An evaluation of the case narratives and timing of deaths relative to the last dose of study medication suggested that there were also no apparent patterns in terms of subject demographics or time to onset of AE leading to fatal events.

Clinical Reviewer's Comment: *Based on the Agency's previous meta-analysis, the incidence of death in drug vs. placebo treated subjects over the course of a typical 10-week controlled trial was 4.5% vs. 2.6%, respectively (e.g., 1.7 times greater relative risk). However, the overall incidence of death was relatively lower (0.86% vs. 4.1%) in the presented safety database relative to the 2005 database. Given the imbalance of deaths between the brexpiprazole vs. placebo groups and the similarity in causes of death to previous findings, the increased mortality risk in elderly patients cannot be ruled out for brexpiprazole. Due to confounders related to age, prior medical history, concomitant medication use, and underlying disease progression (consistent with an AD patient population), direct causality assessment based solely on narratives for each death would not be conclusively informative for inferring overall drug-related mortality risk.*

It is also important to contextualize the incidence of death observed with antipsychotics with other alternatives for the treatment of AAD. A review of the literature revealed a very limited number of head-to-head studies evaluating mortality associated with treatments in AD patients with BPSD symptoms. In a matched, registry-based, cohort study consisting of community dwelling patients with AD in Finland during 2005 to 2011, Saarelainen et al estimated the risk of death associated with taking a new benzodiazepine. The cohorts included community dwelling patients diagnosed with mild to moderate AD based on the NINCDS-ADRDA criteria. After matching cohorts based on age, gender, and time since AD diagnosis, the 180-day all-cause mortality rates was 13.4 per 100 person-years among benzodiazepine users (N=10,380; deaths=440; person-years=3,319) vs. 8.5 per 100 person-years among nonusers (N=20,760; deaths=785; person-years=9,282). After adjusting for duration of benzodiazepine use, the 120-day all-cause mortality rate among benzodiazepine users was 15.2 per 100 person-years (Saarelainen L, et al., 2018). In comparison, the mortality rate observed in this study among subjects receiving brexpiprazole was 2.9 per 100 person-years; this estimate is over four-fold smaller than the mortality rate observed with benzodiazepines. This reviewer also acknowledges the general limitations of cross-study comparison and the use of prescription and hospital discharge data to identify patient cohorts. The registered-based cohort study included only community-dwelling patients without specifying that patients had to exhibit symptoms of agitation (or even other BPSD) symptoms. The cohort study also did not exclude patients with background comorbidities that could elevate the risk of mortality (e.g., cardiovascular and cerebrovascular disease, immune deficiency, neurological conditions).

Table 57: Summary of Deaths Across the AAD Development Program

Protocol/ Subject ID	Randomized Treatment (last dose)	Age/ Gender/ Race	Study Day of Last Dose	Study Day of Death	Fatal Adverse Event	Summary Narrative	Direct Causality Assessment
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.	Possible Given the subject's past medical history of chronic heart failure, it is unclear whether brexpiprazole was related to the exacerbation of congestive heart failure, which indirectly led to respiratory pneumonia. The subject may have also been immunocompromised due to type 2 diabetes. The findings of bacterial meningitis could be attributed to possible bacteremia; however, it is unclear whether the bacterial source was due to pneumonia.
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	Unlikely Although the case report indicated that the subject hit the back of her head, follow-up assessments by a neurologist did not suggest any signs or symptoms of head trauma. It is unlikely that the fall resulted in an intracranial bleed 22 days later. Autopsy results also confirmed that there were no

Protocol/ Subject ID	Randomized Treatment (last dose)	Age/ Gender/ Race	Study Day of Last Dose	Study Day of Death	Fatal Adverse Event	Summary Narrative	Direct Causality Assessment
						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 neurobehavior 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 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.	obvious skin bruises, hematoma, or skull fractures that were consistent with head trauma. Notably, the subject had a history of a subarachnoid hemorrhage several years prior to this event.

Protocol/ Subject ID	Randomized Treatment (last dose)	Age/ Gender/ Race	Study Day of Last Dose	Study Day of Death	Fatal Adverse Event	Summary Narrative	Direct Causality Assessment
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 a 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.	Unlikely The subject experienced sudden respiratory arrest after choking on an orange 25 days after discontinuing treatment. Given that the half-life of brexpiprazole is approximately 90 hours, the subject would not have had any detectable level of brexpiprazole in the systemic circulation. The subject was also receiving treatment with chlorprothixene, a typical antipsychotic associated with anticholinergic effects. Because elderly subjects with AD are known to have trouble swallowing, the event of choking could be confounded due to the underlying disease or use of other concomitant medications.
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	Unlikely The initial onset of a possible respiratory infection is confounded by the subject's past medical history of chronic obstructive pulmonary disease and use of benzodiazepines (possible decreased respiratory drive). However, the subject remained on the study drug for

Protocol/ Subject ID	Randomized Treatment (last dose)	Age/ Gender/ Race	Study Day of Last Dose	Study Day of Death	Fatal Adverse Event	Summary Narrative	Direct Causality Assessment
						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 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.	another 5 days. At the time of subject transport, the event of aspiration was likely due to the unresolved respiratory condition.
331-12-283/ (b) (6)	BREX 2 mg (2 mg/day)	86/ Female/ White	86	95	End-stage AD	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 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. There was no autopsy report.	Unlikely Based on the case narrative, the cause of death was likely related to natural disease progression. Evaluation of laboratory tests, vital signs, and ECG did not reveal any safety concerns. The subjects uncontrolled dehydration and hypertension was a result of refusing any additional treatment.

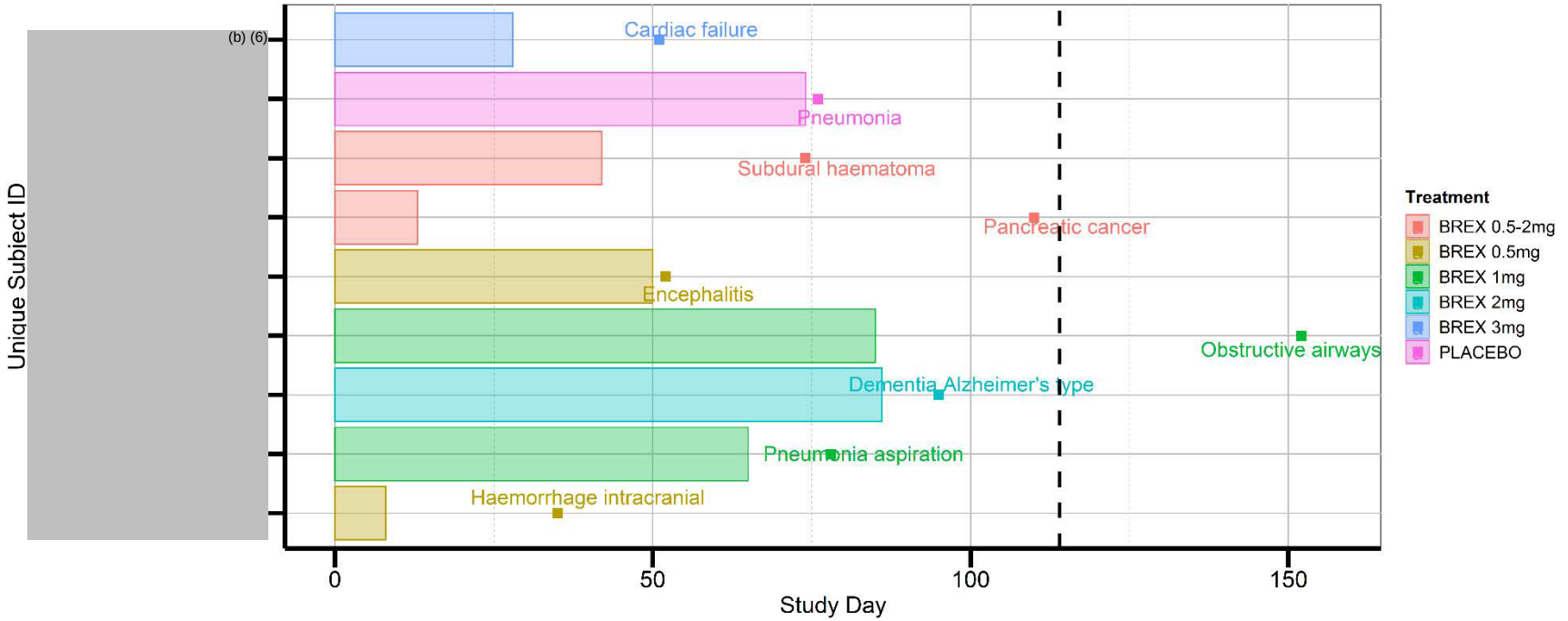
Protocol/ Subject ID	Randomized Treatment (last dose)	Age/ Gender/ Race	Study Day of Last Dose	Study Day of Death	Fatal Adverse Event	Summary Narrative	Direct Causality Assessment
331-12-284/ (b) (6)	PLACEBO	86/ Male/ White	74	76	Pneumonia	Past medical history: anxiety, bladder catheterization, benign prostatic hyperplasia, urine retention The subject was bedbound due to hip pain after a fall in (b) (6) 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.	Not related Subject received placebo during the treatment period.
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 a cardiac failure. Autopsy reports indicated coronary atherosclerosis.	Unlikely Although it is unclear whether the subject had any ongoing or previous cardiac conditions, coronary atherosclerosis (as identified at autopsy) could contribute to worsening heart function. The subject was also receiving concomitant levofloxacin which has also been associated with increased risk of cardiac arrhythmias (e.g., QT prolongation)

Protocol/ Subject ID	Randomized Treatment (last dose)	Age/ Gender/ Race	Study Day of Last Dose	Study Day of Death	Fatal Adverse Event	Summary Narrative	Direct Causality Assessment
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, pneumonectasia, 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.	Unlikely Although there were reports of head trauma, it is unclear whether the preceding event of subdural hematoma was related to the study medication. However, the subdural hematoma was successfully treated with surgery. The subject's underlying medical history for stage III dyscirculatory encephalopathy could have contributed to the resulting brain edema and the fatal AE. The subject discontinued study treatment 32 days prior to the fatal AE. Given that the half-life of brexpiprazole is approximately 90 hours, the subject would not have had any detectable level of brexpiprazole in the systemic circulation.

Protocol/ Subject ID	Randomized Treatment (last dose)	Age/ Gender/ Race	Study Day of Last Dose	Study Day of Death	Fatal Adverse Event	Summary Narrative	Direct Causality Assessment
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).	Unlikely Non-clinical and clinical data collected from prior studies suggest that brexpiprazole is not carcinogenic. There is no additional information to assess whether the subject had pancreatic cancer at the time of study drug initiation.

Source: Clinical Reviewer-created using Applicant's subject case narratives from individual Clinical Study Reports
*The subject was included in table listing even though the death event occurred 2 days after the 30-day follow-up period
Note: The clinical reviewer's causality assessment was based on the World Health Organization standardized case causality assessment criteria.

Figure 28: 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).

When evaluating the timing of deaths relative to reports of AEs and drug exposure, the previous 2005 database suggested that antipsychotic exposure was not usually the direct cause of death but was associated with worsening outcomes over time. In most antipsychotic trials evaluating elderly patients, AEs were a common reason for study discontinuation. Non-fatal adverse reactions to drug could prevent subjects from further study participation, but those subjects could still die at a later date. After these study dropouts occur, even though there is little ambiguity in recognizing deaths, there is often difficulty in deciding which deaths are relevant and in gathering accurate mortality data in subjects as they become lost to follow-up. Therefore, it is important when conducting mortality analysis in this context that an appropriate and uniform sample time frame to count deaths is specified in order to accurately estimate the risk of mortality.

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 withdrew 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 deaths [0.92%]; placebo = one death [0.26%]) 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 if they had 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 the aforementioned bias, this review used 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 deaths in the brexpiprazole and placebo treatment groups. This sampling time frame assumes the possibility of a significant lag between an adverse reaction and death resulting from the event and limits the 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). Using the 114-day sampling time frame, the analysis included seven deaths in the brexpiprazole group and one death in the placebo

group. In comparison with the Applicant's findings, these counts include one additional death in the brexpiprazole group.

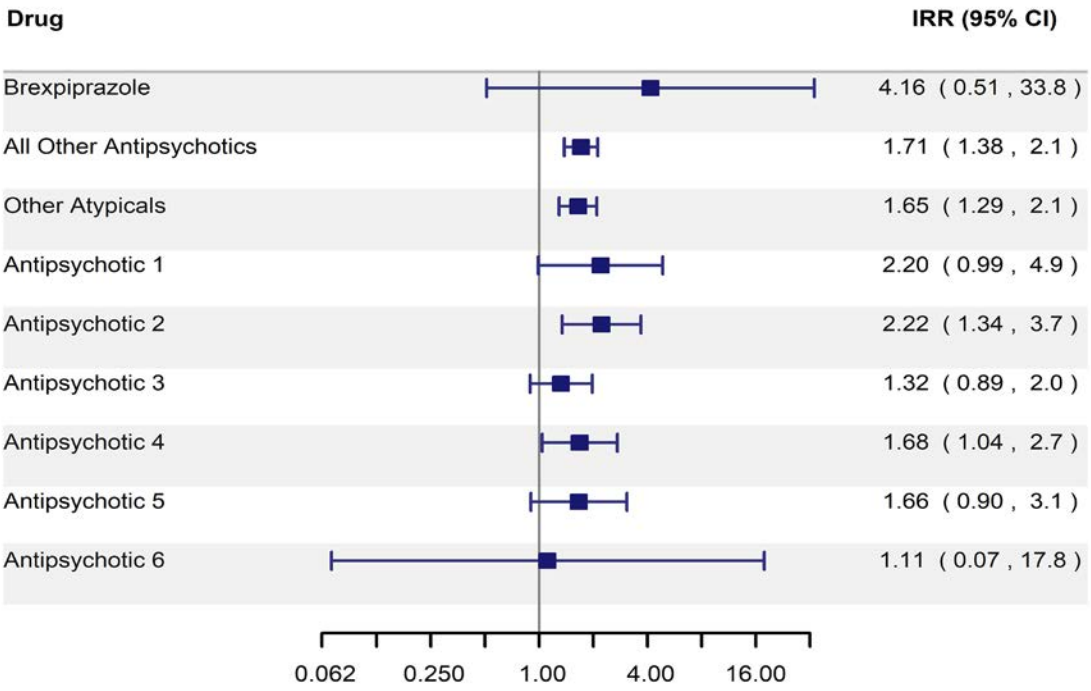
Refer to Table 58 for a summary of deaths occurring by study and treatment arm and for the estimated incident rate ratio (IRR) relative to placebo. Based on the 114-day sampling time frame, the risk of death associated with brexpiprazole was approximately four times higher relative to placebo (IRR = 4.16 [95% CI: 0.51, 33.83). 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]). Figure 29 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. Due to the small number of events in the program, there is great uncertainty in estimating the mortality risk relative to the previous findings as depicted by the wide confidence interval for the IRR estimate.

Table 58: Mortality Analysis of Deaths Across All 12-Week Phase 3 Studies for AAD

Study ID	Treatment	Sample Size	Deaths Observed in the Intended Period of Observation + 30 Days Follow-up Analysis (114 days)		All Observed Deaths Analysis (152 days)	
			Deaths	Exposure Days	Deaths	Exposure Days
(b) (6)	BREX	297	4	33662	5	44796
	PLACEBO	135	0	15390	0	20520
	BREX	132	2*	15004	2*	19944
	PLACEBO	137	1	15580	1	20748
	BREX	226	1	25701	1	34251
	PLACEBO	116	0	13224	0	17632
Total	BREX	655	7	74,367	8	98,991
	PLACEBO	388	1	44,194	1	58,900
IRR (95% CI)			4.16 (0.51, 33.83)		4.75 (0.59, 38.08)	

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 29: 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.

Clinical Reviewer's Comment: *The relatively low overall number of deaths, particularly in the placebo arm, in this program as compared to the incidence observed from prior studies included in the 2005 database adds to the uncertainty of the estimated mortality risk and may also be insufficient to characterize the background rate of death in this population. However, the types of fatal AEs and the imbalance of deaths between treatment groups follows a similar trend observed in previous findings (even if most of the individual cases for this program likely do not seem to exhibit any conclusive drug-related causality).*

Because the use of antipsychotics to treat psychosis and agitation is associated with higher mortality in elderly patients, the Boxed Warning should remain to inform health care providers of this risk. However, it is difficult to identify whether subjects with agitation met the typical diagnostic criteria for dementia-related psychosis. More than 50% of subjects also had other comorbid BPSD symptoms including irritability, anxiety, aberrant motor behavior, apathy, and sleep disorder. The observed mortality risk might not be specific to "dementia-related psychosis," but more general to patients with various BPSD symptoms. Additional analyses are needed to assess the studied population included in the Agency's 2005 database to evaluate whether subjects also met criteria for other BPSD symptoms and to generalize the mortality risk described in the Boxed Warning for future class labeling.

Serious Adverse Events

During the study period, the Applicant reported serious AEs (SAE) among 42 subjects (6.1%) receiving brexpiprazole and 16 subjects receiving placebo (4.1%). The Applicant indicated that SAEs reported in at least two subjects in the brexpiprazole group included: urinary tract infection (six subjects; 0.9%); agitation (three subjects; 0.5%); and pneumonia, fall, dementia, seizure, and chronic obstructive pulmonary disease, each in two subjects (0.3%). The Applicant did not report these events in the placebo group except for pneumonia (two subjects; 0.5%) and urinary tract infection and seizure, each in one subject (0.3%). Table 59 provides a summary of SAEs.

Table 59:Serious Adverse Events Across All 12-Week Phase 3 Studies

System Organ Class[1] /Adverse Event	BREX ≤ 1 mg (N=157)	BREX 0.5 to 2 mg (N=132)	BREX 2 mg (N=213)	BREX 3 mg (N=153)	ALL BREX (N=655)	Placebo (N=388)
Subjects with 1 or more serious AEs	16 (10%)	7 (5.3%)	13 (6.1%)	6 (3.9%)	42 (6.4%)	16 (4.1%)
Blood and lymphatic disorders	-	-	2 (0.9%)	-	2 (0.3%)	-
Anemia	-	-	2 (0.9%)	-	2 (0.3%)	-
Cardiac Disorders	-	-	-	1 (0.7%)	1 (0.2%)	-
Cardiac failure	-	-	-	1 (0.7%)	1 (0.2%)	-
Gastrointestinal Disorders	1 (0.6%)	-	-	-	1 (0.2%)	2 (0.5%)
Gastrointestinal hemorrhage	-	-	-	-	-	2 (0.3%)
Pancreatitis	1 (0.6%)	-	-	-	1 (0.2%)	-
General Disorders	1 (0.6%)	1 (0.8%)	-	-	2 (0.3%)	-
Non-cardiac chest pain	-	1 (0.8%)	-	-	1 (0.2%)	-
Pyrexia	1 (0.6%)	-	-	-	1 (0.2%)	-
Infections	5 (3.2%)	1 (0.8%)	4 (1.9%)	4 (2.6%)	14 (2.1%)	4 (1.0%)
Bacterial Sepsis	1 (0.6%)	-	-	-	1 (0.2%)	-
Cellulitis	1 (0.6%)	-	-	-	1 (0.2%)	-
Colitis	1 (0.6%)	-	-	-	1 (0.2%)	-
COVID-19	-	-	-	1 (0.7%)	1 (0.2%)	1 (0.3%)
Encephalitis	1 (0.6%)	-	-	-	1 (0.2%)	-
Pneumonia	1 (0.6%)	1 (0.8%)	-	1 (0.7%)	3 (0.5%)	2 (0.5)
Urinary tract infection	-	-	4 (1.9%)	2 (1.3%)	6 (0.9%)	1 (0.3%)
Injury, poisoning, and procedural complications	2 (1.3%)	1 (0.8%)	-	1 (0.7%)	4 (0.6%)	4 (1.0%)
Fall	1 (0.6%)	-	-	1 (0.7%)	2 (0.3%)	-
Bone fracture	1 (0.6%)	-	-	1 (0.7%)	2 (0.3%)	4 (1.0%)
Subdural hematoma	-	1 (0.8%)	-	-	1 (0.2%)	-
Metabolism and nutrition	-	-	-	2 (1.3%)	2 (0.3%)	2 (0.5%)
Cachexia	-	-	-	1 (0.7%)	1 (0.2%)	1 (0.3%)
Dehydration	-	-	-	1 (0.7%)	1 (0.2%)	1 (0.3%)

System Organ Class[1] /Adverse Event	BREX ≤ 1 mg (N=157)	BREX 0.5 to 2 mg (N=132)	BREX 2 mg (N=213)	BREX 3 mg (N=153)	ALL BREX (N=655)	Placebo (N=388)
Metabolic Acidosis	-	-	-	1 (0.7%)	1 (0.2%)	-
Nervous system disorders	5 (3.2%)	4 (3.0%)	2 (0.9%)	-	11 (1.7%)	4 (1.0%)
Cerebrovascular accident	1 (0.6%)	-	-	-	1 (0.2%)	-
Alzheimer's dementia	1 (0.6%)	-	1 (0.5%)	-	2 (0.3%)	-
Epilepsy	1 (0.6%)	-	-	-	1 (0.2%)	1 (0.3%)
Intracranial hemorrhage	1 (0.6%)	-	-	-	1 (0.2%)	-
Lacunar infarction	1 (0.6%)	-	-	-	1 (0.2%)	-
Loss of consciousness	-	1 (0.8%)	-	-	1 (0.2%)	-
Syncope	1 (0.6%)	1 (0.8%)	-	-	2 (0.3%)	2 (0.5%)
Psychomotor hyperactivity	-	-	1 (0.5%)	-	1 (0.2%)	-
Transient ischemic attack	-	-	-	-	-	1 (0.3%)
Psychiatric disorders	4 (2.5%)	-	2 (0.9%)	1 (0.7%)	7 (1.1%)	2 (0.5%)
Agitation	2 (1.3%)	-	1 (0.5%)	-	3 (0.5%)	-
Behavior disorder	1 (0.6%)	-	-	-	1 (0.2%)	-
Intentional self-injury	-	-	-	-	-	1 (0.3%)
Mental status change	-	-	-	1 (0.7%)	1 (0.2%)	-
Psychosis	1 (0.6%)	-	1 (0.5%)	-	2 (0.3%)	1 (0.3%)
Renal and urinary disorder	-	-	-	1 (0.7%)	1 (0.2%)	-
Acute kidney injury	-	-	-	1 (0.7%)	1 (0.2%)	-
Respiratory, thoracic, and mediastinal disorders	2 (1.3%)	1 (0.8%)	2 (0.9%)	-	5 (0.8%)	-
COPD	1 (0.6%)	-	1 (0.5%)		2 (0.3%)	-
Dyspnea	-	1 (0.8%)	-	-	1 (0.2%)	-
Hypoxia	-	-	1 (0.5%)	-	1 (0.2%)	-
Obstructive airway	1 (0.6%)	-	-	-	1 (0.2%)	-
Pulmonary edema	-	-	1 (0.5%)	-	1 (0.2%)	-
Vascular disorders	-	1 (0.8%)	1 (0.5%)	1 (0.7%)	3 (0.5%)	-
Hypertension	-	-	-	1 (0.7%)	1 (0.2%)	-
Hypertensive crisis	-	1 (0.8%)	-	-	1 (0.2%)	-
Venous thrombosis limb	-	-	1 (0.5%)	-	1 (0.2%)	-

Source: Reviewer-created using Applicant's Summary of Clinical Safety adae.xpt dataset
Abbreviations: COPD = chronic obstructive pulmonary disease
[1]Subjects were counted once per term for the most severe of multiple occurrences of a specific MedDRA preferred term. Subjects with AEs in multiple organ classes were counted once towards the total
Note: Anemia includes: anemia and microcytic anemia; Gastrointestinal hemorrhage includes: duodenal ulcer hemorrhage and gastrointestinal hemorrhage; Pneumonia includes: pneumonia and aspiration pneumonia; Bone fracture includes: femur fracture, hip fracture, humerus fracture, and patella fracture; COVID-19 includes: COVID-19 infection, and Sars-COV-2 test positive; Cachexia includes: cachexia and failure to thrive; Epilepsy include: epilepsy and seizure; Syncope includes: syncope and presyncope

Dropouts and/or Discontinuations Due to Adverse Effects

Out of the 131 subjects who discontinued from the three phase 3 studies, 56 subjects (42.7%) discontinued due to an AE. Table 60 provides a summary of AEs leading to study drug discontinuation. The Applicant reported at least one AE resulting in study discontinuation for 6.3% and 3.4% of subjects receiving brexpiprazole and placebo, respectively. AEs resulting in discontinuation for three or more subjects in the brexpiprazole groups were agitation (four subjects; 0.6%), seizure (three subjects; 0.5%), and pneumonia (three subjects; 0.5%). Similarly, three subjects (0.8%) in the placebo group experienced potentially worsening agitation and discontinued study medication. There were also no apparent dose-related trends in AEs leading to study drug discontinuation.

Table 60: Adverse Events Leading to Study Drug Discontinuation Across All 12-Week Phase 3 Studies

System Organ Class[1] /Adverse Event	BREX ≤ 1 mg (N=157)	BREX 0.5 to 2 mg (N=132)	BREX 2 mg (N=213)	BREX 3 mg (N=153)	ALL BREX (N=655)	Placebo (N=388)
Subjects with 1 or more serious AEs	14 (8.9%)	9 (6.8%)	7 (3.3%)	11 (7.2%)	41 (6.3%)	13 (3.4%)
Blood and lymphatic disorders	-	-	-	1 (0.7%)	1 (0.2%)	-
Anemia	-	-	-	1 (0.7%)	1 (0.2%)	-
Cardiac Disorders	-	1 (0.8%)	-	-	1 (0.2%)	-
Atrial fibrillation	-	1 (0.8%)	-	-	1 (0.2%)	-
Gastrointestinal Disorders	-	-	-	-	-	1 (0.3%)
Duodenal ulcer hemorrhage	-	-	-	-	-	1 (0.3%)
General Disorders	-	1 (0.8%)	-	2 (0.3%)	3 (0.5%)	1 (0.3%)
Asthenia	-	-	-	2 (0.3%)	2 (0.3%)	-
Gait Disturbance	-	-	-	-	-	1 (0.3%)
General deterioration	-	1 (0.8%)	-	-	1 (0.2%)	-
Infections	2 (1.3%)	1 (0.8%)	1 (0.5%)	2 (1.3%)	6 (0.9%)	2 (0.5%)
COVID-19	-	-	1 (0.5%)	-	1 (0.2%)	2 (0.5%)
Pneumonia	2 (1.3%)	1 (0.8%)	-	1 (0.7%)	4 (0.6%)	-
Urinary tract infection	-	-		1 (0.7%)	1 (0.2%)	-
Viral infection	-	-	1 (0.5%)	-	1 (0.2%)	-
Injury, poisoning, and procedural complications	1 (0.6%)	1 (0.8%)	-	1 (0.7%)	3 (0.5%)	1 (0.3%)
Fall	1 (0.6%)	-	-	1 (0.7%)	2 (0.3%)	-
Bone fracture	-	-	-	1 (0.7%)	1 (0.2%)	1 (0.3%)
Subdural hematoma	-	1 (0.8%)	-	-	1 (0.2%)	-
Investigations	2 (1.3%)	2 (1.5%)	-	2 (1.3%)	6 (0.9%)	2 (0.5%)
Liver enzyme increase	-	2 (1.5%)		2 (1.3%)	4 (0.6%)	-
Lab value increase	-	2 (1.5%)	-	-	2 (0.3%)	2 (0.5%)

System Organ Class[1] /Adverse Event	BREX ≤ 1 mg (N=157)	BREX 0.5 to 2 mg (N=132)	BREX 2 mg (N=213)	BREX 3 mg (N=153)	ALL BREX (N=655)	Placebo (N=388)
Blood pressure increase	-	-	-	1 (0.7%)	1 (0.2%)	-
QT Prolongation	2 (1.3%)	-	-	-	2 (0.3%)	-
Metabolism and nutrition	-	-	1 (0.5%)	1 (0.7%)	2 (0.3%)	-
Feeding disorder			1 (0.5%)	-	1 (0.2%)	-
Dehydration	-	-	-	1 (0.7%)	1 (0.2%)	-
Metabolic Acidosis	-	-	-	1 (0.7%)	1 (0.2%)	-
Nervous system disorders	4 (2.5%)	3 (2.3%)	3 (1.4%)	2 (1.3%)	12 (1.8%)	1 (0.3%)
Akathisia	-	-	-	1 (0.7%)	1 (0.2%)	-
Balance disorder	1 (0.6%)	-	-	-	1 (0.2%)	-
Dementia	1 (0.6%)	-	-	-	1 (0.2%)	-
Dizziness	-	-	-	1 (0.7%)	1 (0.2%)	-
EPS	-	-	3 (1.4%)	-	3 (0.5%)	1 (0.3%)
Lacunar infarction	1 (0.6%)	-	-	-	1 (0.2%)	-
Seizure	-	3 (2.3%)	-	-	3 (0.5%)	-
Somnolence	-	-	-	1 (0.7%)	1 (0.2%)	-
Psychiatric disorders	6 (3.8%)	-	1 (0.5%)	3 (2.0%)	10 (1.5%)	6 (1.5%)
Agitation	3 (1.9%)	-	1 (0.5%)	-	4 (0.6%)	3 (0.8%)
Behavior disorder	1 (0.6%)	-	-	-	1 (0.2%)	-
Intentional self-injury	-	-	-	-	-	1 (0.3%)
Mental status change	-	-	-	1 (0.7%)	1 (0.2%)	-
Psychosis	1 (0.6%)	-	-	1 (0.7%)	2 (0.3%)	1 (0.3%)
Insomnia	1 (0.6%)	-	-	1 (0.7%)	2 (0.3%)	-
Disorientation	-		-	-	-	1 (0.3%)
Renal and urinary disorder	-	-	-	1 (0.7%)	1 (0.2%)	-
Acute kidney injury	-	-	-	1 (0.7%)	1 (0.2%)	-
Respiratory, thoracic, and mediastinal disorders	-	-	-	1 (0.7%)	1 (0.3%)	-
Respiratory disorder	-	-	-	1 (0.7%)	1 (0.3%)	-
Vascular disorders	-	1 (0.8%)	1 (0.5%)	-	2 (0.3%)	1 (0.3%)
Hypertensive crisis	-	1 (0.8%)	-	-	1 (0.2%)	1 (0.3%)
Venous thrombosis limb	-	-	1 (0.5%)	-	1 (0.2%)	-

Source: Reviewer-created using Applicant's Summary of Clinical Safety adae.xpt dataset
[1]Subjects were counted once per term for the most severe of multiple occurrences of a specific MedDRA preferred term. Subjects with AEs in multiple organ classes were counted once towards the total
Note: Pneumonia included: pneumonia and pneumonia aspiration; Bone fracture included: hip and patella fracture; Liver enzyme increase included: alanine aminotransferase increased, aspartate aminotransferase increase, blood alkaline phosphatase increased, and hepatic enzyme increased; Lab value increase included: hypokalemia, blood bicarbonate increased, blood creatinine increased, and blood lactate dehydrogenase increase; EPS included: dysarthria, extrapyramidal disorder, hypokinesia, parkinsonism, psychomotor hyperactivity, and tremor; Psychosis included: delusion, hallucination, and psychotic disorder

Treatment Emergent Adverse Events and Adverse Reactions

A summary of the incidence of AEs occurring in at least 2% of patients in either the brexpiprazole or placebo groups is presented in Table 61. Although the total incidence of patients reporting AEs was greater among subjects receiving brexpiprazole vs. placebo (51% vs. 46%, respectively), there were no dose-dependent trends across dosages 1 through 3 mg/day. AEs reported across the fixed dose studies (Studies 331-12-283 and 331-14-213) in at least 2% of subjects in the total brexpiprazole group with an incidence greater than in the placebo group included: nasopharyngitis, urinary tract infection, headache, somnolence, and insomnia. Only nasopharyngitis, headache, and somnolence met the same criteria and are reported in the product label for subjects who received brexpiprazole for MDD and schizophrenia. The Applicant also did not identify any new AEs for brexpiprazole compared with AEs observed with prior brexpiprazole studies for other indications and for other atypical antipsychotic products.

Table 61: Incidence of Adverse Events Reported by At least 2% of Subjects in the All Brexpiprazole or Placebo Group Across All 12-week Phase 3 Studies

Adverse Event (FDA Medical Query)[1]	BREX ≤ 1 mg (N=157)	BREX 0.5 to 2 mg (N=132)	BREX 2 mg (N=213)	BREX 3 mg (N=153)	ALL BREX (N=655)	Placebo (N=388)
Agitation	5 (3.2%)	6 (4.5%)	5 (2.3%)	-	16 (2.4%)	10 (2.6%)
Cardiac conduction disturbance	6 (3.8%)	2 (1.5%)	6 (2.8%)	-	14 (2.1%)	5 (1.3%)
Decreased appetite	1 (0.6%)	3 (2.3%)	6 (2.8%)	1 (1.5%)	10 (1.5%)	10 (2.6%)
Dizziness	1 (0.6%)	7 (5.3%)	10 (4.7%)	5 (3.3%)	23 (2.9%)	13 (3.4%)
Fatigue	6 (3.8%)	2 (1.5%)	5 (2.3%)	6 (3.9%)	19 (3.2%)	6 (1.5%)
Fall	2 (1.3%)	2 (1.5%)	5 (2.3%)	2 (1.3%)	11 (1.7%)	10 (2.6%)
Headache	12 (7.6%)	10 (7.6%)	18 (8.5%)	10 (6.5%)	50 (7.6%)	36 (9.3%)
Insomnia	7 (4.5%)	5 (3.8%)	11 (5.2%)	4 (2.6%)	27 (4.1%)	12 (3.1%)
Nasopharyngitis	6 (3.8%)	6 (4.5%)	8 (3.8%)	5 (3.3%)	25 (3.8%)	23 (5.9%)
Renal and urinary tract infection	3 (1.9%)	4 (3.0%)	9 (4.2%)	7 (4.6%)	23 (3.5%)	9 (2.3%)
Somnolence	2 (1.3%)	9 (6.8%)	7 (3.3%)	6 (3.9%)	24 (3.6%)	7 (1.8%)

Source: Reviewer-created using Applicant's Summary of Clinical Safety adae.xpt dataset
[1]FDA Medical Query (FDA) narrow definitions were utilized to group Applicant's MedDRA preferred terms. Subjects were counted once per FMQ. Adverse events included only those that started after the start of the study drug or if the event was continuous from baseline and was serious, drug-related, or resulted in death, discontinuation, or interruption or reduction of study treatment.
Note: Agitation included: agitation and irritability; Cardiac conduction disturbance included: atrioventricular block first degree, bundle branch block left, bundle branch block right, electrocardiogram QT prolonged; Decreased appetite included: cachexia, decreased appetite, diet refusal, feeding disorder; Dizziness included: dizziness, presyncope, vertigo; Fatigue included: asthenia, fatigue, and malaise; Insomnia included: initial insomnia, insomnia, poor quality sleep, sleep disorder; Nasopharyngitis included: acute sinusitis, nasopharyngitis, pharyngitis, rhinitis, upper respiratory tract infection; Renal and urinary tract infection included: cystitis, pyelonephritis, pyelonephritis acute, pyuria, urinary tract infection; Somnolence included: somnolence and sedation

Taking into consideration the known safety concerns associated with antipsychotics (particularly in elderly patients), the Applicant examined multiple AEs of special interest (AESI) in their pooled safety database.

Table 62 describes the incidence of AESIs across all 12-weeks phase 3 studies after grouping preferred terms into categories commonly described in patients receiving antipsychotic treatment. AESI categories including somnolence, EPS-related events, akathisia, and

cardiovascular events were numerically larger in the brexpiprazole group vs. placebo. However, incidences of AESI for the selected categories were generally low. Refer to the Laboratory Assessments subsection and Section 8.2.5 for additional analyses of each AESI category.

Table 62: 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)	All BREX (N=655)	Placebo (N=388)
Extrapyramidal Symptom Related Events	5 (3.2%)	9 (6.8%)	10 (4.7%)	4 (2.6%)	28 (4.3%)	12 (3.1%)
Akathisia	-	4 (3.0%)	1 (0.5%)	2 (1.3%)	7 (1.1%)	1 (0.3%)
Dizziness, Syncope, or Orthostatic Hypotension Related Events	4 (2.5%)	9 (6.8%)	12 (5.6%)	5 (3.3%)	30 (4.6%)	19 (4.9%)
QT Prolongation	4 (2.5%)	1 (0.8%)	3 (0.8%)	-	8 (1.2%)	2 (0.5%)
Somnolence	2 (1.3%)	9 (6.8%)	7 (3.3%)	6 (3.9%)	24 (3.7%)	7 (1.8%)
Accidents and Falls	5 (3.2%)	2 (1.5%)	5 (2.3%)	3 (2.0%)	15 (2.3%)	16 (4.1%)
Seizures	1 (0.6%)	3 (2.3%)	-	-	4 (0.6%)	2 (0.5%)
Cardiovascular Events	7 (4.5%)	7 (5.3%)	9 (4.2%)	1 (0.7%)	24 (3.7%)	9 (2.3%)
Cerebrovascular Events	2 (1.3%)	1 (0.8%)	-	-	3 (0.5%)	1 (0.3%)

Source: Reviewer-created using Applicant's Summary of Clinical Safety Report and adae.xpt dataset
Note: Adverse events included only those that started after the start of the study drug or if the event was continuous from baseline and was serious, drug-related, or resulted in death, discontinuation, or interruption or reduction of study treatment.
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

Clinical Reviewer's Comment: *Although the incidence for most of the AESI categories was slightly higher for the overall brexpiprazole group than placebo, the overall incidences are low. There were also no apparent dose-response trends for any of the AESI categories. Further examination of these subjects who experienced severe and serious AESI events also suggested confounding medical histories and use of concomitant medications that could preclude conclusions regarding causality in this study population.*

The product label for brexpiprazole describes that the incidence of EPS-related events, excluding akathisia, in the brexpiprazole vs. placebo group was 6% vs. 3% in subjects participating in 6-week MDD studies and 6% vs. 5% in subjects participating in 6-week schizophrenia studies. Given that the majority of subjects participating in this program received prior antipsychotic therapy and other psychotropic medications, tolerance to AESI could possibly explain the lower reporting of AE relative to subjects with schizophrenia and MDD. Inadequate caregiver reporting of AEs could also be a concern and limit the comparison of findings with other clinical populations. However, there were no apparent safety signals that emerged that were not reported for other antipsychotics.

Laboratory Findings

The Applicant collected laboratory measures based on the schedule of events for each study presented in Section 8.1. The effects of brexpiprazole on chemistry and hematological measures, based on mean change from baseline to the subject's last visit and the incidence of potentially clinically relevant changes in each measure are presented in Table 63. The criteria for identifying laboratory values of potential clinical relevance are described in each of the study protocols. Overall, analysis of laboratory measures did not indicate any clinically relevant differences between any of the brexpiprazole treatment arms and placebo. There were also no apparent dose-dependent trends across any of the laboratory assessments.

Analysis of hepatic measures also confirmed no subjects meeting the criteria for Hy's Law. There were also no differences observed with regards to AEs associated with changes in hepatic (BREX: 1.2% vs. placebo: 1.0%) and renal function (BREX: 1.8% vs. placebo: 1.6%). Across all treatment arms, mean baseline values and mean changes from baseline to last visit for all coagulation-related parameters (i.e., activated partial prothrombin time, platelets, prothrombin time, and INR) were similar. The incidence of AEs associated with electrolytes across the 12-week trials was < 1%, and there were no differences between treatment groups (BREX: 0.2% vs. placebo: 0.5%).

The Applicant also evaluated changes in other clinical laboratory tests including adrenocorticotropic hormone (ACTH) and cortisol. Mean change from baseline to the last study visit for each of these laboratory measures were minimal and similar across all treatment groups (ACTH: brexpiprazole = 0.5 ng/mL vs. placebo =-1.47 ng/mL; cortisol: brexpiprazole = 0.62 ug/dL vs. placebo: -0.02). The Applicant did not define criteria for potentially clinically relevant abnormal values for these measures.

Table 63: Baseline and Mean Changes in Laboratory Assessments During the Treatment Period Across All 12-week Phase 3 Studies

Laboratory Measure[1]	Value	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)
Alanine aminotransferase (U/L)	Mean baseline (SD)	16.7 (10)	17.5 (19)	18.4 (14)	18.2 (16)	16.4 (8.9)
	Mean change (SD)	2.0 (34)	0.6 (8.2)	-1.6 (11)	-0.7 (18)	0.2 (10.0)
	Potentially clinically relevant changes, n (%)	2 (1.3%)	1 (0.8%)	1 (0.5%)	-	1 (0.4%)
Alkaline phosphatase (U/L)	Mean baseline (SD)	81.6 (30)	83.7 (24)	84.6 (48)	81.0 (27)	81.3 (27)
	Mean change (SD)	3.7 (41)	0.4 (16)	0.03 (39)	-1.9 (24)	1.9 (31)
	Potentially clinically relevant changes, n (%)	2 (1.3%)	-	-	-	3 (0.8%)
Aspartate Aminotransferase	Mean baseline (SD)	18.5 (6.2)	19.7 (12)	20.0 (11)	20.0 (7.7)	19.1 (7)
	Mean change (SD)	2.7 (36)	-0.3 (5.8)	-1.0 (11)	0.4 (10)	-0.4 (7.3)

Laboratory Measure[1]	Value	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)
(U/L)	Potentially clinically relevant changes, n (%)	1 (0.6%)	1 (0.8%)	-	-	3 (0.8%)
Bilirubin (mg/L)	Mean baseline (SD)	0.5 (0.2)	0.6 (0.3)	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)
	Mean change (SD)	-0.03 (0.2)	-0.05 (0.2)	-0.01 (0.3)	-0.06 (0.2)	-0.001 (0.3)
	Potentially clinically relevant changes, n (%)	1 (0.6%)	-	-	-	5 (1.3%)
Blood urea nitrogen (mg/L)	Mean baseline (SD)	15.5 (5.5)	14.9 (4.7)	15.9 (5.9)	-	16.2 (6.1)
	Mean change (SD)	-0.4 (5.6)	0.4 (5.4)	-0.01 (5.1)		-0.3 (5.3)
	Potentially clinically relevant changes, n (%)	2 (1.3%)	3 (2.3%)	8 (5.8%)	-	14 (5.2%)
Calcium (mg/dL)	Mean baseline (SD)	9.4 (0.5)	9.5 (0.5)	9.4 (0.5)	9.5 (0.5)	9.5 (0.5)
	Mean change (SD)	-0.003 (0.5)	-0.095 (0.4)	0.003 (0.5)	0.014 (0.5)	-0.056 (0.4)
	Potentially clinically relevant changes, n (%)	6 (3.8%)	3 (2.3%)	7 (3.3%)	2 (1.3%)	12 (3.1%)
Chloride (mEq/L)	Mean baseline (SD)	102 (3.0)	101 (3.3)	102 (3.5)	103 (3.1)	102 (3.4)
	Mean change (SD)	-0.4 (3.4)	0.7 (3.7)	0.2 (3.5)	0.4 (3.1)	-0.2 (3.3)
	Potentially clinically relevant changes, n (%)	1 (0.6%)	2 (1.5%)	-	1 (0.7%)	4 (1.0%)
Cholesterol, fasting (mg/dL)	Mean baseline (SD)	190 (40)	198 (48)	194 (42)	189 (45)	196 (46)
	Mean change (SD)	4.8 (42)	-2.7 (36)	-1.9 (34)	-0.5 (39)	-0.1 (41)
	Potentially clinically relevant changes, n (%)	16 (12%)	16 (13%)	16 (8.4%)	11 (8.3%)	39 (11%)
Creatine kinase (u/L)	Mean baseline (SD)	92.6 (67)	89.3 (56)	102 (98)	97.0 (91)	104 (104)
	Mean change (SD)	3.4 (80)	7.6 (85)	2.3 (145)	9.0 (170)	6.9 (117)
	Potentially clinically relevant changes, n (%)	3 (1.9%)	5 (3.8%)	4 (1.9%)	6 (4.1%)	11 (2.9%)
Creatinine (mg/dL)	Mean baseline (SD)	0.86 (0.2)	0.89 (0.2)	0.88 (0.2)	0.88 (0.2)	0.88 (0.2)
	Mean change (SD)	-0.016 (0.2)	-0.007 (0.1)	0.004 (0.2)	0.003 (0.2)	0.002 (0.2)
	Potentially clinically relevant changes, n (%)	1 (0.6%)	1 (0.8%)	1 (0.5%)	-	4 (1.0%)
Glucose, fasting (mg/dL)	Mean baseline (SD)	96.6 (21)	96.7 (17)	100 (24)	100 (21)	101 (25)
	Mean change (SD)	-2.6 (23)	2.6 (22)	1.3 (26)	6.6 (27)	0.2 (28)
	Potentially clinically relevant changes, n (%)	35 (25%)	39 (32%)	59 (31%)	32 (24%)	81 (23%)
	Mean baseline (SD)	163 (33)	169 (29)	176 (43)	176 (46)	170 (35)

Laboratory Measure[1]	Value	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)
Lactate dehydrogenase (U/L)	Mean change (SD)	2.8 (45)	-0.5 (31)	-3.5 (41)	1.2 (40)	-4.2 (32)
	Potentially clinically relevant changes, n (%)	-	-	-	-	1 (0.3%)
Potassium (mEq/L)	Mean baseline (SD)	4.2 (0.5)	4.3 (0.5)	4.3 (0.4)	4.5 (0.4)	4.3 (0.5)
	Mean change (SD)	-0.01 (0.6)	-0.09 (0.5)	-0.01 (0.5)	-0.14 (0.5)	-0.03 (0.5)
	Potentially clinically relevant changes, n (%)	1 (0.6%)	-	-	-	2 (0.5%)
Sodium (mEq/L)	Mean baseline (SD)	140 (2.8)	140 (2.7)	140 (3.1)	142 (2.6)	140 (3.1)
	Mean change (SD)	-0.10 (2.9)	0.53 (3.6)	0.51 (3.4)	0.09 (3.1)	-0.18 (3.2)
	Potentially clinically relevant changes, n (%)	-	1 (0.8%)	-	-	3 (0.8%)
Triglycerides, Fasting (mg/dL)	Mean baseline (SD)	115 (50)	123 (56)	127 (65)	125 (56)	127 (75)
	Mean change (SD)	10.9 (62)	1.5 (57)	4.6 (83)	-3.7 (51)	5.1 (75)
	Potentially clinically relevant changes, n (%)	39 (28%)	22 (18%)	42 (22%)	15 (11%)	70 (20%)
Urate (mg/dL)	Mean baseline (SD)	4.7 (1.3)	5.0 (1.4)	4.9 (1.4)	5.0 (1.4)	5.0 (1.5)
	Mean change (SD)	0.03 (1.1)	-0.05 (1.0)	0.05 (1.0)	-0.08 (1.0)	-0.02 (1.1)
	Potentially clinically relevant changes, n (%)	2 (1.3%)	-	1 (0.5%)	-	9 (2.4%)
Eosinophils/ Leucocytes (%)	Mean baseline (SD)	2.8 (2.1)	2.4 (1.5)	2.8 (2.1)	2.8 (2.3)	2.7 (1.7)
	Mean change (SD)	0.04 (2.1)	0.09 (1.6)	0.18 (2.1)	-0.47 (1.8)	0.13 (1.8)
	Potentially clinically relevant changes, n (%)	5 (3.2%)	-	3 (1.4%)	-	4 (1.0%)
Hematocrit (%)	Mean baseline (SD)	40.7 (3.9)	41.2 (4.2)	40.9 (4.7)	40.4 (4.4)	40.5 (3.9)
	Mean change (SD)	-0.53 (3.0)	-0.56 (3.6)	-0.71 (3.9)	-0.73 (3.0)	-0.18 (3.6)
	Potentially clinically relevant changes, n (%)	16 (10%)	7 (5.3%)	21 (10%)	19 (13%)	32 (8.4%)
Hemoglobin (g/dL)	Mean baseline (SD)	13.6 (1.3)	13.5 (1.4)	13.5 (1.6)	13.4 (1.5)	13.4 (1.4)
	Mean change (SD)	-0.11 (1.0)	-0.03 (1.0)	-0.11 (1.3)	-0.41 (1.2)	0.05 (1.2)
	Potentially clinically relevant changes, n (%)	5 (3.2%)	4 (3.1%)	11 (5.3%)	7 (4.8%)	13 (3.4%)
Neutrophils ($x10^9$/L)	Mean baseline (SD)	3.95 (1.6)	3.90 (1.3)	3.93 (1.3)	4.11 (1.4)	4.09 (1.5)
	Mean change (SD)	0.11 (1.8)	0.38 (1.7)	0.22 (2.0)	0.24 (1.8)	-0.18 (1.6)
	Potentially clinically relevant changes, n (%)	-	1 (0.8%)	3 (1.4%)	-	2 (0.5%)
Platelets ($x10^9$/L)	Mean baseline (SD)	236 (71)	240 (70)	243 (67)	252 (79)	247 (66)

Laboratory Measure[1]	Value	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)
	Mean change (SD)	-0.6 (63)	-3.9 (64)	9.9 (61)	0.2 (56)	1.3 (60)
	Potentially clinically relevant changes, n (%)	-	-	-	1 (0.7%)	1 (0.3%)
Prolactin (ng/mL)	Mean baseline (SD)	14.3 (16)	13.2 (21)	12.7 (14)	11.7 (15)	13.2 (17)
	Mean change (SD)	-0.75 (17)	-2.2 (20)	0.44 (15)	1.4 (13)	-2.6 (17)
	Potentially clinically relevant changes, n (%)	21 (14%)	6 (4.6%)	31 (15%)	12 (9.2%)	26 (7.0%)

Source: Clinical Reviewer-created using Summary of Clinical Safety adlb.xpt dataset
[1]Calculation of mean baseline and change from baseline for each parameter is based only on subjects with both baseline and evaluation at the last visit for each given parameter
Note: Potential clinically relevant changes include both abnormally low and high values based on the Applicant's pre-specified criteria listed in the Clinical Summary of Safety Report.

Table 64: Shift Analysis of Fasting Glucose During the Treatment Period Across All 12-week Phase 3 Studies

Shift Parameter (Baseline to any post-baseline assessment), n (%)	BREX ≤ 1 mg	BREX 0.5 to 2 mg	BREX 2 mg	BREX 3 mg	Placebo
Normal (< 100 mg/dL) to High (≥ 126 mg/dL)	11 (12%)	11 (13%)	10 (8.3%)	10 (13%)	17 (8.2%)
Impaired (100 to < 126 mg/dL) to High (≥ 126 mg/dL)	4 (14%)	7 (21%)	11 (22%)	10 (22%)	27 (25%)
Normal or Impaired (< 126 mg/dL) to High (≥ 126 mg/dL)	15 (12%)	18 (15%)	21 (12%)	20 (16%)	44 (14%)
Increase of ≥ 10 mg/dL from baseline	47 (36%)	51 (43%)	63 (35%)	54 (42%)	122 (36%)

Source: Clinical Reviewer-adapted using Applicant's Summary of Clinical Safety Table 2.7.4.2.2.1.3-1
Note: Sample size for each parameter and treatment group is based on the total number of treated subjects who met the baseline criteria and had a post-baseline result for the given lab test. Sample size can be derived for each parameter and treatment group using the percent incidence and the number of subjects with the clinically relevant shift.

Summaries of treatment-emergent shifts in fasting glucose levels (based on the American Diabetes Association guidelines) and fasting lipids during the treatment period across all 12-weeks studies are presented in Table 64 and Table 65. The proportions of subjects with shifts from normal baseline fasting glucose to high or from impaired to high at any post-baseline assessment were similar across treatment arms. Similarly, the percentage of subjects reporting an AE for changes in glucose was 0.9% in the brexpiprazole group vs. 0.8% in the placebo group. Incidences of treatment-emergent shifts from baseline fasting serum lipids were also similar for LDL-cholesterol, HDL-cholesterol, and total cholesterol across treatment groups. However, the proportion of subjects with a shift in serum triglycerides from borderline to high was notably

higher in the total brexpiprazole group vs. placebo (29% vs. 12%, respectively). The percentage of subjects reporting an AE for clinically relevant changes in fasting lipids was 0.4% in both brexpiprazole and placebo groups.

Table 65: Shift Analysis of Fasting Lipids During the Treatment Period Across All 12-week Phase 3 Studies

Shift Parameter (Baseline to any post-baseline assessment), n (%)	BREX ≤ 1 mg	BREX 0.5 to 2 mg	BREX 2 mg	BREX 3 mg	Placebo
Total Cholesterol					
Normal (< 200 mg/dL) to High (≥ 240 mg/dL)	8 (10%)	4 (7.4%)	3 (2.9%)	6 (7.5%)	17 (9.4%)
Borderline (200 to < 240 mg/dL) to High (≥ 240 mg/dL)	8 (22%)	11 (26%)	12 (23%)	5 (15%)	21 (21%)
Normal or Borderline (< 240 mg/dL) to High (≥ 240 mg/dL)	16 (14%)	15 (16%)	15 (9.6%)	11 (9.6%)	38 (14%)
Normal (< 200 mg/dL) to Borderline or High (≥ 200 mg/dL)	28 (35%)	12 (22%)	29 (28%)	22 (28%)	59 (32%)
Increase of ≥ 40 mg/dL from baseline	27 (21%)	17 (14%)	29 (16%)	23 (18%)	54 (16%)
Triglycerides					
Normal (< 150 mg/dL) to High (200 to < 500 mg/dL)	9 (7.9%)	5 (5.6%)	17 (13%)	6 (6.4%)	20 (7.9%)
Normal (< 150 mg/dL) to Very High (≥ 500 mg/dL)	1 (0.9%)	-	1 (0.8%)	-	1 (0.4%)
Borderline (150 to < 200 mg/dL) to High (200 to < 500 mg/dL)	2 (29%)	7 (32%)	7 (28%)	3 (26%)	5 (12%)
Normal or Borderline (< 200 mg/dL) to High (200 to < 500 mg/dL)	11 (9.1%)	12 (11%)	24 (15%)	12 (10%)	25 (8.5%)
Increase of ≥ 50 mg/dL from baseline	36 (28%)	32 (27%)	50 (28%)	21 (16%)	76 (23%)

Source: Reviewer-adapted from Applicant's Clinical Summary of Safety Table 2.7.4.2.2.1.3-4 and 2.7.4.2.2.1.3-5
Note: Sample size for each parameter and treatment group is based on the total number of treated subjects who met the baseline criteria and had a post-baseline result for the given lab test. Sample size can be derived for each parameter and treatment group using the percent incidence and the number of subjects with the clinically relevant shift.

The Applicant also used the Adult Treatment Panel III criteria to evaluate subjects for the presence of metabolic syndrome. The Applicant identified cases of metabolic syndrome if subjects met at least three of the following criteria at the same visit: waist circumference ≥ 102 cm for males or ≥ 88 cm for females; triglycerides ≥ 150 mg/dL; HDL < 40 mg/dL for males or < 50 mg/dL for females; systolic blood pressure (SBP) ≥ 130 mmHg and diastolic blood pressure (DBP) ≥ 85 mmHg; and fasting serum glucose ≥ 110 mg/dL. The overall incidence of metabolic syndrome was low (< 5%) in all treatment groups but was slightly higher in several brexpiprazole treatment arms relative to placebo (BREX ≤ 1 mg: 1.7%; BREX 0.5 to 2 mg: 3.7%; BREX 2 mg: 4.5%; BREX 3 mg: 1.6%; placebo: 1.7%)

Clinical Reviewer's Comment: *In general, analysis of laboratory assessments did not reveal any new safety signals. Similar to the laboratory assessments, there were no dose-dependent trends in clinically relevant shifts in fasting glucose and lipids. The lack of clinically relevant differences between brexpiprazole and placebo when comparing changes in glucose and lipids is likely attributed to the background rate of endocrine-related comorbidities in the elderly patient population (approximately 50% of subjects had either impaired glucose or lipids at baseline). A comparison of clinically relevant shifts in fasting glucose and lipids in previous studies evaluating brexpiprazole for MDD and schizophrenia also described consistent results.*

Vital Signs

Summaries for mean changes from baseline to the last study visit for SBP, DBP, and heart rate (HR) across all 12-week phase 3 studies are presented in Table 66. The overall percentage of subjects with clinically relevant changes in vital sign measures was very low (< 1%) across treatment groups. Mean changes in the vital sign measure also suggested that brexpiprazole did not affect SBP, DBP, or HR during the 12-week treatment period. There were also no dose-dependent trends for any of the vital sign measures.

The Applicant defined orthostatic hypotension as ≥ 20 mmHg decrease in SBP and ≥ 25 bpm increase in heart rate when going from supine to sitting or ≥ 20 mmHg decrease in SBP and ≥ 25 bpm increase in heart rate when going from supine to standing. Based on this definition, the incidence of orthostatic hypotension was low and similar across treatment groups (BREX ≤ 1 mg: 1 [0.6%]; BREX 0.5-2 mg: 2 [1.5%]; BREX 2 mg: 2 [0.9%]; BREX 3 mg: 0; placebo: 2 [0.5%]). Across the 12-week trials, the incidence of orthostatic hypotension-related AEs in the brexpiprazole group vs. placebo group was identical (0.5%). The incidence of dizziness (3.2% vs. 3.4%) and syncope (0.2% vs. 0.8%) were also slightly higher in the placebo group.

Table 66: Changes in Heart Rate, Systolic Blood Pressure, and Diastolic Blood Pressure During the Treatment Period Across all 12-Week Phase 3 Studies

Vital Sign Measure	Value[1]	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)
Supine						
	Mean baseline (SD)	68.7 (8.9)	69.2 (8.7)	68.6 (9.5)	68.8 (9.0)	69.1 (9.1)

Vital Sign Measure	Value[1]	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)
Supine						
HR (beats/min)	Mean change (SD)	0.9 (8.1)	-0.5 (8.4)	1.0 (8.4)	0.8 (7.8)	0.7 (8.8)
	Potentially clinically relevant changes, n (%)[2]	1 (0.6%)	-	1 (0.5%)	-	-
SBP (mmHg)	Mean baseline (SD)	126.7 (12.5)	126.0 (10.6)	127.6 (9.6)	127.5 (11.7)	127.8 (11.0)
	Mean change (SD)	0.1 (10.9)	-0.2 (9.9)	-1.1 (9.8)	-0.6 (10.9)	-0.9 (11.3)
	Potentially clinically relevant changes, n (%)[2]	1 (0.6%)	-	-	-	3 (0.8%)
DBP (mmHg)	Mean baseline (SD)	76.6 (8.0)	75.9 (7.4)	76.9 (7.2)	77.5 (7.4)	76.5 (7.3)
	Mean change (SD)	-0 (7.3)	-0.6 (6.6)	-0.5 (6.9)	-0.5 (6.9)	-0.1 (7.6)
	Potentially clinically relevant changes, n (%)[2]	-	-	1 (0.5%)	-	2 (0.5%)
Standing						
HR (beats/min)	Mean baseline (SD)	73.1 (9.8)	75.4 (9.9)	73.1 (9.7)	73.4 (9.3)	74.0 (9.8)
	Mean change (SD)	1.1 (8.6)	-1.0 (9.5)	0.9 (9.0)	-0.1 (8.5)	0.4 (9.0)
	Potentially clinically relevant changes, n (%)[2]	1 (0.6%)	1 (0.8%)	-	-	-
SBP (mmHg)	Mean baseline (SD)	126.6 (12.7)	124.0 (12.0)	125.5 (9.5)	126.0 (10.9)	126.5 (11.0)
	Mean change (SD)	-0.8 (10.0)	1.0 (10.0)	-0.9 (10.0)	-1.1 (10.2)	-0.4 (10.9)
	Potentially clinically relevant changes, n (%)[2]	-	-			6 (1.5%)
DBP (mmHg)	Mean baseline (SD)	76.5 (7.9)	76.1 (7.3)	76.8 (7.1)	78.0 (6.9)	77.1 (7.5)
	Mean change (SD)	0.1 (5.9)	-0.7 (6.6)	-0.2 (6.8)	-0.2 (6.4)	0.3 (7.6)
	Potentially clinically relevant changes, n (%)[2]	1 (0.6%)	-	1 (0.5%)	-	3 (0.8%)

Source: Reviewer-adapted from Applicant's Clinical Summary of Safety CT-ST-9.3.1.1 and CT-ST-9.3.1.2
[1]Calculation of mean baseline and change from baseline for each parameter is based only on subjects with both baseline and evaluation at the last visit for each given parameter
[2]Includes the following clinically abnormal (low and high) vital signs: HR < 50 bpm and decrease ≥ 15 bpm; HR > 120 bpm and increase ≥ 12 bpm; SBP < 90 mmHg and decrease ≥ 20; SBP > 180 mmHg and increase ≥ 20 mmHg; DBP < 50 mmHg and decrease ≥ 15 mmHg; DBP > 105 and increase ≥ 15 mmHg.

Clinical Reviewer's Comment: *Further examination of the range of changes in vital sign measurements indicated small and similar changes between treatment groups. In short-term clinical studies evaluating brexpiprazole in subjects with MDD, the incidence of orthostatic hypotension and dizziness in the brexpiprazole group vs. placebo group was similar (dizziness: 2% vs. 2%; orthostatic hypotension: 0.1% versus 0%, respectively). In short-term trials evaluating subjects with schizophrenia, the incidence for dizziness (2% vs. 2%, respectively) and orthostatic hypotension (0.4% vs. 0.2%, respectively) was also similar. Although elderly patients are often more vulnerable to orthostatic hypotension-related AEs, the exclusion of subject with known cardiovascular and cerebrovascular disease likely led to the low overall incidence observed across the AAD studies.*

Table 67 describes the mean change in body weight from baseline to the last study visit during the treatment period across all 12-week studies. The mean changes in body weight, body mass index, and waist circumference from baseline to the last visit were minimal and similar between subjects in the brexpiprazole groups and in the placebo group. The proportion of subjects with a ≥ 7% increase in body weight (kg) at any visit was 1.7% for the total brexpiprazole group compared with 0.8% for the placebo. More than two-thirds of subjects in these trials were at normal weight (BMI ≥ 18.5 and < 25) at baseline. AEs associated with weight gain abnormalities (preferred terms including BMI increased, increased appetite obesity, weight gain, waist circumference increased, and weight increased) was 2.0% in the brexpiprazole group compared with 0.8% in the placebo group.

Table 67: Changes in Body Weight, Body Mass Index, and Weight Circumference During the Treatment Period Across all 12-Week Phase 3 Studies

Measure	Value[1]	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)
Body Weight (kg)	Mean baseline (SD)	69.1 (14.3)	68.6 (14.8)	69.3 (14.7)	70.2 (15.5)	69.6 (14.1)
	Mean change (SD)	-0.1 (2.0)	0.2 (1.6)	0.2 (2.0)	0.1 (2.9)	-0.2 (2.0)
	Increase ≥ 7%, n (%)	3 (1.9%)	2 (1.5%)	4 (1.9%)	2 (1.3%)	3 (0.8%)
	Decrease ≥ 7%, n (%)	6 (3.8%)	-	5 (2.4%)	3 (2.0%)	11 (2.9%)
Body Mass Index (kg/m^2)	Mean baseline (SD)	25.3 (4.8)	25.4 (4.4)	25.6 (4.3)	26.1 (4.6)	25.9 (4.8)
	Mean change (SD)	0 (0.7)	0.1 (0.6)	0.1 (0.7)	0 (1.1)	-0.1 (0.8)
Weight Circumference (cm)	Mean baseline (SD)	89.8 (14.8)	88.8 (12.2)	92.3 (14.8)	92.3 (14.8)	90.5 (13.5)
	Mean change (SD)	-0.4 (3.7)	-0.1 (2.6)	0.2 (5.1)	-0.2 (4.4)	-0.7 (4.7)

Source: Reviewer-adapted using advs.xpt dataset and Applicant's Summary of Clinical Safety Report CT-ST.9.2.1.1, CT-ST-9.2.2.1, and CT-ST-9.2.3.1
[1]Calculation of mean baseline and change from baseline for each parameter is based only on subjects with both baseline and evaluation at the last visit for each given parameter

Clinical Reviewer's Comment: *Further examination of the range of changes in body weight suggested only small and similar changes between treatment groups. In the short-term clinical studies evaluating brexpiprazole in subjects with MDD, the proportion of subjects with at least 7% increase in body weight at any visit was 6% in the brexpiprazole group and 2% in the placebo group. In short-term trials evaluating subjects with schizophrenia, the proportion of subjects with at least 7% increase in body weight at any visit was approximately 10% in the brexpiprazole group and 4% in the placebo group. Of note, the proportion of subjects with weight loss was higher in both the brexpiprazole and placebo groups. Because elderly patients with dementia may be more likely to experience general weight loss due to underlying comorbidities, loss of appetite, and difficulties swallowing and chewing, the evaluation of brexpiprazole's effect on weight might be confounded.*

Electrocardiograms (ECGs)

The Applicant collected resting 12-lead ECGs at screening, baseline, Week 8, and Week 12 visits. Table 68 describes the mean baseline and mean change from baseline for each ECG parameter across treatment groups in all 12-week studies. In general, changes in each parameter were small and not considered to be clinically meaningful. No subjects in either the brexpiprazole or placebo groups met criteria for HR abnormalities or had ECG findings indicative of acute or subacute infarctions. The most frequently observed abnormality in the brexpiprazole and placebo groups was associated with cardiac rhythm and included supraventricular premature beats (brexpiprazole: 7.9% vs. placebo: 8.6%). No subjects experienced ventricular tachycardia.

Table 68 also provides a summary of changes in the QT interval corrected for heart rate. The most frequent change in QTC interval was in the 30 to 60 msec category with a higher incidence in the placebo group (QTcB: brexpiprazole = 4.9% vs. placebo = 15%; QTcF: brexpiprazole = 10% vs. placebo = 12%). Only five subjects (0.8%) that received brexpiprazole and 11 subjects (2.9%) that received placebo experienced a QTcB interval increase of greater than 60 msec. No brexpiprazole treated subjects exhibited a QTc value > 500 msec by either correction method; four placebo-treated subjects (1.0%) had a QTcB value > 500 msec. The percentage of subjects with reported AEs for QT prolongation were also generally low in both groups (brexpiprazole: 1.2% vs. placebo: 0.5%).

Table 68: Changes in ECG Parameters During the Treatment Period Across all 12-Week Phase 3 Studies

ECG Parameter (msec)	Value[1]	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)
PR Interval	Mean baseline (SD)	163.3 (28)	163.4 (25)	163.2 (26)	162.1 (25)	164.5 (27)
	Mean change (SD)	0.7 (20)	-0.1 (17)	0.6 (15)	-1.2 (17)	1.1 (18)
QRS Interval	Mean baseline (SD)	91.8 (12)	92.2 (13)	91.6 (11)	90.8 (14)	92.9 (12)
	Mean change (SD)	1.1 (9.4)	0.1 (8.2)	0.9 (9.2)	1.5 (9.3)	0.1 (8.6)
RR Interval	Mean baseline (SD)	883 (155)	893 (141)	906 (150)	930 (146)	898 (148)
	Mean change (SD)	-7.1 (125)	8.8 (132)	-13 (144)	-14 (136)	-7.8 (148)
QT Interval	Mean baseline (SD)	398.5 (33)	401.0 (31)	399.7 (31)	301 (32)	398.2 (31)
	Mean change (SD)	-1.6 (24)	1.6 (31)	-1.5 (27)	-3.9 (27)	-0.9 (28)
QTcB Interval	Mean baseline (SD)	426.5 (23)	426.4 (22)	422.2 (24)	417.8 (23)	422.5 (24)
	Mean change (SD)	0.1 (24)	-0.3 (19)	1.3 (24)	2.4 (24)	1.6 (22)
QTcF Interval	Mean baseline (SD)	416.6 (21)	417.5 (21)	414.2 (21)	411.8 (21)	413.9 (22)
	Mean change (SD)	-0.4 (19)	0.3 (19)	0.3 (19)	0.2 (20)	1.1 (19)
QTcN Interval	Mean baseline (SD)	418.7 (21)	419.4 (20)	416.0 (23)	413.1 (21)	415.7 (22)
	Mean change (SD)	-0.3 (20)	0.2 (19)	0.5 (20)	0.7 (20)	1.2 (19)

Source: Reviewer-adapted using Applicant's Summary of Clinical Safety Report CT-ST-10.1.1 and CT-ST-10.1.2
Abbreviations: QTcB = corrected QT interval based on Bazett formula ($QTcB = QT/(RR)^{0.5}$); QTcF = corrected QT interval based on Fridericia formula ($QTcF = QT/(RR)^{0.33}$); QTcN = corrected QT interval based on the Office of Neurology/FDA formula ($QTcN = QT/(RR)^{0.37}$)
[1]Calculation of mean baseline and change from baseline for each parameter is based only on subjects with both baseline and evaluation at the last visit for each given parameter

Clinical Reviewer's Comment: *During previous development programs, the Applicant conducted a thorough QTc Study (331-10-242) to evaluate brexpiprazole's effect on the QT interval. The*

results of the study suggested no clinically significant QTc prolongation at doses three times and four times the maximum recommended human dose for the treatment of schizophrenia and adjunctive treatment for MDD, respectively (see original NDA review and product label). Although elderly patient populations are likely more vulnerable to cardiac rhythm abnormalities due to underlying comorbidities, the findings across this development program confirms the lack of an association with QTc prolongation.

8.2.5 Analysis of Submission-Specific Safety Issues

Extrapyramidal Symptoms

The Applicant used AE reporting and prospective evaluation of EPS-specific rating scale scores to inform the occurrence and severity of EPS-related symptoms in the AAD study population. The incidences of EPS-related AE during the treatment period across all 12-weeks studies are presented in Table 69. The Applicant reported only one subject with akathisia (preferred term of psychomotor hyperactivity) as a serious AE. The incidence of EPS-related AEs was slightly higher among subjects receiving brexpiprazole vs. placebo (5.3% vs. 3.1%). Akathisia, extrapyramidal disorder, and tremor were the only EPS-related preferred AE terms reported in at least two subjects in any of the brexpiprazole dosage groups. Mean global scores captured using the BARS, SAS, and AIMS described no clinically meaningful change from baseline to the last study visit for either brexpiprazole or placebo Table 70. Assessment of EPS-related symptoms based on the three rating scales were consistent with the incidence of reported EPS-related AEs.

Table 69: Adverse Events Related to Extrapyramidal Symptoms During the Treatment Period Across All 12-week Phase 3 Studies

Adverse Events[1]	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)
Subjects with any EPS-Related Events	5 (3.6%)	13 (9.8%)	11 (5.2%)	6 (3.9%)	12 (3.1%)
Akathisia	-	4 (3.0%)	1 (0.5%)	2 (1.3%)	1 (0.3%)
Dyskinesia	-	2 (1.5%)	-	-	1 (0.3%)
Dystonia	1 (0.6%)	-	2 (0.9%)	-	2 (0.5%)
Parkinsonism	4 (2.5%)	9 (6.8%)	8 (3.8%)	4 (2.6%)	9 (2.3%)

Source: Reviewer-created using Applicant's Summary of Clinical Safety Report and adae.xpt dataset
Abbreviations: EPS = extrapyramidal symptoms
[1]Subjects only counted once if they exhibited multiple AEs within each category. Based on the Applicant's grouping of preferred terms; Akathisia includes: akathisia, psychomotor hyperactivity and restlessness; Dyskinesia includes dyskinesia; Dystonia includes gait instability, muscle spasms, and musculoskeletal stiffness; Parkinsonism includes akinesia, bradykinesia, bradyphrenia, gait disturbance, hypertonia, hypokinesia, muscle rigidity, parkinsonism, and tremor.

Table 70: EPS-Related Symptoms Assessed by Rating Scale Measures During the Treatment Period Across All 12-week Phase 3 Studies

EPS-Related Measure	Value[1]	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)
AIMS Total Score	Mean baseline (SD)	0.2 (1.0)	0.1 (0.5)	0.2 (0.6)	0.2 (1.0)	0.2 (1.0)
	Mean change (SD)	0 (0.5)	0 (0.3)	0 (0.4)	-0.1 (0.9)	0 (0.5)
BARS Global Clinical Rating Score	Mean baseline (SD)	0.1 (0.4)	0 (0.2)	0.1 (0.4)	0.1 (0.3)	0.1 (0.4)
	Mean change (SD)	0 (0.3)	0 (0.2)	0 (0.3)	0 (0.3)	0 (0.3)
	Potentially clinically relevant changes, n (%)[2]	1 (0.6%)	1 (0.8%)	-	-	3 (0.3%)
SAS Total Score	Mean baseline (SD)	1.0 (2.0)	0.7 (1.7)	0.8 (1.6)	0.8 (1.7)	1.0 (1.9)
	Mean change (SD)	-0.1 (1.0)	0.2 (1.7)	0.3 (2.6)	0.3 (1.5)	-0.2 (1.2)
	Potentially clinically relevant changes, n (%)[3]	6 (3.8%)	8 (6.1%)	16 (7.7%)	6 (4.3%)	44 (4.3%)

Source: Reviewer-adapted using Applicant's Clinical Summary of Safety Report CT-ST-11.1.1 through CT-ST-11.4.1.2
[1]Calculation of mean baseline and change from baseline for each parameter is based only on subjects with both baseline and evaluation at the last visit for each given parameter
[2]Includes subjects with BARS Global Clinical Rating Score ≤ 2 at baseline and any post-baseline value > 2
[3]Includes subjects with a SAS Total Score ≤ 3 at baseline and any post-baseline value > 3

Clinical Reviewer's Comment: *In previous studies evaluating brexpiprazole in adults, the incidence of EPS-related AEs, excluding akathisia was 5% in the brexpiprazole group and 4% in the placebo group for subjects with schizophrenia and 6% in the brexpiprazole group and 3% in the placebo group for subjects with MDD. The incidence of akathisia was also higher in subjects with schizophrenia and MDD receiving brexpiprazole (6% and 9%, respectively) vs. placebo (5% and 2%, respectively). Reports of EPS-related AEs in the AAD population appear to be consistent with previous findings in patients with schizophrenia and MDD.*

Suicidal Ideation and Behavior

To evaluate brexpiprazole's risk for suicidal ideation and behavior (SI/B), the Applicant collected AEs related to SI/B and prospectively monitored for SI/B using the Sheehan Suicidality Tracking Scale (Sheehan-STS). Across all three phase 3 studies, only two subjects reported AEs associated with SI/B. Both subjects received placebo treatment; one subject (67-year-old, white female) reported severe intentional self-injury starting on Study Day 4 and one subject (76-year-old, white female) reported mild suicidal ideation starting on Study Day 10. No subjects reported suicidal behavior at baseline or at Week 12/ET visit. The average change from baseline in the Sheehan-STS total score, Sheehan-STS suicidal ideation subscale, and Sheehan-STS suicidal behavior subscale at Week 12 was 0 across all treatment groups. The percentage of subjects with a S-SSTS total score > 0 at any time during the treatment period by treatment group was the following: placebo = 13 (3.4%); BREX ≤ 1 mg = 6 (3.8%); BREX 0.5 to 2 mg = 5 (3.8%); BREX 2 mg = 8 (3.8%); and BREX 3 mg = 3 (2.0%). These incidences were identical for the Sheehan-STS suicidal ideation subscale score, given that there were no cases of suicidal behavior.

Clinical Reviewer's Comment: *Overall, the incidence of SI/B based on AE data and responses on the Sheehan-STS was low and similar across all treatment groups. A review of SI/B data reported in previous schizophrenia and MDD studies in adults revealed that seven subjects reported an AE for SI/B (four subjects [0.1%] in prior MDD trials and three subjects [0.1%] in prior schizophrenia trials. Given that both events of suicidal ideation occurred among elderly subjects receiving placebo in the AAD program and the low incidence in other psychiatric trials, it is unlikely that brexpiprazole is associated with an increased risk for SI/B in elderly patients.*

Cerebrovascular and Cardiovascular Events

The incidences of cardiovascular and cerebrovascular events for each treatment arm are described in Table 71. Overall, the incidences were low in all treatment groups over the 12-week study duration. The most common events were in the category of cardiac arrhythmias (incidence of QT prolongation was 1.2% in the overall brexpiprazole group compared to 0.5% in the placebo group; see a description of ECG findings above). Of the 24 subjects in the brexpiprazole group, two subjects reported a serious AE:

- An 87-year-old female (Study 331-12-283) reported moderate pulmonary edema on Day 35 while receiving BREX 2 mg. The subject halted treatment and the event was considered resolved. Relevant medical history included hypertension, hyperlipidemia, chronic kidney disease, cardiac valve disease, and congestive heart failure.

- A 78-year-old male (Study 331-14-213) reported severe cardiac failure on Day 51 while receiving treatment with brexpiprazole 3 mg and discontinued treatment due to hallucinations after 28 days on the study medication. After 24 days following study discontinuation, the subject died due to cardiac failure. Refer to the subject case narrative in Table 57. Relevant medical history included pneumonia.

Similarly, the incidence of cerebrovascular events was low in all treatment groups (0.5% in the overall brexpiprazole group vs. 0.3% in the placebo group). The Applicant did not report any events in the BREX 2 mg or 3 mg arms. A total of three subjects reported four events in the brexpiprazole group and one subject in the placebo group:

- A 60-year-old female (331-12-283) experienced a cerebrovascular accident on Day 27 and lacunar infarction on Day 40 while receiving BREX 1 mg. The Applicant categorized both events as serious (hospitalization), but mild in severity. Investigators withdrew the study medication, and the event was resolved during the trial period. The Applicant did not disclose any relevant medical history.

- An 87-year-old female (331-12-283) reported a serious fall on Day 8 and a fatal serious adverse event of intracranial hemorrhage on Day 30 while receiving BREX 0.5 mg. Refer to the subject case narrative in Table 57.

- An 80-year-old male (331-12-284) reported a serious adverse event of severe subdural hematoma on Day 42 while receiving brexpiprazole 2 mg. Investigators withdrew the study medication and the event was resolved during the trial period. Relevant medical history included ischemic heart disease, arterial hypertension, diffuse cardiosclerosis, and retinal angiopathy. Refer to the subject case narrative in Table 57.

- An 82-year-old female (331-12-283) experienced a transient ischemic attack on Day 84 while receiving placebo. The Applicant did not disclose any relevant medical history.

Table 71: Incidence of Cardiovascular and Cerebrovascular AEs Reported Across All 12-week Phase 3 Studies

Adverse Events[1]	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)
Cardiovascular Events	7 (4.5%)	7 (5.3%)	9 (4.2%)	1 (0.7%)	9 (2.3%)
Arrhythmias	7 (4.5%)	5 (3.8%)	7 (3.3%)	-	9 (2.3%)
Ischemic heart disease	-	2 (1.5%)	1 (0.5%)	-	-
Cardiac failure	-	-	1 (0.5%)	1 (0.7%)	-
Cerebrovascular Events	2 (1.3%)	1 (0.8%)	-	-	1 (0.3%)
Cerebrovascular accident	1 (0.6%)	-	-	-	1 (0.3%)
Intracranial hemorrhage	1 (0.6%)	-	-	-	-
Lacunar infarction	1 (0.6%)	-	-	-	-
Subdural hematoma	-	1 (0.8%)	-	-	-

Source: Reviewer-adapted using Applicant's Summary of Clinical Safety Table 2.7.4.2.2.16-1 and 2.7.4.2.2.17-1
[1]Aahythmias includes: atrial fibrillation, atrioventricular block first degree, bundle branch block left, bundle branch block right, QT prolongation, sinus bradycardia, supraventricular extrasystoles, and ventricular extrasystoles. Ischemic heart disease includes angina pectoris and myocardial ischemia. Cardiac failure includes cardiac failure and pulmonary edema. Cerebrovascular accident includes transient ischemic attack and cerebrovascular accident.

Cognitive Impairment

The Applicant prospectively monitored for changes in cognitive function using the MMSE. Across all 12-week studies, the mean baseline MMSE total score was similar across all treatment groups (see Section 8.1). Table 72 below describes change from baseline in the MMSE total score at the last study visit. Only one subject in Study 331-12-283 receiving BREX 1 mg reported worsening cognition (mild) as an AE after approximately 1 week of treatment (baseline MMSE = 18; Week 12 MMSE = 15). The mean change from baseline in the MMSE total score in all treatment groups suggests that there was no change, on average, in cognitive function across all treatment arms.

Clinical Reviewer's Comment: *In the current literature, several studies have suggested that patients with AD typically show an annual decline of 3 points on the MMSE total score (Bernard BA, et al., 2010). Therefore, this reviewer conducted several additional analyses to evaluate the percentage of subjects with at least a 3-point and 6-point decrease in the MMSE total score by the last study visit (Table 72). Approximately 9% of subjects across all brexpiprazole arms and 8% of subjects in the placebo arm experienced at least a 3-point decrease in MMSE total score.*

Given the lack of difference and no apparent dose-dependent relationship, it appears that the change in cognitive impairment was due to the natural course of disease rather than an effect due to the drug. In contrast, the percent of subjects with an improvement in cognitive function (MMSE total score increase of at least 3 points) was greater among subjects receiving brexpiprazole dosages ≥ 2 mg (18%) relative to placebo (11%). However, it is unclear whether improvements in neurobehavioral symptoms, including agitation, led to changes in cognitive impairment. Mechanistically, the Applicant hypothesizes that brexpiprazole exerts its effects on agitation by neurobehavior modulation rather than a direct effect on AD and cognitive function. Therefore, this review evaluated changes in cognitive function from a safety perspective only.

Table 72: Change in Cognitive Impairment Assessed by MMSE Total Score During the Treatment Period Across All 12-week Phase 3 Studies

MMSE Total Score Value	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)
Baseline, mean (SD)	13.1 (3.8)	14.7 (4.1)	14.7 (3.6)	15.5 (3.9)	14.8 (4.1)
Change from baseline at last visit, mean (SD)	0.1 (2.1)	-0.2 (2.0)	0.3 (2.6)	0.6 (2.6)	0.1 (2.2)
> 3-point decrease, n (%)	12 (7.6%)	15 (11%)	22 (10%)	10 (6.5%)	30 (7.7%)
> 6-point decrease, n (%)	2 (1.3%)	1 (0.8%)	3 (1.4%)	4 (2.6%)	4 (1.0%)
> 3-point increase, n (%)	13 (8.3%)	11 (8.3%)	35 (16%)	29 (19%)	43 (11%)

Source: Reviewer-created using Applicant's Summary of Clinical Safety admmse.xpt dataset
Abbreviation: MMSE = Mini Mental Status Exam; SD = standard deviation

8.2.6 Safety Analyses by Demographic Subgroups

The Applicant conducted several post-hoc subgroup analyses of AEs by age (< 65 years, 65 to < 75 years, and ≥ 75 years), sex, race, region, baseline psychosis status (defined as an NPI delusion item score ≥ 4 or an NPI hallucination score ≥ 4 or both), and by visit week during dose titration (Week 1, 2, and 3 to 4). The Applicant did not power the study to conduct meaningful subgroup analyses; nominal comparisons by age, sex, race, and region did not suggest any clinically meaningful differences in incidence of AEs. Overall incidence of AEs was similar between subjects who had baseline psychosis (81 subjects; 52.9%) and those who did not (253 subjects; 50.6%). Distribution of AEs, including serious and severe AEs and AEs leading to study discontinuation, based on preferred terms were also comparable between the two groups. Of the nine reported deaths across the three phase 3 efficacy studies, only two subjects exhibited baseline psychotic symptoms. During each week of the titration period (Week 1 through 4), the incidence of AEs was similar between the brexpiprazole dose groups (0.5 to 2 mg/day) vs. placebo. There were no specific events or trends in AE reporting during the titration period.

Clinical Reviewer's Comment: *Exploratory subgroup analyses of AEs and other safety findings did not reveal any predictors for risks commonly associated with antipsychotic use. The lack of any differences in the types and frequency of AEs between brexpiprazole and placebo during the titration period suggests that the proposed initial dose of 0.5 mg/day and titration over the initial 4 weeks was reasonable. This reviewer also conducted additional analyses based on subject care-setting and cognitive impairment. In general, the incidences of AEs were greater in*

institutionalized subjects relative to community-dwelling subjects (55% vs. 42%) and subjects with severe cognitive impairment relative to subjects with moderate or mild cognitive impairment (56% vs. 46%). Similar to the other subgroups, there were no clinically relevant differences between brexpiprazole vs. placebo within these subgroups.

8.2.7 Specific Safety Studies/Clinical Trials

Study 331-12-211

Given that other regulatory agencies expressed concerns that late-occurring AEs could develop due to the relatively long half-life of brexpiprazole (~90 hours), the Applicant designed Study 331-13-211 to extend the duration of the safety follow-up period from 30 days to 3 months (i.e., 30 days from previous phase 3 trials plus 2 months) for subjects who previously received brexpiprazole or placebo treatment during Studies 331-12-283 or 331-12-284. Because Study 331-13-211 was an observation trial, subjects did not receive any treatment. Although the Applicant did not monitor efficacy during the observational period, safety assessments, including evaluation of cognition, AEs, concomitant medications, and non-pharmacological interventions were collected.

The Applicant enrolled a total of 450 subjects, 262 subjects previously received brexpiprazole and 188 previously received placebo. Only three subjects (0.7%) discontinued from the trial due to lost to follow-up, cerebrovascular accident, and withdrawal of consent. Demographic and baseline disease characteristics were similar to the parent studies (331-12-283 and 331-12-284). During the trial period, the Applicant reported only one death:

- A 71-year-old white female that previously received brexpiprazole in Study 331-12-284, experienced a serious event of a femoral neck fracture from a fall on Day 17. The subject underwent an operation on Day 22 and was discharged in good condition. On Day 45 (75 days after the last dose of study medication) the subject experienced sudden cardiac arrest as a result of stroke. The subject did not report any relevant medical history or any relevant concomitant medications.

Three subjects also experienced three serious adverse events during the trial period (one of the subjects experienced a fatal outcome listed above):

- A 75-year-old white male previously received BREX 2 mg in Study 331-12-283 and experienced mild pulmonary edema during on Day 27 (56 days after the last dose of the study medication). The subject medical history consisted of hypertension and asthma.

- A 76-year-old white male received placebo in Study 331-12-284 and experienced psychomotor hyperactivity on Day 8 (38 days after the last dose of the study medication). The subject was hospitalized for approximately 1 week while his condition worsened. Clinical notes suggested that the subject did not sleep at night and was anxious, irritable, and aggressive. Treatments included chlorprothixene and

chlorpromazine.

Overall, the incidence of AEs was similar between subjects who received prior brexpiprazole (22%) vs. placebo (20%). The most frequently reported AE in the brexpiprazole vs. placebo group were headache (5.3% vs. 4.8%), agitation (3.1% vs. 2.7%), dizziness (1.9% vs. 0.5%), upper respiratory tract infection (1.5% vs. 1.6%), and fall (1.9% vs. 0%). The Applicant categorized the majority of AEs as mild or moderate. None of the subjects initiated new concomitant medications for the treatment of AAD during the trial. The mean change from baseline to Month 2 in the MMSE total score was similar between subjects who previously received brexpiprazole (-0.34; range: -11 to 8) vs. subjects who previously received placebo (-0.46; range: -8 to 7). In general, there were no new safety findings identified in this trial that suggest an increased risk of late-occurring AE after treatment discontinuation.

Clinical Reviewer's Comment: *The study population consisted of all subjects who completed 12 weeks of study treatment (brexpiprazole or placebo) in Studies 331-12-283 and 331-12-284. At the end of both preceding studies, there was no dosage taper, and subjects immediately stopped receiving study medication at the end-of-study visit. Abrupt discontinuation of antipsychotics has been associated with withdrawal symptoms (e.g., nausea, vomiting, abdominal pain, diarrhea, headache, tachycardia, anxiety, hyperkinesia, and insomnia) with onset typically within several weeks after discontinuation. However, the incidence of AEs associated with potential withdrawal symptoms were similar between subjects receiving prior brexpiprazole vs. placebo (nausea and vomiting: 0.8% vs. 0.5%; diarrhea: 0.4% vs. 0.5%; headache: 5.3% vs. 4.8%; anxiety: 0.8% vs. 0%, insomnia: 0.8% vs. 0.5%, hyperkinesia: 0.4% vs. 0.5%, respectively).*

Additional analyses of AEs indicated that the percentage of subjects exhibiting symptoms of agitation and irritability was similar between treatment groups (brexpiprazole: 3.4% vs. placebo: 3.2%). However, AE reporting may be unreliable (e.g., due to caregiver reporting or inability to communicate symptoms by the subject) to assess persistence of effect after receiving brexpiprazole treatment in Studies 331-12-283 and 331-12-284. Given that the Applicant did not collect efficacy measures (i.e., CMAI) during the observation period, there is additional uncertainty whether subjects will experience recurrent symptoms of agitation after 12 weeks of treatment and the relative timing at which worsening symptoms occur after drug discontinuation.

Study 331-201-00182

During a 2018 Type C guidance meeting, the Division expressed concerns regarding the lack of long-term treatment data for brexpiprazole in subjects with AD. Although the Division reiterated to the Applicant that a long-term safety study would not be a preapproval requirement, as a matter of convenience, the Division suggested to gather long-term safety data as an extension to Study 331-14-213. Based on the results from the prior phase 3 efficacy studies, the Applicant designed Study 331-201-00182 as an active-treatment extension study to

Study 331-14-213, with the aim to confirm the safety and tolerability of brexpiprazole when administered for up to an additional 12 weeks.

Study 331-201-00182 included subjects who completed Week 12 of Study 331-14-213 and had no substantial protocol deviations. Assessments from the last visit of Study 331-14-213 served as the baseline measures for this study. Subjects randomized to BREX 2 mg and BREX 3 mg treatment arms in Study 331-14-213 began with the same dose at baseline. Although this was an active-treatment extension study (subjects and investigators aware of only brexpiprazole administration), all subjects remained blinded to their dose assignment. The Applicant's dose administration and titration criteria included the following:

- All subjects who received placebo in Study 331-14-213 received an initial brexpiprazole dosage of 0.5 mg/day for 1 week, followed by 1 mg/day for 1 week, and then were titrated up to 2 mg/day by Week 3. Subjects could receive 3 mg/day beginning at the Week 6 visit and could decrease to 2 mg/day once at any time following Week 6.
- Subjects who previously received BREX 3 mg could decrease to BREX 2 mg at any time beginning at Week 4 through the end of the treatment period. If a subject decreased to BREX 2 mg prior to Week 6, they could increase back to BREX 3 mg at the Week 6 visit, but no further changes were permitted.
- Subjects who previously received BREX 2 mg and requested a dose decrease prior to Week 6 could have their dose increased to BREX 3 mg at the Week 6 visit and decrease to BREX 2 mg once at any time following the Week 6 visit.

The Applicant enrolled a total of 259 subjects who completed Study 331-14-213 (163 subjects previously received brexpiprazole and 96 subjects previously received placebo). Approximately 12% of subjects discontinued from the study, 13% from the prior brexpiprazole group and 9% from the prior placebo group. The major reason for study discontinuation was due to AEs (5% in both groups). Given that this was an active-treatment extension study, demographic and baseline disease characteristics were similar to the parent study. Among the subjects who received prior brexpiprazole treatment, 142 subjects (87%) continued to receive brexpiprazole for at least 12 weeks (total brexpiprazole exposure of at least 24 weeks).

The Applicant did not report any deaths, SI/B, or cerebrovascular events during the trial period. Although there were no serious or severe AEs reported for subjects receiving prior placebo treatment, six subjects (3.7%) and five subjects (3.1%) who received prior brexpiprazole treatment reported serious and severe AEs, respectively. Serious AEs (by preferred term) included: hemorrhoids, elevated liver enzymes, fall (two subjects), hip fracture, and syncope. Based on the summary case narratives, causality assessments were confounded by concomitant medications and underlying comorbidities. The overall percentage of subjects who experienced AEs was 26% in the prior brexpiprazole group vs. 27% in the prior placebo group. Incidence of AEs greater than 2% and AEs of special interest are displayed in
Table 73 and Table 74.

Table 73: Incidence of AEs Reported by At least 2% of Subjects in Study 331-201-00182

Adverse Event (FDA Medical Query)[1]	Prior BREX (N=163)	Prior Placebo (N=96)
Nasopharyngitis	-	5 (5.2%)
Headache	6 (3.7%)	3 (3.1%)
Agitation	1 (0.6%)	3 (3.1%)
Bacterial Infection	5 (3.1%)	-
Fall	5 (3.1%)	1 (1.0%)
Dizziness	4 (2.5%)	1 (1.0%)
Somnolence	4 (2.5%)	1 (1.0%)
Hypotension	-	2 (2.1%)

Source: Reviewer-created using Applicant's adae.xpt dataset
[1]FDA Medical Query (FDA) narrow definitions were utilized to group Applicant's MedDRA preferred terms. Subjects were counted once per FMQ
Note: Bacterial infection included cholecystitis, erysipelas, urinary tract infection, wound infection.

Table 74: Incidence of Adverse Events of Special Interest in Study 331-201-00182

AE of Special Interest	Prior BREX (N=163)	Prior Placebo (N=96)
Extrapyramidal Symptom Related Events	6 (3.7%)	2(2.1%)
Akathisia	2 (1.2%)	2(2.1%)
Dizziness, Syncope, or Orthostatic Hypotension Related Events	5 (3.1%)	3 (3.1%)
QT Prolongation	1 (0.6%)	-
Accidents and Falls	5 (3.1%)	1 (1.0%)
Cardiovascular Events	1 (0.6%)	-
Cerebrovascular Events	-	-

Source: Reviewer-created using Applicant's Summary of Clinical Safety Report and adae.xpt dataset
Note: *Extrapyramidal symptoms* include: extrapyramidal disorder, muscle rigidity, bradykinesia, hypokinesia, parkinsonism, and tremor; *Akathisia* includes: psychomotor hyperactivity, and restlessness; *Dizziness* includes: dizziness, hypotension, and syncope, Accidents and Falls includes: fall, femur fracture, and hip fracture; *Cardiovascular events* include: atrial fibrillation

Overall, the safety profile was similar between subjects who received prior brexpiprazole vs. placebo. The incidence of subjects with ≥ 7% increase in body weight was lower in the prior brexpiprazole group vs. placebo (2.1% vs. 4.7%). The incidence of EPS-related AE was relatively low compared to Study 331-14-213 and there were no clinically meaningful changes in the AIMS, SAS, or BARS total scores at the Week 12 visit. The mean change from baseline to Week 12 in the MMSE total score was also similar between subjects who previously received brexpiprazole (-0.26; range: -7 to 6) vs. subjects who previously received placebo (0.17; range: -7 to 5).

Clinical Reviewer's Comment: *In general, longer-term use of brexpiprazole (daily dosing with 2 or 3 mg for up to 24 weeks) appeared to be safe and well tolerated, with no new deaths and no new safety signals. The incidence of AEs and changes in laboratory assessments among subjects receiving prior placebo treatment was similar to subjects who initiated brexpiprazole treatment in Study 331-14-213. Although the Applicant evaluated subjects for an additional 12 weeks, it is unclear whether the current long-term safety database of 142 subjects receiving up to 24 weeks is sufficient to characterize the safety profile among patients receiving brexpiprazole for AAD in*

the real-world setting. The current literature describes varying durations of antipsychotic use in patients with AAD (typical range: 1 to 8 months) based on response and tolerability (Aigbogun MS, et al., 2020 and Mauleon AD, et al., 2021). Although previous long-term, open-label safety studies evaluating antipsychotics, including brexpiprazole, for at least 1 year in adults with MDD and schizophrenia did not reveal any significant safety findings, it is unclear at this time whether an open-label safety study evaluating primarily elderly patients with dementia would result in any new safety findings. Additional justification for longer-term treatment duration would be needed to consider another long-term safety study as a post-marketing requirement.

8.2.8 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The application did not include new human carcinogenicity studies.

Human Reproduction and Pregnancy

The application did not include new human reproduction or pregnancy data.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The application did not include any formal assessments related to drug abuse potential, withdrawal, and rebound. Because the proposed product is likely to be administered by a caregiver, the potential for overdose is limited.

8.2.9 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's estimate for the number of patient-years of treatment with marketed brexpiprazole is 1,269,878, as of June 30, 2022 (exposure from the 2022 Periodic Safety Update Report). The most frequently reported indication for cases of AEs in patients aged 65 years and older was for the treatment of depression and schizophrenia. There were 21 cases reported for AD, of which one case had a diagnosis of AAD. The Applicant identified a total of 58 deaths, none of which included subjects with AD. The estimated fatal case reporting rate was 3.2 per 100,000 patient-years. Based on reports that included sufficient information, causes for death included: fall, suicide, pneumonia, pneumonia aspiration, myocardial infraction, hypoglycemia, gastrointestinal perforation, interstitial lung disease. Although limited information was available in most cases that precluded any meaningful causal assessments, the Applicant highlighted several cases that were confounded due to the patient's underlying disease status, comorbidities, and use of concomitant medications. The most frequently reported serious AEs (reported in ≥ five cases; per 100,000 patient-years) included: tardive dyskinesia (1.7), neuro-malignant syndrome (1.3), fall (1.0), cerebrovascular accident (0.6), transient ischemic attacks (0.6), pneumonia (0.6), parkinsonism (0.5), akathisia (0.4), and gait disturbance (0.4).

Due to the imbalance of deaths across treatment arms in the brexpiprazole AAD development program, the Office of Surveillance and Epidemiology (OSE) 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 (refer to Dr. Clayton English's DPV review for additional information). Using the FAERS database, the Agency identified 22 assessable cases of serious AEs with brexpiprazole leading to hospitalization or 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.

Using the IQVIA National Sales Perspective and Total Patient Tracker database, the OSE team also assessed the extent of real-world brexpiprazole use among patients aged 65 years or older, its relative use among all patients, as well as possible reasons for use, to contextualize the AE reports from the FAERS database. In 2022, approximately (b) (4) patients aged 65 years or older received a prescription for brexpiprazole (representing approximately (b) (4) of the total patient population of brexpiprazole users). Brexpiprazole use among patients aged 65 years or older more than doubled from 2017 to 2022. During the study period, among patients aged 65 years or older, the majority of brexpiprazole use was observed among patients aged 65 to 74 years. Depression accounted for 42% of brexpiprazole use, followed by bipolar disorder at approximately 20%, and schizophrenia at approximately 19%. There were no mentions for the use of brexpiprazole for AAD.

Expectations on Safety in the Postmarket Setting

Based on current drug utilization data reported in the literature, antipsychotics are still considered first-line pharmacological treatment options for the treatment of AAD despite the Boxed Warning (Aigbogun MS, et al., 2021). However, duration of antipsychotic treatment in the real-world varies and often ranges from "as needed" use to chronic long-term dosing. Data from the brexpiprazole AAD development program suggests an onset of efficacy starting approximately after 4 weeks of once daily dosing. Although the dosage and administration instructions in the product label does describe a once daily dosing treatment paradigm, there are currently no statements proposed to avoid "as-needed" or shorter-term use. Given that health-care providers could prescribe brexpiprazole indefinitely for the treatment of AAD, evaluation of post-marketing data will continue in order to identify any new signals attributed to long-term use.

In addition to agitation, antipsychotics are commonly used for the treatment of other BPSD

symptoms including psychosis and irritability. Therefore, it is likely that brexpiprazole could be used off-label for the treatment of other BPSD symptoms caused by various etiologies. Across the brexpiprazole AAD development program, more than 85% of subjects exhibited other co-morbid BPSD symptoms, with 25% of subjects reporting symptoms related to psychosis. Although subgroup analyses did not suggest any differences in treatment effect on agitation between subjects with and without psychosis, it is unclear whether brexpiprazole is efficacious in patients with psychosis alone. It is also possible that brexpiprazole could be used off-label for the treatment of agitation associated with other dementia etiologies (e.g., vascular dementia, dementia with Lewy bodies, frontotemporal dementia, Parkinson's disease). Even though there is no data to evaluate whether antipsychotics, in general, exert a similar effect across these varying etiologies, there are no specific safety concerns in the event of off-label use we can determine for now.

8.2.10 Integrated Assessment of Safety

Overall, the Applicant submitted sufficient safety information to adequately assess brexpiprazole's short-term (12 weeks) safety profile in elderly patients with AAD. Since the initial approval of brexpiprazole in 2015, the Applicant has reported significant clinical experience with 10,291 subjects exposed across clinical studies (892 subjects were > 65 years of age) and a cumulative exposure rate of over 1,260,000 patient-years.

In comparison with the current literature, trials evaluating other antipsychotics and alternative treatments for AAD suggest very limited evidence of efficacy with significant risks and tolerability concerns. Given the established risk for mortality associated with antipsychotic use in elderly patients with dementia, the review of safety primarily included a mortality assessment of observed deaths across the AAD clinical development program. Across the three 12-week phase 3 studies, the Applicant reported a total of eight deaths (1.2%) among subjects receiving brexpiprazole and one death (0.26%) in a subject receiving placebo. Although the number of deaths were imbalanced between treatment groups, there was no clear pattern in the cause of death and cases were often confounded by underlying comorbidities, advanced age, and concomitant medications that are consistent with an AD population. Based on the review team's mortality analysis, the estimated incident risk ratio for death was 4.16 (95% CI: 0.51 to 33.83). Due to the small number of deaths reported in this program relative to the Agency's previous meta-analysis, there is still great uncertainty regarding the true mortality risk in this population that would be prescribed brexpiprazole in the real world. Therefore, the data available at this time suggests that the Boxed Warning should remain to inform providers, caregivers, and patients of this risk.

Even though the study population consisted of an older dementia population with subjects aged ≥ 51 years (mean age: 74 years), safety findings were generally similar to brexpiprazole's known safety profile in adults with schizophrenia and depression. Any lack of similarity could have been attributed to the lower enrollment of subjects > 75 years relative to the expected average age for subjects with moderate to severe AD (~ 80 years). AESIs generally occurred at a higher rate in the brexpiprazole treatment group; overall incidences of AESIs were also similar

to adults with schizophrenia and depression. However, there were no apparent dose-dependent trends or new safety concerns identified. There was also no evidence of worsening of cognitive function with brexpiprazole compared to placebo over the course of a 12-week treatment period. Although the safety database contained only 142 subjects who were exposed to at least 6 months of brexpiprazole treatment, the safety findings were consistent with the drug's known safety profile over 12 weeks. Further analyses of the safety data did not reveal any specific subgroups of patients at higher risk with brexpiprazole use. Evaluation of post-marketing data also did not reveal any new safety signals and suggested consistent findings with brexpiprazole's extensive clinical experience in other development programs and with other atypical antipsychotics.

Overall, this safety review did not identify any new safety signals that warrant the need for additional warnings in the product label or that would preclude the approval of this sNDA.

8.3 Statistical Issues

The review team did not identify any major statistical issues that could impact the overall conclusions.

8.4 Conclusions and Recommendations

To support the development program for the treatment of AAD, the Applicant conducted three double-blind, placebo-controlled, 12-week phase 3 studies, one observational post-treatment study, and one active-treatment extension safety study. Results from two adequate and well controlled studies 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 depression. Although there were few deaths across the development program, the imbalance and causes of deaths suggest that brexpiprazole's effect on mortality may be similar with the known risk with other antipsychotics. AAD is a serious unmet medical need without any currently available FDA-approved treatment options. Given that brexpiprazole's clinically meaningful benefit in reducing symptoms of agitation outweighs brexpiprazole's known risks that appear to be similar with other antipsychotics and with other approved indications, the Applicant has demonstrated that brexpiprazole has a favorable benefit-risk profile for the treatment of AAD.

9 Advisory Committee Meeting and Other External Consultations

The Agency convened a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Peripheral and Central Nervous System Drugs Advisory Committee on April 14, 2023. The purpose of this Advisory Committee meeting was to discuss the use of brexpiprazole for the treatment of AAD. 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 was asked to opine on the relative benefits and risks of brexpiprazole for the proposed indication.

The committee was charged with the following discussion and voting questions (complete record of the committee member's discussion and voting statements will be available to the public via the online transcript of the meeting):

1. **DISCUSSION:** Discuss the overall benefit/risk assessment of brexpiprazole for the treatment of agitation associated with Alzheimer's dementia. In your discussion, 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.

Committee Discussion**:** *Many members of the committee agreed that brexpiprazole had an effect on agitation and fulfilled a serious unmet medical need; the efficacy profile was not in question. Several committee members also highlighted that brexpiprazole had a positive dose-response relationship that further adds to the evidence of efficacy. Several other committee members acknowledged that the short duration of the trial (12 weeks) and the small effect size are a deterrent to the benefit and should be further characterized. Committee members also highlighted the high placebo response rate in the AAD population and agreed that it was consistent with placebo response rates observed in trials evaluating other psychiatric conditions. Regarding risks, several committee members noted that extrapolating data from a 12-week trial was difficult, and that the clinical community would not know how this would translate in the real world, where patients will be administered this medication more broadly. A majority of the committee members also agreed that continuing with the Boxed Warning would provide the opportunity to educate patients and families about the risks and the benefits. Committee members also noted the wide confidence intervals for the estimated mortality risk and recognized that there was great uncertainty. Several committee members recommended more data collection on brexpiprazole's long-term safety and what it will translate to in the real world. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** Discuss whether there is a population of patients with Alzheimer's dementia for whom the benefit/risk of brexpiprazole appears acceptable. Is there a population for whom the benefit/risk does not appear to be favorable?

***Committee Discussion*:** *Many of the committee members agreed that brexpiprazole could be a reasonable option for patients with moderate to severe agitation. Several members noted that patients with mild agitation would likely benefit from non-pharmacological treatment alone. Regarding a population where brexpiprazole would not be favorable, committee members agreed that there is not a clear discernible subgroup (possibly due to insufficient data) that would not benefit from brexpiprazole, but if any it would be patients with very severe agitation and those with acute agitation. Please see the transcript for details of the committee discussion.*

3. **VOTE:** Has the Applicant provided sufficient data to allow identification of a population in whom the benefits of treating agitation associated with Alzheimer's dementia 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 Alzheimer's dementia?

Vote Result: Yes: 9 No: 1 Abstain: 0

Committee Discussion: *The majority of the panel agreed that the Applicant provided sufficient data to allow identification of a population in whom the benefits of treating agitation associated with Alzheimer's dementia with brexpiprazole outweigh its risks. The one panel member who did not agree had concerns and stated more data is needed to demonstrate that brexpiprazole is effective and safe. However, the panel member did not specify what additional data would be needed to support the use of brexpiprazole for AAD. Please see the transcript for details of the committee discussion.*

Clinical Reviewer's Comment*: The committee raised multiple points to consider, including: the extrapolation of benefit observed in 12-weeks to long-term use; uncertainty regarding how the observed mortality risk would translate to the real-world; lack of a specific population where brexpiprazole's benefits do not outweigh its risk; and the possibility of limiting treatment to patients with moderate to severe agitation. The committee's conclusion that the Applicant's available evidence support the effectiveness of brexpiprazole for the treatment of AAD aligns with the review conclusions. Feedback from the committee will be of use in determining the need for additional long-term studies.*

10 Pediatrics

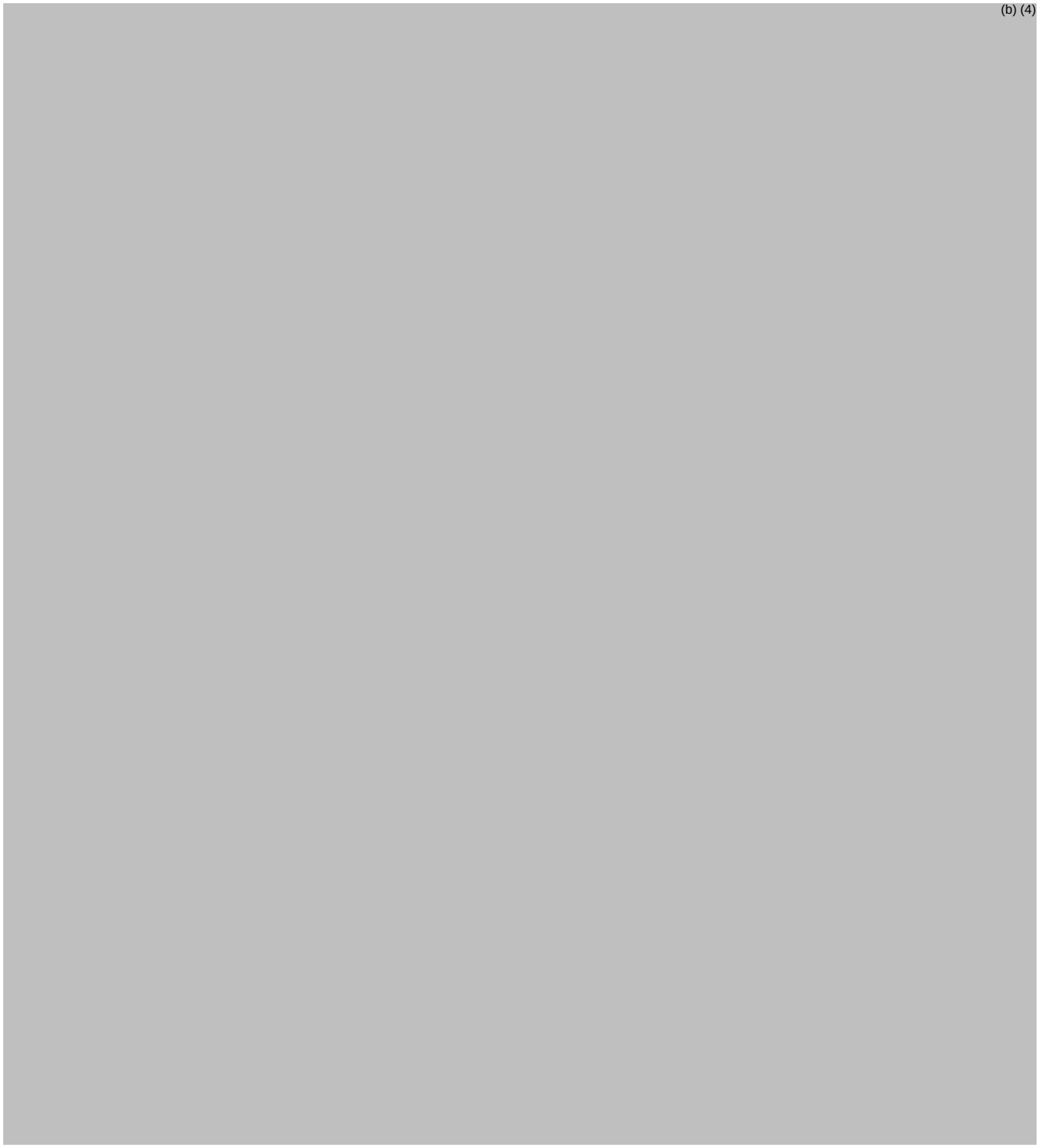
Given that necessary studies are impossible or highly impractical as AD does not occur in children, the Applicant submitted a request for a full waiver of pediatric studies. The Agency agreed with the Applicant's initial Pediatric Study Plan on March 23, 2017.

11 Labeling Recommendations

11.1 Prescription Drug Labeling

The table below summarizes significant high-level changes to the proposed prescribing information. The product label was under negotiation at the completion of this review.

(b) (4)



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12 Risk Evaluation and Mitigation Strategies (REMS)

12.1 REMS Proposed by Applicant

The applicant did not submit a proposed REMS or risk management plan with this application.

12.2 REMS Considerations

The increased risk of death associated with elderly patients with dementia treated with an antipsychotic is well-substantiated based on the Agency's previous 2005 meta-analysis. This risk is conveyed in the class-wide Boxed Warning for antipsychotics, including brexpiprazole. The treatment population for the proposed indication of brexpiprazole will likely be elderly patients who have an increased risk of mortality, potentially exacerbating the risk. The review team explored whether a REMS would be necessary to ensure the benefits outweigh the risk of increased risk of death in elderly patients with dementia-related psychosis treated with antipsychotics for the proposed indication of AAD.

Risk mitigation elements, such as narrowing the indicated population, minimizing the risk by early detection, and reducing the negative impact of the risk once it occurred were considered. Although the mortality risk is well-substantiated, the cause of death varied making it difficult to mitigate the risk. Deaths in the analyses that prompted the Boxed Warning for antipsychotics, as well as in this clinical program were varied, although there were more deaths attributed to cardiovascular and infectious causes. However, no specific risk factors were identified that predispose patients to higher mortality or could decrease the risk.

The Agency considered a strategy to ensure that healthcare providers and patients are informed of the risk of increased death for brexpiprazole. Despite the lack of clear understanding of the causes of increased mortality, the risk is well known. The risk that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death is conveyed in the Boxed Warning, which was approved in 2005, and multiple publications and consensus guidelines (Reus et al., 2016; American Geriatrics Society, 2019) have highlighted the risk. Feedback from the AC also indicated that continuing with the Boxed Warning would provide the opportunity to educate patients and families about the risks and the benefits (see Section 9). Hence, healthcare providers who are likely to prescribe brexpiprazole should be aware of the associated risk and a REMS is not needed to further convey the existence of the risk. Additionally, implementing a REMS to ensure informed decision-making for brexpiprazole would not be feasible. For some products, a REMS has been required to ensure that there is informed decision-making prior to the patient starting treatment. Such REMS would include elements to assure safety that would require certification of prescribers, pharmacies, and patients. Because brexpiprazole is approved for other indications and is currently distributed and dispensed with just a prescription for these indications, a REMS that includes restricting the distribution to certified and enrolled

stakeholders could not be put into place without impacting access for patients who are prescribed the drug for the other indications.

12.3 REMS Conclusions

The Agency did not identify any risk mitigation strategies (e.g., identification of specific patient risk factors, dose reductions or specific monitoring) that can prevent or reduce the increased risk of mortality, due to the varied causes of mortality and unknown pathophysiology. Lastly, a strategy to ensure that healthcare providers and patients are informed of the risk of increased death is not necessary as information about the risk is well established and is communicated though labeling, the published literature, practice guidelines, and general practice. Therefore, the Agency determined that a REMS is not necessary to ensure that the benefits of brexpiprazole outweigh its risks.

13 Postmarketing Requirements and Commitment

The review team identified several uncertainties regarding's brexpiprazole's observed benefit/risk profile for the treatment of AAD. Given the low overall incidence of death across the development program relative to the Agency's findings that led to the Boxed Warning, brexpiprazole's true mortality risk in the real-world is unclear. On April 21, 2023, the Agency met with the Applicant to discuss potential post-marketing studies that could quantitatively estimate brexpiprazole's mortality risk or confirm whether the risk was similar to that described in the Boxed Warning (70% increased risk of death among patients treated with an antipsychotic relative to placebo). The Division convened several internal meetings to discuss potential post-marketing study designs and their feasibility. The list below describes the identified uncertainties and possible post-marketing studies that could be recommended (but were ultimately determined to all have major limitations in either methodology or feasibility) in order to obtain additional safety and efficacy information:

1. Given the low overall incidence of deaths observed across the AAD development program, brexpiprazole's estimate of mortality in elderly patients with dementia is unclear.

   Proposed strategies and general studies:

   - Randomized, double-blind, placebo-controlled study intended to evaluate brexpiprazole's mortality risk in elderly subjects with AAD

Discussion: *A dedicated randomized controlled study adequately powered to detect a statistically significant incident risk ratio of 1.7 (previously estimated using in the Agency's 2005 analysis) or a hazard ratio of 2 (a conservative estimate based on time-to-event meta-analysis reported by Ralph SJ, et al.) would require a sample size of more than 800 patients per treatment arm. For comparison, the Applicant completed each of their 12-week phase 3 studies in approximately 4 years. A study that would include at least 1600 subjects (800 per arm) with staggered enrollment would be significantly longer than the Applicant's previously conducted studies and may not be feasible.*

There are also additional ethical concerns for exposing subjects to placebo, given the post-approval availability of brexpiprazole for the treatment of AAD. Subjects receiving placebo will likely also experience various intercurrent events (e.g., use of brexpiprazole as a rescue medication, concomitant use of other psychotropic drugs, study dropout due to lack of efficacy or natural disease progression) that would either prolong study recruitment or limit the interpretability of study results.

The lower overall incidence of death observed in the AAD development program relative to the Agency's previous findings (1% vs. 4%, respectively) could be attributed to lack of elderly frail

subjects (average age: 74 years vs. 81 years, respectively). However, even a dedicated randomized, placebo-controlled trial in frail elderly patients (where one would expect a higher incidence of death) would still likely require a large sample size and may not be feasible for the same reasons outlined already.

- Observational matched-cohort study intended to evaluate brexpiprazole's mortality risk in elderly patients with AAD

Discussion: *The current literature includes several observational studies that confirmed the mortality risk estimated in the Agency's 2005 meta-analysis. Although an observational study avoids the limitations of enrolling and prospectively monitoring a large number of subjects, real-world data (e.g., prescription claims data, registry data) used to support an observational study may be limited in identifying the intended use of brexpiprazole, diagnostic confirmation of AD and AAD, comorbid medical conditions, concomitant medication use, and exposure and duration of treatment. Although several strategies could limit biases associated with observational studies, identifying a matched cohort to represent a control group may also be difficult.*

- Enhanced pharmacovigilance surveillance plan to obtain and evaluate all fatal events in elderly patients with AAD treated with brexpiprazole

Discussion: *The Applicant proposed an enhanced pharmacovigilance plan to capture fatal events using a developed structured reporting form with a targeted questionnaire. The Applicant plans to collect comprehensive data for all fatal events, including start and stop dates of drug therapy, duration of treatment, concomitant medications, medical comorbidities, details of hospitalization, concurrent AE, and details of autopsy reports if performed. In addition to individual case medical review, the Applicant proposes to conduct a cumulative review and submit a summarized Annual Surveillance Report to the Agency.*

The enhanced pharmacovigilance plan would represent a convenience sample of fatal reports and would likely not capture all deaths associated with brexpiprazole. Similar to conducting an open-label study, there would be no control group for comparison. Because the proposed targeted questionnaire also appears consistent with FDA's Safety Information and AE Reporting Program MedWatch, there are similar concerns regarding reliability and completeness of the reported data that would limit causality assessments.

2. Study 331-201-00182 evaluated 142 subjects who received brexpiprazole for 6 months. Because AD is a progressive disease and symptoms of agitation could worsen as AD severity increases, health-care providers could prescribe brexpiprazole for indefinite-use. It is unclear whether brexpiprazole's long-term safety profile (> 6 months) in elderly patients would differ from the current experience with brexpiprazole in the AAD development program and relative to the long-term safety profile with other atypical antipsychotics.

Proposed strategies and general studies:

- Open-label, long-term, active-treatment safety study to evaluate brexpiprazole's long-term safety profile in elderly subjects with AAD

Discussion: *During the AC meeting held on April 14, 2023, several committee members commented on the need for long-term data safety data due to the likelihood that clinicians might prescribe brexpiprazole indefinitely. The safety profile among subjects who received brexpiprazole for 6 months did not reveal any new safety signals. Generally, open-label studies evaluating long-term safety of other antipsychotics (up to 1 year) did not reveal any new safety signals relative to safety information collected during shorter randomized, placebo-controlled studies. Given the lack of a control-arm, progressive nature of AD, high degree of concomitant medication use, and numerous underlying comorbidities, the interpretability of study results from any open-label safety study is limited.*

3. The Applicant did not characterize brexpiprazole's persistence of effect after continued treatment for 12 weeks. Given the risks associated use of antipsychotics (e.g., mortality, cardiovascular and cerebrovascular events), health-care providers could taper and discontinue brexpiprazole treatment after agitated behaviors are controlled. However, it is unclear when patients would experience worsening of agitation after halting treatment and whether continued use of brexpiprazole prevents future exacerbations.

   Proposed strategies and general studies:

   - Double-blind, placebo-controlled, randomized withdrawal study to evaluate the use of brexpiprazole to prevent worsening symptoms of agitation in elderly subjects with AAD

Discussion: *From a clinical perspective, it is difficult to consider AAD as an episodic illness due to the chronic and progressive nature of the underlying condition (AD). Therefore, there is a high probability that patients would experience worsening symptoms of agitation after brexpiprazole treatment is discontinued. The PK profile of brexpiprazole exposures suggests that time to steady state is approximately 3 week (half-life ~ 90 hours). Given that onset of brexpiprazole's efficacy is approximately 4 weeks, there does not appear to be a significant delay in brexpiprazole's pharmacodynamic effect relative to achieving PK steady state. Therefore, one could hypothesize that patients who stopped brexpiprazole treatment after experiencing benefit would likely experiencing worsening symptoms after 3 to 4 weeks.*

Similar to conducting a randomized, double-blind, placebo-controlled study to evaluate mortality, a randomized withdrawal study would require a large sample size. Dropouts due to lack of efficacy, residual drug effects with varying withdrawal rates, and use of concomitant rescue medications among subjects randomized to placebo also limit the interpretability of the study results.

4. The implementation of the Boxed Warning in 2005 has led to efforts to reduce off-label antipsychotic prescribing, with a subsequent increase in use of alternative treatments (e.g., benzodiazepines, antiepileptics, antidepressants) that have modest efficacy and significant risks. With this approval, brexpiprazole will be the only treatment (and antipsychotic) indicated for the treatment of AAD. However, there is limited data comparing risks of antipsychotics to alternative treatments.

   Proposed strategies and general studies:

   - Randomized, double-blind, active-controlled study to compare brexpiprazole's risk of mortality relative to other antipsychotics and alternative treatments for AAD

Discussion: *Although favorable safety data comparing brexpiprazole to alternative treatments could further justify brexpiprazole's benefit/risk profile, the use of unapproved treatments as active controls when they have not been shown to be safe or effective is an ethical and regulatory challenge. Similar to conducting a randomized, double-blind, placebo-controlled study to evaluate mortality, this study would also require a large sample size to detect differences in safety.*

Overall, the Agency determined that no additional post-marketing studies are warranted at this time. There are major feasibility, ethical, and logistical constraints associated with the aforementioned studies, combined with a high likelihood of uninterpretable or inconclusive data yielded by most of these designs, given the progressive nature of the illness and the population's background morbidities. For now, the Applicant's proposed enhanced pharmacovigilance plan including the structured reporting form appears to be the most pragmatic post-marketing data collection method available in order to attempt to monitor the potential increased risk of mortality among real-world patients prescribed brexpiprazole for AAD.

14 Division Director Comments

The content of this Unireview reflects the issues discussed in the marketing application assessment and regulatory decisions and actions taken. My feedback and edits have been incorporated above. I agree with the findings as documented by the primary review team.

15 Appendices

15.1 References

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15.2 Financial Disclosure

Covered Clinical Study (Name and/or Number): 331-12-283

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 94		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

(b) (6) received payments for speaking engagements on Lundbeck's behalf. (b) (6) did not screen or randomize any subjects. (b) (6) is the spouse of (b) (6) (see below). (b) (6) site randomized (b) (6) out of 433 randomized subjects. (b) (6) received payments for speaking engagements on the Applicant's behalf. Dr. Malik's site randomized (b) (6) out of 433 randomized subjects and he did not rate any efficacy or safety scales on the subjects. Based on the design of the study and operational structure and procedures, the Applicant considered the concern for potential bias to be minimal.

Covered Clinical Study (Name and/or Number): 331-12-284

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 85		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 331-14-213

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 122		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

(b) (6) received payments for speaking engagements on Otsuka's and/or Lundbeck's behalf. (b) (6) was delegated as the primary rater at this site conducting all scales, including the primary efficacy measure. (b) (6) randomized (b) (6) out of a total of 345 subjects. Given the above information, and the double- blind study design of the 331-14-213 trial, the Applicant indicated that there was no possibility that bias could be introduced by this investigator.

15.3 Additional Efficacy Analyses

Table 75: Study 331-12-283 Change from Baseline to Week 12 in CMAI Total Score in Subgroups—MMRM (Efficacy Sample)

Subgroup	Treatment Group	Baseline		Mean Change from Baseline		Treatment Difference vs. Placebo
		N	Mean (SD)	N	LS Mean (SE)[1]	LS Mean Diff (95% CI)[1]
Female	BREX 1mg	76	70.68 (15.58)	69	-14.3 (1.74)	1.92 (-3.1, 6.94)
	BREX 2mg	78	71.15 (17.05)	66	-21.1 (1.73)	-4.94 (-9.95, .07)
	Placebo	68	72.63 (19.16)	58	-16.2 (1.86)	
Male	BREX 1mg	58	70.22 (16.55)	50	-18.5 (2.00)	-1.22(-6.65, 4.2)
	BREX 2mg	60	70.77 (16.05)	54	-19.1 (1.96)	-1.8 (-7.16, 3.56)
	Placebo	63	71.83 (16.46)	60	-17.3 (1.88)	
White	BREX 1mg	131	70.08 (15.79)	116	-15.6 (1.33)	1.3 (-2.44, 5.04)
	BREX 2mg	131	71.00 (16.80)	114	-19.7 (1.33)	-2.78 (-6.51, 0.96)
	Placebo	125	72.46 (17.80)	112	-16.9 (1.35)	
All other races	BREX 1mg	3	88.33 (14.57)	3	-37.2 (6.86)	-26.3 (-45.1, -7.52)
	BREX 2mg	7	70.71 (12.28)	6	-31.5 (4.26)	-20.6 (-34.1, -7.2)
	Placebo	6	67.67 (19.96)	6	-10.9 (4.57)	
AGE < 65	BREX 1mg	24	68.75 (11.87)	21	-8.32 (3.22)	2.99 (-6.86, 12.84)
	BREX 2mg	22	69.45 (12.59)	19	-16.0 (3.36)	-4.68 (-14.7, 5.33)
	Placebo	18	73.67 (18.68)	18	-11.3 (3.69)	
65 ≤ AGE < 75	BREX 1mg	34	70.09 (16.94)	30	-15.5 (2.52)	0.14 (-6.65, 6.92)
	BREX 2mg	46	71.17 (15.72)	39	-17.1 (2.17)	-1.42 (-7.7, 4.86)
	Placebo	40	71.05 (17.81)	36	-15.7 (2.30)	
AGE ≥ 75	BREX 1mg	76	71.21 (16.73)	68	-18.9 (1.68)	0.09 (-4.65, 4.84)
	BREX 2mg	70	71.34 (18.28)	62	-23.8 (1.76)	-4.84 (-9.7, 0.01)
	Placebo	73	72.55 (17.88)	64	-19.0 (1.72)	
North America	BREX 1mg	36	72.56 (17.89)	29	-21.4 (2.76)	-2.88 (-10.5, 4.71)
	BREX 2mg	41	73.78 (20.52)	35	-26.3 (2.54)	-7.76 (-15.1, -0.48)
	Placebo	38	72.92 (22.17)	32	-18.5 (2.65)	
ROW	BREX 1mg	98	69.72 (15.20)	90	-14.1 (1.44)	1.95 (-2.12, 6.02)
	BREX 2mg	97	69.80 (14.54)	85	-17.7 (1.46)	-1.63 (-5.73, 2.47)
	Placebo	93	71.97 (15.88)	86	-16.0 (1.48)	
Non-Hispanic	BREX 1mg	110	69.85 (15.33)	98	-14.8 (1.43)	0.96 (-3.02, 4.94)
	BREX 2mg	115	69.41 (14.32)	100	-18.8 (1.40)	-3.03 (-6.97, 0.91)
	Placebo	107	71.86 (16.47)	98	-15.8 (1.43)	
Hispanic	BREX 1mg	24	74.58 (18.14)	20	-22.2 (3.30)	-0.28 (-9.67, 9.10)

Subgroup	Treatment Group	Baseline		Mean Change from Baseline		Treatment Difference vs. Placebo
		N	Mean (SD)	N	LS Mean (SE)[1]	LS Mean Diff (95% CI)[1]
	BREX 2mg	23	78.87 (23.82)	20	-26.8 (3.31)	-4.85 (-14.3, 4.66)
	Placebo	23	74.17 (23.90)	19	-22.0 (3.33)	

Source: Study 331-12-283 Clinical Study Report, CT-6.1.1 (females), CT-6.1.2 (males), CT-6.3.1 (< 65 years), CT-6.3.2 (≥ 65 and < 75 years), and CT-6.3.3 (≥ 75 years), CT-6.2.1 (whites), CT-6.2.2 (all other races), and CT-6.2.3 (whites and all other races at Week 12), CT-6.4.1 (North America) and CT-6.4.2 (other regions) confirmed by statistical reviewer. The subgroup analysis of ethnic status was conducted by statistical reviewer.
Abbreviations: MMRM = Mixed Effects Model for Repeated Measures; LS = Least Squares; SE = Standard Error; n = number of subjects with data.
[1]In each subgroup stratum, MMRM was conducted with model Terms: treatment, visit, treatment by visit and baseline by visit interaction.

Table 76: Study 331-12-284 Change from Baseline to Week 12 in CMAI Total Score in Subgroups—MMRM (Efficacy Sample)

Subgroup	Treatment Group	Baseline		Mean Change from Baseline		Treatment Difference vs. Placebo
		N	Mean (SD)	N	LS Mean (SE)[1]	LS Mean Diff (95% CI)[1]
Female	BREX 0.5-2 mg	81	72.04 (16.62)	75	-19.3 (1.41)	-3.55 (-7.46, 0.36)
	Placebo	87	68.83 (15.79)	73	-15.7 (1.38)	
Male	BREX 0.5-2 mg	50	70.68 (17.31)	41	-16.7 (1.89)	0.47 (-4.75, 5.69)
	Placebo	48	68.15 (16.57)	44	-17.2 (1.83)	
White	BREX 0.5-2 mg	126	71.06 (16.66)	111	-17.6 (1.11)	-1.36 (-4.43, 1.7)
	Placebo	127	68.27 (16.11)	111	-16.3 (1.09)	
All other races	BREX 0.5-2 mg	5	83.00 (19.20)	5	-35.6 (8.36)	-22 (-46.4, 2.36)
	Placebo	8	73.63 (14.31)	6	-13.6 (6.71)	
AGE < 65	BREX 0.5-2 mg	23	66.74 (11.65)	21	-16.4 (2.07)	0.1 (-6.09, 6.29)
	Placebo	19	65.42 (17.55)	18	-16.5 (2.25)	
65 ≤ AGE < 75	BREX 0.5-2 mg	46	71.54 (17.37)	43	-15.8 (1.69)	-0.47 (-5.14, 4.2)
	Placebo	49	68.78 (16.36)	45	-15.3 (1.63)	
AGE ≥ 75	BREX 0.5-2 mg	62	73.27 (17.91)	52	-21.2 (1.85)	-4.39 (-9.48, 0.7)
	Placebo	67	69.34 (15.44)	54	-16.8 (1.77)	
North America	BREX 0.5-2 mg	27	70.96 (18.03)	23	-17.6 (2.77)	-2.17 (-9.63, 5.28)
	Placebo	33	66.70 (15.38)	26	-15.4 (2.46)	
Other	BREX 0.5-2 mg	104	71.66 (16.60)	93	-18.7 (1.23)	-2.28 (-5.71, 1.15)
	Placebo	102	69.20 (16.24)	91	-16.4 (1.23)	
Non-Hispanic	BREX 0.5-2 mg	124	71.30 (16.64)	108	-18.2 (1.19)	-2.57 (-5.84, 0.71)
	Placebo	128	68.56 (16.22)	108	-15.7 (1.16)	
Hispanic	BREX 0.5-2 mg	6	80.33 (16.05)	6	-23.3 (2.76)	-0.6 (-8.60, 7.41)
	Placebo	9	67.11 (11.90)	9	-22.7 (2.15)	

Source: Study 331-12-284 Clinical Study Report, CT-6.1.1 (females), CT-6.1.2 (males), CT-6.3.1 (< 65 years), CT-6.3.2 (≥ 65 and < 75 years), and CT-6.3.3 (≥ 75 years), CT-6.2.1 (whites), CT-6.2.2 (all other races), and CT-6.2.3 (whites and all other races at Week 12), CT-6.4.1 (North America) and CT-6.4.2 (other regions) confirmed by statistical reviewer. The subgroup analysis of ethnic status was conducted by statistical reviewer.
Abbreviations: MMRM = Mixed Effects Model for Repeated Measures; LS = Least Squares; SE = Standard Error; n = number of subjects with data.
[1] In each subgroup stratum, MMRM was conducted with model Terms: treatment, visit, treatment by visit and baseline by visit interaction.

Table 77: Study 331-14-213 Change from Baseline to Week 12 in CMAI Total Score in Subgroups—MMRM (Efficacy Sample)

Subgroup	Treatment Group	Baseline		Mean Change from Baseline		Treatment Difference vs. Placebo
		N	Mean (SD)	N	LS Mean (SE)[1]	LS Mean Diff (95% CI)[1]
Female	BREX 2 and 3 mg	132	82.24 (15.46)	114	-22.2 (1.32)	-4.73 (-9.48, 0.01)
	Placebo	60	76.95 (18.58)	50	-17.4 (1.99)	
Male	BREX 2 and 3 mg	93	78.15 (18)	78	-22 (1.72)	-5.16 (-10.7, 0.34)
	Placebo	56	81.55 (16.14)	53	-16.8 (2.17)	
White	BREX 2 and 3 mg	211	80.84 (16.7)	180	-21.7 (1.09)	-4.83 (-8.43, -1.22)
	Placebo	114	79.3 (17.6)	101	-16.9 (1.47)	
All other races	BREX 2 and 3 mg	14	76.14 (15.7)	12	-28.7 (2.44)	2.02 (-12.6, 16.65)
	Placebo	2	72 (14.14)	2	-30.7 (6.29)	
AGE < 65	BREX 2 and 3 mg	23	77.61 (20.38)	21	-26.9 (2.85)	-4.98 (-14.7, 4.74)
	Placebo	13	83.92 (13.22)	12	-21.9 (3.8)	
65 ≤ AGE < 75	BREX 2 and 3 mg	83	79.42 (18.55)	73	-22.5 (1.63)	-6.62 (-11.8, -1.45)
	Placebo	54	78.11 (18.5)	47	-15.8 (2.04)	
AGE ≥ 75	BREX 2 and 3 mg	119	81.91 (14.31)	98	-21.2 (1.55)	-4.46 (-10.1, 1.16)
	Placebo	49	79.08 (17.51)	44	-16.8 (2.38)	
North America	BREX 2 and 3 mg	100	77.32 (17.05)	86	-21.8 (1.68)	0.32 (-5.53, 6.18)
	Placebo	49	75.67 (19.77)	41	-22.1 (2.44)	
Other	BREX 2 and 3 mg	125	83.14 (15.91)	106	-22.5 (1.27)	-8.99 (-13.2, -4.81)
	Placebo	67	81.73 (15.32)	62	-13.5 (1.7)	
Non-Hispanic	BREX 2 and 3 mg	157	82.35 (15.82)	133	-22.2 (1.25)	-8.3 (-12.5, -4.07)
	Placebo	79	80.53 (15.31)	71	-13.9 (1.74)	

Subgroup	Treatment Group	Baseline		Mean Change from Baseline		Treatment Difference vs. Placebo
		N	Mean (SD)	N	LS Mean (SE)[1]	LS Mean Diff (95% CI)[1]
Hispanic	BREX 2 and 3 mg	68	76.4 (17.83)	59	-22.2 (1.81)	1.66 (-4.42, 7.74)
	Placebo	37	76.27 (21.45)	32	-23.9 (2.47)	

Source: Study 331-14-213 Clinical Study Report, CT-6.1.1 (females), CT-6.1.2 (males), CT-6.3.1 (< 65 years), CT-6.3.2 (≥ 65 and < 75 years), and CT-6.3.3 (≥ 75 years), CT-6.2.1 (whites), CT-6.2.2 (all other races), and CT-6.2.3 (whites and all other races at Week 12), CT-6.4.1 (North America) and CT-6.4.2 (other regions) confirmed by statistical reviewer. The subgroup analysis of ethnic status was conducted by statistical reviewer.
Abbreviations: MMRM = Mixed Effects Model for Repeated Measures; LS = Least Squares; SE = Standard Error; n = number of subjects with data.
[1]In each subgroup stratum, MMRM was conducted with model Terms: treatment, visit, treatment by visit and baseline by visit interaction.

15.4 Additional Clinical Outcome Assessment Analyses

Refer to Dr. Swett's DCOA review for additional analyses on the CMAI's psychometric properties and interpretations of a clinically meaningful within-patient change.

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