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Brexpiprazole (Rexulti) for the Treatment of Agitation Associated with Alzheimer's dementia

Joint Meeting of the Psychopharmacologic and the Peripheral and Central Nervous System Drugs Advisory Committee Meeting

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Brexpiprazole (Rexulti) for the Treatment of Agitation Associated with Alzheimer's dementia

FDA Opening Remarks

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Alzheimer's Dementia (AD)

- Alzheimer's disease (AD) is the most common cause of dementia, with an estimated US prevalence of 6.5 million people aged ≥ 65 years
- Although cognitive decline is the predominant symptom, behavioral and psychological symptoms of dementia (BPSD), including agitation, aggression, and irritability, are common
- BPSD symptoms are associated with a higher risk of accelerated disease progression, functional decline, decreased quality of life, greater caregiver burden, increased out-of-home placement, and earlier death
- Clinical presentation and frequency of BPSD symptoms may vary; most patients experience initial onset of symptoms in later stages of AD and worsening symptoms as AD progresses

Agitation Associated with Alzheimer's Dementia (AAD)

- Agitation is among the most persistent and challenging aspects of care among patients with BPSD
  - Estimated pooled prevalence of agitation associated with AD is approximately 40% with higher rates observed in patients living in long-term care facilities relative to those living in the community
- In 2015, the International Psychogeriatric Association (IPA) formed the Agitation Definition Working Group to establish a consensus definition of agitation in cognitive disorders (finalized and updated in 2022). The definition includes four criteria that must be met:
  - Presence of cognitive impairment or dementia
  - Types and duration of behavior to be considered
  - Symptoms must be associated with excess distress or produce excess disability
  - Symptoms must not be attributable to some other condition

Unmet Medical Need for AAD

- Clinical management of agitation remains a challenge:
  - Non-pharmacological approaches include: cognitive stimulation, group therapy, exercise, music therapy, and multisensory therapy
  - No FDA-approved pharmacological options
  - Off-label pharmacological options include: benzodiazepines, antihistamines, antidepressants, antiepileptics, and antipsychotics
- Studies evaluating off-label pharmacologic treatments are highly heterogeneous in design and patient population
- Results have demonstrated only small improvements in efficacy with serious risk and tolerability concerns

Antipsychotics for the Treatment of AAD

- Antipsychotics currently used as a first-line treatment choice
  - American Psychiatric Association Practice Guideline recommends the use of “non-emergency antipsychotic medications” for the treatment of agitation in patients with dementia
- Boxed Warning since 2005 for the increased risk of mortality (70%) in elderly patients with dementia-related psychosis receiving antipsychotic treatment
- After the implementation of the Boxed Warning, various regulatory bodies and healthcare institutions have taken action to decrease off-label antipsychotic prescribing
- Drug utilization data indicate a decrease in antipsychotic use and an increase in the use of opioids, antiepileptics, and benzodiazepines among elderly patients with dementia

Clinical Implications

- With limited evidence to support alternatives to antipsychotics, healthcare providers are left with unclear choices for treatment
- Although there are currently no FDA-approved treatments for AAD, antipsychotics are still commonly prescribed off-label, despite the limited benefit described in the current literature and the increased risk of mortality

Questions to the Committee

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

Brexpiprazole (Rexulti) for the Treatment of Agitation Associated with Alzheimer's dementia

FDA Presentation

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Outline

1. Summary of Efficacy
2. Summary of Safety
3. Overall Assessment and Conclusions

Brexpiprazole

- Brexpiprazole is an atypical antipsychotic that is FDA-approved for:
  - Treatment of schizophrenia in patients > 13 years of age (2 to 4 mg/day)
  - Adjunctive treatment to antidepressants for major depressive disorder in adults (2 to 3 mg/day)
- Mechanism of Action:
  - Hypothesized to exert its pharmacological effect through a combination of partial agonist activity at 5-HT_{1a} and D_2 receptors, and antagonist activity at 5-HT_{2a} receptors
- Applicant's proposed indication: treatment of agitation associated with Alzheimer's dementia (AAD)
  - Proposed target dose of 2mg/day with a maximum dose of 3 mg/day

Brexpiprazole for AAD: Clinical Program

- Three double-blind, randomized, placebo-controlled, multi-center, 12-week phase 3 studies
  - Applicant initiated Studies 331-12-283 and 331-12-284 in 2013 and initiated Study 331-14-213 in 2018
  - Differences in the study population (e.g., diagnostic criteria for probable AD and agitation) attributed to the Agency's evolving advice
- One observational post-treatment study (331-13-211) in subjects who completed Studies 331-12-283 and 331-12-284
- One active-treatment extension safety study (331-201-00182) in subjects who completed Study 331-14-213

Initial Discussions: 2012 Type B Pre-IND Meeting

- Agency agreed that AAD is an important target for treatment and that the Applicant should collaborate with clinical experts to identify the appropriate target population (e.g., agitation as a broad indication, or a subgroup of patients with “aggressive agitation”)
- The Applicant proposed a clinical development program of two 12-week, phase 3, double-blind, placebo-controlled trials. For both studies, the Applicant proposed the Cohen Mansfield Agitation Inventory (CMAI) as the primary efficacy measure.
- Because the Applicant had not yet settled on a specific target (agitation vs. aggressive agitation), the Agency did not provide more specific advice and indicated that the general study designs appeared reasonable.

Studies 283 and 284: Trial Design

Trial Characteristics	331-12-283	331-12-284
Design	Randomized, double-blind, placebo-controlled, multi-center, 12-week phase 3 study	
Treatment Paradigm/Arms	Fixed-dose • BREX 1 mg • BREX 2 mg • Placebo	Flexible-dose • BREX 0.5 to 2 mg • Placebo
Study Periods	• Screening period (up to 42 days) to assess eligibility criteria and washout prohibited concomitant pharmacotherapy prior to randomization • 12-week double-blind treatment period • 30-day follow-up safety evaluation after receiving the last dose of study medication • Week 16 mortality assessment for all subjects who terminated early	

Studies 283 and 284: Study Population

Inclusion Criteria	Studies 331-12-283 and 331-12-284
Age and Setting	Subjects between 55 to 90 years of age, living either in an institutionalized setting or non-institutionalized setting where the subject was not living alone
Probable AD	NINCDS-ADRDA criteria
AD Severity	MMSE score 5 to 22
Agitation	• NPI-NH or NPI/NPI-NH Agitation/ Aggression Item score ≥ 4 • Symptom onset at least 2 weeks prior to screening • Previous trial of non-pharmacological interventions and who did not exhibit an insufficient response to at least two previous antipsychotics for the treatment of AAD

Abbreviations: AAD = agitation associated with Alzheimer's dementia; MMSE = Mini Mental Status Exam; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association; NPI-NH = Neuropsychiatric Inventory – Nursing Home; NPI/NPI-NH = Neuropsychiatric Inventory/Neuropsychiatric Inventory – Nursing Home

Studies 283 and 284: Population Rationale

- Although the IPA provisional consensus definition for agitation was established in 2015 after the initiation of both studies, the proposed study population appears to closely approximate to a study population potentially enrolled based on the IPA criteria
  - Criteria for having symptoms not related to another neurological or psychiatric condition is aligns with IPA Criteria D
  - Criteria for duration of symptoms (2 weeks) aligns with IPA Criteria B
  - Enrollment based on an NPI-NH Agitation/Aggression score ≥ 4 could include subjects with agitated behaviors, similar to IPA Criteria B
- Results from these studies could be generalizable to a population that meets the current IPA consensus definition

Studies 283 and 284: Population Rationale

- Inclusion of subjects with probable AD (mild to severe)
  - Use of the NINCDS-ADRDA criteria to identify subjects with probable AD was reasonable due to lack of biomarker-based diagnostic criteria
  - The Agency currently recommends sponsors to follow the draft guidance for industry for industry Early Alzheimer's Disease: Developing Drugs for Treatment (February 2018) and the 2018 National Institute of Aging – Alzheimer's Association (NIA-AA) criteria to assess eligibility and characterize subjects with AD
  - Inclusion of subjects with mild to severe dementia reflects a range of patients who are likely to have AAD

Studies 283 and 284: Treatment Paradigm

Trial Characteristics	331-12-283	331-12-284
Randomization	1:1:1 to either BREX 1 mg, BREX 2 mg, or placebo	1:1 to either flexible dose brexpiprazole (0.5 mg to 2 mg) or placebo
Titration Scheme	• Initial dosage of 0.25 mg/day • Forced-titration to target fixed dose • Dosage decrease was not allowed at any time • Subjects were withdrawn if unable to tolerate their assigned dosage	• Initial dosage of 0.25 mg/day • Flexible-dose titration based on response and tolerability (after Week 4, dosage could increase from 1 mg/day to 2 mg/day) • Subjects withdrawn if unable to tolerate brexpiprazole 0.5 mg/day or matching placebo

Cohen-Mansfield Agitation Inventory (CMAI)

- Primary efficacy measure across all three efficacy studies was the CMAI (Long Form)
- CMAI-Long Form is a caregiver-reported 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)
- CMAI total score is the sum of ratings from all 29 items (possible total score range from 29 to 203)
- A large-scale factor analysis of the CMAI collected in nursing home patients demonstrated the presence of four subscales: aggressive behaviors (Factor 1), physically non-aggressive behaviors (Factor 2), verbally agitated behaviors (Factor 3), and hiding and hoarding (Factor 4).

CMAI Subscales

Subscales	CMAI Items	Possible Score Range
Factor 1: Aggressive Behaviors	hitting, kicking, scratching, grabbing, pushing, hurting self or others, throwing things, cursing or verbal aggression, spitting, tearing things or destroying property, screaming, and biting	12 to 84
Factor 2: Physically Non-aggressive Behaviors	Pace or aimless wandering, trying to get to a different place, general restlessness, inappropriate dress or disrobing, handling things inappropriately, performing repetitious mannerisms	6 to 42
Factor 3: Verbally Agitated Behaviors	complaining, constant unwarranted request for attention or help, repetitious sentences or questions, negativism	4 to 28
Factor 4: Hiding and Hoarding	hiding things, hoarding things	2 to 14

Source: Rabinowitz, J et al., 2005

Study Endpoints

Endpoint	Definition
Primary	Change from baseline in CMAI total score at Week 12
Secondary (multiplicity adjusted)	Change from baseline in the Clinical Global Impression of Severity (CGI-S) scale score, as related to agitation, at Week 12
Exploratory*	Change from baseline to Week 12 in CMAI subscale scores (Factors 1, 2, and 3)

*To explicate the findings from the primary efficacy endpoint, the treatment effects were evaluated for the three major subscales (Factors 1, 2, and 3) that closely aligned with the diagnostic criteria for agitation. Subscale scores were calculated based on the summation of responses of all items within the subscale. Between-treatment group results for each subscale were provided descriptively (i.e., not in the statistical testing hierarchy).

Caregiver Requirements

- Applicant identified the subject's caregiver as the person who had sufficient contact with the subject to describe the subject's symptoms and could directly observe the subject's behavior in order to participate in trial assessments, including completion of a diary
- 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).

Statistical Analysis and Considerations

- Primary endpoint analysis was based on an MMRM analysis
  - Secondary endpoint analysis was identical to the primary statistical methodology
  - Model adjusted for the following prespecified covariates: treatment, pooled trial center, visit week, an interaction term of treatment by visit week, and an interaction term for baseline values of CMAI total score by visit week
- Hierarchical testing procedure used to control type I error rate.
  - For Study 283, the primary efficacy endpoint was tested in the order of: 1) comparison of BREX 2 mg versus placebo and 2) comparison of BREX 1 mg versus placebo. If the primary efficacy analysis for the CMAI total score yielded statistically significant results for both comparisons, the Applicant repeated the hierarchical testing procedure for the key secondary efficacy variable (CGI-S score).

Study 331-12-283 Results

Study 331-12-283: Disposition and Baseline Characteristics

- 433 subjects randomized into the double-blind treatment period
- Most frequent reason for study discontinuation across all treatment groups was adverse events (BREX 1 mg: 5.9%; BREX 2 mg: 7.3%; placebo: 4.3%)
- Majority white (96%), non-Hispanic (83%) subjects with a mean age of 74 years
- Most subjects resided in an institutionalized setting (67%) and exhibited moderate or severe cognitive impairment (91%); comorbid psychotic symptoms present among only 26% of subjects
- Majority of subjects exhibited agitation with aggressive behaviors (86%), physically non-aggressive behaviors (93%), or verbally agitated behaviors (83%) at baseline (70% exhibited significant symptoms across all three domains of agitation)

Study 331-12-283: Primary and Secondary Endpoint Analysis

	Placebo (N=131)	BREX 1 mg (N=134)[2]	BREX 2 mg (N=138)
Primary Efficacy Endpoint (CMAI)			
Mean CMAI Total Score at Baseline (SD)	72.2 (17.85)	70.5 (15.95)	71.0 (16.56)
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		0.9015	**0.0404**
Secondary Efficacy Endpoint (CGI-S)			
Mean CGI-S Score at Baseline (SD)	4.5 (0.66)	4.5 (0.62)	4.5 (0.70)
LSM Change from Baseline (SE)	-1.1 (0.08)	-1.0 (0.08)	-1.3 (0.08)
Placebo-subtracted difference (95% CI)[1]		0.09 (-0.14, 0.32)	-0.16 (-0.39, 0.06)
P-value		0.4440	0.1566

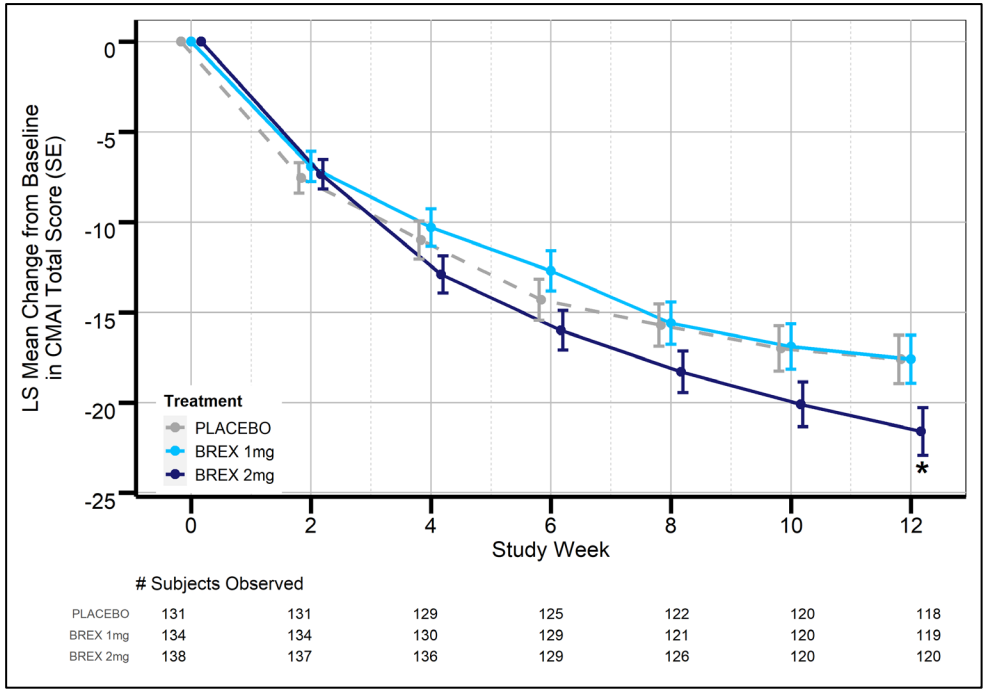
Source: Reviewer's analysis

Abbreviations: CGI-S = Clinical Global Impression-Severity Scale; LSM = least squares mean; SD=standard deviation, SE=standard error; 95% CI = unadjusted 95% confidence interval (p-value also unadjusted for multiple dose arms)

[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

[2]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.

Study 331-12-283: Primary and Secondary Endpoint Analysis



Source: Reviewer's Analysis
Note: Gray dashed line represents the placebo arm

- Statistically significant treatment effect only for BREX 2 mg vs. placebo observed at Week 12 in change from baseline in CMAI total score
- Treatment differences did not reach statistical significance for either BREX 1 mg or BREX 2 mg arms for the secondary efficacy endpoint

Exploratory Analyses on CMAI Subscales

- Although the developers of the CMAI do not recommend the use of a total score, the Applicant selected to use the CMAI total score as their primary efficacy endpoint.
- The Applicant conducted exploratory analyses to evaluate whether there were consistent directional improvements observed across all three CMAI subscale domains and whether there was any compensatory change in one subscale compared with another.
- CMAI Factor 1 (aggressive behavior), Factor 2 (physically non-aggressive behavior), and Factor 3 (verbal agitation) closely aligned with the behaviors outlined in the IPA consensus definition and were the major subscales of interest

Study 331-12-283: Exploratory Analyses on CMAI Subscales

- CMAI Factor Score Analyses

Variable	Placebo (N=131)	BREX 1 mg (N=134)	BREX 2 mg (N=138)
Factor 1: Aggressive Behaviors			
LSM Change from Baseline (SE)	-6.59 (0.50)	-6.58 (0.50)	-7.57 (0.49)
Placebo-subtracted difference (95% CI)		0.02 (-1.31, 1.34)	-0.97 (-2.29, 0.35)
Factor 2: Physically Non-aggressive Behaviors			
LSM Change from Baseline (SE)	-5.74 (0.51)	-5.31 (0.51)	-6.92 (0.51)
Placebo-subtracted difference (95% CI)		0.42 (-0.97, 1.81)	-1.18 (-2.57,0.20)
Factor 3: Verbally Agitated Behaviors			
LSM Change from Baseline (SE)	-3.19 (0.38)	-3.46 (0.38)	-4.45 (0.37)
Placebo-subtracted difference (95% CI)		-0.28 (-1.30, 0.75)	-1.26 (-2.29, -0.24)

Source: Reviewer's analysis

Abbreviations: CI = unadjusted confidence interval (p-value unadjusted); SD: standard deviation; SE = standard error

- Treatment effect across all three CMAI Factor subscales indicated greater improvement with the BREX 2-mg arm vs. placebo

Study 331-12-284 Results

Study 331-12-284: Disposition and Baseline Characteristics

- 270 subjects randomized into the double-blind treatment period
- Most frequent reason for study discontinuation across all treatment groups was due to adverse events (BREX: 6.8%; placebo: 1.5%)
- Majority white (95%), non-Hispanic (94%) subjects with a mean age of 74 years
- Most subjects resided in an institutionalized setting (55%) and exhibited moderate or severe cognitive impairment (76%); comorbid psychotic symptoms present among only 22% of subjects
- Majority of subjects exhibited agitation with aggressive behaviors (85%), physically non-aggressive behaviors (87%), or verbally agitated behaviors (87%) at baseline (67% exhibited significant symptoms across all three domains of agitation)

Study 331-12-284: Primary and Secondary Endpoint Analysis

	Placebo (N=135)	BREX 0.5 to 2 mg (N=131)[2]
Primary Efficacy Endpoint (CMAI)		
Mean CMAI Total Score at Baseline (SD)	68.6 (16.01)	71.5 (16.84)
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
Secondary Efficacy Endpoint (CGIS)		
Mean CGI-S Score at Baseline (SD)	4.5 (0.74)	4.5 (0.77)
LSM Change from Baseline (SE)	-1.0 (0.09)	-1.3 (0.09)
Placebo-subtracted difference (95% CI)[1]		-0.31 (-0.55, -0.06)
P-value (nominal)		0.0164

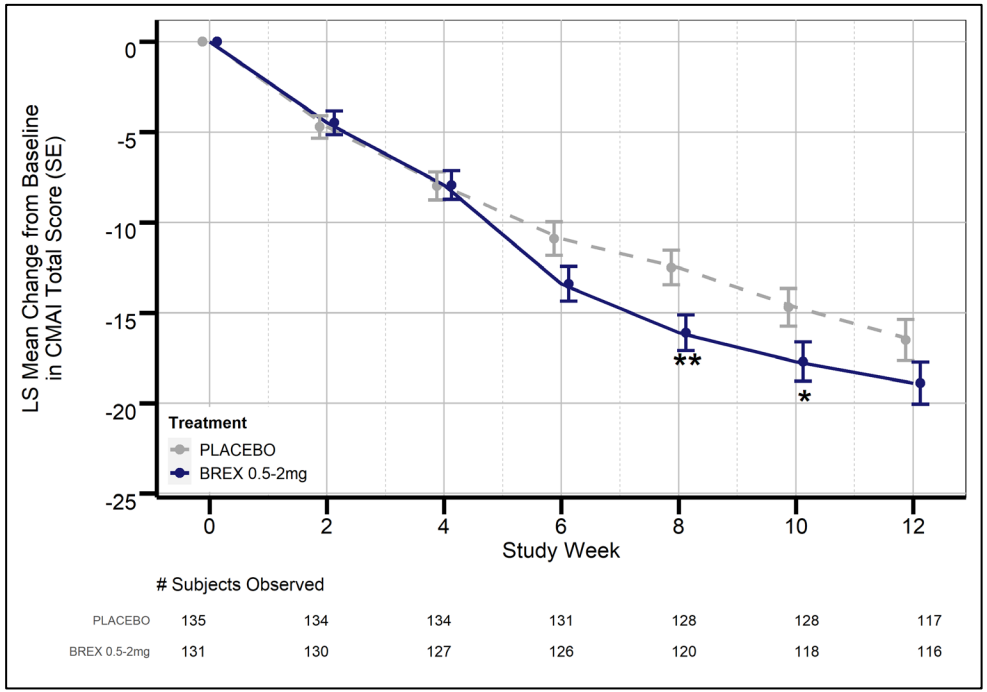
Source: Reviewer's analysis

Abbreviations: CMAI = Cohen Mansfield Agitation Inventory; LSM = least squares mean; MMRM = mixed-effect model for repeated measures; SD=standard deviation; SE=standard error; 95% CI = 95% confidence interval

[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

[2]Two subjects in the placebo group and one subject in the BREX group had only single post-baseline assessments at Week 1, not a planned schedule assessment time. As a result, those three subjects were not captured in the primary analysis although they were in the Efficacy Sample.

Study 331-12-284: Primary and Secondary Endpoint Analysis



Source: Reviewer's Analysis
Note: Gray dashed line represents the placebo arm

- Result for the primary efficacy endpoint (LSMD: -2.34 [95% CI: -5.49, 0.82]; p = 0.1454) was not statistically significant
- Analysis of the secondary efficacy endpoint yielded a -0.31 point numerical improvement for the BREX group over placebo (95% CI: -0.55, -0.06). However, the result is considered solely descriptive

Study 331-12-284: Exploratory Analyses on CMAI Subscales

- CMAI Factor Score Analyses

Variable	Placebo (N=135)	BREX 0.5 to 2 mg (N=131)
Factor 1: Aggressive Behaviors		
LSM Change from Baseline (SE)	-6.13 (0.42)	-7.22 (0.43)
Placebo-subtracted difference (95% CI)		-1.09 (-2.24, 0.05)
Factor 2: Physically Non-aggressive Behaviors		
LSM Change from Baseline (SE)	-5.17 (0.42)	-5.52 (0.43)
Placebo-subtracted difference (95% CI)		-0.35 (-1.51, 0.81)
Factor 3: Verbally Agitated Behaviors		
LSM Change from Baseline (SE)	-3.54 (0.33)	-4.23 (0.34)
Placebo-subtracted difference (95% CI)		-0.69 (-1.59, 0.21)

Source: Reviewer's analysis

Abbreviations: CI = unadjusted confidence interval (p-value unadjusted); SD: standard deviation; SE = standard error

- Treatment effect across all three CMAI Factor subscales indicated a greater improvement with the brexpiprazole arm vs. placebo

Study 331-12-284: Post-hoc Exploratory Analyses

- 59% of subjects receiving brexpiprazole and 55% of subjects receiving placebo required an increase in dosage from 1 mg/day to 2 mg/day after the Week 4 visit
- Subgroup analyses of subjects whose dosage was titrated to 2 mg/day after the Week 4 visit indicated a numerical improvement with brexpiprazole over placebo
- Subgroup analyses of subjects whose modal dosage ≥ 2 mg/day indicated a numerical improvement with brexpiprazole over placebo

2017 Type C Guidance Meeting

- The Applicant discussed their top-line results from Studies 283 and 284 including several subgroup post-hoc analyses that suggested a robust treatment effect among subjects with significant aggressive behaviors at baseline
- Agency did not consider Study 283 to be “statistically persuasive” and emphasized that post-hoc analyses could not serve as the primary support for an application
- Agency recommended the Applicant conduct another 12-week, double-blind, placebo-controlled, fixed-dose study to evaluate a higher dosage than previously studied (e.g., 3 mg/day)
- Agency emphasized that subjects do not need to exhibit aggressive behaviors to be suitable for enrollment and recommended use of the IPA provisional consensus definition for agitation to ensure subjects exhibited sufficient agitation at baseline

2018 Type C Guidance Meeting

- The Applicant met with the Agency to discuss key design elements for Study 213 and proposed an enrichment strategy to include subjects with aggressive behavior at baseline
  - Agency noted that limiting enrollment may narrow the product's final indication for use and that generalizability of the study results to individuals with non-aggressive AAD was unclear
- To obtain sufficient safety data at higher brexpiprazole dosages, the Applicant agreed to planned sample size of 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

Studies 213: Trial Design

Trial Characteristics	Study 331-14-213
Design	Randomized, double-blind, placebo-controlled, multi-center, 12-week phase 3 study
Treatment Paradigm/Arms	• 2:1 randomization ratio to either brexpiprazole or placebo (further randomized to 1:2 to BREX 2 mg or BREX 3 mg) • Initial dosage of 0.5 mg/day with forced titration to target dose • Dosage decrease was not allowed at any time during the study
Study Periods	• Screening period (up to 42 days) for washout of prohibited concomitant pharmacotherapy prior to randomization and to assess eligibility criteria • 12-week double-blind treatment period • 30-day follow-up safety evaluation after receiving the last dose of study medication • Week 16 mortality assessment for all subjects who terminated early

Study 213: Study Population

Inclusion Criteria	Study 331-14-213
Age and Setting	Subjects between 55 to 90 years of age, living either in an institutionalized setting or non-institutionalized setting where the subject was not living alone
Probable AD	NINCDS-ADRDA criteria
AD Severity	MMSE score 5 to 22
Agitation	Criteria identical to Studies 283 and 284 • NPI-NH or NPI/NPI-NH Agitation/ Aggression Item score ≥ 4 • Symptom onset at least 2 weeks prior to screening • Previous trial of non-pharmacological interventions and who did not exhibit an insufficient response to at least 2 previous antipsychotics Additional Criteria: • Meets 2015 IPA provisional consensus definition • Meet criteria for CMAI Factor 1 (aggressive) agitation (e.g., ≥ one aggressive behavior occurring several times per week)

Study 213: Statistical Analysis and Considerations

- Same analyses as in the other two studies, but this study had an unblinded interim analysis for a potential early stop for efficacy.
- The Applicant performed the interim analysis after the first 255 randomized subjects completed the Week 12 visit or discontinued from the trial. After reviewing the unblinded interim analysis results, the Applicant tested the primary efficacy endpoint at a two-sided 3.5% nominal significance level for the final analysis to control the overall type I error rate.

Study 331-14-213 Results

Study 331-14-213: Disposition and Baseline Characteristics

- 345 subjects randomized into the double-blind treatment period
- Most frequent reason for study discontinuation across all treatment groups was due to adverse events (BREX 2 mg: 9.3%; BREX 3 mg: 15%; placebo: 11%)
- Majority white (95%), non-Hispanic (69%) subjects with a mean age of 74 years
- Most subjects resided in an non-institutionalized setting (56%) and exhibited moderate or severe cognitive impairment (76%); comorbid psychotic symptoms present among only 19% of subjects
- Majority of subjects exhibited agitation with physically non-aggressive behaviors (94%) or verbally agitated behaviors (94%) at baseline (89% exhibited significant symptoms across all three domains of agitation)

Study 331-14-213: Primary and Secondary Endpoint Analysis

	Placebo (N=116)	BREX 2 and 3 mg (N=225)[2]
Primary Efficacy Endpoint (CMAI)		
Mean CMAI Total Score at Baseline (SD)	79.2 (17.52)	80.6 (16.64)
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**
Secondary Efficacy Endpoint (CGI-S)		
Mean CGI-S Score at Baseline (SD)	4.7 (0.69)	4.7 (0.66)
LSM Change from Baseline (SE)	-0.9 (0.08)	-1.2 (0.06)
Placebo-subtracted difference (95% CI)[1]		-0.27 (-0.47, -0.07)
P-value (nominal)		0.0078

Source: Reviewer's analysis

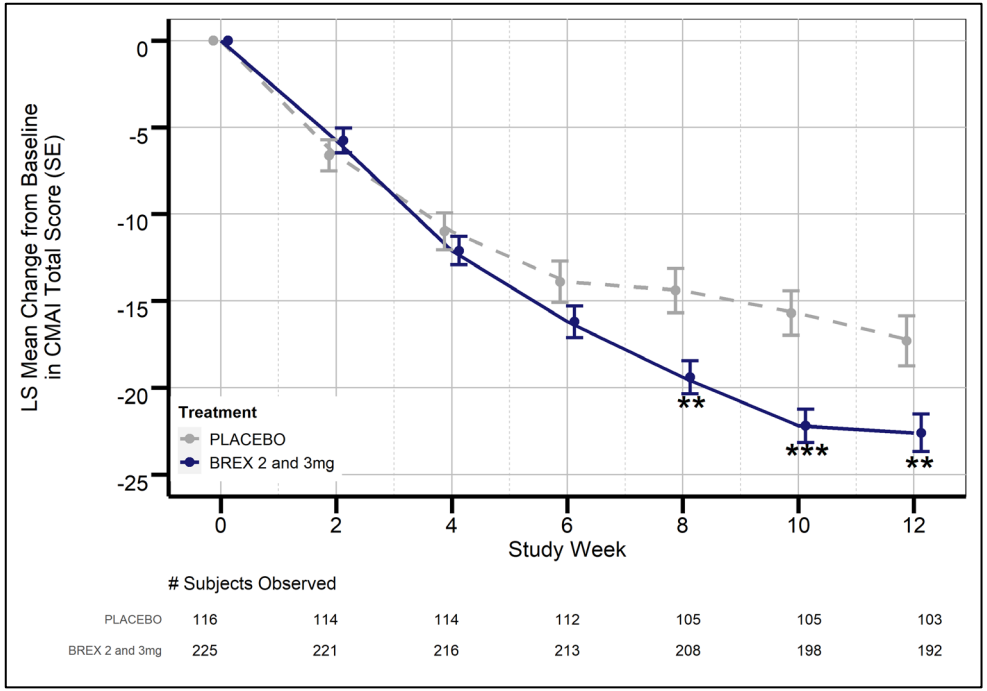
Abbreviations: CMAI = Cohen Mansfield Agitation Inventory; LSM = least squares mean, MMRM = mixed-effect model for repeated measures; SD=standard deviation, SE=standard error, 95% CI = 95% confidence interval.

[1]MMRM method with model terms: treatment, trial site, visit, treatment by visit and baseline by visit interaction.

[2]One subject in the BREX 2 and 3 mg group had only one post-baseline assessment and it was at Week 7, not a planned schedule assessment time. As a result, this subject was not captured in the primary analysis although this subject was in the Efficacy Sample.

Note: The p-values should be compared with the significance level of 0.035 due to an interim analysis conducted.

Study 331-14-213: Primary and Secondary Endpoint Analysis



Source: Reviewer's Analysis
Note: Gray dashed line represents the placebo arm

- The combined brexpiprazole group demonstrated a statistically significant improvement compared to placebo on the primary efficacy endpoint (LSMD = -5.32 [95% CI: -8.77, -1.87]; p = 0.0026)
- Statistical significance also observed with the combined brexpiprazole group over placebo for the secondary efficacy endpoint

Study 331-14-213: Exploratory Analyses on CMAI Subscales

- CMAI Factor Score Analyses

Variable	Placebo (N=116)	BREX 2 and 3 mg (N=225)
Factor 1: Aggressive Behaviors		
LSM Change from Baseline (SE)	-7.13 (0.56)	-9.09 (0.42)
Placebo-subtracted difference (95% CI)		-1.95 (-3.28, -0.63)
Factor 2: Physically Non-aggressive Behaviors		
LSM Change from Baseline (SE)	-5.04 (0.53)	-6.45 (0.40)
Placebo-subtracted difference (95% CI)		-1.41 (-2.68, -0.41)
Factor 3: Verbally Agitated Behaviors		
LSM Change from Baseline (SE)	-3.14 (0.40)	-4.39 (0.31)
Placebo-subtracted difference (95% CI)		-1.24 (-2.21, -0.28)

Source: Reviewer's analysis

Abbreviations: CI = unadjusted confidence interval (p-value unadjusted); SD: standard deviation; SE = standard error

- Treatment effect across all three CMAI Factor subscales indicated greater improvement with brexpiprazole relative to placebo

Overall Conclusions Regarding Efficacy

- Applicant submitted three adequate and well-controlled trials to contribute to substantial evidence of effectiveness
- Statistically significant treatment effects demonstrated with the BREX 2-mg treatment group in Study 331-12-283 and with the combined BREX 2-mg and 3-mg treatment group in Study 331-14-213
- Supportive evidence from Study 331-12-284 that suggests a numerical improvement with brexpiprazole over placebo among subjects titrated to BREX 2 mg after Week 4, which was consistent with findings observed with Studies 331-12-283 and 331-14-213
- Consistent numerical improvements across all three major CMAI subscales in each study

Previously Observed Benefit/Risk Profile of Antipsychotics

- Current literature on other antipsychotics for AAD suggests no regulatory level of evidence of efficacy in the context of serious risks and tolerability concerns
- The benefit/risk analysis for brexpiprazole in AAD requires weighing the benefits as outlined in previous slides against the risk of mortality in elderly patients with dementia-related psychosis as described in the current Boxed Warning
- A comparison with the previous findings of the mortality risk associated with antipsychotics is needed to better contextualize underlying mortality risk observed in this program

Safety Evaluation in Brexpiprazole AAD Trials

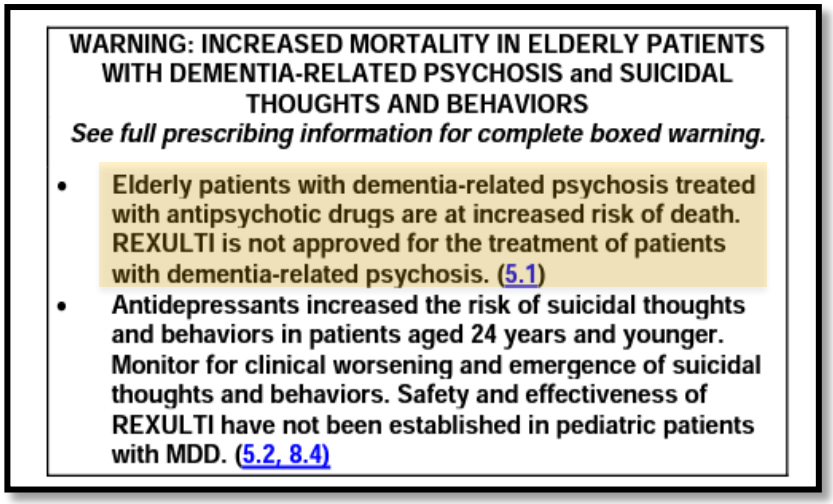
- Primarily based on the three phase 3 studies and two additional safety studies:
  - Study 331-13-211: a 2-month observational, post-treatment rollover phase 3 study that included subjects who completed Studies 331-12-283 and 331-12-284
  - Study 331-201-00182: an active-treatment extension study that included subjects who completed Study 331-14-213
- Evaluation included a mortality assessment of the observed deaths across the clinical development program and other safety findings (e.g., adverse events, laboratory assessments, physical examinations) to compare with the known safety profile observed in adults with schizophrenia and major depressive disorder

FDA's 2005 Meta-Analysis on Antipsychotics in Older People with Dementia

- Starting in 2001, FDA received a cluster of cases of serious cerebrovascular events among subjects with dementia-related psychosis receiving antipsychotic treatment. FDA issued warning statements to risperidone (2003), olanzapine (2004), and aripiprazole (2005) product labels.
- In 2005, FDA conducted a meta-analysis to systematically assess the available data to estimate the mortality risk
  - Databased included 17 randomized, short-term, placebo-controlled trials evaluating six different antipsychotics in elderly subjects with dementia (N_{Total} = 5,377; N_{Drug} = 3,611; $N_{Placebo}$ = 1,766)
  - Average age of population: 81 years
  - Study Duration: Seven studies of 10 weeks and four studies of 12 weeks

FDA's 2005 Meta-Analysis

- Analysis revealed a 70% increased risk of death among subjects receiving antipsychotic treatment vs. placebo
- Over the course of a typical 10-week trial, the incidence of death was 4.5% in the antipsychotic arm vs. 2.6% in the placebo arm
- Causes of death varied and the specific mechanism by which antipsychotics increase the risk of death was unclear

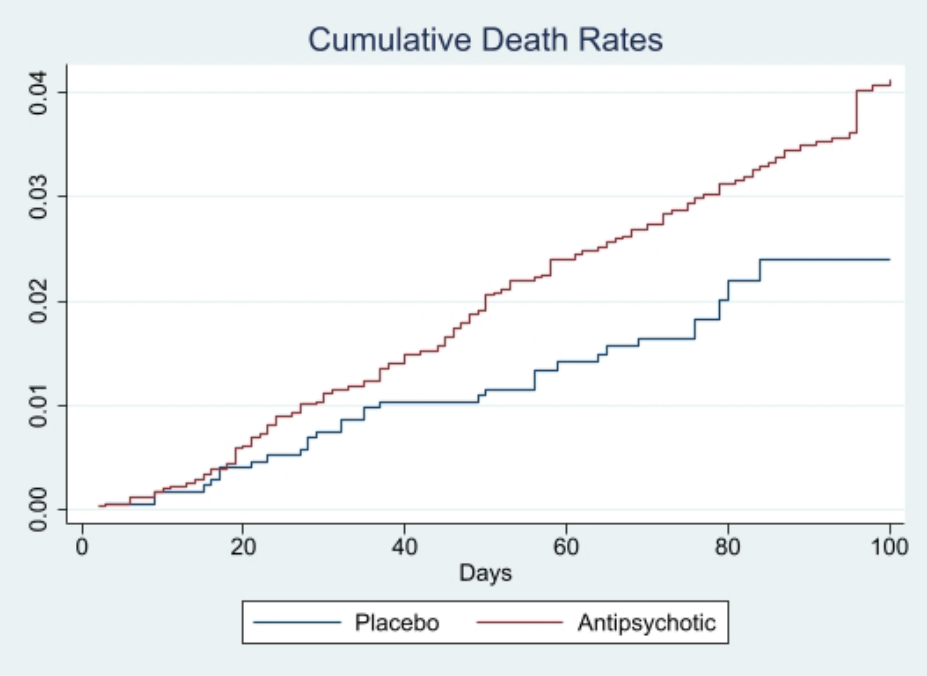


WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. REXULTI is not approved for the treatment of patients with dementia-related psychosis. (5.1)**
- **Antidepressants increased the risk of suicidal thoughts and behaviors in patients aged 24 years and younger. Monitor for clinical worsening and emergence of suicidal thoughts and behaviors. Safety and effectiveness of REXULTI have not been established in pediatric patients with MDD. (5.2, 8.4)**

Interpretation of Mortality Data from Meta-Analysis



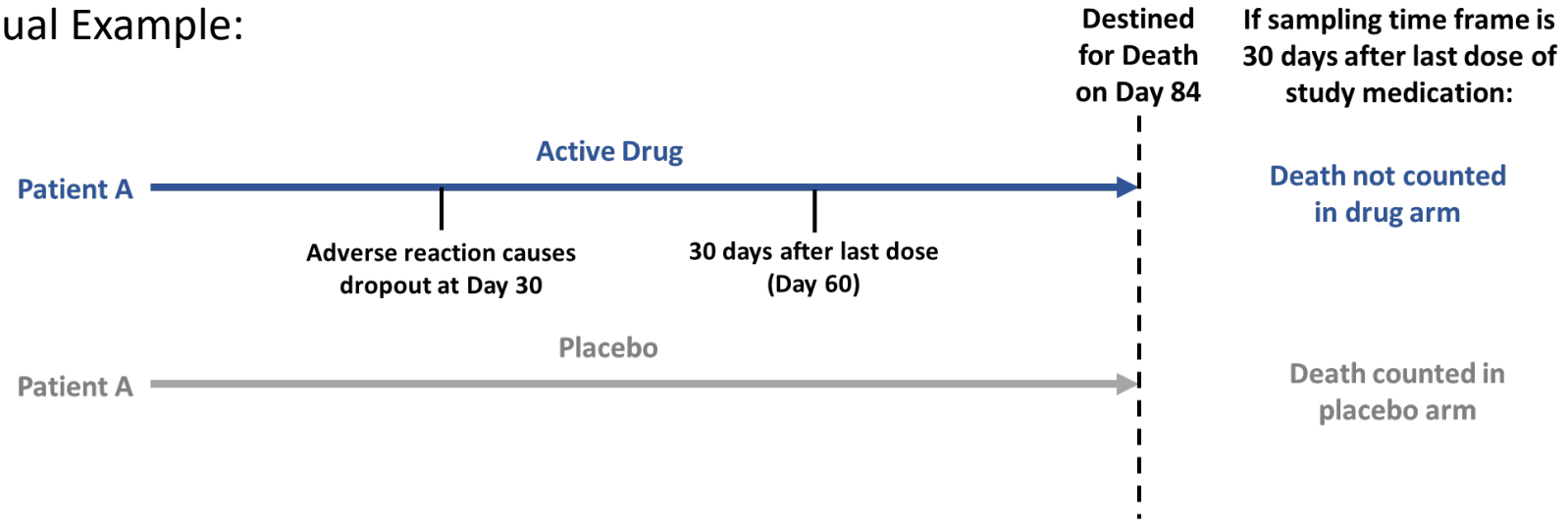
- Hazard for death is persistent and proportional
  - The lack of a concentration of deaths closer to the time of drug initiation suggests that antipsychotics may not be a major direct cause of death
  - A steady rise in cumulative deaths at a higher rate relative to placebo suggests an indirect effect on death rates from exogenous causes

Deaths from Exogenous Events during Antipsychotic Trials

- Previous reports of the timing of a death relative to reports of adverse event and the time of the last dose of study medication suggest that the drug was not usually the direct cause of death but may be associated with worsening outcomes
- Non-fatal adverse reactions to drug may prevent subjects from further study participation and could still increase the risk of death over time
  - Specifying appropriate sampling time frames to count deaths are important to accurately estimate the risk for mortality

Potential Bias Associated with Sampling Time Frames

Visual Example:

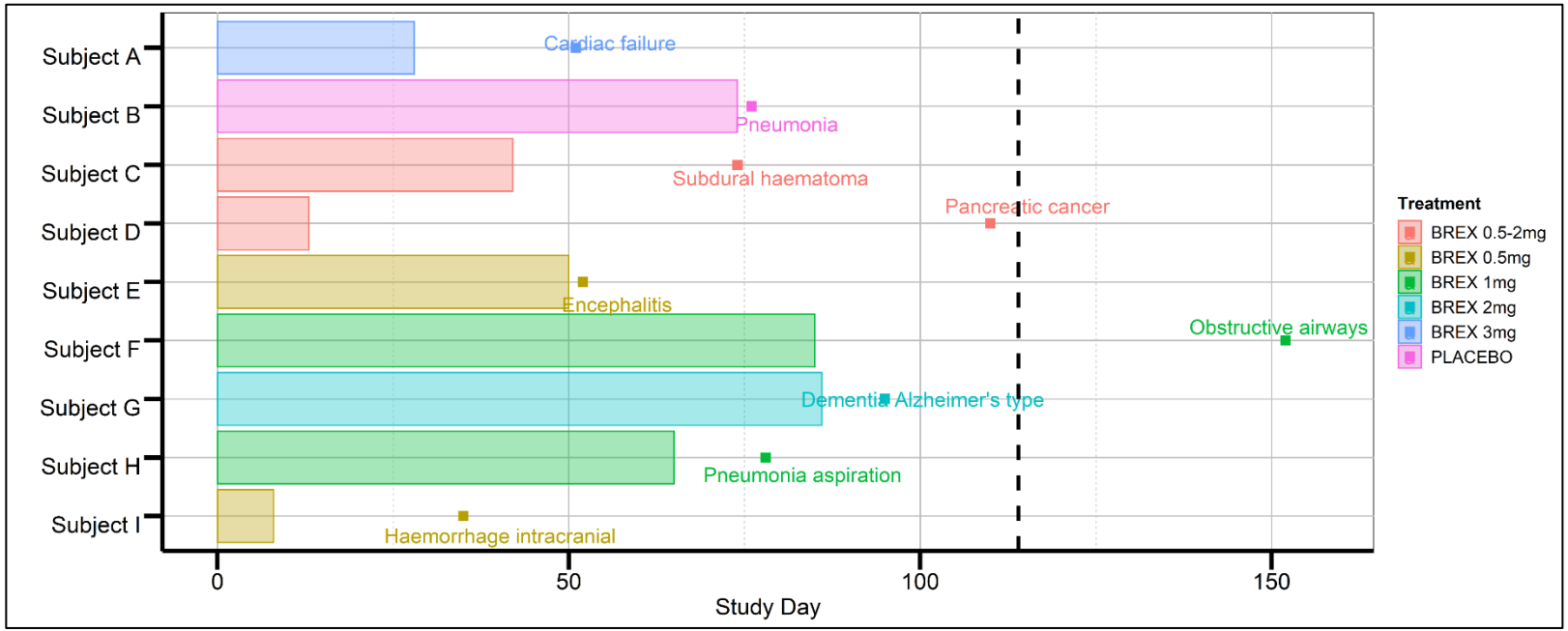


The proposed sampling time frame to count deaths could artificially lower the background rate in the drug arm, underestimating the mortality risk.

Mortality Assessment in Brexpiprazole AAD Trials

- Given the similar duration of treatment and follow-up observation period, the review team focused on deaths observed across all three 12-week, phase 3 studies.
- Across the three studies, the Applicant reported a total of nine deaths; eight of these subjects received brexpiprazole (1.2% of N=655) and one received placebo (0.26% of N=388).
- The Applicant also reported one death in a subject enrolled in Study 211 that previously received brexpiprazole in Study 284. There were no deaths reported in Study 00182 (active-treatment extension study).

Mortality Assessment in Brexpiprazole AAD Trials



Source: Reviewer's Analysis

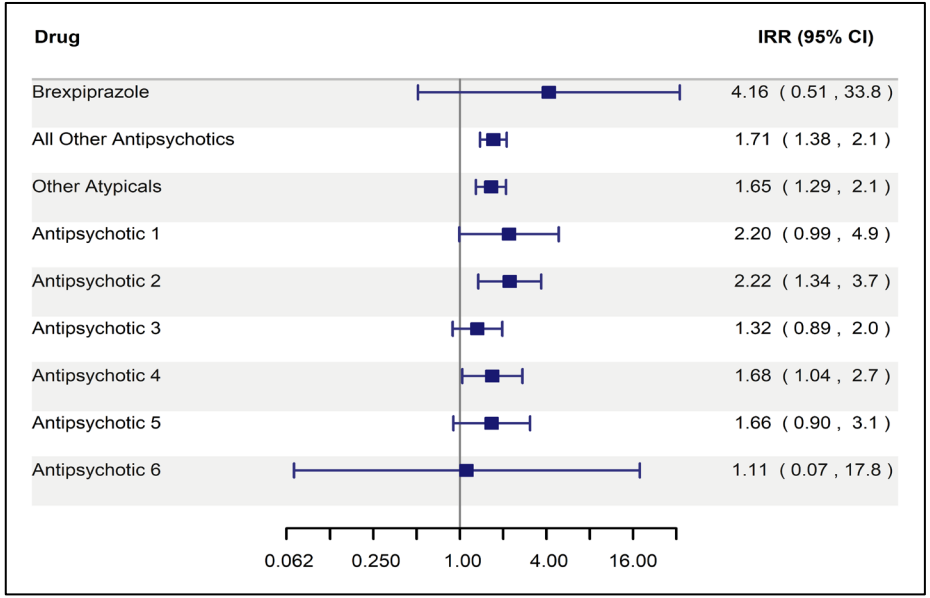
Note: Shaded region represents duration of study treatment. Points represent time of fatal AE/outcome. Vertical dashed line represents the intended period of observation up to the Week 16 mortality assessment (I.e.,114 days).

Mortality Assessment in Brexpiprazole AAD Trials

- The Applicant estimated the incidence of death for each treatment group based on deaths that occurred within 30 days after the last dose of the study medication (BREX = 6 events [0.92%]; placebo = one event [0.26%])
  - One of the deaths in the brexpiprazole treated group occurred after the fatal AE started 25 days after study drug discontinuation
- To juxtapose the current findings with FDA's previous meta-analysis, the review team utilized a similar statistical approach to estimate brexpiprazole's mortality risk
  - Given the confidence in collecting mortality information throughout the study period and follow-up, the review team selected a sampling time frame of 114 days (deaths observed in the intended period of observation [12 weeks] + 30 days of follow-up) to count the number of death events for each treatment group

Mortality Assessment with Brexpiprazole vs. Other Antipsychotics

- Based on the selected sampling time frame, the analysis included seven deaths in the brexpiprazole-treated group (one more than the Applicant reported count) vs. one death in the placebo-treated group
- Incident Rate Ratio (IRR) for brexpiprazole was 4.16 (95% CI: 0.51, 33.83)
- Due to the small number of deaths in this program, including the relatively lower incidence in the placebo arm, there is greater uncertainty regarding the true estimate of the mortality risk relative to the previous findings



Source: Reviewer's Analysis
Abbreviations: CI = confidence interval; IRR = incident rate ratio

Overall Conclusions Regarding Safety

- Although the mortality risk for brexpiprazole appears to follow a similar trend with other antipsychotics, the relatively lower number of deaths casts additional uncertainty regarding the risk amongst the real-world population of patients that will be prescribed the drug
- Because the use of antipsychotics to treat psychosis and agitation is associated with higher mortality in elderly patients, the Boxed Warning should remain to adequately inform health-care providers, patients, and caregivers.
- Other safety findings with this older dementia population were generally similar with brexpiprazole's known safety profile in adult patients with schizophrenia and depression
- Based on the results of the active-treatment extension safety study, continued treatment with brexpiprazole (up to 24 weeks) did not reveal any new safety signals

Overall Conclusion

- Serious unmet medical need for the treatment of AAD
- Applicant appears to have provided substantial evidence of effectiveness for brexpiprazole's use in AAD
- Brexpiprazole's mortality risk appears to be consistent with other antipsychotics used in elderly patients with dementia

Questions to the Committee

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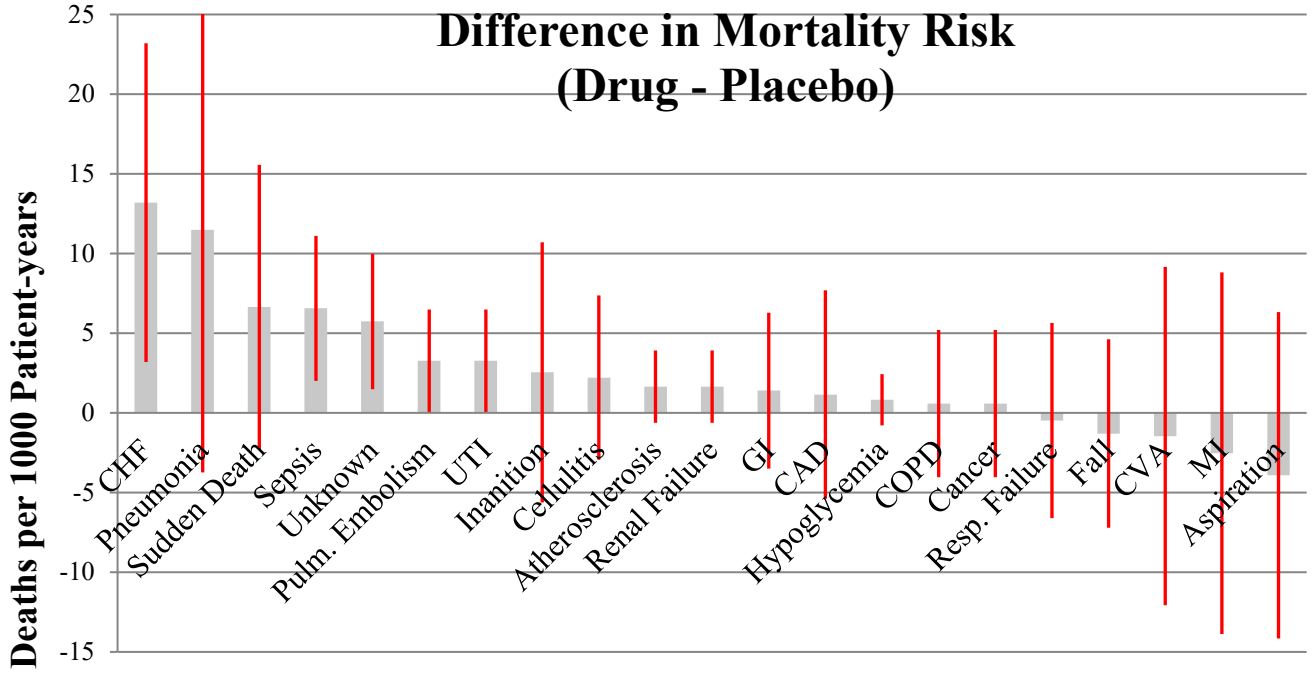
Back-up Slides

Causes of Death



Original Antipsychotic Studies vs. Brexpiprazole Program

	2005 FDA Meta-Analysis	Brexpiprazole
Mean Age of Population	81 years	74 years
Annualized Mortality Rate		
Placebo	8%	0.8%
Antipsychotic	13%	3.5%
CDC Mortality Risk-Equivalent Age Cohort[1]		
Placebo	81 years	59 years
Antipsychotic	86 years	77 years

Source: Reviewer's Analysis

[1]Calculations based on the 2000 and 2019 CDC Life Tables for the 2005 FDA meta-analysis and brexpiprazole program, respectively