BREXIPRAZOLE sNDA for Agitation Associated with Alzheimer’s Dementia (AAD)

April 14, 2023

Psychopharmacologic Drugs Advisory Committee and Peripheral and Central Nervous System Drugs Advisory Committee
Otsuka Pharmaceutical Co.
Lundbeck Inc.
Introduction
Mary Hobart, PhD
Vice President, Global Regulatory Affairs
Otsuka Pharmaceutical
Agitation Associated with Alzheimer’s Dementia (AAD)

- Poor Health Outcomes
- Increased Institutionalization
- Caregiver Distress

No approved treatments
Seeking Supplemental Indication for Brexpiprazole

Proposed sNDA Indication

Treatment of agitation associated with AD

Recommended Dosing

- Target dose: 2 mg QD
- Maximum dose: 3 mg QD

Boxed Warning

- Not proposing to remove boxed warning
Brexpiprazole (REXULTI®) – Atypical Antipsychotic Approved for Schizophrenia and Major Depressive Disorder

- Approved in US for treatment of schizophrenia and for adjunctive treatment of major depressive disorder
  - First approved in US in 2015
  - Approved in > 60 countries, including EU and Canada

- 1,269,877 patient-years experience from clinical studies and post-approval
# Brexpiprazole sNDA Key FDA Regulatory Interactions

## Phase 3 Studies
- **283**: (fixed 1 and 2 mg dose)
- **284**: (flexible 0.5 – 2 mg dose)

## Open-label Extension Study 182

<table>
<thead>
<tr>
<th>Year</th>
<th>2012</th>
<th>2015</th>
<th>2018</th>
<th>2022</th>
</tr>
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<tbody>
<tr>
<td><strong>Pre-IND meeting</strong> &amp; <strong>IND submitted</strong></td>
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<td><strong>Fast Track Designation granted</strong></td>
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<tr>
<td><strong>FDA meeting to discuss Study 213 design</strong></td>
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<tr>
<td><strong>Pre-sNDA meeting &amp; sNDA submission</strong></td>
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</table>
Three Phase 3 Studies Support Efficacy and Safety of Brexpiprazole

**Study 283**
Fixed-dose
1 or 2 mg/day
Randomized, double-blind, placebo-controlled
12 Weeks

**Study 284**
Flexible-dose
0.5 to 2 mg/day
Randomized, double-blind, placebo-controlled
12 Weeks

**Study 213**
Fixed-dose
2 or 3 mg/day
Randomized, double-blind, placebo-controlled
12 Weeks
Brexpiprazole Positive Benefit / Risk for Treatment of AAD When Dosed 2 or 3 mg QD

Statistically significant and clinically meaningful improvements in key measures of agitation vs placebo

Favorable tolerability profile
AEs consistent with those previously reported for brexpiprazole and observed in this patient population

Addresses critical unmet clinical need and provides substantial improvement relative to currently utilized off-label treatments for AAD
Agenda

Unmet Need

Zahinoor Ismail, MD, FRCPC
Professor of Psychiatry, Neurology, Epidemiology, and Pathology
Hotchkiss Brain Institute & O'Brien Institute for Public Health
University of Calgary

Efficacy

Robert McQuade, PhD
Executive Vice President and Chief Strategy Officer
Otsuka Pharmaceutical

Safety

John Kraus, MD, PhD
Executive Vice President and Chief Medical Officer
Otsuka Pharmaceutical

Clinical Perspective

Alireza Atri, MD, PhD
Director
Banner Sun Health Research Institute

Benefit / Risk Summary

Mary Hobart, PhD
Vice President, Global Regulatory Affairs
Otsuka Pharmaceutical
### Additional Responders

**Gus Alva, MD, DFAPA**  
ATP Clinical Research, Inc

**Matthew Harlin, MS**  
Director, Quantitative Pharmacology  
Otsuka Pharmaceutical

**Jyoti Aggarwal, MHS**  
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Otsuka Pharmaceutical

**Pralay Mukhopadhyay, PhD**  
Vice President, Head of Clinical Analytics  
Otsuka Pharmaceutical
Unmet Need in AAD

Zahinoor Ismail, MD, FRCPC

Professor of Psychiatry, Neurology, Epidemiology, and Pathology
Hotchkiss Brain Institute & O’Brien Institute for Public Health
University of Calgary
Alzheimer’s Dementia Is Highly Prevalent and Expected to Increase Significantly in Coming Decades

Alzheimer’s is the most common form of dementia.

- Approximately 6.5 million in 2022
- Approximately 12.7 million in 2050

Alzheimer’s Disease Facts and Figures, 2022
International Psychogeriatric Association (IPA) defines agitation in dementia as ≥ 1 behavior persistent or frequently recurrent for ≥ 2 weeks\textsuperscript{1,2}

- **Excessive Motor Activity Behaviors**
  - Pacing
  - Rocking
  - Gesturing
  - Pointing fingers
  - Restlessness
  - Performing repetitious mannerisms

- **Verbal Aggression Behaviors**
  - Yelling
  - Speaking in an excessively loud voice
  - Using profanity
  - Screaming
  - Shouting

- **Physical Aggression Behaviors**
  - Grabbing
  - Shoving
  - Pushing
  - Resisting
  - Hitting self
  - Slamming doors
  - Tearing things
  - Destroying property

\textsuperscript{1} Cummings et al. 2015; 2. Sano et al. 2023
AAD Worsens Impact of Already Devastating and Burdensome Disease for Patient and Caregiver

### PATIENT¹⁻⁵
- Accelerated disease progression
- Functional decline
- Poorer quality of life
- Greater mortality
- Higher rates of institutionalization

### CAREGIVER⁶⁻¹⁰
- Anxiety and depression
- Further increases burden of care
- > 20 hours per week supervising and providing care to patients
- Caregiver distress can lead to institutionalization

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Evidence Based Approach to Treating AAD

- Nonpharmacological strategies are first line
- Both pharmacological and non-pharmacological treatments often initiated only after clinical emergency
  - Poor recognition of agitation
  - Lack of indicated treatments
  - Reluctance to treat early
- Goal is to reduce agitation and calm patient without sedation
Current pharmacotherapy requires balance of risks and benefits.

Choice of medications (all off-label) can depend on acuity of agitation (i.e., frequency, severity, and safety issues):

- Benzodiazepines, antihistamines, antidepressants, antiepileptics, and antipsychotics (both typical and atypical).

Off-label medications show inconsistent and modest effects and carry several notable safety limitations:

- Sedation, extrapyramidal symptoms, falls, worsened cognitive performance, and cardiovascular and cerebrovascular events.

No labeling to guide use.

1. Ismail et al. 2019
Need for Better Identification of AAD and Approved, Well-Documented Pharmacological Treatments

- AAD worsens impact of already devastating and burdensome disease for patients, caregivers, and healthcare system

- Need for FDA-approved product that communicates efficacy and safety expectations in label
- Reduce AAD symptoms with better risk / benefit profile than currently used off-label pharmacotherapy
- Ultimate goal to not sedate patients but reduce AAD symptoms
Efficacy

Robert McQuade, PhD
Executive Vice President and Chief Strategy Officer
Otsuka Pharmaceutical
Three Phase 3 Studies Support Efficacy of Brexpiprazole 2 and 3 mg

- **Study 283**
  - Fixed-dose
  - 1 or 2 mg/day
  - Randomized, double-blind, placebo-controlled
  - 12 Weeks

- **Study 284**
  - Flexible-dose
  - 0.5 to 2 mg/day
  - Randomized, double-blind, placebo-controlled
  - 12 Weeks

- **Study 213**
  - Fixed-dose
  - 2 or 3 mg/day
  - Randomized, double-blind, placebo-controlled
  - 12 Weeks
Studies 283 and 284: Similar Clinical Designs

**Patients with AAD**

**Study 283**
- Fixed-dose
- Brexpiprazole 2 mg/day (N = 140)
- Brexpiprazole 1 mg/day (N = 137)
- Placebo (N = 136)

**Study 284**
- Flexible-dose
- Brexpiprazole 0.5–2 mg/day (N = 133)
- Placebo (N = 137)

**Titration, Study 283**
- Brexpiprazole 2 mg: Days 1–3, 0.25 mg; Days 4–14, 0.5 mg; Weeks 3 and 4, 1 mg/day; Weeks 5–12, 2 mg/day
- Brexpiprazole 1 mg: Days 1–3, 0.25 mg; Days 4–14, 0.5 mg; Weeks 3 and 4, 1 mg/day; Weeks 5–12, 1 mg/day

**Titration, Study 284**
- Brexpiprazole 0.5–2 mg: Days 1–3, 0.25 mg; Days 4–14, 0.5 mg; Weeks 3 and 4, 1 mg/day; Weeks 5–12, 2 mg/day

**Note:** Study 283 originally had a 0.5 mg group which was removed based on new information from completed studies in other indications.
Studies 283 and 284: Endpoint Selection

**Primary Endpoint**
Mean change in Cohen-Mansfield Agitation Inventory (CMAI) Total Score at Week 12

**Key Secondary Endpoint**
Mean change on Clinical Global Impression of Severity (CGI-S) score as related to agitation at Week 12
Cohen-Mansfield Agitation Inventory (CMAI): Well-Established Tool

<table>
<thead>
<tr>
<th>Behaviors</th>
<th>Factor 1</th>
<th>Factor 2</th>
<th>Factor 3</th>
<th>Other Behaviors (Non-subscale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors</td>
<td>Aggressive</td>
<td>Physical Non-Aggressive</td>
<td>Verbally Agitated</td>
<td></td>
</tr>
<tr>
<td>1. Hitting</td>
<td></td>
<td>Pace, aimless wandering</td>
<td>Complaining</td>
<td>Hiding things</td>
</tr>
<tr>
<td>2. Kicking</td>
<td></td>
<td>Inappropriate dress or disrobing</td>
<td>Constant requests for attention</td>
<td>Hoarding things</td>
</tr>
<tr>
<td>3. Pushing</td>
<td></td>
<td>Trying to get to different place</td>
<td>Negativism</td>
<td>Making strange noises</td>
</tr>
<tr>
<td>4. Scratching</td>
<td></td>
<td>Handling things</td>
<td>Repetitious sentences or questions</td>
<td>Eating/drinking inappropriate substances</td>
</tr>
<tr>
<td>5. Hurting self or others</td>
<td></td>
<td>General restlessness</td>
<td></td>
<td>Intentional falling</td>
</tr>
<tr>
<td>6. Tearing things</td>
<td></td>
<td>Performing repetitive</td>
<td></td>
<td>Verbal sexual advances</td>
</tr>
<tr>
<td>7. Throwing things</td>
<td></td>
<td>mannerisms</td>
<td></td>
<td>Physical sexual advances</td>
</tr>
<tr>
<td>8. Screaming</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Cursing or verbal aggression</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>10. Grabbing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Biting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Spitting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Behaviors (Non-subscale)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>▪ Hitting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Kicking</td>
<td></td>
<td></td>
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<tr>
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<td></td>
</tr>
<tr>
<td>▪ Spitting</td>
<td></td>
<td></td>
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<tr>
<td>Range of possible scores</td>
<td>12 to 84 points</td>
<td>6 to 42 points</td>
<td>4 to 28 points</td>
<td>7 to 49 points</td>
</tr>
</tbody>
</table>

7-point Scale

1. Never
2. < 1 / week but still occurring
3. 1-2x / week
4. Several times / week
5. 1-2x / day
6. Several times / day
7. Several times / hour

Rabinowitz et al. 2005
Studies 283 and 284: Key Enrollment Criteria

**Inclusion Criteria**
- Adults 55-90 years old
- Diagnosis of probable Alzheimer’s disease according to NINCDS-ADRDA criteria and MMSE score 5-22
- Diagnosis of agitation with onset of symptoms ≥ 2 weeks prior to screening
- NPI-NH or NPI/NPI-NH Agitation/Aggression Score ≥ 4 at screening and baseline

**Exclusion Criteria**
- Dementia or memory impairment not due to Alzheimer’s disease
- Axis-1 disorders (schizophrenia, BD, current MDD)
- History of stroke, transient ischemic attack, or pulmonary or cerebral embolism
- Delirium or history of delirium within 30 days of screening
- Serious risk of suicide (Sheehan-STS scale)

MMSE = Mini-Mental State Examination
# Studies 283 and 284: Demographics Similar Across and Within Studies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study 283</th>
<th>Study 284</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mg/day</td>
<td>2 mg/day</td>
</tr>
<tr>
<td></td>
<td>N = 137</td>
<td>N = 140</td>
</tr>
<tr>
<td>Age (years), Mean</td>
<td>74</td>
<td>74</td>
</tr>
<tr>
<td>Female</td>
<td>57%</td>
<td>56%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>98%</td>
<td>95%</td>
</tr>
<tr>
<td>Black / African-American*</td>
<td>1%</td>
<td>4%</td>
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<tr>
<td>Other</td>
<td>0.7%</td>
<td>1%</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>18%</td>
<td>16%</td>
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* Black / African American patients represented 10% and 15% of randomized US patients
Studies 283 and 284: Representative of Patients with AAD with Similar Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study 283</th>
<th>Study 284</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mg/day N = 137</td>
<td>2 mg/day N = 140</td>
</tr>
<tr>
<td>CMAI total score, Mean</td>
<td>70.7</td>
<td>71.0</td>
</tr>
<tr>
<td>CGI severity score, Mean</td>
<td>4.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Dementia severity (MMSE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (&gt; 18)</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Moderate (13 – 18)</td>
<td>55%</td>
<td>62%</td>
</tr>
<tr>
<td>Severe (≤ 12)</td>
<td>39%</td>
<td>30%</td>
</tr>
<tr>
<td>Institutionalized</td>
<td>65%</td>
<td>61%</td>
</tr>
<tr>
<td>Time since diagnosis of Alzheimer’s (months), Mean</td>
<td>36.7</td>
<td>31.3</td>
</tr>
<tr>
<td>Time since onset of current agitation episode (months), Mean</td>
<td>7.0</td>
<td>9.3</td>
</tr>
</tbody>
</table>
Studies 283 and 284: Similar Completion Rates

**Study 283**
- **Randomized**
  - N = 433
- **1 mg/day**
  - N = 137
    - Discontinued: N = 16
      - Completed: N = 121 (88%)
- **2 mg/day**
  - N = 140
    - Discontinued: N = 18
      - Completed: N = 122 (87%)
- **Placebo**
  - N = 136
    - Discontinued: N = 15
      - Completed: N = 121 (89%)

**Study 284**
- **Randomized**
  - N = 270
- **0.5 – 2 mg/day**
  - N = 133
    - Discontinued: N = 16
      - Completed: N = 117 (88%)
- **Placebo**
  - N = 137
    - Discontinued: N = 16
      - Completed: N = 121 (88%)
Studies 283 and 284: Primary CMAI Results Show Improvements with Brexpiprazole

**Study 283**
- Brex 1 mg (N = 134)
- Brex 2 mg (N = 138)
- Placebo (N = 131)

**LS Mean Change from Baseline in CMAI Total Score (SE)**

- Week 0: p = 0.9015
- Week 12: *p = 0.0404

**Study 284**
- Brex 0.5 – 2 mg (N = 131)
- Placebo (N = 135)

**LS Mean Change from Baseline in CMAI Total Score (SE)**

- Week 0: *p = 0.1454

* *p<0.05, **p<0.01 versus placebo; MMRM*
Study 284: Patients Up-Titrated to Brexpiprazole 2 mg Demonstrated Efficacy on CMAI Total Score (Post-Hoc)

- Up-Titration to 2 mg

- LS Mean Change from Baseline in CMAI Total Score (SE)

- Decision to up-titrate to 2 mg

- Brex 0.5 – 2 mg (N = 77)
- Placebo (N = 74)

- *p < 0.05, **p < 0.01 versus placebo; nominal p-values presented; MMRM

- p = 0.0121
Studies 283 and 284: Improvement on Key Secondary (CGI-S) Endpoint with Brexipiprazole

**Study 283**

![Graph showing LS Mean Change from Baseline in CGI-S Score, as Related to Agitation (SE) over 12 weeks for Brex 1 mg (N = 134), Brex 2 mg (N = 138), and Placebo (N = 131).]

- **Brex 1 mg (N = 134)**: p = 0.4440
- **Brex 2 mg (N = 138)**: p = 0.1566
- **Placebo (N = 131)**

* p<0.05 versus placebo; MMRM

**Study 284**

![Graph showing LS Mean Change from Baseline in CGI-S Score, as Related to Agitation (SE) over 12 weeks for Brex 0.5 – 2 mg (N = 131) and Placebo (N = 135).]

- **Brex 0.5 – 2 mg (N = 131)**: *
- **Placebo (N = 135)**: p = 0.0164

* p<0.05 versus placebo; MMRM
Studies 283 and 284: Key Conclusions

- Study 283 met primary endpoint; Study 284 did not
- Data supports efficacy of brexpiprazole 2 mg
  - 2 mg identified as minimum effective dose
Studies 283 and 284: Enrollment of Some Patients with Insufficient Agitation May Have Impacted Results

1. Grossberg et al. 2020; 2. Rabinowitz et al. 2005

Agitation inclusion criterion in 283 and 284 based on NPI-NH Agitation/Aggression item score of ≥ 4\(^1\) not on CMAI

Focused on behaviors that are more prominent and more impactful on patient’s and caregiver’s quality of life

- CMAI Factor 1* encompasses physical and verbal aggressive behaviors\(^2\)

Post-hoc analyses of patients meeting criteria for Factor 1 demonstrated greater baseline frequency and greater effect of treatment over placebo

- ~ 86% met criteria for CMAI Factor 1 with baseline of 71-75 points
- Those who did not meet Factor 1 criteria had baseline of 55-59 points

*To meet criterion, one of following must be displayed: i. ≥ 1 aggressive behaviors occurring several times per week; ii. ≥ 2 aggressive behaviors occurring once or twice per week; iii. ≥ 3 aggressive behaviors occurring less than once per week
1. Grossberg et al. 2020; 2. Rabinowitz et al. 2005
Three Phase 3 Studies Support Efficacy of Brexpiprazole 2 and 3 mg

**Study 283**
Fixed-dose
1 or 2 mg/day
Randomized, double-blind, placebo-controlled
12 Weeks

**Study 284**
Flexible-dose
0.5 to 2 mg/day
Randomized, double-blind, placebo-controlled
12 Weeks

**Study 213**
Fixed-dose
2 or 3 mg/day
Randomized, double-blind, placebo-controlled
12 Weeks
Study 213: Clinical Design Based on FDA Feedback

The study had an interim analysis at 255 patients. Decision to move to full sample of 330. Alpha level for final analysis is 0.035.

For all patients who terminated early from the study, a mortality assessment was obtained from the patient's caregiver by telephone contact at Week 16.

Patients with dementia of Alzheimer’s type who exhibit agitation per IPA criteria and CMAI Factor 1

Brexpiprazole 2 or 3 mg/day (N = 228)
- Randomization 2:1
- Randomization 1:2
  - 2 mg/day (N = 75)
  - 3 mg/day (N = 153)

Placebo (N = 117)

Dosing
- Day 1: 0.5 mg
- Day 8: 1 mg
- Day 15: 2 mg
- Day 29: 2 mg or 3 mg

Screening

12-week double-blind treatment period

Titration ≤ 4 Weeks

30-day safety follow-up
# Study 213: Key Enrollment Criteria Included
## Enrichment for More Prominent Agitated Behaviors

### Inclusion Criteria
- Adults 55-90 years old
- Diagnosis of probable Alzheimer’s disease according to NINCDS-ADRDA criteria and MMSE score 5-22
- Diagnosis of agitation meeting IPA provisional definition and onset of symptoms ≥ 2 weeks prior to screening
- NPI-NH or NPI/NPI-NH Agitation/Aggression Score ≥ 4 at screening and baseline
- Meet criteria for CMAI Factor 1 at baseline

### Exclusion Criteria
- Dementia or memory impairment not due to Alzheimer's disease
- Axis-1 disorders (schizophrenia, BD, current MDE)
- History of stroke, transient ischemic attack, or pulmonary or cerebral embolism
- Delirium or history of delirium within 30 days of screening
- Serious risk of suicide (Sheehan-STS scale)
Study 213: Endpoint Selection Same as 283 and 284

**Primary Endpoint**
Mean change in Cohen-Mansfield Agitation Inventory (CMAI) Total Score at Week 12

**Key Secondary Endpoint**
Mean change on Clinical Global Impression of Severity (CGI-S) score as related to agitation at Week 12
## Study 213: Demographics Consistent Across Arms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2 mg/day N = 75</th>
<th>3 mg/day N = 153</th>
<th>Placebo N = 117</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Mean</td>
<td>74</td>
<td>75</td>
<td>73</td>
</tr>
<tr>
<td>Female</td>
<td>57%</td>
<td>60%</td>
<td>51%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>93%</td>
<td>94%</td>
<td>98%</td>
</tr>
<tr>
<td>Black / African-American*</td>
<td>7%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Other</td>
<td>0%</td>
<td>2%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>33%</td>
<td>30%</td>
<td>32%</td>
</tr>
</tbody>
</table>

* Black / African American patients represented 8% of randomized US patients
# Study 213: Disease Characteristics Similar Across Arms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2 mg/day N = 75</th>
<th>3 mg/day N = 153</th>
<th>Placebo N = 117</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMAI total score, Mean</td>
<td>78.6</td>
<td>81.2</td>
<td>79.4</td>
</tr>
<tr>
<td>CGI severity score, Mean</td>
<td>4.6</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Dementia severity (MMSE)</td>
<td></td>
<td></td>
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<tr>
<td>Mild (&gt; 18)</td>
<td>21%</td>
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</tr>
<tr>
<td>Moderate (13 – 18)</td>
<td>64%</td>
<td>52%</td>
<td>56%</td>
</tr>
<tr>
<td>Severe (≤ 12)</td>
<td>15%</td>
<td>24%</td>
<td>20%</td>
</tr>
<tr>
<td>Institutionalized</td>
<td>43%</td>
<td>42%</td>
<td>46%</td>
</tr>
<tr>
<td>Time since diagnosis of Alzheimer's (months), Mean</td>
<td>34.5</td>
<td>37.8</td>
<td>34.1</td>
</tr>
<tr>
<td>Time since onset of current agitation episode (months), Mean</td>
<td>9.0</td>
<td>10.5</td>
<td>8.9</td>
</tr>
</tbody>
</table>
Study 213: Most Patients Completed Study

Randomized
N = 345

2 – 3 mg/day
N = 228

Discontinued
N = 30

Completed
N = 198 (87%)

Placebo
N = 117

Discontinued
N = 13

Completed
N = 104 (89%)
Study 213: Brexpiprazole 2 or 3 mg Significant Improvement vs Placebo in Primary Endpoint CMAI

- **p<0.01, ***p<0.001 versus placebo; MMRM**

### LS Mean Change from Baseline in CMAI Total Score (SE)

- **Brex 2 or 3 mg (N = 225)**
- **Placebo (N = 116)**

### CMAI Total score at baseline, Mean (SD)

<table>
<thead>
<tr>
<th>Brexpiprazole (N = 225)</th>
<th>Placebo (N = 116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80.6 (16.6)</td>
<td>79.2 (17.5)</td>
</tr>
</tbody>
</table>

### Mean Change in CMAI Total score at Week 12, LS Mean (SE)

<table>
<thead>
<tr>
<th>Brexpiprazole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>-22.6 (1.08)</td>
<td>-17.3 (1.44)</td>
</tr>
</tbody>
</table>

### Treatment Difference at Week 12 (95% CI)

<table>
<thead>
<tr>
<th>Brexpiprazole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5.32</td>
<td>(-8.77, -1.87)</td>
</tr>
</tbody>
</table>

**p = 0.0026**
Study 213: Brexpiprazole 2 or 3 mg Significant Improvement vs Placebo in Key Secondary Endpoint CGI-S

**p<0.01 versus placebo; MMRM**

** LS Mean Change from Baseline in CGI-S Severity of Illness (SE) **

<table>
<thead>
<tr>
<th>Brexpiprazole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGI-S score at baseline, Mean (SD)</td>
<td>4.71 (0.66)</td>
</tr>
<tr>
<td>Mean Change in CGI-S score at Week 12, LS Mean (SE)</td>
<td>-1.20 (0.06)</td>
</tr>
<tr>
<td>Treatment Difference at Week 12 (95% CI)</td>
<td><strong>-0.27 (-0.47, -0.07)</strong></td>
</tr>
</tbody>
</table>
Study 213: CMAI Endpoint Demonstrates Improvement vs Placebo for Both Brexpiprazole 2 and 3 mg

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

*p<0.05, **p<0.01, ***p<0.001 versus placebo; nominal p-values presented; MMRM
Study 213: Brexpiprazole Separated from Placebo Across 3 Key Factors of Agitation

Change from Baseline to Week 12

<table>
<thead>
<tr>
<th>Category</th>
<th>Brex 2 or 3 mg (N = 225)</th>
<th>Placebo (N = 116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressive</td>
<td>-9.09</td>
<td>-7.13</td>
</tr>
<tr>
<td>Physically Non-Aggressive</td>
<td>-6.45</td>
<td>-5.04</td>
</tr>
<tr>
<td>Verbally Agitated</td>
<td>-4.39</td>
<td>-3.14</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01 versus placebo; nominal p-values presented; MMRM
Study 213: Higher Percentage of Responders with Brexpiprazole vs Placebo on CMAI Total Score

Responders at Week 12 (%)

<table>
<thead>
<tr>
<th></th>
<th>Brex 2 or 3 mg (N = 225)</th>
<th>Placebo (N = 116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMAI Total ≥ 20%</td>
<td>RR = 1.41</td>
<td>RR = 1.62</td>
</tr>
<tr>
<td></td>
<td>68%</td>
<td>47%</td>
</tr>
<tr>
<td>95% CI: 1.15, 1.72</td>
<td></td>
<td>95% CI: 1.18, 2.23</td>
</tr>
<tr>
<td>CMAI Total ≥ 30%</td>
<td>RR = 1.62</td>
<td></td>
</tr>
<tr>
<td></td>
<td>43%</td>
<td>26%</td>
</tr>
<tr>
<td>95% CI: 1.00, 2.61</td>
<td></td>
<td>95% CI: 1.00, 2.61</td>
</tr>
<tr>
<td>CMAI Total ≥ 40%</td>
<td>RR = 1.62</td>
<td></td>
</tr>
<tr>
<td></td>
<td>23%</td>
<td>23%</td>
</tr>
<tr>
<td>95% CI:</td>
<td></td>
<td>95% CI: 1.00, 2.61</td>
</tr>
</tbody>
</table>

RR: ratio of response rate
CMAI Reduction Strongly Correlated with Improvement on CGI-S

- Strong correlation between reductions in CMAI Total Score and CGI-S
- Meaningful within patient change threshold in CMAI (20-point reduction) correlated to improvement of CGI-S (2-point reduction)
Higher Percentage of Brexpiprazole-Treated Patients Achieve Meaningful Within Patient Change Threshold

Study 213

Patients Achieving CMAI MWPC Threshold (20-points) in Total Score from Baseline (%)

- Brex 2 and 3 mg (N = 225): 56%
- Placebo (N = 116): 37%

RR = 1.51; 95% CI: 1.17, 1.94

MWPC: meaningful within patient change; RR: ratio of response rate
Study 182: Continued Improvements Observed in 12-Week Extension Trial with Brexpiprazole Treatment

Study 213 Double-Blind
Study 182 Active Extension

**p<0.01, ***p<0.001 versus placebo; MMRM
Brexpiprazole Shows Consistent Efficacy Across 3 Trials Supporting Meaningful Benefit to Patients with AAD

<table>
<thead>
<tr>
<th>Trial Number and Analysis</th>
<th>Daily Dose</th>
<th>CMAI Result</th>
<th>CMAI p-value</th>
<th>CGI-S Result</th>
<th>CGI-S p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-specified Analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 283 ITT</td>
<td>2 mg</td>
<td>-3.77</td>
<td><strong>0.0404</strong></td>
<td>-0.16</td>
<td>0.1566</td>
</tr>
<tr>
<td>Study 213 ITT</td>
<td>2 or 3 mg</td>
<td>-5.32</td>
<td><strong>0.0026</strong></td>
<td>-0.27</td>
<td><strong>0.0078</strong></td>
</tr>
<tr>
<td>Study 284 ITT</td>
<td>0.5 – 2 mg (Mean dose 1.54 mg)</td>
<td>-2.34</td>
<td>0.1454</td>
<td>-0.31</td>
<td><strong>0.0164</strong>*</td>
</tr>
</tbody>
</table>

*Nominal p-values not adjusted for multiple comparisons
Bolded text indicates p-values or nominal p-values < 0.05, and Cohen's-D Effect size of 0.25 to 0.35
Safety

John Kraus, MD, PhD
Executive Vice President and Chief Medical Officer
Otsuka Pharmaceutical
Brexpiprazole AAD Safety Population
Three Phase 3 Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Dose Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 283</td>
<td>432</td>
<td>Fixed-dose (1 or 2 mg/day)</td>
</tr>
<tr>
<td>Study 284</td>
<td>269</td>
<td>Flexible-dose (0.5 to 2 mg/day)</td>
</tr>
<tr>
<td>Study 213</td>
<td>342</td>
<td>Fixed-dose (2 or 3 mg/day)</td>
</tr>
</tbody>
</table>

N = 655  
All Brexpiprazole  
N = 388  
Placebo

In AAD short-term controlled trials, completion rate was 88%
Brexpiprazole Generally Safe and Well-Tolerated in Patients with AAD, Similar with Established Safety Profile

<table>
<thead>
<tr>
<th>N (%)</th>
<th>Brexpiprazole Fixed ≤ 1 mg N = 157</th>
<th>Brexpiprazole Fixed 2 mg N = 213</th>
<th>Brexpiprazole Fixed 3 mg N = 153</th>
<th>All Brexpiprazole N = 655</th>
<th>Placebo N = 388</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 AE</td>
<td>77 (49%)</td>
<td>119 (56%)</td>
<td>64 (42%)</td>
<td>335 (51%)</td>
<td>178 (46%)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>14 (9%)</td>
<td>7 (3%)</td>
<td>11 (7%)</td>
<td>41 (6%)</td>
<td>13 (3%)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>16 (10%)</td>
<td>13 (6%)</td>
<td>6 (4%)</td>
<td>42 (6%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>4 (2.5%)</td>
<td>1 (0.5%)</td>
<td>1 (0.7%)</td>
<td>6 (0.9%)</td>
<td>1 (0.3%)</td>
</tr>
</tbody>
</table>

Brexpiprazole flexible dose 0.5 – 2 mg group from Study 284 not included in this table
## AEs Generally Consistent Across Groups

*Three Phase 3 Studies*

<table>
<thead>
<tr>
<th>MedDRA Preferred Term ≥ 2%, N (%)</th>
<th>Brexpiprazole Fixed 2 to 3 mg N = 366</th>
<th>All Brexpiprazole N = 655</th>
<th>Placebo N = 388</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>28 (8%)</td>
<td>50 (8%)</td>
<td>36 (9%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14 (4%)</td>
<td>21 (3%)</td>
<td>13 (3%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12 (3%)</td>
<td>24 (4%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>12 (3%)</td>
<td>22 (3%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12 (3%)</td>
<td>17 (3%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9 (2%)</td>
<td>18 (3%)</td>
<td>10 (3%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8 (2%)</td>
<td>11 (2%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Fall</td>
<td>7 (2%)</td>
<td>11 (2%)</td>
<td>10 (3%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6 (2%)</td>
<td>10 (2%)</td>
<td>10 (3%)</td>
</tr>
<tr>
<td>Agitation</td>
<td>6 (2%)</td>
<td>16 (2%)</td>
<td>10 (3%)</td>
</tr>
</tbody>
</table>
### Serious Adverse Events Generally Low in Frequency

*Three Phase 3 Studies*

<table>
<thead>
<tr>
<th>MedDRA Preferred Term ≥ 2 Events in All Brexpiprazole or Placebo, N (%)</th>
<th>Brexpiprazole Fixed 2 to 3 mg N = 366</th>
<th>All Brexpiprazole N = 655</th>
<th>Placebo N = 388</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE</td>
<td>19 (5%)</td>
<td>42 (6%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6 (2%)</td>
<td>6 (0.9%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Agitation</td>
<td>1 (0.3%)</td>
<td>3 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (0.3%)</td>
<td>2 (0.3%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>1 (0.3%)</td>
<td>1 (0.2%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1 (0.3%)</td>
<td>2 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Dementia Alzheimer’s type</td>
<td>1 (0.3%)</td>
<td>2 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Fall</td>
<td>1 (0.3%)</td>
<td>2 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Syncope</td>
<td>0</td>
<td>1 (0.2%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Seizure</td>
<td>0</td>
<td>2 (0.3%)</td>
<td>1 (0.3%)</td>
</tr>
</tbody>
</table>
## Safety Topics of Special Interest Expected and Balanced Across Treatment Groups

### Three Phase 3 Studies

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term, N (%)</th>
<th>Brexpiprazole Fixed 2 to 3 mg N = 366</th>
<th>All Brexpiprazole N = 655</th>
<th>Placebo N = 388</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostatic hypotension, dizziness and syncope</td>
<td>17 (5%)</td>
<td>30 (5%)</td>
<td>19 (5%)</td>
</tr>
<tr>
<td>Extrapyramidal symptoms (EPS)¹</td>
<td>17 (5%)</td>
<td>35 (5%)</td>
<td>12 (3%)</td>
</tr>
<tr>
<td>Somnolence, sedation</td>
<td>13 (4%)</td>
<td>24 (4%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Cardiovascular events¹</td>
<td>10 (3%)</td>
<td>24 (4%)</td>
<td>9 (2%)</td>
</tr>
<tr>
<td>Cerebrovascular events¹</td>
<td>0</td>
<td>3 (0.5%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Accidents and injuries¹</td>
<td>8 (2%)</td>
<td>15 (2%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td>Falls</td>
<td>7 (2%)</td>
<td>11 (2%)</td>
<td>10 (3%)</td>
</tr>
</tbody>
</table>

- No worsening in cognition as assessed by MMSE change from baseline compared to placebo

1. Grouped terms

**MMSE** = Mini-Mental State Examination
< 1% Mortality Rate Observed in Brexpiprazole AAD Program Lower than Meta-Analyses for Other Antipsychotics


Lower Mortality Rates with Brexpiprazole Compared to Other Antipsychotics in Elderly Population with Dementia

- Brexpiprazole: 0.9%
- Aripiprazole: 3.7%
- Olanzapine: 2.7%
- Quetiapine: 5.4%
- Risperidone: 2.9%

1. Mühlbauer et al. 2021 – Included majority of studies with AD population, similar age range and study duration with Brexpiprazole AAD program
# Events Within Study or 30-Day Follow-Up Period that Led to Death from Three Phase 3 Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose</th>
<th>Age</th>
<th>Sex</th>
<th>Study Treatment Duration (days)</th>
<th>Days Since Last Dose Prior to Death</th>
<th>Fatal Event Verbatim</th>
<th>Treatment Completion</th>
<th>Relevant Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>283</td>
<td>0.5 mg</td>
<td>87</td>
<td>F</td>
<td>8</td>
<td>27</td>
<td>Intracranial hemorrhage</td>
<td>Withdrew – Fall</td>
<td>History of subarachnoid hemorrhage and recent initiation of clopidogrel</td>
</tr>
<tr>
<td>283</td>
<td>0.5 mg</td>
<td>76</td>
<td>M</td>
<td>50</td>
<td>2</td>
<td>Acute purulent meningencephalitis</td>
<td>Withdrew – Personal reason</td>
<td>Multiple significant medical conditions, incidental infection-related event</td>
</tr>
<tr>
<td>283</td>
<td>1 mg</td>
<td>78</td>
<td>M</td>
<td>65</td>
<td>13</td>
<td>Aspiration pneumonia</td>
<td>Withdrew – Aspiration pneumonia</td>
<td>History of COPD, gastritis, oesophagitis and encephalopathy</td>
</tr>
<tr>
<td>283</td>
<td>1 mg</td>
<td>66</td>
<td>F</td>
<td>85</td>
<td>67</td>
<td>Airway obstruction</td>
<td>Completed</td>
<td>Choked on an orange</td>
</tr>
<tr>
<td>283</td>
<td>2 mg</td>
<td>86</td>
<td>F</td>
<td>86</td>
<td>9</td>
<td>End stage Alzheimer’s dementia</td>
<td>Completed</td>
<td>Transferred to hospice, disease progression</td>
</tr>
<tr>
<td>213</td>
<td>3 mg</td>
<td>78</td>
<td>M</td>
<td>28</td>
<td>23</td>
<td>Heart failure</td>
<td>Withdrew – Hallucinations</td>
<td>Concurrent pneumonia, autopsy showed cerebral and coronary atherosclerosis</td>
</tr>
<tr>
<td>284</td>
<td>Placebo</td>
<td>86</td>
<td>M</td>
<td>74</td>
<td>2</td>
<td>Pneumonia</td>
<td>Completed</td>
<td>Bed bound, lived in nursing home</td>
</tr>
</tbody>
</table>

2 additional deaths not included. One patient in Study 284 died from vascular encephalopathy and brain edema 2 days after 30-day protocol specified safety follow-up period. One patient in Study 284 died from pancreatic cancer > 100 days after last dose.
Patients (N = 259) who completed Study 213 rolled over into Brexpiprazole extension trial (Study 182) for 12 weeks of brexpiprazole. Of these, 163 patients were exposed to brexpiprazole up to 24 weeks. Long-term use generally safe and well-tolerated in patients with AAD. No new safety signals. No deaths. Safety profile similar to double-blind placebo-controlled studies.
Brexpiprazole 2 and 3 mg Safe and Well-Tolerated in Patients with AAD

- AEs comparable between brexpiprazole and placebo
  - Consistent with established safety profile
  - Consistent with events observed from extensive clinical experience
- High tolerability to brexpiprazole with low incidence of discontinuations
- Deaths numerically higher in all brexipiprazole group (0.9%) vs placebo (0.3%)
  - No pattern of time after first administration or time since last dose
  - No consistent cause of death
  - No deaths considered by investigator as related to treatment
Clinical Perspective

Alireza Atri, MD, PhD

Director
Banner Sun Health Research Institute
Dire Need for Approved and Safe Options to Treat AAD

- Clinically meaningful benefits for patients and families
- Favorable benefit/risk profile
- Many patients with AD suffer from severe agitation behaviors
  - Agitated behaviors negatively impact QoL and health of dyads
- Current off-label options are problematic and lacking evidence
  - Limited clinical benefit must be balanced with safety, tolerability, and serious side effects
  - Leads to pharmacological yo-yo

Need better treatment options
### Examples of Agitation-Related Behaviors that Increased Dyad Burden

**Patient Example 1**
- 62-year-old male, physically healthy, 6’2” 220 lbs
- Early onset AD, significant receptive aphasia
- Constant humming and pacing
- Separation anxiety
- Weekly and unprovoked episodes of grabbing, glaring, or pushing

**Patient Example 2**
- 56-year-old female
- Early onset AD
- Good communication but substantial difficulties with visuospatial cognition and praxis
- Repeatedly resistant to hygiene
- Hitting family and caregivers
- Crying and screaming

Pattern of agitated behaviors varies by patient and their impact also dyad specific
Relevant Assessment in Evaluation of Treatment

1. What is overall acuity of condition? What factors could be triggering or exacerbating it?

2. What is frequency, severity, duration, timing, triggers, and impact of relevant behavioral disturbances? Commonly evaluated using holistic observations and scales

3. Could intervention meaningfully help my patient?
20-Point CMAI Reductions Associated with Clinically Meaningful Decreases of 2 Points on CGI-S

CGI-S improvement could prevent downward spiral and clinical / psychosocial tipping point
Reducing Impact of Agitation-Related Behaviors Reduces Burden

- Reduce frequency, severity, duration or “diffusibility” of troubling and volatile symptoms*

<table>
<thead>
<tr>
<th>62-Year-Old Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reducing glaring and grabbing episodes could have kept at home (e.g., 1-point CGI change)</td>
</tr>
<tr>
<td>Shorter or less-intense episodes easier to diffuse</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>56-Year-Old Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reducing resistance, combativeness, to hygiene might lessen medical issues (e.g., 1-point CGI change)</td>
</tr>
<tr>
<td>Preventing escalation to refusal to take medication and food needed to allow patient management</td>
</tr>
</tbody>
</table>

7-point Scale

*Commonly evaluated using CGI tool
Brexipiprazole Is A Needed Treatment Option for Care of AAD
Efficacy with Favorable Tolerability and Benefit-Risk Profile

- Effect size point estimates range between 0.25 – 0.35 for group-level differences
- Clinically meaningful and beneficial within patient changes for individual-level differences
  - 50% greater likelihood that any given patient may benefit from large 2-point CGI improvement
- Tolerability and safety profile allows patients to remain on treatment sufficiently to have opportunity to receive benefit
- Need to stop solely relying on off-label treatment options
  - Need FDA-approved products with favorable and well-defined efficacy and safety profiles, clear dosing directions, and defined appropriate use

Meaningful effectiveness to provide better options for positive impact on patients, families, and caregivers
Benefit / Risk Summary

Mary Hobart, PhD
Vice President, Global Regulatory Affairs
Otsuka Pharmaceutical
Brexpiprazole Has Favorable Benefit/Risk Profile for Treatment of Agitation in Patients with AD

**EFFICACY**
- Substantial evidence of efficacy in multiple measures of agitation
  - Demonstrated across 3 main factors on CMAI scale
  - Improvement in aggressive and non-aggressive behaviors
  - Clinically meaningful benefit

**SAFETY**
- Safety profile in AAD consistent with known safety profile in other indications
- Well-tolerated with no new safety events
- Low mortality overall (< 1%) but greater number of events with brexpiprazole than placebo

Appropriate labelling will guide prescribers on appropriate use of brexpiprazole in elderly patients with dementia.
BREXPIPRAZOLE sNDA for Agitation Associated with Alzheimer’s Dementia (AAD)

April 14, 2023

Psychopharmacologic Drugs Advisory Committee and Peripheral and Central Nervous System Drugs Advisory Committee

Otsuka Pharmaceutical Co.
Lundbeck Inc.
Back-up Slides
# 5-Point Reduction in CMAI Total Score is Associated with Improved Patient and Caregiver Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percent Reduction in Likelihood of Outcome</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital Admissions</td>
<td>19%</td>
<td>1.19 (1.12, 1.25)</td>
</tr>
<tr>
<td>Emergency Room Visits</td>
<td>17%</td>
<td>1.17 (1.10, 1.23)</td>
</tr>
<tr>
<td>Falls</td>
<td>15%</td>
<td>1.15 (1.08, 1.21)</td>
</tr>
<tr>
<td><strong>Caregiver Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Level of Caregiver Burden (Zarit Burden Interview)</td>
<td>19%</td>
<td>1.19 (1.14, 1.25)</td>
</tr>
<tr>
<td>Caregiver Depression (PHQ-2 subscale of PHQ-4)</td>
<td>11%</td>
<td>1.11 (1.07, 1.16)</td>
</tr>
<tr>
<td>Caregiver Generalized Anxiety Disorder (GAD-2 subscale of PHQ-4)</td>
<td>7%</td>
<td>1.07 (1.03, 1.10)</td>
</tr>
</tbody>
</table>

Odds ratios were obtained from logistic regression adjusted for care recipient’s and caregiver’s age and gender, AD severity, and time since AD diagnosis. An Odds Ratio > 1 indicates that the variable is associated with a higher risk of the care recipient having the event in the year prior to the data collection.

1. Caregiver Burden Study, 2022 (data on file)
Deaths in Patients Exposed to Brexpiprazole in Clinical Program Was Low, Without Trend Observed Among Specific Fatal Events

<table>
<thead>
<tr>
<th></th>
<th>AAD N = 751</th>
<th>Schizophrenia N = 3,170</th>
<th>MDD N = 5,265</th>
<th>Placebo N = 2,259</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of Deaths</td>
<td>6 (0.8%)</td>
<td>9 (0.3%)</td>
<td>6 (0.1%)</td>
<td>1 (0.04%)</td>
</tr>
</tbody>
</table>

**Fatal Events**

- Haemorrhage intracranial (1)
- Obstructive airways disorder (1)
- Dementia alzheimer's type (1)
- Cardiac failure (1)
- Encephalitis (1)
- Pneumonia aspiration (1)
- Gun shot wound (1)
- Uterine cancer (1)
- Completed suicide (1)
- Asphyxia (1)
- Cardiac failure (1)
- Coronary artery disease (1)
- Gastric ulcer perforation (1)
- Death (1)
- Peritonitis (1)
- Septic shock (1)
- Acute myocardial infarction (1)
- Metastatic malignant melanoma (1)
- Completed suicide (2)
- Pulmonary embolism (1)
- Myocardial rupture (1)
- Gastric ulcer perforation (1)
- Peritonitis (1)
- Pneumonia

Deaths in completed clinical trials
# Rexulti Dosing Adjustments for Drug Interactions

<table>
<thead>
<tr>
<th>Factors</th>
<th>Dose Adjustment for REXULTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP2D6 or CYP3A4 inhibitors</td>
<td>Administer half the usual dose</td>
</tr>
<tr>
<td>Strong/moderate CYP2D6 with Strong/moderate CYP3A4 inhibitors</td>
<td>Administer a quarter of the usual dose</td>
</tr>
<tr>
<td>Known CYP2D6 poor metabolizers taking strong/moderate CYP3A4 inhibitors</td>
<td>Administer a quarter of the usual dose</td>
</tr>
<tr>
<td>Strong CYP3A4 inducers</td>
<td>Double the usual dose and further adjust based on clinical response</td>
</tr>
</tbody>
</table>
### Low Incidence of AEs Leading to Discontinuations

**Pooled Studies**

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term ≥ 1%</th>
<th>Brexpiprazole ≤ 1 mg N = 157</th>
<th>Brexpiprazole Fixed 2 to 3 mg N = 366</th>
<th>Brexpiprazole 0.5 – 2 mg N = 132</th>
<th>All Brexpiprazole N = 655</th>
<th>Placebo N = 388</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs leading to discontinuation</td>
<td>9%</td>
<td>5%</td>
<td>7%</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>4%</td>
<td>1%</td>
<td>0</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>3%</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>1%</td>
<td>0.8%</td>
<td>0.8%</td>
<td>0.9%</td>
<td>0</td>
</tr>
<tr>
<td>Investigations</td>
<td>1%</td>
<td>0.5%</td>
<td>2%</td>
<td>0.9%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>
# AEs Leading to Discontinuation Were Low in Three Phase 3 Studies

**Pooled Studies**

<table>
<thead>
<tr>
<th>Preferred Term &gt; 1 AE</th>
<th>All Brexpiprazole N = 655</th>
<th>Placebo N = 388</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs leading to discontinuation</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Agitation</td>
<td>0.6%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0.5%</td>
<td>0</td>
</tr>
<tr>
<td>Seizure</td>
<td>0.5%</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>0.3%</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0.3%</td>
<td>0</td>
</tr>
<tr>
<td>Fall</td>
<td>0.3%</td>
<td>0</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>0.3%</td>
<td>0</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>0.3%</td>
<td>0</td>
</tr>
<tr>
<td>Electrocardiogram QT prolonged</td>
<td>0.3%</td>
<td>0</td>
</tr>
<tr>
<td>Positive COVID-19 test</td>
<td>0</td>
<td>0.5%</td>
</tr>
</tbody>
</table>
## Categorical Changes in QTcB/QTcF Were Higher in Placebo Than Brexpiprazole in Three Phase 3 Studies

### Pooled Studies

<table>
<thead>
<tr>
<th>Classification</th>
<th>Category</th>
<th>All Brexpiprazole N = 645</th>
<th>Placebo N = 382</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Onset (&gt; 500 MSEC)</td>
<td>0</td>
<td>4 (1%)</td>
<td></td>
</tr>
<tr>
<td>QTcB</td>
<td>30 – 60 MSEC</td>
<td>96 (15%)</td>
<td>58 (15%)</td>
</tr>
<tr>
<td></td>
<td>≥ 60 MSEC</td>
<td>5 (0.8%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>New Onset (&gt; 500 MSEC)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTcF</td>
<td>30 – 60 MSEC</td>
<td>66 (10%)</td>
<td>44 (12%)</td>
</tr>
<tr>
<td></td>
<td>≥ 60 MSEC</td>
<td>2 (0.3%)</td>
<td>6 (2%)</td>
</tr>
</tbody>
</table>
## Study 283 and 284: Quality of Life

<table>
<thead>
<tr>
<th>Endpoint/Variable</th>
<th>Placebo</th>
<th></th>
<th>Brexpiprazole</th>
<th></th>
<th>Treatment Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Mean</td>
<td>LS Mean Change</td>
<td>Baseline Mean</td>
<td>LS Mean Change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 283</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QoL Alzheimer's Disease Score – Patient</td>
<td>28.96</td>
<td>1.41</td>
<td>28.96</td>
<td>1.20</td>
<td>-0.21 (-1.31, 0.88)</td>
<td>0.7026</td>
</tr>
<tr>
<td>QoL Alzheimer's Disease Score – Family Member or Caregiver</td>
<td>26.05</td>
<td>1.78</td>
<td>24.89</td>
<td>1.39</td>
<td>-0.39 (-1.35, 0.58)</td>
<td>0.4331</td>
</tr>
<tr>
<td>Study 284</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QoL Alzheimer's Disease Score – Patient</td>
<td>30.36</td>
<td>1.18</td>
<td>29.35</td>
<td>1.64</td>
<td>0.45 (-0.53, 1.44)</td>
<td>0.3634</td>
</tr>
<tr>
<td>QoL Alzheimer’s Disease Score – Family Member or Caregiver</td>
<td>26.65</td>
<td>1.52</td>
<td>25.97</td>
<td>2.21</td>
<td>0.69 (-0.29, 1.67)</td>
<td>0.1668</td>
</tr>
</tbody>
</table>
Pooled: Brexpiprazole Separated from Placebo Across 3 Key Factors of Agitation

Change from Baseline to Week 12

- Aggressive
  - Brex 2 or 3 mg (N = 363): -8.73 (p = 0.0009)
  - Placebo (N = 247): -7.17

- Physically Non-Aggressive
  - Brex 2 or 3 mg (N = 363): -6.64 (p = 0.0125)
  - Placebo (N = 247): -5.49

- Verbally Agitated
  - Brex 2 or 3 mg (N = 363): -4.56
  - Placebo (N = 247): -3.33

*p<0.05, **p<0.01 versus placebo; nominal p-values presented; MMRM
Study 213 and 283: Brexpiprazole Demonstrates Reduction in Mean Frequency Across Aggressive, Physically Non-Aggressive, and Verbally Agitated Behaviors
Brexpiprazole Efficacy Results Across 2 Phase 3 Trials Support Meaningful Benefit to Patients with AAD

Study 283

- Brex 1 mg (N = 134)
- Brex 2 mg (N = 138)
- Placebo (N = 131)

LS Mean Change from Baseline in CMAI Total Score (SE)

Week

0 2 4 6 8 10 12

p = 0.040

Study 213

- Brex 2 or 3 mg (N = 225)
- Placebo (N = 116)

Week

0 2 4 6 8 10 12

p = 0.003

*p<0.05, **p<0.01, ***p<0.001 versus placebo; MMRM
### Pooled: Agitated Behaviors Are Reduced to Lower Frequencies in Brexpiprazole-Treated Patients Compared to Placebo

<table>
<thead>
<tr>
<th>Baseline Frequency</th>
<th>Several times an hour</th>
<th>Several times a day</th>
<th>1-2 x a day</th>
<th>Several times a week</th>
<th>1-2 x per week</th>
<th>&lt; 1 per week</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>191</td>
<td>119</td>
<td>941</td>
<td>597</td>
<td>873</td>
<td>587</td>
<td>1159</td>
</tr>
<tr>
<td>Mean Pt Reduction</td>
<td>-2.87</td>
<td>-1.94</td>
<td>-2.45</td>
<td>-2.00</td>
<td>-2.01</td>
<td>-1.61</td>
<td>-1.50</td>
</tr>
</tbody>
</table>

#### Graphical Representation

- **Several times an hour**: [Bars for Brex (2 or 3 mg) and Placebo]
- **Several times a day**: [Bars for Brex (2 or 3 mg) and Placebo]
- **1-2 x a day**: [Bars for Brex (2 or 3 mg) and Placebo]
- **Several times a week**: [Bars for Brex (2 or 3 mg) and Placebo]
- **1-2 x per week**: [Bars for Brex (2 or 3 mg) and Placebo]
- **< 1 per week**: [Bars for Brex (2 or 3 mg) and Placebo]
- **Never**: [Bars for Brex (2 or 3 mg) and Placebo]
Increased Response in the Placebo Group Over Time in Acute Schizophrenia Trials

Mean Change From Baseline on PANSS Total In Placebo Arm

Note: Latuda and Brexp data was not part of the original paper and has been added in based on the package insert
Kemp et al. 2010
Study 213: Brexpiprazole Separated from Placebo Across 3 Key Factors of Agitation

![Bar chart showing change from baseline to week 12 for Aggressive, Physically Non-Aggressive, and Verbally Agitated categories for Brex 2 or 3 mg (N = 225) and Placebo (N = 116).]

- Aggressive: Brex 2 or 3 mg = -9.09, Placebo = -7.13, p = 0.004
- Physically Non-Aggressive: Brex 2 or 3 mg = -6.45, Placebo = -5.04, p = 0.030
- Verbally Agitated: Brex 2 or 3 mg = -4.39, Placebo = -3.14, p = 0.011

*p<0.05, **p<0.01 versus placebo; nominal p-values presented; MMRM