Headline results from AAD trial

A Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Brexpiprazole in the Treatment of Patients with Agitation in Alzheimer's Dementia (AAD)

Investor presentation; June 2022

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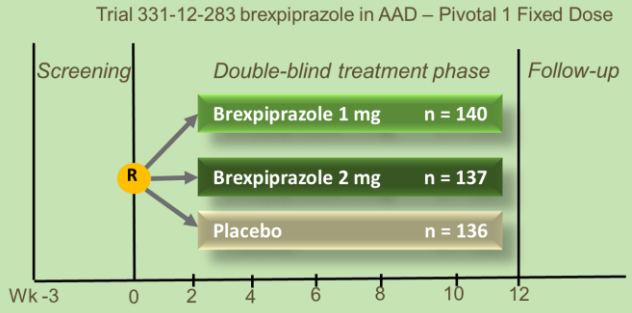
Introductory remarks about agitation in Alzheimer's dementia

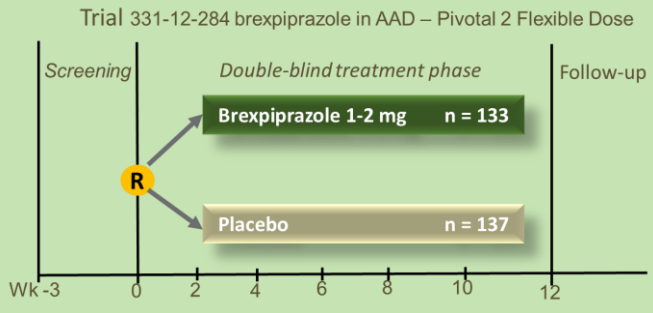
- There are no FDA-approved pharmacological treatments for agitation in Alzheimer’s Dementia[1]
- Comes with a high burden for the patients and has been associated with accelerated disease progression, functional decline, decreased quality of life, increased risk of institutionalization, and earlier death[2-4]
- Relieving agitation in patients with Alzheimer’s dementia reduces the burden of caring and enables a better quality of life for caregivers[5,6]
- Associated with significantly higher healthcare resource utilization and costs compared to non-agitated patients[7,8]
- Prevalent across dementia severity in the U.S. community setting, with a prevalence of 56% in mild, 75% in moderate to severe, and 68% in severe Alzheimer’s disease[3]
- Prevalent across care settings in the U.S., with a prevalence of approximately 45% within a community setting and 53% in nursing home residents[3,9]

1: Porsteinsson & Antonsdottir. Expert Opin Pharmacother 2017;18(6):611–620. 2. Lanctôt KL et al. Alzheimer’s Dement (NY) 2017; 3: 440–449. 3. Halpern R et al. Int J Geriatr Psychiatry 2019; 34: 420–431. 4. Koenig AM et al. Curr Psychiatry Rep 2016; 18: 3. 5. Gitlin LN et al. Int J Geriatr Psychiatry 2016; 31: 1056–1063. 6. Brodaty H et al. Am J Psychiatry 2012; 169: 946–953. 7. Cloutier M et al. Alzheimers Dement (NY) 2019; 6: 851–861. 8. Jones E et al. J Alzheimers Dis 2021; 83: 89–101. 9. Fillit H et al. Int J Geriatr Psychiatry 2021; 36: 1959–1969

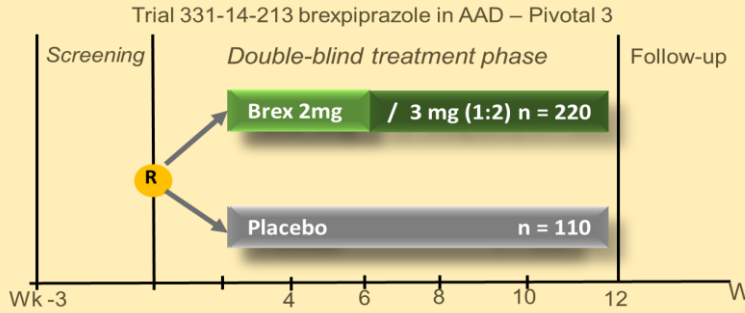
Clinical development program - Brexpiprazole in Agitation in Alzheimer´s Dementia



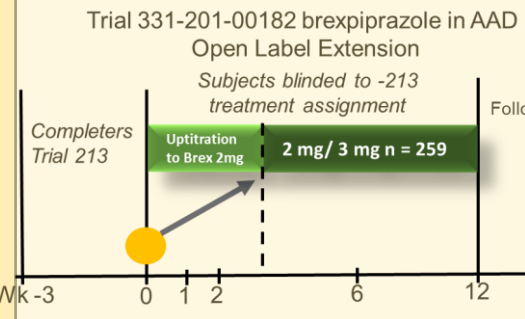
Study 1 (NCT01862640)
Completed



Study 2 (NCT01922258)
Completed



Study 3 (NCT03548584)
Completed



Study 4 (NCT03594123)
Ongoing

Open Label Extension

Study 1 - Efficacy and safety of fixed-dose brexpiprazole for the treatment of agitation in Alzheimer's type dementia[1]

Study I (NCT01862640)

N = 433 patients

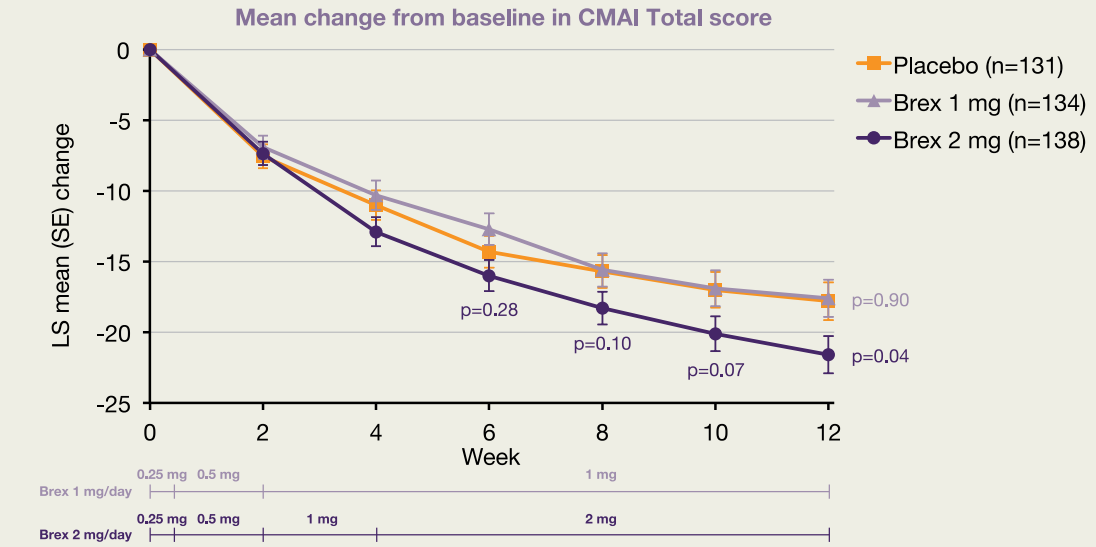
Male or female, aged 55-90 years

1 mg, 2 mg and placebo

12 weeks' treatment duration

Primary endpoint: CMAI Total

Key secondary endpoint: CGI-S as related to agitation



MMRM

CMAI Total baseline (SD): placebo, 72.2 (17.9); 1 mg, 70.5 (16.0); 2 mg, 71.0 (16.6)

CMAI=Cohen-Mansfield Agitation Inventory; LS=least squares; MMRM=mixed model for repeated measures; SD=standard deviation; SE=standard error

CMAI: Brexpiprazole 2 mg/day statistically significant improvement over placebo[1]

CGI-S score: Brexpiprazole 2 mg/day not statistically superior to placebo. Numerical improvement was observed for 2 mg/day from Week 6-12 over placebo[1]

No new safety signals were observed[1]

1. Grossberg GT et al. Am J Geriatr Psychiatry. 2020;28(4):383-400

Study 2 - Efficacy and safety of flexibly-dosed brexpiprazole for the treatment of agitation in Alzheimer's type dementia[1]

Study II (NCT01922258)[1]

N = 270 patients

Male or female, aged 55-90 years

Flexible dose: 0.5-2 mg/day

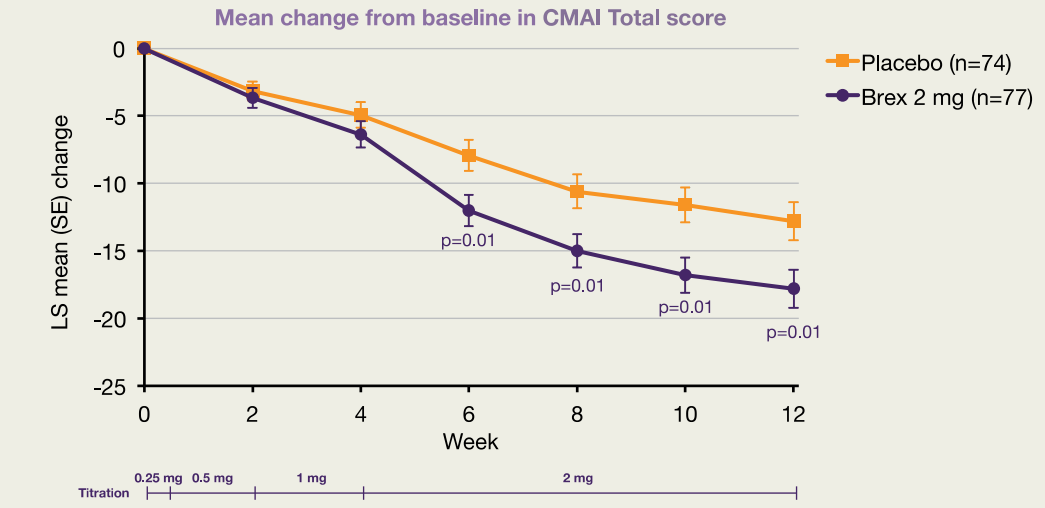
12 weeks' treatment duration

Primary endpoint: CMAI Total

Key secondary endpoint: CGI-S as related to agitation

Post-hoc analysis

– subgroup of patients titrated to 2mg



MMRM

CMAI Total baseline (SD), dose increase at Week 4: placebo, 68.3 (16.2); 0.5–2 mg, 69.2 (15.4)

CMAI: Numerically favourable for flexibly-dosed brexpiprazole (0.5–2 mg/day) over placebo, but not statistically significant[1]

CGI-S: Greater improvement for flexibly-dosed brexpiprazole (0.5–2 mg/day) over placebo, with $p<0.05$[1]

Post hoc: Patients titrated to brexpiprazole 2 mg/day at Week 4 had greater improvement over matched placebo patients on both the primary and secondary endpoint, with $p<0.05$ [1]

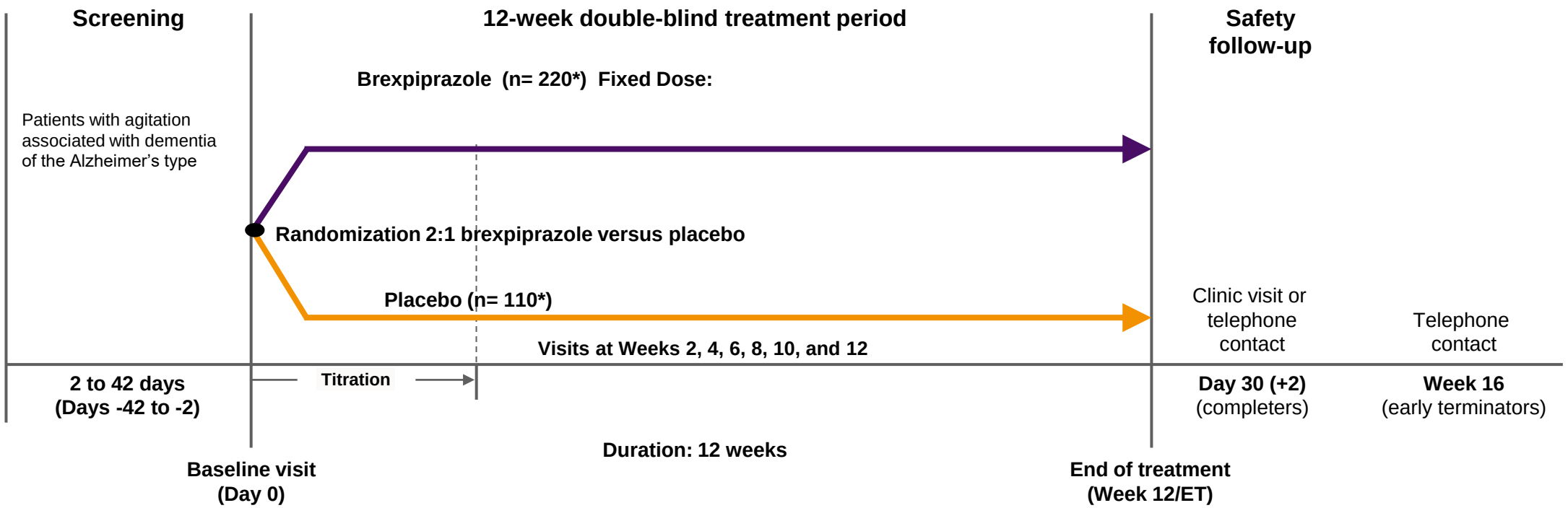
No new safety signals were observed[1]

1. Grossberg GT et al. Am J Geriatr Psychiatry. 2020;28(4):383-400

The two prior phase III studies laid the basis for the third phase III study

Design	12-week, multicenter, randomized, double-blind, placebo-controlled, fixed-dose trial designed to assess the efficacy, safety, and tolerability of brexpiprazole
Dosing	2 mg/day, 3 mg/day or placebo
Size	345 patients with agitation associated with dementia of the Alzheimer's type who are residing either in an institutionalized setting or in a non-institutionalized setting where the subject is not living alone
Participating countries	Bulgaria, Hungary, Serbia, Slovakia, Spain, Ukraine, and USA
Primary endpoint	Cohen-Mansfield Agitation Inventory (CMAI) total score
Key secondary endpoint	Clinical Global Impression Severity of Illness (CGI-S) score

Study 3 - Design



Planned subject numbers total 330; Interim Analysis after 255 have had chance to complete

Brexpiprazole arm 2:1 randomization to 3 mg/day brexpiprazole and 2 mg/day brexpiprazole; primary analysis as one group brexpiprazole

ET = Early Termination

Study 3 - Key eligibility criteria

- **Key inclusion criteria**
  - Male or female out-patients or institutionalized, 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 at least 2 weeks prior to screening
  - NPI-NH Agitation/Aggression score ≥4 at screening and baseline[a]
  - Identified caregiver spending at least 2hours/day and minimally 4 days/week with the patient
  - Requiring pharmacological treatment for agitation according to investigator after
    - Evaluation of reversible factors, and
    - Trial of non-pharmacological interventions

- **Key exclusion criteria**
  - Other types of dementia than Alzheimer's disease, or DSM-5 Axis-1 disorders (schizophrenia, BD, current MDE)
  - History of stroke, TIA, pulmonary or cerebral embolism, epilepsy or seizures, NMS
  - Use of high-dose antipsychotics in past 90 days
  - Uncontrolled diabetes or hypertension, or symptomatic hypotension
  - Having received immunotherapy, such as vaccines, to treat Alzheimer's disease within 6 months prior to randomization

[a]The NPI-NH was completed by a clinician based on an interview with the patient's caregiver; Agitation/aggression domain score was obtained by multiplying the frequency rating (from 1 [rarely] to 4 [very often]), by the severity rating (from 1 [mild] to 3 [severe])

BP=bipolar disorder; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, 5th edition; IPA=International Psychogeriatric Association; MDE=major depressive episode; MMSE=Mini-Mental State Examination; NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NMS=neuroleptic malignant syndrome; NPI-NH=Neuropsychiatric Inventory − Nursing Home version; TIA=transient ischemic attack

Overall Efficacy and safety conclusions (Study 331-14-213)

Efficacy:

- The treatment effects of brexpiprazole demonstrated statistically significant difference (p=0.0026) in comparison to placebo in the primary endpoint (CMAI difference)
- The treatment effects of brexpiprazole demonstrated statistically significant difference (p=0.0055) in comparison to placebo in the key secondary endpoint (CGI-S)
- The efficacy of Brexpiprazole in Study 213 ***was consistent*** with the prior studies 283 and 284

Safety and Tolerability:

- The only Treatment Emergent Adverse Event (TEAE) with more than 5% incidence in patients treated with brexpiprazole was headache (6.6% vs. 6.9% for placebo)
- There was 1 death observed in brexpiprazole 3mg/day treatment group, assessed as not related
- The safety and tolerability profile of brexpiprazole in Study 213 ***was consistent*** with the prior two studies 283 and 284

Summary

- Study 3 demonstrated statistically significant difference (p=0.0026) in the mean change from baseline to Week 12 in the Cohen-Mansfield Agitation Inventory (CMAI) total score between brexpiprazole and placebo, as well as on change from baseline to Week 12 in the Clinical Global Impression – Severity of Agitation (CGI-S, p=0.0055)
- Fast Track designation granted February 2016
- Lundbeck and Otsuka are planning to submit a sNDA to the FDA later in 2022