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Enclosure:

- POSTER: Porsteinsson A, Chumki S, Palma A et al. Presented at Alzheimer's Association International Conference (AAIC) , July 27-31, 2025, Toronto, Canada

Sustained clinically meaningful efficacy and consistent safety in patients with agitation associated with dementia due to Alzheimer's disease treated with brexpiprazole: a 24-week *post hoc* analysis

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Wednesday-853

Introduction

- Agitation is a common neuropsychiatric symptom of Alzheimer's dementia,[1,2] which is associated with substantial health and financial burden for patients and caregivers.[1-4]
- Antipsychotics can provide some improvement in agitation for people with dementia.[1] However, people with dementia may be particularly vulnerable to adverse events.[5] As a result, there may be caution in the dosing and duration of antipsychotic treatment.[5-7]
- Agitation symptoms may result from dysfunction in noradrenergic, serotonergic, and dopaminergic neurotransmitter systems.[8] Brexpiprazole is an atypical antipsychotic with activity in these three systems,[9] and is approved in the United States,[10] Canada[11] and other regions for the treatment of agitation associated with dementia due to Alzheimer's disease.
- In clinical trials of brexpiprazole in this patient population, agitation symptoms reduced in frequency, and brexpiprazole was generally well tolerated.[12-14]
- This *post hoc* analysis aimed to evaluate clinically meaningful efficacy, and safety, of brexpiprazole throughout 24 weeks of treatment.

Methods

Sample

- Data were included from two brexpiprazole trials in patients with agitation associated with dementia due to Alzheimer's disease: a Phase 3, 12-week, fixed-dose, randomized, placebo-controlled trial (ClinicalTrials.gov identifier: NCT03548584 [Trial 213])[13] and a Phase 3, 12-week, single-arm, active-treatment extension trial (NCT03594123 [Trial 182]).[14]
- Trial 182 enrolled patients who completed treatment with brexpiprazole or placebo in Trial 213; thereafter, patients received brexpiprazole 2 or 3 mg/day.
- ***For additional trial design information, please scan the QR code.***
- In order to capture up to 24 weeks' treatment, the present analyses include patients from Trial 213 who continued into Trial 182.

Efficacy analyses

- Data were included for:
  - Patients who received brexpiprazole 2 or 3 mg/day in both trials ('prior brexpiprazole' subgroup)
  - Patients who received placebo in Trial 213, then brexpiprazole 2 or 3 mg/day in Trial 182 ('prior placebo' subgroup)
- The proportion of patients who achieved a sustained clinically meaningful response was determined, defined as a 20-point reduction from baseline of Trial 213 in Cohen-Mansfield Agitation Inventory (CMAI) Total score that was maintained until the end of Trial 182. In this population, a 20-point reduction represents a meaningful change in agitation.[15]
- Kaplan–Meier curves for the cumulative proportion achieving sustained clinically meaningful response were calculated.

Safety analyses

- Safety was assessed throughout 24 weeks in the prior brexpiprazole subgroup only, reflecting the longest evaluable brexpiprazole treatment duration.
- Safety outcomes were based on treatment-emergent adverse events (TEAEs):
  - Time to first TEAE (Kaplan–Meier methodology)
  - Percentage of patients who reported a new TEAE ('incidence'), or a new or ongoing TEAE ('prevalence')
  - Median TEAE duration (TEAEs overall, and TEAEs of interest)

Results

Efficacy

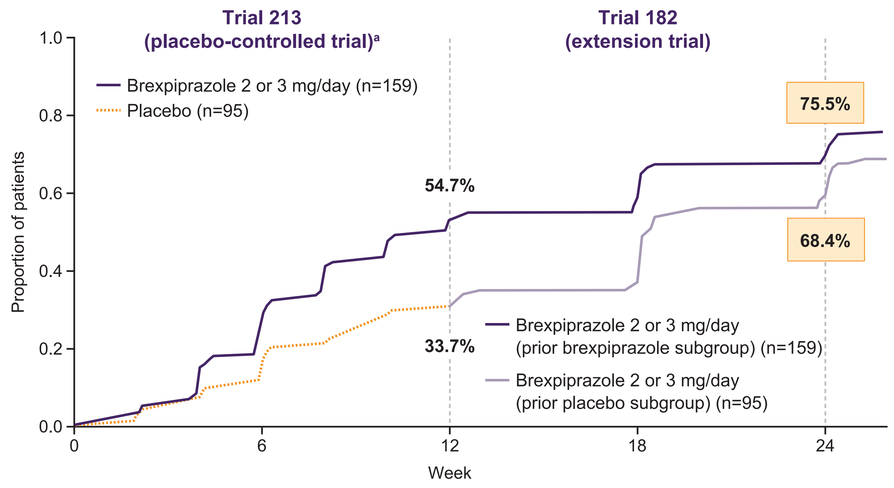
- Data were analyzed for 254 patients:
  - 159 patients who received brexpiprazole in both trials
  - 95 patients who received placebo in Trial 213, and brexpiprazole in Trial 182
- Rate of sustained clinically meaningful response is shown in Figure 1.

Safety

- Data were analyzed for 163 patients who received brexpiprazole in both trials.
- Among patients who had not already experienced a TEAE in Trial 213, TEAEs were rare throughout Trial 182 (Figure 2).
- The percentage of patients with a new TEAE ('incidence'), or a new or ongoing TEAE ('prevalence'), is presented in Figure 3.
- TEAE duration is shown in Figure 4.

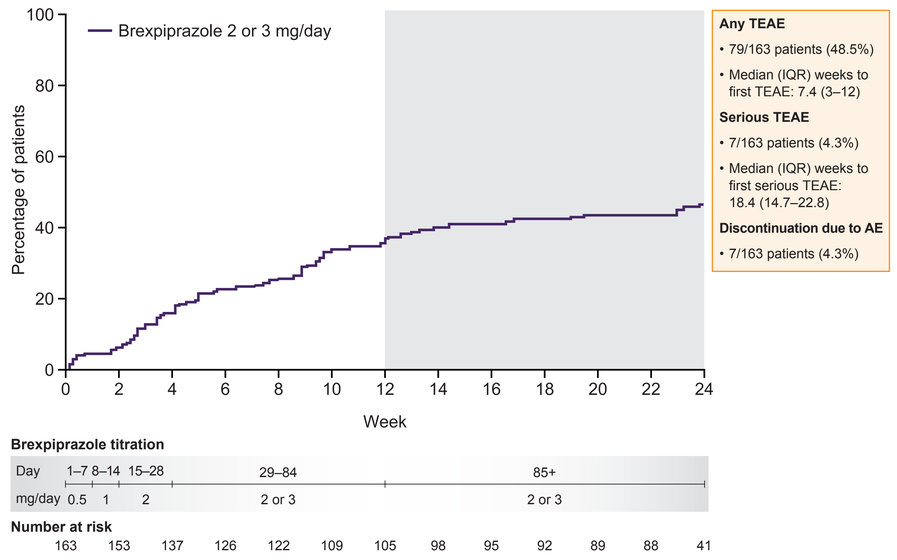
Results

Figure 1: Cumulative proportion of patients achieving sustained clinically meaningful response over 24 weeks



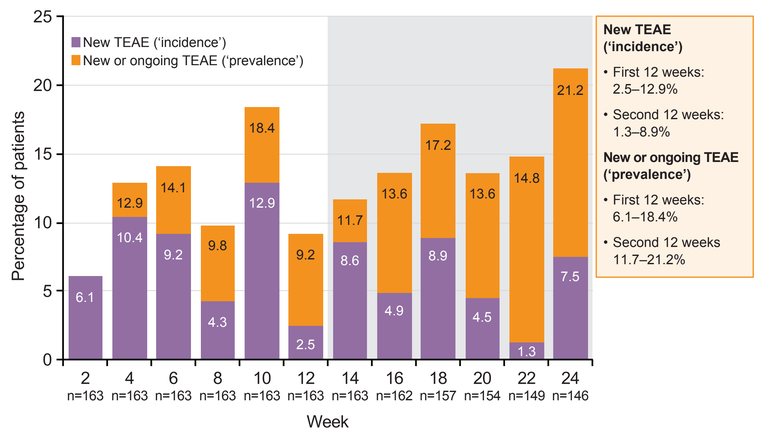
[a]Subset of patients who continued into Trial 182
n-values reflect all analyzed patients; observed cases n-values were lower than stated at Week 18 (prior brexpiprazole, n=155; prior placebo, n=94) and at Week 24 (prior brexpiprazole, n=140; prior placebo, n=86)
Sustained clinically meaningful response is defined as 20-point reduction from baseline in CMAI Total score that was maintained to the end of Trial 182
CMAI=Cohen-Mansfield Agitation Inventory

Figure 2: Time to first TEAE over 24 weeks



AE=adverse event; IQR=interquartile range; TEAE=treatment-emergent adverse event

Figure 3: TEAEs in 2-week intervals over 24 weeks



At Week 2, incidence and prevalence values are both 6.1%
TEAE=treatment-emergent adverse event

Figure 4: Duration of TEAEs over 24 weeks – TEAEs overall and TEAEs of interest

	Patients with TEAEs (n=163)	Median TEAE duration
TEAEs overall		
Any TEAE	79 (48.5%)	**Any TEAE:** 3 (IQR 1–8) days
Serious TEAE	7 (4.3%)	
TEAEs of interest		
Dizziness	8 (4.9%)	
EPS-related[a]	12 (7.4%)	
Any akathisia[b]	5 (3.1%)	
Insomnia	2 (1.2%)	
Somnolence or sedation	8 (4.9%)	

[a]EPS-related TEAEs included akathisia, bradykinesia, drooling, extrapyramidal disorder, hypokinesia, Parkinsonism, restlessness, and tremor; [b]a subcategory of EPS that includes akathisia, extrapyramidal disorder, and restlessness
Duration data not presented for cardiovascular events (duration could not be estimated because the end of the TEAEs were not observed), or for falls (duration not applicable)
EPS=extrapyramidal symptoms; IQR=interquartile range; TEAE=treatment-emergent adverse event

Conclusions

- For patients who received 24 weeks of brexpiprazole 2 or 3 mg/day, rates of meaningful agitation response continued to increase throughout 24 weeks.
- The incidence of adverse events was low over 24 weeks. Longer-term treatment with brexpiprazole was not associated with additional safety signals over time.
- Analysis limitation: There was no placebo group in the 24-week analysis, and findings therefore cannot be solely attributed to brexpiprazole.

Please also visit posters **Monday-519** (brexpiprazole NNT and NNH analysis) and **Wednesday-849** (efficacy of brexpiprazole on caregiver-identified bothersome agitation symptoms)

References

1. Antonsdottir et al. Expert Opin Pharmacother 2015; 16 (11): 1649–1656.
2. Halpern et al. Int J Geriatr Psychiatry 2019; 34 (3): 420–431.
3. Morris et al. BMJ Open 2015; 5 (3): e007382.
4. Khoo et al. Int Psychogeriatr 2013; 25 (12): 1991–1999.
5. Mok et al. BMJ 2024; 385: e076268.
6. Schneider et al. Am J Geriatr Psychiatry 2006; 14 (3): 191–210.
7. Schneider et al. N Engl J Med 2006; 355 (15): 1525–1538.
8. Cummings et al. CNS Spectr 2024: 1–10.
9. Maeda et al. J Pharmacol Exp Ther 2014; 350 (3): 589–604.
10. Rexulti (brexpiprazole) US prescribing information. Otsuka Pharmaceutical Co. Ltd. May 2025.
11. Rexulti (brexpiprazole) Canadian product monograph. Otsuka Canada Pharmaceutical Inc. January 2024.
12. Grossberg et al. Am J Geriatr Psychiatry 2020; 28 (4): 383–400.
13. Lee et al. JAMA Neurol 2023; 80 (12): 1307–1316.
14. Behl et al. J Alzheimers Dis 2024; 102 (2): 520–529.
15. Meunier et al. Front Neurol 2024; 15: 1379062.

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