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Enclosure:

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Brexpiprazole for agitation associated with dementia due to Alzheimer's disease: number needed to treat, number needed to harm, and likelihood to be helped or harmed

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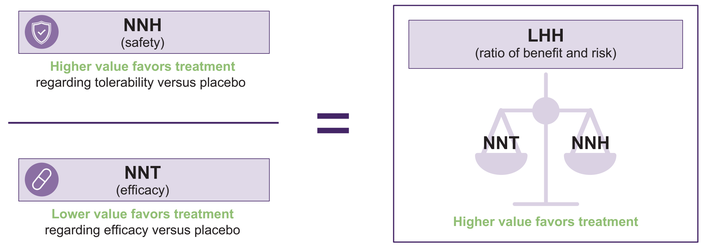
28

Introduction

- Agitation is a common and challenging set of neuropsychiatric symptoms in Alzheimer's disease, which is associated with considerable burden to patients and caregivers.[1-3]
- Older adults are especially vulnerable to the side effects of treatment.[4,5] As such, it is important to maximize benefits, minimize risks, and understand expected treatment outcomes in this patient population.
- The efficacy and safety of brexpiprazole in patients with agitation associated with dementia due to Alzheimer's disease – the first (and currently only) FDA-approved treatment for this condition – has been demonstrated in Phase 3 trials.[6-8] Brexpiprazole has subnanomolar affinity for receptors in the noradrenergic, serotonergic, and dopaminergic monoamine systems,[9] which may underlie efficacy on agitation symptoms.[10]
- Number needed to treat (NNT), number needed to harm (NNH), and likelihood to be helped or harmed (LHH) analyses provide quantitative efficacy and safety information, and help to inform clinical decisions.[11,12] Lower NNT values, and higher NNH and LHH values, are more supportive of treatment versus placebo (Figure 1).[12]
- In schizophrenia and major depressive disorder, in which brexpiprazole is an approved treatment, NNT, NNH, and LHH data indicated a favorable efficacy and safety profile for brexpiprazole.[13]
- The aim of this practice-relevant *post hoc* analysis was to delineate the clinical benefit and risk profile of brexpiprazole in patients with agitation associated with dementia due to Alzheimer's disease, using NNT, NNH, and LHH.

Figure 1: Overview of NNH, and LHH[12]



LHH=likelihood to be helped or harmed; NNH=number needed to harm; NNT=number needed to treat

Methods

- Data were pooled from two 12-week trials of fixed-dose brexpiprazole in patients aged 55–90 years with agitation associated with dementia due to Alzheimer's disease (ClinicalTrials.gov: NCT01862640 [Study 283];[7] NCT03548584 [Study 213][8]).
- The primary efficacy measure in each trial was the Cohen-Mansfield Agitation Inventory (CMAI), described in Figure 2.[7,8] The key secondary efficacy measure was Clinical Global Impression – Severity of illness (CGI-S), as related to agitation.[7,8]
- In Study 283, patients were randomized 1:1:1 to brexpiprazole 1 mg/day, brexpiprazole 2 mg/day, or placebo.[7] In Study 213, patients were randomized 2:1 to brexpiprazole 2 or 3 mg/day or placebo.[8]
- This *post hoc* analysis analyzes data for the FDA-approved recommended-to-maximum brexpiprazole doses of 2 or 3 mg/day.

NNT (efficacy)

- Response analyses were conducted based on change from baseline to Week 12 in clinical scale scores:
  - **Main analysis: CMAI Total score ≥20-point reduction**, reflecting the magnitude of change that can be considered clinically relevant at the individual-patient level.[14]
  - CMAI Total score ≥17-point reduction, reflecting an alternative definition of meaningful within-patient improvement, derived using different methodology.[15]
  - CGI-S score ≥2-point reduction, which approximately corresponds to ≥20-point reduction in CMAI Total score.[14]
- Response data are based on last observation carried forward analyses.
- NNT values were calculated for each response rate definition.

NNH (safety)

- Safety outcomes throughout 12 weeks were analyzed:
  - **Main analysis: Incidence of discontinuation due to treatment-emergent adverse events (TEAEs).**
  - Other safety outcomes included incidence of: TEAEs by severity (mild, moderate, severe; based on investigator judgment); death; and individual TEAEs of interest.
- NNH values were calculated for each safety outcome.

LHH (overall benefit–risk profile)

- LHH was calculated based on response rates relative to discontinuation due to TEAEs.

Figure 2: CMAI

The Cohen-Mansfield Agitation Inventory (CMAI)[16]

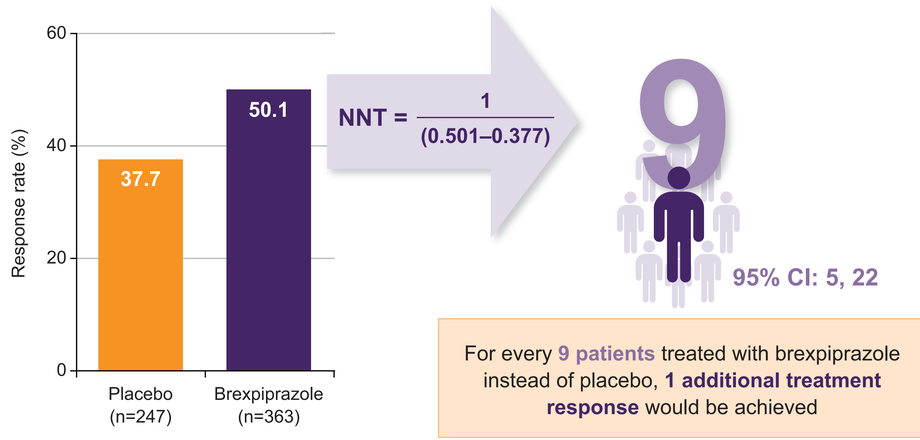
1. Pacing, aimless wandering
2. Inappropriate dressing or disrobing
3. Spitting (include at meals)
4. Cursing or verbal aggression
5. Constant unwarranted requests for attention/help
6. Repetitive sentences or questions
7. Hitting (including self)
8. Kicking
9. Grabbing onto people or things inappropriately
10. Pushing
11. Throwing things
12. Making strange noises
13. Screaming
14. Biting
15. Scratching
16. Trying to get to a different place
17. Intentional falling
18. Complaining
19. Negativism
20. Eating or drinking inappropriate substances
21. Hurting self or others
22. Handling things inappropriately
23. Hiding things
24. Hoarding things
25. Tearing things/destroying property
26. Performing repetitious mannerisms
27. Making verbal sexual advances
28. Making physical sexual advances
29. General restlessness

1 Never · 2 Less than once a week · 3 Once or twice a week · 4 Several times a week · 5 Once or twice a day · 6 Several times a day · 7 Several times an hour

Results

- Data for 617 patients were analyzed for safety (brexpiprazole, n=366; placebo, n=251), and 610 patients for efficacy (brexpiprazole, n=363; placebo, n=247).
- Response rates, and associated NNT values, are shown in Figure 3 and Table 1.
- The incidence of adverse events, and associated NNH values, are shown in Figure 4 and Table 2.
- LHH values are shown in Figure 5.

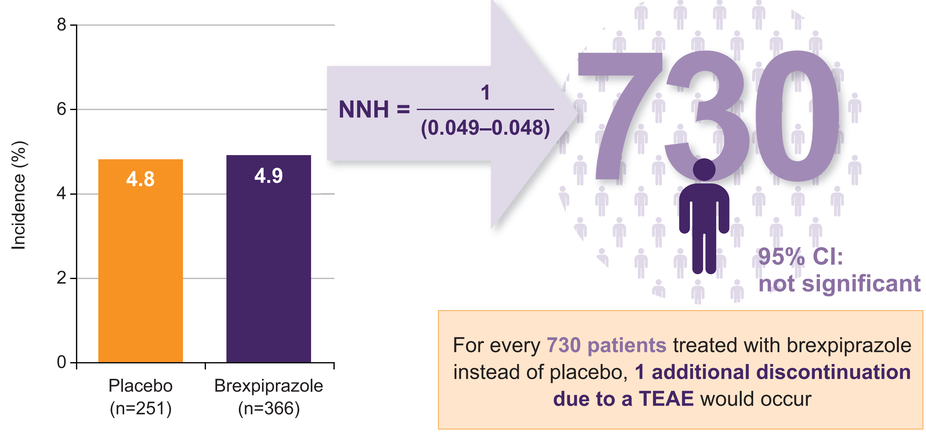
Figure 3: NNT for response (≥20-point reduction in CMAI Total score from baseline to Week 12)



For every **9 patients** treated with brexpiprazole instead of placebo, **1 additional treatment response** would be achieved

Non-rounded response rates were used for the calculation of NNT
CI=confidence interval; CMAI=Cohen-Mansfield Agitation Inventory; NNT=number needed to treat

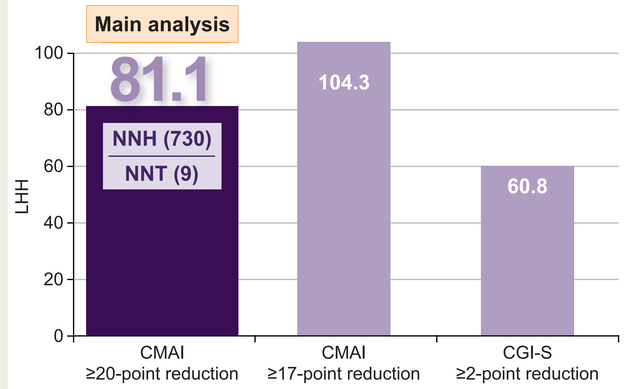
Figure 4: NNH for discontinuation due to TEAEs



For every **730 patients** treated with brexpiprazole instead of placebo, **1 additional discontinuation due to a TEAE** would occur

Non-rounded response rates were used for the calculation of NNH
CI=confidence interval; NNH=number needed to harm; TEAE=treatment-emergent adverse event

Figure 5: LHH for response relative to discontinuation due to TEAEs



81 times more likely
that brexpiprazole results in treatment response (≥20-point CMAI Total score reduction) than discontinuation due to a TEAE

CGI-S=Clinical Global Impression – Severity of illness; CMAI=Cohen-Mansfield Agitation Inventory; LHH=likelihood to be helped or harmed; NNH=number needed to harm; NNT=number needed to treat; TEAE=treatment-emergent adverse event

Table 1: Summary of response rates and NNT values

Definition of response	Response rate, n (%)		NNT	95% CI
	Placebo (n=247)	Brexpiprazole (n=363)		
Main analysis: CMAI ≥20-point reduction	93 (37.7)	182 (50.1)	9	(5, 22)
CMAI ≥17-point reduction	106 (42.9)	211 (58.1)	7	(5, 14)
CGI-S ≥2-point reduction	69 (27.9)	134 (36.9)	12	(7, 67)

CGI-S=Clinical Global Impression – Severity of illness; CI=confidence interval; CMAI=Cohen-Mansfield Agitation Inventory; NNT=number needed to treat

Table 2: Summary of safety and NNH values

	Incidence, n (%)		NNH	95% CI
	Placebo (n=251)	Brexpiprazole (n=366)		
Main analysis: Discontinuation due to TEAEs	12 (4.8)	18 (4.9)	730	(ns)
Mild TEAEs	76 (30.3)	142 (38.8)	12	(7, 105)
Moderate TEAEs	35 (13.9)	63 (17.2)	31	(ns)
Severe TEAEs	8 (3.2)	19 (5.2)	50	(ns)
Deaths	0 (0.0)	2 (0.5)[a]	183	(ns)
TEAEs of interest				
Somnolence and sedation	2 (0.8)	14 (3.8)	34	(19, 129)
Insomnia	8 (3.2)	12 (3.3)	1,000[b]	(ns)
EPS-related events (excluding akathisia)	3 (1.2)	12 (3.3)	48	(ns)
Urinary tract infection	3 (1.2)	12 (3.3)	48	(ns)
Cardiovascular	5 (2.0)	10 (2.7)	136	(ns)
Nasopharyngitis	4 (1.6)	9 (2.5)	116	(ns)
Falls	4 (1.6)	7 (1.9)	314	(ns)
Akathisia	0 (0.0)	6 (1.7)	61	(35, 296)
Weight gain ≥7%	1 (0.4)	5 (1.4)	104	(ns)
Cerebrovascular	1 (0.4)	0 (0.0)	1,000[c]	(ns)

[a]End-stage Alzheimer's disease symptoms that occurred after end of the treatment period and heart failure, both considered unrelated to the study drug; [b]values >1,000 were truncated at 1,000; [c]the NNH value for cerebrovascular TEAEs was negative (-251), and thus was imputed as 1,000 consistent with past practice[17]
Mild, moderate, and severe TEAEs were defined as follows, based on investigator judgment: mild=discomfort noticed, but no disruption to daily activity; moderate=discomfort sufficient to reduce or affect normal daily activity, severe=inability to work or perform normal daily activity
CI=confidence interval; EPS=extrapyramidal symptoms; NNH=number needed to harm; ns=not significant; TEAE=treatment-emergent adverse event

Conclusions

In this *post hoc* analysis in patients with agitation associated with dementia due to Alzheimer's disease, NNT and NNH values indicated that brexpiprazole 2 or 3 mg/day is efficacious on symptoms of agitation and generally well tolerated compared with placebo.

In this patient sample, brexpiprazole 2 or 3 mg/day is 81 times more likely to result in a treatment response (≥20-point reduction in CMAI Total score) than a discontinuation due to a TEAE.

These data add to the body of evidence for brexpiprazole in patients with agitation associated with dementia due to Alzheimer's disease, and provide meaningful clinical interpretation of benefits and risks.

References

1. Halpern et al. Int J Geriatr Psychiatry 2019; 34 (3): 420–431.
2. Fillit et al. Int J Geriatr Psychiatry 2021; 36 (12): 1959–1969.
3. Antonsdottir et al. Expert Opin Pharmacother 2015; 16 (11): 1649–1656.
4. Rogowska et al. Drugs Aging 2023; 40 (1): 21–32.
5. Steinberg et al. Am J Psychiatry 2012; 169 (9): 900–906.
6. Rexulti® (brexpiprazole). US prescribing information. Otsuka Pharmaceutical Co. Ltd. May 2024.
7. Grossberg et al. Am J Geriatr Psychiatry 2020; 28 (4): 383–400.
8. Lee et al. JAMA Neurol 2023; 80 (12): 1307–1316.
9. Maeda et al. J Pharmacol Exp Ther 2014; 350 (3): 589–604.
10. Jain et al. J Clin Psychiatry 2024; 85 (4): plunaro2417ah.
11. Citrome. Innov Clin Neurosci 2014; 11 (5–6): 26–30.
12. Citrome. J Clin Psychiatry 2011; 72 (3): 412–413.
13. Citrome. Int J Clin Pract 2015; 69 (9): 978–997.
14. Meunier et al. Front Neurol 2024; 15: 1379062.
15. De Mauleon et al. Alzheimers Dement 2021; 17 (10): 1687–1697.
16. Cohen-Mansfield J. Instruction Manual for the Cohen-Mansfield Agitation Inventory (CMAI). Rockville, MD: The Research Institute of the Hebrew Home of Greater Washington; 1991.
17. Citrome et al. CNS Spectrums 2021; 26 (2): 146.

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