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Enclosure:

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Evidence-based dosing of brexpiprazole in patients with agitation associated with dementia due to Alzheimer's disease: an exposure–response analysis

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Introduction

- Symptoms of agitation are common among people with Alzheimer's dementia, and are associated with substantial burden to patients and caregivers.[1-3]
- Achieving the right treatment at the right dose is critical to ensuring meaningful improvement, while minimizing risks associated with suboptimal treatment, particularly in this vulnerable population.
- Brexpiprazole is approved by the FDA for the treatment of agitation associated with dementia due to Alzheimer's disease, with a recommended dose of 2 or 3 mg/day.[4]
- Brexpiprazole has a high binding affinity for noradrenergic, serotonergic, and dopaminergic receptors,[5] which may underlie efficacy on agitation.[6]
- In fixed-dose Phase 3 trials, there was significantly greater improvement from baseline to Week 12 in the frequency of agitation behaviors (Cohen-Mansfield Agitation Inventory [CMAI] Total score) with brexpiprazole 2 or 3 mg/day versus placebo, but not with brexpiprazole 1 mg/day versus placebo.[7-9] Safety data suggest no notable differences between brexpiprazole doses.[7,8]
- However, given the treatment guideline recommendation that antipsychotics should be prescribed at the lowest effective dose,[10] there may be hesitancy to dose brexpiprazole above 1 mg/day in this patient population.
- The aim of this analysis was to support evidence-based dosing of brexpiprazole in patients with agitation associated with dementia due to Alzheimer's disease, through an exposure–response analysis.

Methods

Dataset

- Data were analyzed from two Phase 3, 12-week, placebo-controlled trials of fixed-dose brexpiprazole in patients with agitation associated with dementia due to Alzheimer's disease (ClinicalTrials.gov: NCT01862640 [Trial 283];[7] NCT03548584 [Trial 213][8]).
- The trials were conducted in the US, Europe, and Russia.
- In Trial 283, patients were randomized 1:1:1 to brexpiprazole 1 mg/day, brexpiprazole 2 mg/day, or placebo (a fourth arm [brexpiprazole 0.5 mg/day] was removed in a protocol amendment).[7] In Trial 213, patients were randomized 2:1 to brexpiprazole 2 or 3 mg/day (further randomized 1:2 to 2 mg/day or 3 mg/day) or placebo.[8]
- The primary endpoint in each trial was the change from baseline to Week 12 in CMAI Total score.[7,8]
  - The CMAI is a clinically validated measure of the frequency of 29 agitated behaviors, each scored from 1 (never) to 7 (several times an hour), with a total score range of 29–203.[9,11]
  - Caregivers have reported that a reduction in the frequency of agitation behaviors reflects a meaningful improvement.[12] Based on anchor- and distribution-based analyses, a 20-point reduction in CMAI Total score is considered to constitute a meaningful within-patient improvement.[13]

Exposure–response analysis

- Data were evaluated as follows:
  - Placebo – data from Trial 283 and 213 pooled
  - Brexpiprazole 0.5 mg/day – data from Trial 283 (subsequently removed due to small sample size)
  - Brexpiprazole 1 mg/day – data from Trial 283
  - Brexpiprazole 2 mg/day – data from Trial 283 and 213 pooled
  - Brexpiprazole 3 mg/day – data from Trial 213
- The pharmacokinetic (PK) analysis sample comprised brexpiprazole-treated patients with evaluable PK data, and CMAI Total score data at baseline and Week 12.
- The average brexpiprazole blood concentration at steady state ($C_{avg,ss}$) was predicted for each patient using a population PK model. Using PK data from two trials of brexpiprazole,[7] the model was validated in this patient population. Patients treated with placebo were assigned $C_{avg,ss}$ of 0.
- Efficacy was evaluated by percentage change from baseline in CMAI Total score at Week 12. Percentage change (rather than absolute change) was chosen to account for the effect of baseline CMAI Total score on the exposure-response relationship.
- An exposure–response analysis using a sigmoid Emax model characterized the relationship between average blood concentration and percentage change from baseline in CMAI Total score.

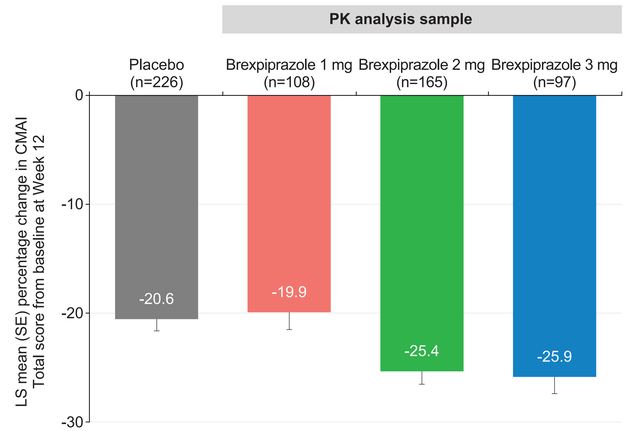
Table 1: Summary of patient characteristics at baseline

	Placebo (n=226)	PK analysis sample		
		Brexpiprazole 1 mg (n=108)	Brexpiprazole 2 mg (n=165)	Brexpiprazole 3 mg (n=97)
Age, years, mean (SD)	73.4 (7.6)	73.9 (8.8)	73.8 (7.8)	75.0 (8.1)
Female, n (%)	112 (49.6)	60 (55.6)	92 (55.8)	62 (63.9)
Body weight, kg, mean (SD)	70.3 (13.7)	68.9 (14.6)	68.9 (14.4)	68.0 (14.7)
Race, n (%)				
Asian	2 (0.9)	1 (0.9)	2 (1.2)	2 (2.1)
Black	6 (2.7)	1 (0.9)	6 (3.6)	3 (3.1)
White	218 (96.5)	106 (98.1)	157 (95.2)	92 (94.8)
CMAI Total score, mean (SD)	75.4 (17.1)	70.8 (16.1)	75.3 (17.1)	80.9 (15.6)

The PK analysis sample comprised brexpiprazole-treated patients with evaluable PK data, and CMAI Total score data at baseline and Week 12
CMAI=Cohen-Mansfield Agitation Inventory; PK=pharmacokinetic; SD=standard deviation

Results

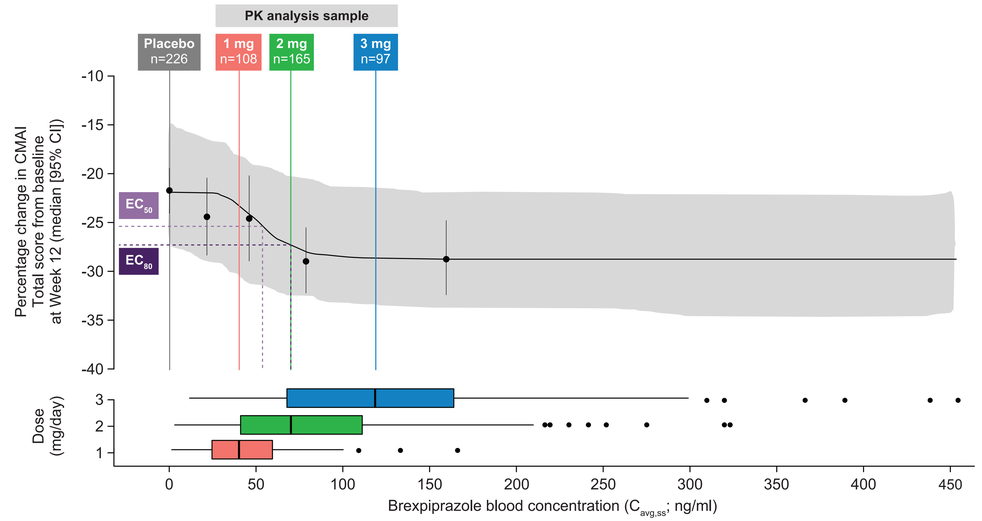
Figure 1: Percentage change in CMAI Total score by administered brexpiprazole dose



The PK analysis sample comprised brexpiprazole-treated patients with evaluable PK data, and CMAI Total score data at baseline and Week 12
Mean (SD) CMAI Total score at baseline: placebo, 75.4 (17.1); brexpiprazole 1 mg, 70.8 (16.1); brexpiprazole 2 mg, 75.3 (17.1); brexpiprazole 3 mg, 80.9 (15.6)
LS mean (SE) data were derived from a mixed model for repeated measures, with baseline by visit interaction, treatment by visit interaction, and study protocol interaction
CMAI=Cohen-Mansfield Agitation Inventory; LS=least squares; PK=pharmacokinetic; SD=standard deviation; SE=standard error

- Data were analyzed for 608 patients. Following exclusion of the brexpiprazole 0.5 mg arm (due to small sample size), data for 596 patients were summarized, of whom 370 patients comprised the brexpiprazole PK analysis sample, and 226 patients were treated with placebo.
- Patient characteristics at baseline are shown in Table 1.
- Figure 1 shows percentage change in CMAI Total score with each administered dose of brexpiprazole.
- Figure 2 shows percentage change in CMAI Total score as a function of brexpiprazole blood level resulting from each administered dose.
- Brexpiprazole 1 mg/day did not demonstrate additional efficacy compared with placebo. For the 1 mg dose, the predicted median blood concentration was lower than the level required to achieve the half-maximal effect (EC_{50}) on the CMAI Total score.
- For brexpiprazole 2 mg and 3 mg, the predicted median blood concentration exceeded the EC_{50}.
- Model-predicted percentage change from baseline in CMAI Total score plateaued beyond the 3 mg dose, indicating no further increase in efficacy beyond this dose.

Figure 2: Percentage change in CMAI Total score by brexpiprazole blood level resulting from each administered dose



The PK analysis sample comprised brexpiprazole-treated patients with evaluable PK data, and CMAI Total score data at baseline and Week 12; $C_{avg,ss}$ for participants treated with placebo was set to 0
Upper panel: data points and error bars show the observed median and 95% CI of percentage change from baseline in CMAI Total score at Week 12, by placebo and brexpiprazole $C_{avg,ss}$ quartiles; the black line and shaded region show the model predicted median and 95% CI of percentage change from baseline in CMAI Total score at Week 12
Lower panel: boxplots show the brexpiprazole $C_{avg,ss}$ distribution at 1, 2, and 3 mg/day doses
$C_{avg,ss}$=average blood concentration at steady state; CI=confidence interval; CMAI=Cohen-Mansfield Agitation Inventory; $EC_{50/80}$=blood level of brexpiprazole required to achieve 50%/80% of the maximal drug effect; PK=pharmacokinetic

Conclusions

- Supportive of clinical trial results, this analysis demonstrated an exposure–response relationship for brexpiprazole in patients with agitation associated with dementia due to Alzheimer's disease.
- Brexpiprazole doses of 2 or 3 mg/day are expected to achieve meaningful reductions in agitation frequency, while brexpiprazole 1 mg/day is unlikely to be effective in reducing the frequency of agitation symptoms.
- These findings should be considered when selecting appropriate treatment for individual patients.

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