

Population Pharmacokinetic And Exposure-response Analysis Of Brexpiprazole In Japanese Patients With Agitation In Alzheimer’s Dementia

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Background

Brexpiprazole is approved for the agitation in Alzheimer’s dementia (AAD), schizophrenia, adjunct treatment of major depressive. In Japan, a phase 2/3 study for AAD demonstrated that treatments with brexpiprazole 1 and 2 mg/day achieved statistically significant and clinically meaningful improvements in AAD compared with placebo based on the primary endpoint, mean change in the Cohen-Mansfield Agitation Inventory (CMAI) Total Score from baseline to week 10¹). To characterize the pharmacokinetics and exposure-response (ER) relationship in Japanese patients with AAD, population pharmacokinetics (PopPK) was utilized, and ER modeling was conducted.

Methods

A previously established PopPK model for brexpiprazole using data from Japanese healthy subjects and schizophrenia patients was used²) to perform an external validation of the previous PopPK model against data from the phase 2/3 study in patients with AAD in Japan. Numerical predictive check (NPC) and prediction-corrected visual predictive check (pcVPC), goodness-of-fit (GOF) diagnostic plots, and normalized prediction distribution errors (NPDE) analyses were used in the external validation. Furthermore, exposure-response analysis was conducted using data from Japanese patients with AAD. The systemic exposure metric used in this exposure-response analysis was average concentration at steady state (Cavg,ss), obtained from Study 331-102-00088. The efficacy response measure was the percent change from baseline (PCFB) in the CMAI response at Week 10.

Results

For the population PK analysis, 185 Japanese AAD patients with PK observations after brexpiprazole administration were included (185 PK sampling points). A total of 300 patients with a CMAI Total Score at both baseline and Week 10 were included in the exposure-efficacy analysis. Key baseline patient characteristics are summarized in Table 1. The external validation demonstrated that the previously established PopPK model was able to predict brexpiprazole concentrations in Japanese patients with AAD (Figure 1). In the exposure-response analysis, a sigmoid Emax model adequately described the effect of brexpiprazole exposure (Cavg,ss) on the percent change from baseline in the CMAI Total Score (Table 2). In addition, a daily dose of brexpiprazole 1 and 2 mg was expected to show > 50% and > 80% of the maximum efficacy (Figure 2).

Table 1. Summary Statistics for covariates explored in the exposure-efficacy response analyses

Covariate	Treatment			
	Overall (N = 300)	1mg (N = 82)	2mg (N = 102)	Placebo (N = 116)
Age (years)				
Median [Min, Max]	81 [60, 90]	81 [60, 90]	80 [60, 90]	82 [60, 90]
Body weight (kg)				
Median [Min, Max]	47.8 [30.1, 85.1]	47.8 [32.6, 82.1]	49.6 [30.1, 85.1]	47.2 [30.1, 79.3]
Sex				
Female	183 (61%)	49 (59.8%)	65 (63.7%)	69 (59.5%)
Baseline CMAI Total Score				
Mean (SD)	62.8 (12.1)	62.7 (11.0)	63.5 (13.2)	62.4 (11.9)
Median [Min, Max]	61.5 [39, 107]	62.5 [41, 92]	63 [39, 104]	60 [45, 107]

Abbreviations: Max = maximum; Min = minimum; N = number of subjects; SD = standard deviation

Table 2. Parameter estimation of the Exposure-Response model

Parameter	Description	Estimate	RSE%	95% CI
E ₀	placebo effect on PCFB CMAI	-13.8	10.2	-16.5 to -11.0
EC ₅₀ (ng/mL)	C _{avg,ss} to achieve half-maximum drug effect on PCFB CMAI	46.5	62.0	-10.0 to 103
E _{max}	maximum drug effect on PCFB CMAI	-11.0	40.7	-19.8 to -2.23
γ	sigmoidicity factor	2.42	113	-2.95 to 7.80
σ ²	additive residual error	16.9	4.04	15.5 to 18.2

* EC80 = 82.5 ng/mL.

Abbreviations: Cavg,ss = average concentration at steady-state, CI = confidence interval, PCFB = percent change from baseline, RSE = relative standard error.

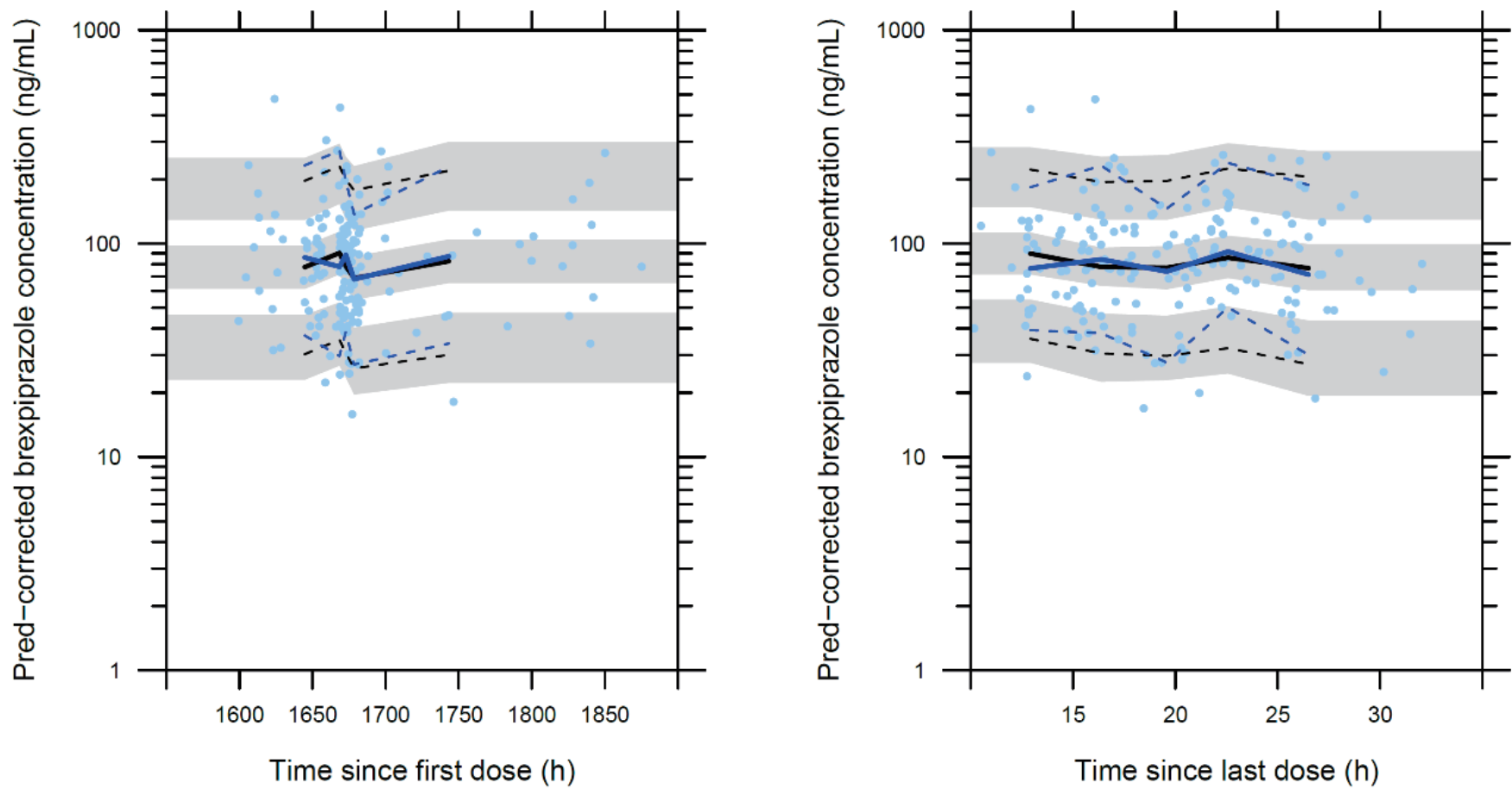


Figure 1: pcVPCs - Brexpiprazole concentrations versus time

* Brexpiprazole PK was characterized using a two-compartment model with apparent first-order clearance (CL/F) from the central compartment and delayed transit compartment absorption rate constant (Ktr). Covariate effects included age, cytochrome P450 (CYP) 2D6 phenotype and the eGFR on CL/F, a study phase factor on bioavailability (F), and a dose effect on Ktr.

Author Disclosure Information

K. Shimizu: Employee/Owner; Self; Otsuka Pharmaceutical Co., Ltd.

Conclusion

Brexpiprazole 2 mg/day would provide close to maximum reduction in the CMAI Total Score for Japanese patients with agitation in Alzheimer’s dementia.

References

- 1) Nakamura, Y. et al.: Alzheimer’s Dement. 2024; 20 (11): 8002–8011.
- 2) Higashi, K. et al.: Drug Metab Pharmacokinet. 2025; 62: 101057.

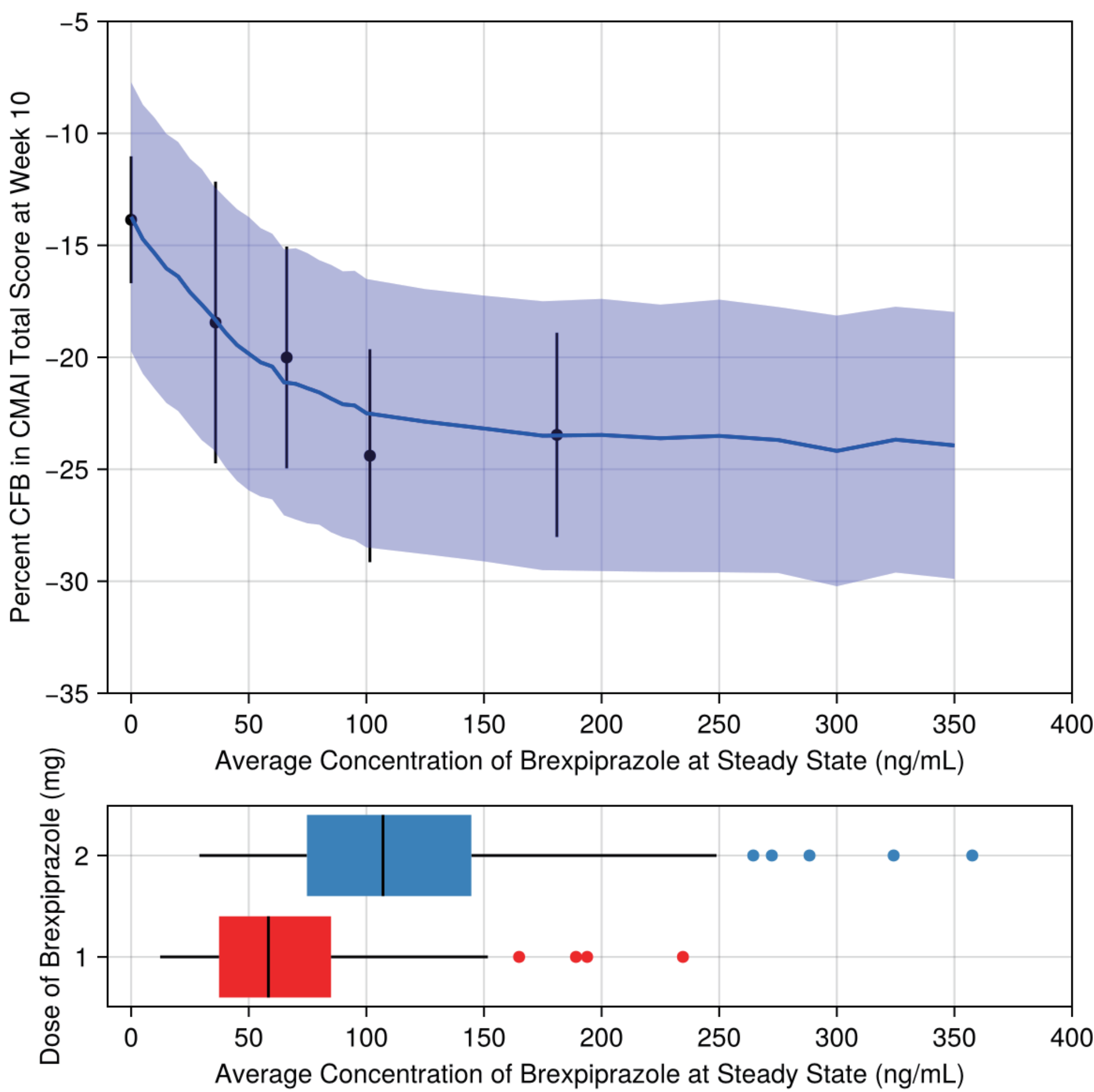


Figure 2: Observed and model predicted mean and 95% confidence interval of the percent change from baseline in CMAI Total Score versus Cavg,ss

* The proportions of subjects exceeding EC50 and EC80 were 59.8% and 29.3% at 1 mg, and 94.1% and 67.6% at 2 mg, respectively.