

Supplemental Methods.

Noncompartmental Pharmacokinetic Analysis

First dose PK parameters were calculated using noncompartmental methods (Phoenix WinNonlin 7.0, Certara Pharsight Corp, Cary, NC). Any plasma concentration measured below the LLOQ was excluded from analyses. The maximum plasma concentration (C_{MAX}) and time to C_{MAX} (T_{MAX}) were recorded as observed values. The area under the plasma concentration vs time curve to the last observed time point (AUC_{LAST}) was calculated using the Linear Up Log Down trapezoidal rule. The elimination rate (k_{EL}) was calculated as the slope of the log-transformed concentrations vs terminal time points. AUC extrapolated to time infinity (AUC_{INF}) was calculated as $AUC_{LAST} + C_{LAST}/k_{EL}$, where C_{LAST} is the concentration at the last observed time point. Half-life ($t_{1/2}$) was calculated as $\ln 2/k_{EL}$. Apparent oral clearance (CL/F) was calculated as $dose/AUC_{INF}$; apparent oral volume of distribution (Vz/F) was calculated as CL/F divided by k_{EL} . PK parameters at steady-state (Cycle 2 Day 1) were calculated the same except AUC was calculated over the dosing interval $\tau = 24$ hr (AUC_{TAU}), clearance (CL_{SS}/F) as $dose/AUC_{TAU}$, and Vz/F as CL_{SS}/F divided by k_{EL} . The number of subjects included in the pharmacokinetic analysis was insufficient for proper statistical testing.

Supplemental Table 1. Adverse Events with an Attribution of at Least Possible Occurring in Greater than 15% of Patients Who Received Study Treatment (N=17) Sorted by Dosing Strategy

Adverse Event	450 mg Twice Daily N = 7		750 mg Once Daily N = 6		600 mg Once Daily N = 4	
	Grade 1/2	Grade 3	Grade 1/2	Grade 3	Grade 1/2	Grade 3
<i>Concentration Impairment</i>	6 (86)	0 (0)	5 (83)	1 (17)	2 (50)	0 (0)
<i>Fatigue</i>	5 (71)	0 (0)	4 (67)	0 (0)	2 (50)	0 (0)
<i>Tremor</i>	3 (43)	0 (0)	5 (83)	0 (0)	2 (50)	0 (0)
<i>Nausea</i>	4 (57)	1 (14)	0 (0)	0 (0)	3 (75)	1 (25)
<i>Dizziness</i>	2 (29)	1 (14)	1 (17)	1 (17)	1 (25)	0 (0)
<i>Blurred Vision</i>	1 (14)	0 (0)	1 (17)	0 (0)	2 (50)	0 (0)
<i>Hypotension</i>	3 (43)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25)
<i>Vomiting</i>	1 (14)	0 (0)	0 (0)	0 (0)	2 (50)	0 (0)
<i>Edema (limbs)</i>	1 (14)	0 (0)	1 (17)	0 (0)	1 (25)	0 (0)
<i>Fall</i>	1 (14)	1 (14)	0 (0)	0 (0)	1 (25)	0 (0)
<i>Gait Disturbance</i>	3 (43)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<i>Malaise</i>	1 (14)	0 (0)	2 (33)	0 (0)	0 (0)	0 (0)
<i>Presyncope</i>	3 (43)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)