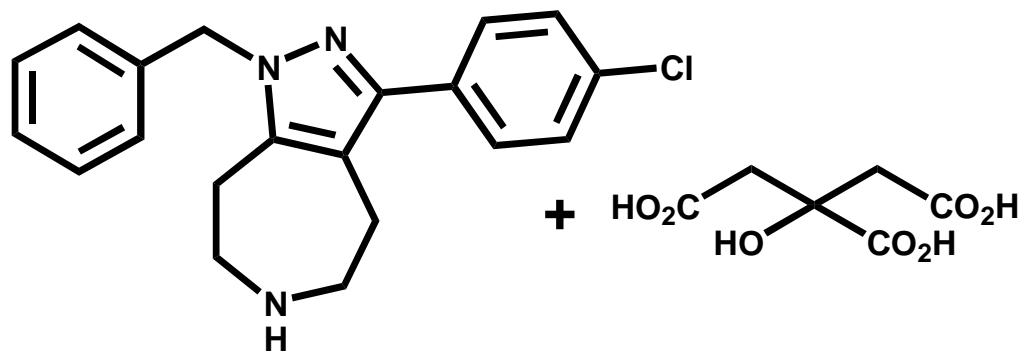


**Translational evaluation of JNJ-18038683, a 5-HT<sub>7</sub> receptor antagonist, on  
REM sleep and in major depressive disorder**

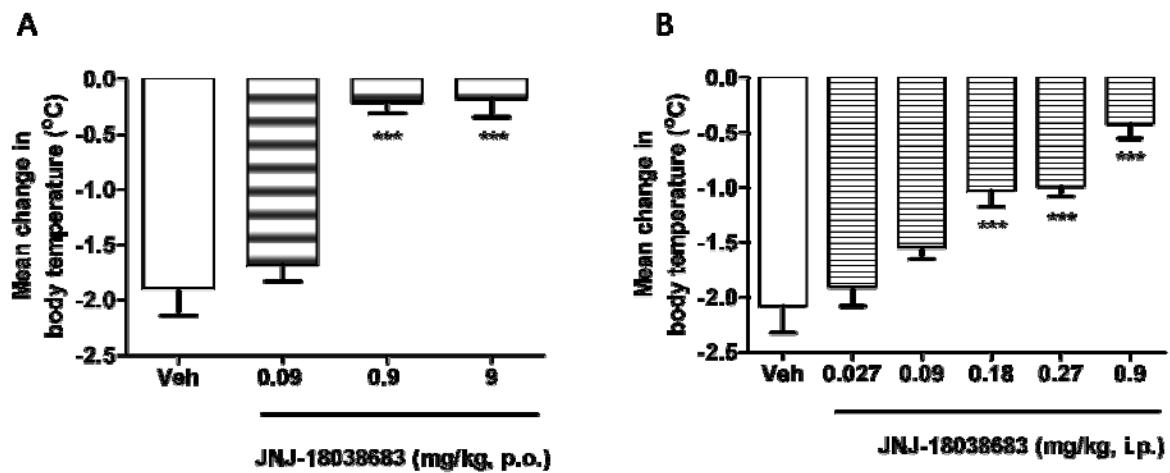
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**Supplemental data files JPET#193995**

**Supplemental Figure 1:** Chemical structure of JNJ-18038683(3-(4-chlorophenyl)-1,4,5,6,7,8-hexahydro-1-(phenylmethyl)pyrazolo[3,4-d]azepine 2-hydroxy-1,2,3-propanetricarboxylate).



**Supplemental Figure 2:** Effect of oral administration (A) and intraperitoneal (B) of JNJ-18038683 on 5-CT-induced hypothermia in rats. JNJ-18038683 was administered orally 6 hours before 5-CT administration or intraperitoneally 20 minutes before 5-CT administration. 5-CT was administered intraperitoneally (0.1 mg/kg). Data bars represent the mean  $\pm$  S.E.M. (n = 5). \*\*\* P < 0.001 compared to 5-CT alone group (Veh = vehicle).



**Supplemental Table 1:** In vitro selectivity profile of JNJ-18038683. Data were obtained using standard radioligand binding assays. Data are the mean  $\pm$  S.E.M from at least three separate experiments unless indicated by an asterisk.

r = rat; h = human, c = canine. \* Indicate single value

	In vitro binding	Fold selectivity
	pK <sub>i</sub>	versus h5-HT <sub>7</sub>
<u>Serotonin receptors</u>		
r5-HT <sub>1A</sub>	6.39 $\pm$ 0.38	65
h5-HT <sub>1A</sub>	6.50 $\pm$ 0.28	50
h5-HT <sub>1B</sub>	6.90 $\pm$ 0.14	20
r5-HT <sub>1B</sub>	6.54*	46
c5-HT <sub>1D</sub>	6.20*	100
r5-HT <sub>2A</sub>	6.50 $\pm$ 0.08	50
h5-HT <sub>2A</sub>	7.03 $\pm$ 0.03	14
h5-HT <sub>2B</sub>	6.81 $\pm$ 0.16	25
h5-HT <sub>2C</sub>	7.06 $\pm$ 0.23	14
h5-HT <sub>3</sub>	<5	>1000
r5-HT <sub>4</sub>	<5	>1000
h5-HT <sub>5A</sub>	5.50*	>100
h5-HT <sub>6</sub>	7.20*	10
<u>Dopamine receptors</u>		
rD <sub>1</sub>	6.06 $\pm$ 0.21	>100

hD <sub>1</sub>	6.15*	>100
rD <sub>2</sub>	6.69*	32
hD <sub>2</sub>	<5	>1000

Adrenergic receptors

rα <sub>1</sub>	7.04 ± 0.13	15
hα <sub>1B</sub>	7.00*	15
rα <sub>2</sub>	<5	>1000

Histamine receptors

hH <sub>1</sub>	<5	>1000
hH <sub>3</sub>	<5	>1000

Transporters

hNE uptake	<5	>1000
hDAT uptake	<5	>1000
r5-HT uptake	5.52*	>100
h5-HT uptake	< 5	>1000

CEREP panel

adenosine (A1,A2A,A3), angiotensin (AT1),	>100
bradykinin (B2), cholecystokinin (CCKA),	
galanin (GAL2), melatonin ML1), muscarinic	
(M1, M2, M3), neuropeptides (NT1), neurokinin	
(NK2, NK3), opiate (μ, κ, δ), somatostatin,	
vasopressin (V1a), ion channels (sodium,	
calcium, potassium and chloride)	< 50% inh at 1 μM

**Supplemental Table 2:** Summary of secondary efficacy results from the MDD study at week 7  
(placebo n = 71, JNJ-18038683 n = 72, escitalopram n = 75). CI = confidence interval.

Efficacy endpoints	JNJ-18038683 vs. Placebo		Escitalopram vs. Placebo	
	Mean (95% CI)	p-value <sup>a, b, c</sup>	Mean (95% CI)	p-value <sup>a, b, c</sup>
CGI-S	-0.3 (-0.71,0.14)	0.192	-0.2 (-0.59,0.25)	0.432
MADRS Responder %	4.9 (-11.46,21.28)	0.931	-1.2 (-17.32,15.03)	0.896
MADRS-6	-1.1 (-3.37,1.14)	0.332	-0.6 (-2.83,1.60)	0.583
HAMD-17	-0.9 (-3.48,1.77)	0.522	-1.1 (-3.69,1.46)	0.394
HAMD-17 Responder %	-4.9 (-21.23,11.49)	0.538	-4.0 (-20.25,12.17)	0.820
HAMD-6	-0.4 (-1.85,1.03)	0.575	-0.5 (-1.90,0.92)	0.492
ESS	0.4 (-1.10,1.83)	0.622	1.1 (-0.31,2.56)	0.124
GAF	2.1 (-2.17,6.42)	0.330	1.0 (-3.21,5.20)	0.642
SA Item-1 (Sleep Latency)	-3.5 (-25.65,18.69)	0.757	9.4 (-12.60,31.44)	0.400
SA Item-2 (# of Awakenings)	-0.2 (-0.74,0.30)	0.401	-0.1 (-0.59,0.42)	0.744
SA Item-3 (Sleep Time)	-18.8 (-50.28,12.61)	0.239	-5.8 (-36.54,24.90)	0.709
SA Item-4 % (Sleep Quality) <sup>d</sup>	6.3 (-9.93,22.65)	0.733	3.0 (-13.01,19.17)	0.569

- (a): For CGI-S, MADRS-6, HAMD-17, HAMD-6, ESS, GAF, SA Items 1-3, analysis based on an ANCOVA model with treatment, (pooled) center and sex as factors and baseline as covariate.
- (b): For MADRS responder, HAMD-17 responder and SA Item-4, analysis based on the generalized Cochran-Mantel-Haenszel test for row mean scores differ, with (pooled) center and sex as stratification factors.
- (c): Pairwise comparison without adjustment of multiplicity.
- (d): Mean and CI given based on subcategories ‘Excellent’ and ‘Good’, p-values given based on all 4 subcategories.

**Supplemental Table 3:** HAMD-17 total score - change from baseline to end point (LOCF)  
 excluding sites with mean HAMD-17 total score in the placebo arm less or equal to 10 at end  
 point.

	Placebo (n = 52)	JNJ-18038683 (n = 53)	Escitalopram (n = 57)
<b>Baseline</b>			
Mean (SD)	27.5 (2.31)	27.1 (1.92)	27.1 (1.99)
<b>End Point</b>			
Mean (SD)	18.2 (7.53)	14.1 (8.71)	14.7 (7.47)
<b>Change from Baseline</b>			
Mean (SD)	-9.4 (7.33)	-13.1 (8.45)	-12.4 (7.03)
P-value (minus placebo) (a)		0.0125	0.0291
Difference of LS Means (SE)		-4.0 (1.56)	-3.3 (1.51)
(a) Based on Analysis of covariance (ANCOVA) model with treatment, sex, and center as factors, and baseline value as a covariate.			
Note: Negative change in score indicates improvement.			