Poster No. F13

Safety, tolerability, pharmacokinetic and pharmacodynamic properties of the selective orexin-1 receptor antagonist JNJ-61393215: Results from the first-in-human and multiple ascending dose studies

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BACKGROUND

- JNJ-61393215, a first-in-class, selective, high affinity and potent orexin-1 receptor (OX1R) antagonist is currently under development for the treatment of neuropsychiatric disorders associated with panic, anxiety, addictive behaviors, and mood dysregulation.
- Pharmacological studies have shown OX1R involvement in physiological processes that regulate emotion, the reward system and the autonomic nervous system.[1,2]
- In this first-in-human single ascending dose (SAD) and multiple ascending dose (MAD) study, the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) properties of OX1R antagonist JNJ-61393215 were evaluated.

Study objectives

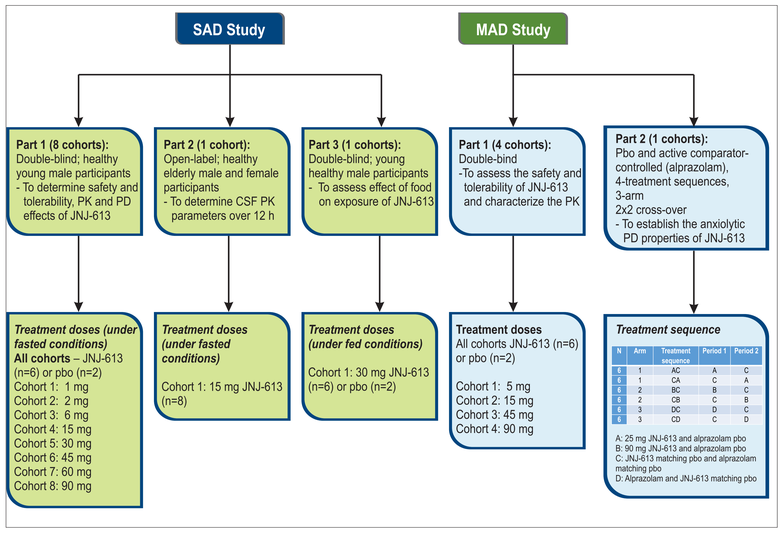
- Determine safety and tolerability of JNJ-61393215 versus placebo after single dose (under fasted and fed condition) and multiple dose administrations.
- Characterize the PK profile of JNJ-61393215 in plasma and cerebrospinal fluid (CSF) and the effect of food (high fat/high calorie meal) following single dose administration.
- Investigate effect of JNJ-61393215 on subjective fear response and anxiety symptoms by 35% CO_2 double breath inhalation challenge (Methodology and Results will be described separately).

METHODS

Study design: Single- and multiple-ascending dose study of JNJ-61393215 in healthy participants

This was a phase 1, randomized, double-blind, placebo-controlled 3-part SAD and 2-part MAD study to assess safety and tolerability, PK and PD of JNJ-61393215 in healthy participants.

Figure 1. Study design



JNJ-613, JNJ-61393215; CSF, cerebrospinal fluid; MAD, multiple-ascending dose; N, number of patients; Pbo, placebo; PD, pharmacodynamics; PK, pharmacokinetic; SAD, single-ascending dose. JNJ-61393215 was administered orally once-daily; alprazolam 1 mg twice-daily.

Assessments

- ***PK parameters***: C_{max}, C_{last}, t_{max}, AUC_{last}, AUC_{∞}, $t_{½\ term}$, CL/F, Vd/F, CLcr in SAD study and C_{max}, t_{max}, AUC_{24h}, unbound fraction, CL/F, Vd/F in MAD study were estimated in all participants who received a dose of JNJ-61393215.
- The PD effects of JNJ 61393215 were investigated in every cohort of the SAD study using the NeuroCart, a multidimensional CNS test battery that has been validated at the Centre for Human Drug Research (CHDR) and has previously been shown to be sensitive to PD effects of centrally active compounds,[3] including dual orexin and selective orexin-2 receptor antagonists.[4] The Neurocart test battery included the following assessments: saccadic eye movements, smooth pursuit eye movements, adaptive tracking, body sway, subjective drug effects (Bond & Lader Visual Analogue Scale [VAS], Bowdle VAS), Visual Verbal Learning test (VVLT) – immediate recall and delayed recall.
- ***Safety***: Treatment-emergent adverse events (TEAEs), clinical laboratory tests, physical examinations, vital signs were monitored and recorded.

RESULTS

Study population

- In SAD study, 72 healthy participants (mean [SD] age: 31 [15.06] years; BMI: 23.1 kg/m^2) were included. Overall, 32 male participants (mean [SD] age: 30.5 [11.2] years) in Part 1 and 39 male participants (mean [SD] age: 28.2 [8.0] years) in Part 2 were included in MAD study.
- In JNJ-61393215 treatment group, the majority (~80%) of participants were white, with mean BMI of 22.9 (2.8) kg/m^2 (range 17.9 to 29.4).

Table 1. Participant disposition

	Participants in JNJ-61393215, N	Number of cohorts	Participants per cohort	Dose range of JNJ-61393215
SAD study				
Part 1	48 [males]	8	6	1 to 90 mg under fasted conditions
Part 2	8 [3 males; 5 females]	1	8	15 mg under fasted conditions
Part 3	6 [males]	1	6	30 mg under fed conditions
MAD study				
Part 1	24 [males]	4	6	5 to 90 mg

Except for Part 2 of SAD study, all parts were placebo-controlled.

Concentration-time profiles of JNJ-61393215

- Quantifiable JNJ-61393215 concentrations were observed for all participants at all dose levels:
  SAD: From 30 min postdose to 72 h postdose, under fed and fasted conditions.
  MAD: From 20 min postdose on day 1 up to 72 h postdose on day 7.
- Total plasma concentrations increased to peak concentrations occurring ~1.5 h postdose for lower doses (1, 2, 6, 15, and 30 mg), and ~2.5 h postdose for higher doses (45, 60, and 90 mg).
- C_{max} and AUC were approximately 50% lower when 30 mg JNJ-613983215 was administered with food vs fasted conditions .
- CSF concentrations were lower than the corresponding unbound JNJ-61393215 plasma concentrations.
  - Mean ratios of CSF versus unbound JNJ-61393215 15 mg plasma concentrations increased over time ranging from 0.420 at 1.5 h after dosing to 0.752 at 12 h after dosing in elderly patients under fasted conditions.
  - The t_{max} was reached approximately 3 h postdose in CSF and the mean CSF concentration-time profile of JNJ-61393215 paralleled the mean plasma concentration-time profile.

Figure 2. Mean total plasma concentration-time profiles of JNJ-61393215 after administration of single oral doses (1 to 90 mg) under fasted conditions in healthy male participants

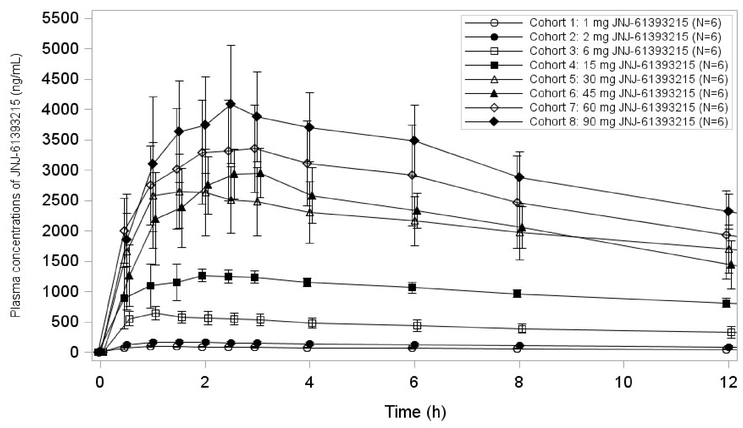
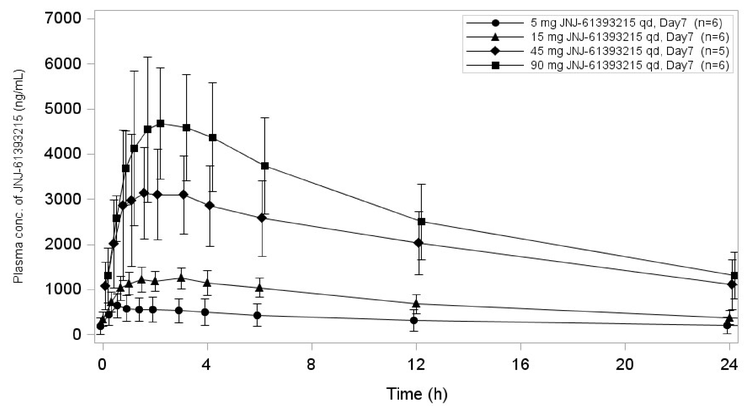


Figure 3. Mean plasma-concentration-time profiles of JNJ-61393215 on 7 day following multiple doses of 5, 15, 45, and 90 mg QD



Pharmacokinetic parameters

- Dose proportional increase of C_{max}, AUC_{last} and AUC_{∞} was observed for dose range of 1 to 30 mg. For doses >30 mg, C_{max}, AUC_{last} and AUC_{∞} increased in less than dose-proportional manner.
  - Under fed conditions, the geometric mean ratios for C_{max}, AUC_{last} and AUC_{∞} of JNJ-61393215 were approximately 53%, 59% and 57% of the corresponding values obtained after administration under fasted conditions. Food-effect data were not confirmed in a follow-up cross-over study (data on file).
- For 5 to 90 mg dose range, dose-normalized PK parameters (day 1 and 7) increased in a less than dose-proportional manner.
- Unbound fraction increased with increasing drug plasma concentrations (1.4% and 3% at 2.5 h after a 1 and 90 mg dose, respectively); unbound fraction decreased with increasing α1-acid glycoprotein concentrations.
  - Accumulation ratios for C_{max}, AUC_{24h} were low and decreased with dose from 147% at 5 mg QD to 103% at 90 mg QD.
- Median t_{max} was 1.0 to 1.5 h for lower dose (1 to 30 mg dose range) and 2.25 to 2.26 h for higher dose levels (45, 60, and 90 mg).
- Mean $t_{1/2term}$ was comparable between dose levels (range 13.6 to 24.6 h across cohorts under fasted conditions).
- Apparent CL/F and Vd/F
  - The amount of JNJ-61393215 excreted unchanged in urine was low. JNJ-61393215 was found to be a low-clearance drug with mean CL/F ranging from 0.419 L/h at 30 mg to 1.18 L/h at 90 mg under fasted conditions and Vd ranging 11.3 L at 6 mg and 22.3 L at 90 mg under fasted conditions.
  - Mean CL/F value increased with increasing dose with the corresponding values at 0.789, 0.878, 1.02, and 1.45 L/h after 5, 15, 45, and 90 mg QD JNJ 61393215, respectively. Mean Vd/F value increased with increasing dose with corresponding values at 16.3, 17.4, 24.5, and 27.0 L after 5, 15, 45, and 90 mg doses of JNJ 61393215, respectively.

Table 2. Pharmacokinetic results of JNJ-61393215 following single oral administration under fasted and fed conditions

	SAD, JNJ-61393215									
PK parameters	Part 1 (fasted)								Part 2 (fasted)	Part 3 (fed)
	Cohort 1 1 mg	Cohort 2 2 mg	Cohort 3 6 mg	Cohort 4 15 mg	Cohort 5 30 mg	Cohort 6 45 mg	Cohort 7 60 mg	Cohort 8 90 mg	Elderly 15 mg	30 mg
N	6	6	6	6[a]	6	6	6	6	8	6
C_{max}, ng/mL	97.4 ± 10.1	177 ± 24.3	643 ± 111	1390 ± 171	2850 ± 701	3122 ± 336	3552 ± 736	4497 ± 664	1524 ± 276	1482 ± 258
t_{max}, h, median (range)	1.00 (1.00 – 2.00)	1.26 (1.00 – 2.48)	1.00 (1.00 – 1.02)	1.50 (0.50 – 3.03)	1.50 (1.00 – 6.00)	2.26 (1.00 – 3.10)	2.25 (1.00 – 6.00)	2.25 (1.03 – 6.00)	1.50 (0.50 – 2.52)	5.00 (2.50 – 12.00)
C_{last}, ng/mL	5.56 ± 4.13	9.99 ± 6.60	28.9 ± 38.8	155 ± 137	281 ± 187	103 ± 128	148 ± 165	104 ± 66.1	137 ± 88.2	142 ± 132
AUC_{last}, ng.h/mL	1974 ± 484	3795 ± 1129	11804 ± 4560	36101 ± 8898	72100 ± 23112	55232 ± 20288	70482 ± 30326	78253 ± 18009	35439 ± 13491	42984 ± 16036
AUC_{∞}, ng.h/mL	2148 ± 636	4068 ± 1323	12778 ± 6127	35858 ± 5760	82306 ± 30685	58186 ± 24756	74467 ± 35958	80461 ± 19572	40460 ± 17077	47894 ± 21754
$t_{1/2term}$, h	18.2 ± 5.7	16.7 ± 4.4	16.0 ± 6.6	24.6 ± 12.4	21.5 ± 6.7	14.5 ± 5.3	15.0 ± 4.2	13.6 ± 2.3	22.5 ± 5.5	18.0 ± 7.6
CL/F, L/h	0.501 ± 0.144	0.545 ± 0.211	0.551 ± 0.221	0.427 ± 0.0685	0.419 ± 0.180	0.874 ± 0.295	0.922 ± 0.306	1.18 ± 0.309	0.445 ± 0.206	0.751 ± 0.355
Vd/F, L	12.2 ± 1.26	12.0 ± 1.56	11.3 ± 1.91	11.9 ± 1.30	11.6 ± 1.30	16.6 ± 2.34	18.5 ± 3.32	22.3 ± 2.21	13.2 ± 3.58	16.7 ± 1.96
CLcr, mL/min	142 ± 22.8	147 ± 39.6	142 ± 17.5	136 ± 30.2	121 ± 44.5	117 ± 11.0	132 ± 22.0	136 ± 31.2	82.0 ± 24.1	–
$C_{max\ unbound,\ dose\ normalized}$, ng/mL	1.40 ± 0.360	1.50 ± 0.308	2.10 ± 0.217	1.47 ± 0.187	1.89 ± 0.562	1.81 ± 0.334	1.45 ± 0.469	1.52 ± 0.334	–	–
$AUC_{last,\ unbound,\ dose\ normalized}$, ng.h/mL/mg	27.1 ± 2.73	31.0 ± 4.61	37.4 ± 8.41	37.8 ± 6.82	45.7 ± 8.90	31.0 ± 8.14	28.2 ± 10.9	25.8 ± 4.74	–	–

[a]N=5 for AUC_{∞}, CL/F, Vd/F and AUC_{∞}, AUC_{∞}, AUC_{∞}, area under the plasma concentration-time curve from time 0 to infinite time; AUC_{last}, area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentrations; C_{last}, last quantifiable plasma concentration; C_{max}, maximum plasma concentration; CLcr, creatinine clearance; CL/F, total clearance of drug after extravascular administration; SAD, single-ascending dose; $t_{1/2term}$, elimination half-life associated with the terminal slope (λz) of the semi-logarithmic drug concentration-time curve; t_{max}, time to reach maximum plasma concentration; Vd/F, apparent volume of distribution.

Table 3. Pharmacokinetic results of JNJ-61393215 following multiple oral doses

	MAD			
PK parameters, Day 7	**5 mg JNJ-61393215**	**15 mg JNJ-61393215**	**45 mg JNJ-61393215**	**90 mg JNJ-61393215**
N	**6**	**6**	**5**	**6[a]**
C_{max}, ng/mL	627 (272)	1380 (248)	3528 (1227)	4784 (1454)
t_{max}, median (range)	1.25 (0.67-2.02)	2.00 (0.67-3.00)	1.50 (0.67-3.00)	1.50 (1.00-3.00)
AUC_{24h}, ng.h/mL	8401 (5604)	18170 (4611)	48187 (17359)	66403 (20245)
FU, 0h	0.0194 (0.00413)	0.0234 (0.00742)	0.0184 (0.00517)	0.0226 (0.00698)

Values are presented as mean±SD unless specified; [a]n=5 for C_{max}, t_{max}.
AUC_{24h}, area under the plasma concentration-time curve from time 0 to 24 h; C_{max}, maximum plasma concentration; FU, Unbound fraction; JNJ-613, JNJ-61393215; MAD, multiple-ascending dose; t_{max}, time to reach maximum plasma concentration.

- JNJ-61393215 didn't show any significant effects on measures of alertness and sedation or cognitive parameters. Similarly, no changes in wake EEG parameters were detected after administration of JNJ-61393215 as compared to placebo.

Safety

- JNJ-61393215 showed no safety concerns in fasted (1 to 90 mg JNJ-61393215) and fed (30 mg JNJ-61393215) conditions.
- The most common TEAEs in all JNJ-61393215 treatment groups were somnolence, and headache. The proportions of participants who manifested somnolence and headache appeared comparable between the placebo and JNJ-61393215 treatment arms. All TEAEs were mild in severity except for lumbar puncture syndrome reported as a moderate TEAE in 2 patients on 15 mg JNJ-61393215.
- No deaths or serious TEAEs were reported. There were no study discontinuations except for 2 premature discontinuations due to TEAE of atrioventricular block and hepatic enzyme increase (n=1 participant each).

Table 4. Summary of TEAEs after single or multiple-administration of JNJ-61393215 doses by preferred term (in ≥5% participants)

SAD											
	Pbo	JNJ-61393215									
		1 mg	2 mg	6 mg	15 mg	30 mg	45 mg	60 mg	90 mg	15 mg (Part 2)	30 mg (Part 3)	Total
Total	**18**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**8**	**6**	**62**
Any TEAE, n (%)	11 (61)	1 (16.7)	2 (33.3)	3 (50)	1 (16.7)	6 (100)	3 (50)	3 (50)	4 (66.7)	8 (100)	3 (50)	34 (54.8)
Headache	6 (33.3)	0	0	0	0	2 (33.3)	1 (16.7)	0	0	4 (50)	1 (16.7)	8 (12.9)
Somnolence	3 (16.7)	0	0	2 (33.3)	1 (16.7)	0	2 (33.3)	2 (33.3)	1 (16.7)	1 (12.5)	0	9 (14.5)

MAD, Part 1 study							
	Pbo	JNJ-61393215				Active Total	Total
		5 mg	15 mg	45 mg	90 mg		
Total	**8**	**6**	**6**	**6**	**6**	**24**	**32**
Any TEAE, n (%)	6 (75)	6 (100)	3 (50)	6 (100)	5 (83.3)	20 (83.3)	26 (81.3)
Headache	3 (37.5)	2 (33.3)	1 (16.7)	2 (33.3)	3 (50)	8 (33.3)	11 (34.4)
Somnolence	3 (37.5)	1 (16.7)	1 (16.7)	3 (50)	2 (33.3)	7 (29.2)	10 (31.3)
Dysgeusia	2 (25)	2 (33.3)	0	1 (16.7)	0	3 (12.5)	5 (15.6)

MAD, multiple-ascending dose; Pbo, placebo; SAD, single-ascending dose; TEAE, treatment-emergent adverse events.

CONCLUSIONS

- In this first-in-human study, the safety profile of OX1R antagonist JNJ-61393215 was acceptable; the majority of TEAEs were mild in severity and their frequency was comparable to placebo.
- After administration of a single dose of JNJ-61393215, peak exposure and total exposure increased in a dose-proportional manner up to 30 mg.
- JNJ-61393215 was found to be a low-clearance drug and the CSF levels confirmed central penetration. Food reduced the bioavailability of JNJ-61393215.
- JNJ-61393215 did not produce any PD effects as a single dose up to 90 mg in healthy male subjects, consistent with preclinical data that show no detectable PD or behavioral effects in naïve/unchallenged animals.
- These results support the evaluation of JNJ-61393215 efficacy in future clinical studies as a potential treatment option for patients with mood and anxiety disorders.

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