Poster No. W52

The selective Orexin-1 receptor inhibitor JNJ-61393215 decreases subjective anxiety evoked by CO_2 inhalation in healthy subjects

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ABSTRACT

Background: JNJ-61393215 is a novel, selective, high affinity/potent orexin-1 receptor (OX1R) antagonist and is a potential first in class therapy for the treatment of panic, anxiety, mood disorders and substance abuse. OX1R inhibitors show anxiolytic effects in several preclinical behavioral paradigms, including fear conditioning, fear potentiated startle, lactate infusion, hypercapnia, and yohimbine challenge. Activation of the OX1R is a critical component of CO_2-mediated anxiety. JNJ-61393215 blocked CO_2-induced anxiety behavior in the social interaction test at 10 and 30 mg/kg (p.o.) in a rat model of CO_2-induced panic.

Inhalation of CO_2 induces anxiety symptoms and panic attacks in subjects with anxiety disorders as well as healthy subjects, and benzodiazepines are able to attenuate those symptoms. In the current study, the anxiolytic effects of JNJ-61393215 were investigated in humans using an experimental medicine model of CO_2 inhalation, which is associated with symptoms of panic/anxiety in healthy volunteers and is known to be sensitive to the anxiolytic effects of marketed anxiolytics (Leibold et al., 2016).

Methods: To investigate the potential anxiolytic effects of JNJ-61393215 in humans, 39 healthy male subjects sensitive to the anxiogenic effects of 35% CO_2 inhalation at screening were randomized to receive JNJ-61393215 25mg (extrapolated peak receptor occupancy: 93%), JNJ-613932159 0mg (extrapolated peak receptor occupancy: 98.5%), alprazolam 1mg bid or placebo for 7 days. The study used an incomplete cross-over design and each subject was randomized to receive either placebo or one of the three active treatments. Subjects underwent a 35% CO_2 inhalation challenge after 6 days of dosing with the study drug in each cross-over period and the anxiety symptoms induced by the CO_2 challenge were measured using the Panic Symptom List (PSL-IV). The CO_2 challenge was performed 2.5 hours after the administration of the study drug (Tmax median: 1.5h; range: 1-3h); alprazolam was used as active comparator to establish assay sensitivity, to compare the magnitude of changes in the PSL-IV induced by JNJ 61393215 or alprazolam versus placebo.

Results: JNJ-61393215 90mg induced a statistically significant reduction of anxiety symptoms induced by inhalation of 35% CO_2 in healthy volunteers according to the primary outcome measure PSL-IV (difference of LS Means: -2.3; p<0.02); a significant anxiolytic effect was also demonstrated for a therapeutic dose of alprazolam (difference of LS Means: -3.4; p<0.03). The anxiolytic effect of JNJ-61393215 was present in most subjects and was driven by a reduction in severity of 9/13 items of the PSL-IV, suggesting a broad anxiolytic effect. The low dose of JNJ-61393215 caused a numerical, statistically non-significant decrease in anxiety symptoms.

Conclusions: JNJ-61393215 90mg showed a statistically significant effect on the PSL-IV total score compared to placebo; a significant anxiolytic effect was also demonstrated for alprazolam at a therapeutic dose. This study demonstrates for the first time in humans the anxiolytic effects of a selective orexin-1 receptor antagonist and provides supporting rationale to test the efficacy of JNJ-61393215 in a patient population.

INTRODUCTION/OBJECTIVE

- JNJ-61393215 is a first-in-class orexin-1 receptor selective antagonist in development for the treatment of mood and anxiety disorders.
- Data from the first-in-human single ascending dose study EDI1001 and from the multiple ascending dose study EDI1002 showed that the compound was safe and well-tolerated at doses up to 90 mg QD in healthy volunteers.
- JNJ-61393515 did not demonstrate CNS effects in healthy volunteers under non-anxious conditions under both single and multiple ascending doses in study EDI1002.
- Activation of the OX1R is a critical component of CO_2-mediated anxiety. JNJ-61393215 blocked CO_2-induced anxiety behavior in the social interaction test at 10 and 30 mg/kg (p.o.) in a rat model of CO_2-induced panic (Bonaventure et al., 2017).
- In the current study, the anxiolytic effects of JNJ-61393215 were investigated in humans using an experimental medicine model of CO_2 inhalation, which is associated with symptoms of panic/anxiety in healthy volunteers and is known to be sensitive to the anxiolytic effects of marketed anxiolytics (Leibold et al., 2016).

MATERIALS/METHODS

- This study was a randomized, placebo and active comparator-controlled, four-treatment three-arm 2x2 cross-over part in healthy male subjects. A double-dummy design was used (Table 1).
- Each group of subjects received different study drugs: either JNJ-61393215 25 mg (receptor occupancy [RO] at Cmax: 93%), JNJ-61393215 90 mg (RO at Cmax: 98.5%), alprazolam or placebo.
- Subjects treated for 7 days; 35% CO_2 double inhalation challenge performed after 6 days of dosing 2.5 hours after the administration of the study drug (Tmax median: 1.5h; range: 1-3h).
- Subjects sensitive to 35% CO_2 challenge performed at screening according to standard prespecified criteria (Poma et al., 2014).

Table 1. Study Design

N	Treatment Sequence	Period1	Period 2
6	AC	A	C
6	CA	C	A
6	BC	B	C
6	CB	C	B
6	DC	D	C
6	CD	C	D

A: 25 mg q.d. oral suspension formulation JNJ-61393215 and alprazolam matching placebo b.i.d.
B: 90 mg q.d. oral suspension formulation JNJ-61393215 and alprazolam matching placebo b.i.d.
C: JNJ-61393215 matching placebo q.d. and alprazolam matching placebo b.i.d.
D: 1 mg b.i.d. alprazolam and JNJ-61393215 matching placebo q.d.
b.i.d=twice daily; q.d=once daily

- Panic Symptom List-IV (PSL-IV), a self-reported scale which captures symptoms of panic/anxiety, was used as the primary outcome measure.
- Secondary analyses investigated the effects of JNJ-61393215 on physiological parameters changes (i.e., heart rate and blood pressure) during the 35% CO_2 challenge.

ANALYSIS

Primary Objective

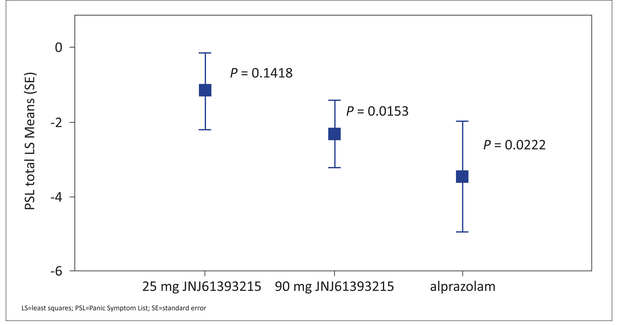
- To investigate if JNJ-61393215 decreases subjective fear and anxiety symptoms elicited by a 35% CO_2 double breath inhalation challenge.

- Within each arm active treatment (alprazolam or JNJ-61393215) was compared to matched placebo by using a linear mixed effects model, controlling for treatment, period and sequence as a fixed effect, subject as a random effect and baseline score as a covariate (if applicable).
- Significance was set with a one-sided p-value <0.10 based on the mixed model with a decrease expected in the active treatment as compared with placebo.

RESULTS

- JNJ-61393215 90 mg induced a statistically significant reduction of panic symptoms induced by inhalation of 35% CO_2 in healthy volunteers according to the primary outcome measure, PSL-IV (difference of LS Means: -2.3; p <0.02).

Figure 1. Anxiety symptoms induced by the 35% CO_2 challenge: LS Means differences between active treatments and placebo



LS=least squares; PSL=Panic Symptom List; SE=standard error

- The positive control alprazolam also showed a statistically significant decrease in panic symptoms compared to placebo; because of the parallel design, a direct comparison of the efficacy of JNJ-61393215 and alprazolam should be done with caution.
- The low dose of JNJ-61393215 caused a numerical, statistically non-significant decrease in panic symptoms.
- The anxiolytic effect of JNJ-61393215 was driven by a numeric reduction of 9/13 items of the PSL-IV (highlighted in Table 2), suggesting a broad anxiolytic effect.

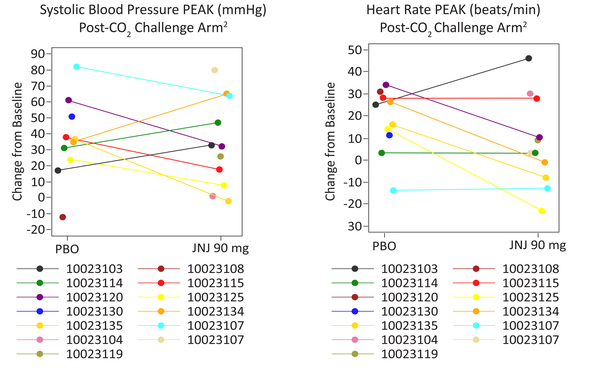
Table 2. Individual PSL-IV anxiety items scores in each treatment group

	PBO	JNJ-61393215 25 mg	PBO	JNJ-61393215 90 mg	PBO	ALPRAZOLAM 1mg
Dizziness	1.9	1.3	2.3	**1.8**	2.1	1.7
Choking/Gasping for breath	1.8	1.9	2.5	**1.8**	2.1	1.9
Hot flashes/Cold shiver	0.3	0.3	0.9	**0.5**	0.8	0.2
Nausea	0.4	0.2	0.7	**0.5**	0.8	0.2
Palipitations	1.9	1.3	1.8	1.8	1.9	1.3
Sweating	0.7	0.8	1.3	**0.9**	1.3	1.0
Shortness of breath	1.6	1.8	2.3	**2.1**	2.2	1.9
Numb/tingling	0.8	0.7	1.5	**1.2**	0.9	0.7
Depersonalization/ derealization	0.5	0.6	1.2	1.2	1.1	0.8
Fear of dying	0.1	0.1	0.3	0.4	0.3	0.1
Fear of losing contract	0.3	0.3	0.4	0.4	0.3	0.4
Chest pain discomfort	0.3	0.2	0.8	**0.7**	0.1	0
Trembling/shaking	1.3	1.3	1.6	**1.4**	1.1	1.2

PBO=placebo; PSL=Panic Symptom List

- Physiological parameters did not show significant effects for any of the active treatments compared to placebo, consistent with previous literature showing no relationship between emotional and cardiovascular response to panicogenic exposure.
- This analysis had two main limitations: the variability of physiological parameters was large and 4 subjects had missing data because of technical issues.

Figure 2. Change from baseline in systolic blood pressure and heart rate peak following the 35% CO_2 challenge



JNJ=JNJ-61393215; PBO=placebo

CONCLUSIONS

- JNJ-61393215 (at 90 mg) showed a statistically significant effect on the PSL-IV total score compared to placebo.
- A significant anxiolytic effect was also demonstrated for alprazolam at a therapeutic dose.
- The anxiolytic effect of JNJ-61393215 was present in most subjects and was driven by a reduction in severity of 9/13 items of the PSL-IV.
- JNJ-61393215 at 25 mg did not show any significant effect on anxiety symptoms.
- This study demonstrates for the first time in humans the anxiolytic effects of a selective orexin-1 receptor antagonist in an experimental panic paradigm and provides supporting rationale to test the efficacy of JNJ-61393215 in a patient population.
- A proof of concept study in subjects with major depressive disorder and anxious distress is currently in preparation.

References:
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Disclosures:
Giacomo Salvadore, Cathy Bleys, Kanaka Tatikola, Bart Remmerie, John Moyer, Abigail Nash, Luc Van Nueten and Wayne Drevets are employees and shareholders of Johnson & Johnson, LLC. Sander Brooks and Gabriel Jacobs are employees of the Center for Human Drug Research, Leiden, NL

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