The selective Orexin-1 receptor inhibitor JNJ-61393215 decreases subjective anxiety evoked by CO2 in healthy subjects

Giacomo Salvadore1, Sander Brooks2, Cathy Bleys3, Kanaka Tatikola4, Bart Remmerie4, Gabriel Jacobs2, John Moyer5, Abigail Nash5, Luc GM Van Nueten4, Wayne C Drevets4

INTRODUCTION/OBJECTIVE

JNJ-61393215 is a first-in-class orexin-1 receptor antagonist in development for the treatment of major mood and anxiety disorders. Data from the preclinical single-dose screening study EDI1001 and from the first ascending dose study EDI1002 showed that the compound was safe and well-tolerated at doses up to 90 mg (p.o.) in a rat model of CO2 anxiety at screening were randomized to receive JNJ-61393215 25mg (metoprolol tartrate peak receptor occupancy: 95%), JNJ-61393215 90mg (metoprolol tartrate peak receptor occupancy: 56%), alprazolam, or placebo for 7 days. The study used an inline crossed-over design and each subject was randomized to receive either placebo or one of the three active treatments. Subjects underwent a 50% CO2 inhalation challenge after 6 days of dosing with the drug in each cross-over period and the anxiety symptoms induced by the CO2 challenge were measured using the Panic Likelihood Scale (PLS-IV). The CO2 challenge was performed 2.5 hours after the administration of the study drug (median: 1.6h range: 1-4h). Alprazolam was used as active comparator to establish assay sensitivity, to compare the magnitude of changes in the PLS-IV induced by JNJ-61393215 or alprazolam versus placebo.

RESULTS

• JNJ-61393215 90mg induced a statistically significant reduction of anxiety symptoms induced by exposure to 35% CO2, 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 trend to a significant decrease in panic symptoms compared to placebo; a significant anxiolytic effect was also demonstrated for alprazolam at a therapeutic dose of alprazolam (difference of LS Means: -3.4; p<0.03). The anxiolytic effect of JNJ-61393215 was investigated in humans using an experimental medicine-model of CO2 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 (Lebold et al., 2016). This analysis had two main limitations: the variability of physiological parameters was large and 4 subjects did not complete the study.

MATERIALS/METHODS

• This study was a randomized, placebo and active comparator controlled, four treatment three 24-hour cross-over in part 1 study subjects. A double-blind dummy placebo was used (Table 1).
• Each group of subjects received different study drugs: either JNJ-61393215 25 mg (metoprolol tartrate occupancy (RC) at 66%, 90mg (metoprolol tartrate occupancy (RC) at 56%), or placebo. Subjects treated for 7 days; 35% CO2 double inhalation challenge performed after 6 days of dosing. The PLS-IV was administered 2.5 hours after the administration of the study drug (median: 1.3h range: 1-3h).
• Subjects sensitive to 35% CO2 challenge performed according to standard specified criteria (Forma et al., 2014.).

Table 1. Study Design

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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0.4</td>
<td>0.2</td>
<td>0.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Breathing</td>
<td>1.6</td>
<td>1.8</td>
<td>2.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Palpitation</td>
<td>0.9</td>
<td>0.3</td>
<td>0.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Somatic symptoms</td>
<td>1.4</td>
<td>1.1</td>
<td>2.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Deathwish</td>
<td>0.7</td>
<td>0.5</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Numb/tingling</td>
<td>0.7</td>
<td>0.7</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Chest pain/discomfort</td>
<td>0.7</td>
<td>0.7</td>
<td>1.2</td>
<td>1.3</td>
</tr>
</tbody>
</table>
| 1 Receptor Antagonist in Two Rat Models of Panic Attack

• 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.

CONCLUSIONS

• JNJ-61393215 90mg (p.o.) 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 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 trend to a significant decrease in panic symptoms compared to placebo; a significant anxiolytic effect was also demonstrated for alprazolam at a therapeutic dose.
• The anxiolytic effect of JNJ-61393215 was driven by a statistically significant reduction of panic symptoms induced by inhalation of 35% CO2 in healthy volunteers according to the primary outcome measure PSL-IV (Wilcoxon Signed Rank test: p<0.02).
• The anxiolytic effect of JNJ-61393215 90mg (extrapolated peak receptor occupancy: 98.5%), alprazolam 1mg bid or placebo was also demonstrated for the primary outcome measure PSL-IV (Wilcoxon Signed Rank test: p<0.02).
• Activation of the OX1R is a critical component of CO2-induced anxiety.
• To investigate the potential anxiolytic effects of JNJ-61393215 in humans, 39 healthy male subjects sensitive to the anxiolytic effects of 35% CO2 inhalation at screening were randomized to receive JNJ-61393215 25mg (metoprolol tartrate peak receptor occupancy: 95%), JNJ-61393215 90mg (metoprolol tartrate peak receptor occupancy: 56%), alprazolam, or placebo for 7 days. The study used an inline crossed-over design and each subject was randomized to receive either placebo or one of the three active treatments. Subjects underwent a 50% CO2 inhalation challenge after 6 days of dosing with the drug in each cross-over period and the anxiety symptoms induced by the CO2 challenge were measured using the Panic Likelihood Scale (PLS-IV). The CO2 challenge was performed 2.5 hours after the administration of the study drug (median: 1.5h range: 1-3h); alprazolam was used as active comparator to establish assay sensitivity, to compare the magnitude of changes in the PLS-IV induced by JNJ-61393215 or alprazolam versus placebo.
• JNJ-61393215 90mg induced a statistically significant reduction of anxiety symptoms induced by inhalation of 35% CO2, compared to placebo; because of the parallel design, a direct comparison of the efficacy of JNJ-61393215 and alprazolam should be done with caution.
• JNJ-61393215 blocked CO2 induced anxiety symptoms and panic attacks in subjects with anxiety disorders as well as healthy volunteers, and JNJ-61393215 anxiolytic also attenuated these symptoms. In this current study, the anxiolytic effects of JNJ-61393215 were investigated in humans using an experimental medicine-model of CO2 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 (Lebold et al., 2016). This analysis had two main limitations: the variability of physiological parameters was large and 4 subjects did not complete the study.
• 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.

This analysis had two main limitations: the variability of physiological parameters was large and 4 subjects did not complete the study.

PREPRINTED AT ACP 2019 Meeting, May 20-21, 2019; Scottsdale, Arizona

This study was supported by funding from Janssen Research & Development LLC, Titusville, NJ, USA

REFERENCES

Lebold et al., 2016. CO2 Receptor Antagonist in Two Rat Models of Panic Attack and provides supporting rationale to test the efficacy of JNJ-61393215 in a patient population. 2 Receptor Antagonist in Two Rat Models of Panic Attack and provides supporting rationale to test the efficacy of JNJ-61393215 in a patient population.