The orexin-2 antagonist JNJ-42847922(MIN-202) improves sleep in patients with major depressive disorder suffering from comorbid insomnia

S. Brooks[1], J. Kent[2], G.E. Jacobs[1], G. van Amerongen[1], R. Zuiker[1], I. Kezic[3], R. Luthringer[4], P. van der Ark[5], J. van Gerven[1], P. de Boer[5].

[1]Centre for Human Drug Research, Clinical Pharmacology, Leiden, The Netherlands, [2]Janssen Research and Development, Neuroscience Development, Titusville NJ, USA, [3]Janssen Research and Development, Quantitative Sciences, Beerse, Belgium, [4]Minerva Neurosciences, Waltham MA, USA. [5]Janssen Research and Development, Neuroscience Development, Beerse, Belgium.

INTRODUCTION

Insomnia is a common symptom in patients suffering from major depressive disorder (MDD)[1]. It is estimated that up to 70% of MDD patients experience difficulties falling and/or staying asleep, early morning insomnia and/or non-restorative sleep during a depressive episode. Although antidepressant drugs (ADs) can improve mood, a proportion of MDD patients still experience insomnia. Also, some ADs may increase sleep problems by impacting sleep architecture negatively[2].

AIM

To investigate the effect of the selective orexin-2 receptor (ORX2R) antagonist JNJ-42847922 (JNJ) on sleep and to explore its possible benefits in treating mood in patients with MDD. A secondary aim was to evaluate the pharmacokinetics of JNJ-42847922.

METHODS

This single dose, double-blind, placebo-controlled study evaluated 20 patients (18-64 years inclusive) with mild to moderate MDD (Diagnostic and Statistical Manual of Mental Disorders version IV, Hamilton Rating Scale for Depression [HAM-D] ≤ 21) and insomnia (latency to sleep *onset* > 20 min, total sleep time < 6.5h) who were stably treated with SSRI or SNRI for at least 30 days. All were treated with 10, 20 , 40 mg JNJ or placebo in a 4-way crossover design with 7 days washout between doses. Latency to persistent sleep (LPS), total sleep time (TST) and sleep efficiency were measured with polysomnography (PSG). The PSG night started 1 hour before the normal sleep time of the subjects. Subjective changes in mood were assessed with the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR_{14}). Safety parameters included vital signs and ECG. Suicidal ideation was determined with the Columbia Suicide Severity Rating Scale.

Pharmacokinetic parameters that were included in the analysis were mean maximal plasma concentration (C_{max}) and area under the curve (AUC).

Treatment	QIDS-SR_{14} (CFB)
Placebo	-0.7
10 mg	-1.4
20 mg	-1.3
40 mg	-2.1

Table1: Mean total QIDS-SR14 change from baseline between Day 1 and Day 2.

RESULTS

- Baseline characteristics: twenty subjects randomized, 60% female, median age [range] 43.0 years [20-62], mean HAM-D (SD) [range] 9.4 (3.68) [4-14].
- For all the dose groups compared to placebo:
  - Mean LPS was significantly* shorter for all dose groups compared to placebo: (figure 1, closed symbols).
  - Mean TST was significantly* longer (figure 1, open symbols).
  - Mean sleep efficiency was significantly† improved.
- Mean QIDS-SR_{14} demonstrated a trend to mood-improvement for the 40 mg group between day 1 and day 2 (table 1). These changes were not limited to sleep-related symptoms only.
- No clinically relevant changes in safety parameters were observed.
- The mean C_{max} and AUC of JNJ-42847922 appeared to increase dose-proportionally.

*** one-sided p-value <0.01 † one sided p-value <0.05**

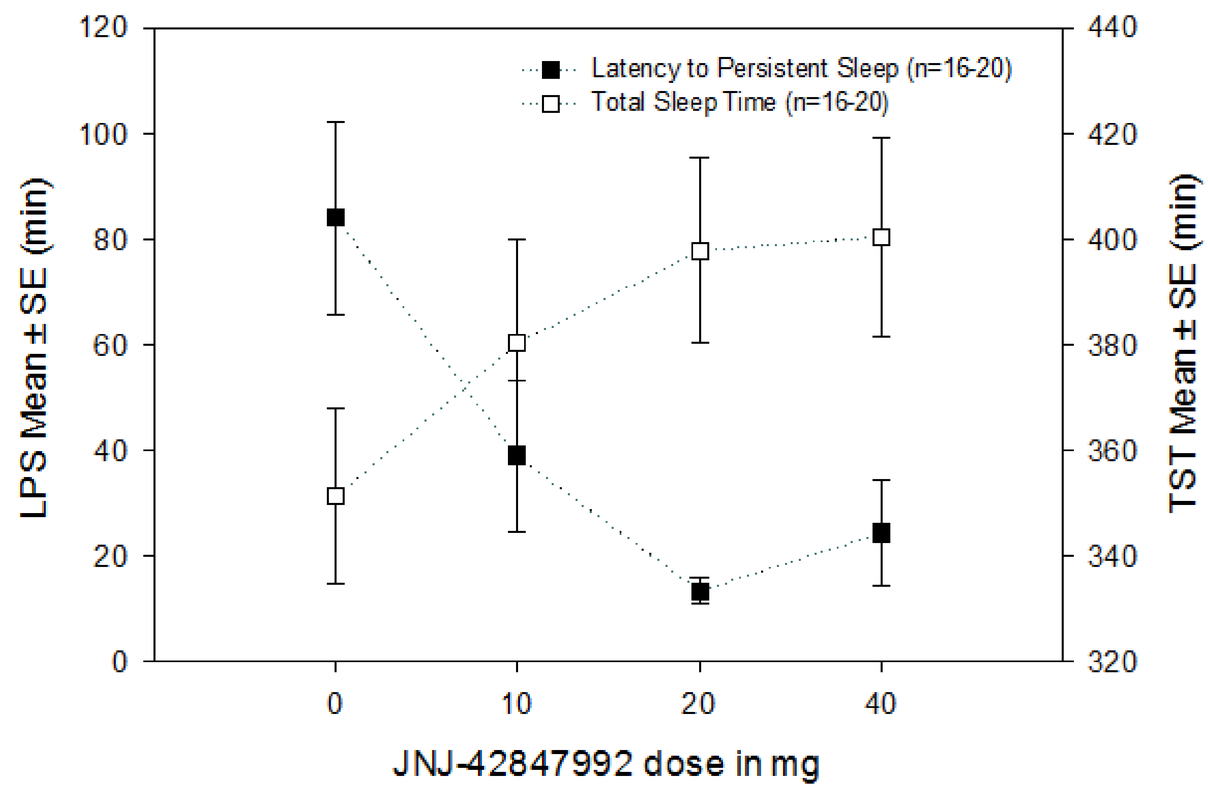

Figure 1: Mean latency to persistent sleep (left Y-axis, closed symbols) and total sleep time (right Y-axis, open symbols) ± SE by different treatments.

CONCLUSIONS

In comparison to placebo the selective ORX2R antagonist JNJ-42847922 resulted in:

- a statistically significant, dose-dependent decrease in LPS.
- a statistically significant increase in TST and SE.
- a tendency toward subjectively improved mood.

1. Fava M., 2004. Daytime sleepiness and insomnia as correlates of depression. J Clin Psychiatry 65 Suppl 1, 27-32.
2. Mayers A.G., Baldwin D.S., 2005. Antidepressants and their effect on sleep. Human psychopharmacology 20, 533-559.