JNJ-42847922/MIN-202, a selective orexin 2 receptor antagonist, demonstrates beneficial effects on mood and sleep in patients with major depressive disorder

K. Recourt[1], G. van Amerongen[1], G. Jacobs[1], R. Zuiker[1], R. Luthringer[2], P. van der Ark[3], J. van Gerven[1].

1Centre for Human Drug Research, CNS, Leiden, The Netherlands. 2Minerva Neurosciences, -, Waltham, USA. 3Janssen Pharmaceutica N.V, Janssen Research and Development, Beerse, Belgium.

INTRODUCTION

Orexins promote wakefulness and are hypothesized to play a role in excessive psychological and/or somatic arousal in patients with major depressive disorder (MDD). JNJ-42847922/MIN-202 (JNJ) is a selective antagonist of the human orexin-2 receptor (OX2R) that may normalize excessive arousal and might therefore attenuate depressive symptoms.

AIM

To investigate the safety and tolerability of JNJ in patients with MDD and to explore its effects on sleep and symptoms of depression.

METHODS

47 men and women (age 18-63 years inclusive) with a diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) and a total Inventory of Depressive Symptomatology (IDS-C30) score of ≥30 at screening were included in a double-blind, diphenhydramine- and placebo-controlled multicenter study. The population was mixed with respect to the presence of insomnia disorders at baseline with latency to persistent sleep values as low as 4.5 minutes. Patients were either antidepressant-naive or treated with a maximum of two concurrent monoaminergic antidepressants. Patients were randomized to receive either diphenhydramine 25mg q.d. (N=13), JNJ 20mg q.d (N=22) or placebo (N=12) for 10 nights.

In order to monitor effects on sleep polysomnography (PSG) was performed. The structured interview guide for the 17-item Hamilton depression rating scale (HAMD-17) was administered to monitor MDD symptoms. To explore JNJ's mood effects independently from effects on sleep, the HAMD-17 was adjusted for its sleep items and a mean score for the six core symptoms of depression derived from the Cleary and Guy's factor analysis of the HDRS17 was calculated (HAMD-6). To investigate the safety and tolerability of JNJ, vital signs, suicidal ideation using the Columbia Suicide Severity Rating Scale (C-SSRS) and adverse events (AE's) were monitored.

Financial disclosure: this research was funded by Janssen Research & Development

RESULTS

- Mean change from baseline in minutes (standard error of the mean) as measured objectively by PSG for total sleep time and wake after sleep onset were 20.7(18.6), 26.6(12.0), 33.9(12.8) and -14.4(13.4), -18.1(8.2), -36.2(8.5) for placebo, JNJ and diphendydramine respectively.
- Compared to placebo and diphenhydramine, JNJ decreased the mean total HAMD-17, the mean adjusted HAMD-17 and the mean HAMD-6 scores compared to baseline (Table 1).
- Treatment with JNJ was associated with mild, self-limiting symptoms of which headache, dizziness, somnolence, abdominal discomfort, diarrhea, nausea, nightmare, insomnia, nasopharyngitis and fatigue were most common.

Table 1.: Summary of HAMD-17 Total Scores and Subscale Scores: Means and Mean Changes from Baseline on Day 11;

	Placebo	JNJ 20 mg	Diphenhydramine 25 mg
	N=12	N=22	N=13
HAMD-17 Total Score			
Baseline	18.7 (5.71)	18.7 (4.65)	20.0 (5.12)
Day 11 Change from baseline	-3.6 (4.03)	-5.5 (3.86)	-4.1 (3.66)
Effect Size JNJ vs Placebo		-0.48	
HAMD-17 Adjusted Total Score			
Baseline	13.7 (4.98)	14.4 (3.36)	15.1 (4.41)
Day 11 Change from baseline	-2.3 (3.03)	-4.5 (2.76)*	-2.3 (2.81)
Effect Size JNJ vs Placebo		-0.55	
HAMD-6 Score			
Baseline	9.0 (3.57)	10.4 (2.09)	10.6 (3.31)
Day 11 Change from baseline	-1.5 (2.15)	-3.8 (2.22)**	-1.8 (2.01)
Effect Size JNJ vs Placebo		-1.05	

* = $p < 0.05$, ** = $p < 0.01$, test for no difference between JNJ42847922 and placebo from post hoc ANCOVA model on change from baseline with treatment and sex as factors and baseline score as covariate.
Results shown are mean (SD)
Cohen's D effect size for JNJ versus placebo on Day 11 Change from baseline

CONCLUSIONS

JNJ was safe and demonstrated beneficial effects on both sleep and mood in a sample of patients with mild to moderate MDD. Mood improving effects seemed to occur independently from effects on sleep, suggesting that JNJ may display mood improving effects in itself.