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A Phase 3, Randomized, Placebo-Controlled, Double-Blind, Multicenter, 12-Week Study of the Safety and Efficacy of JZP-110 in the Treatment of Excessive Sleepiness in Patients With Obstructive Sleep Apnea: SF-36 and EQ-5D-5L Measures

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Heike Benes, MD[1,2]; Stephen G. Thein, PhD[3]; James M. Andry Sr., MD[4]; John D. Hudson, MD[5]; Kathleen F. Villa, MS[6]; Dan Chen, MD[6]; Lawrence P. Carter, PhD[6,7]; Hao Wang, PhD[6]; Yuan Lu, MS[6]; Jed Black, MD[6,8]; James Maynard, MD[9]

[1]Medical Center University of Rostock, Rostock, Germany; [2]Somni Bene Institute for Medical Research and Sleep Medicine, Schwerin, Germany; [3]Pacific Research Network, San Diego, CA, USA; [4]Sleep Therapy & Research Center, San Antonio, TX, USA; [5]Future Search Trials of Neurology, Austin, TX, USA; [6]Jazz Pharmaceuticals, Palo Alto, CA, USA; [7]University of Arkansas for Medical Sciences, Little Rock, AR, USA; [8]Stanford University Sleep Medicine Center, Redwood City, CA, USA; [9]CTI Clinical Research Center, Cincinnati, OH, USA

Background

- Excessive sleepiness (ES) is a frequent symptom of obstructive sleep apnea (OSA) that persists in 13%–65% of patients who are utilizing continuous positive airway pressure[1-3]
- ES adversely impacts specific domains of health-related quality-of-life (HRQoL) in patients with OSA
  - Studies using the 36-item Short Form Health Survey (SF-36) have shown that Vitality and Role Physical domains were particularly affected[4-7]
- JZP-110 is a selective dopamine norepinephrine reuptake inhibitor with wake-promoting effects that is being evaluated for the treatment of ES in patients with OSA, narcolepsy, and Parkinson's disease
  - The primary efficacy analyses from this phase 3 clinical trial are presented in APSS **Poster #349**[8]

Objectives

- Evaluate the effects of JZP-110 on patient-reported HRQoL in adult patients with OSA and ES using the SF-36 version 2 (SF-36 v2)[9] and the 5-dimension, 5-level EuroQol (EQ-5D-5L)[10]

Methods

DESIGN

- This was a 12-week, double-blind, placebo-controlled, parallel-design study with the co-primary endpoints described in detail in APSS **Poster #349**[8]
- Patients were randomized (1:1:2:2:2) to JZP-110 37.5 mg, 75 mg, 150 mg, or 300 mg, or placebo for 12 weeks, and were stratified by adherence or nonadherence with primary OSA therapy

ENDPOINTS

- Two pre-specified endpoints are described:
  - The SF-36 v2 consists of 2 summary scales (Physical Component Summary and Mental Component Summary) and 8 specific health status domains (Physical Function, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, Mental Health)[9]
  - The EQ-5D-5L consists of 5 questions/dimensions (Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression) that have 5 response levels each (no problems, slight problems, moderate problems, severe problems, and extreme problems/unable to do) that are used to derive an overall EQ-5D-5L index score (0=death, 1=perfect health), and a health status visual analog scale (VAS) that is anchored at 0 with "the worst health you can imagine" and at 100 with "the best health you can imagine"[10]

ANALYSES

- Efficacy analyses were based on the modified intent-to-treat (mITT) population; there was no multiplicity adjustment for the SF-36 v2 or EQ-5D-5L
- SF-36 v2 scores were scaled from 0 to 100 (higher scores on all scales represent better health), transformed to norm-based scores using US general-population data from SF-36 Manuals,[9] and were analyzed using a mixed-effect model with repeated measures (MMRM); and baseline value of the efficacy endpoint was used to determine differences in changes from baseline
- EQ-5D-5L VAS and index-score data were analyzed using an MMRM model
- Safety and tolerability were assessed based on treatment-emergent adverse events (TEAEs), vital signs, electrocardiogram test, physical exams, and laboratory tests

Results

Table 1. Baseline Demographic and Clinical Characteristics of the Safety Population

Variable	Placebo (n=119)	JZP-110 37.5 mg (n=58)	JZP-110 75 mg (n=62)	JZP-110 150 mg (n=117)	JZP-110 300 mg (n=118)
Baseline Demographics					
Age, years, mean (SD)	54.1 (11.4)	57.1 (10.2)	54.4 (11.5)	52.7 (10.6)	53.2 (10.6)
Sex, n (%)					
Male	77 (64.7)	39 (67.2)	35 (56.5)	72 (61.5)	74 (62.7)
Female	42 (35.3)	19 (32.8)	27 (43.5)	45 (38.5)	44 (37.3)
Race, n (%)					
Asian	4 (3.4)	3 (5.2)	1 (1.6)	3 (2.6)	6 (5.1)
Black or African American	26 (21.8)	10 (17.2)	14 (22.6)	18 (15.4)	21 (17.8)
White	87 (73.1)	45 (77.6)	46 (74.2)	93 (79.5)	90 (76.3)
Other	2 (1.6)	0	1 (1.6)	3 (2.6)	1 (0.8)
BMI, kg/m², mean (SD)	33.1 (5.2)	34.1 (5.3)	33.4 (5.7)	33.3 (4.8)	32.9 (5.6)
Baseline Clinical Characteristics					
MWT sleep latency, minutes, mean (SD)	12.4 (7.2)	13.6 (8.1)	13.1 (7.2)	12.5 (7.2)	12.0 (7.3)
ESS score, mean (SD)	15.6 (3.3)	15.1 (3.5)	14.8 (3.5)	15.1 (3.4)	15.2 (3.1)
Baseline CGI-S, n (%)					
1=Normal, not at all ill	0	0	0	0	0
2=Borderline ill	3 (2.5)	1 (1.7)	1 (1.6)	2 (1.7)	1 (0.8)
3=Mildly ill	8 (6.7)	5 (8.6)	4 (6.5)	7 (6.0)	10 (8.5)
4=Moderately ill	48 (40.3)	28 (48.3)	31 (50.0)	53 (45.3)	44 (37.3)
5=Markedly ill	39 (32.8)	14 (24.1)	15 (24.2)	41 (35.0)	44 (37.3)
6=Severely ill	15 (12.6)	9 (15.5)	7 (11.3)	14 (12.0)	17 (14.4)
7=Among the most extremely ill	4 (3.4)	1 (1.7)	3 (4.8)	0	2 (1.7)
Missing	2 (1.7)	0	1 (1.6)	0	0
SF-36v2, mean (SD)[a]					
Physical Function	48.2 (8.0)	46.1 (8.6)	49.4 (7.8)	48.0 (8.0)	48.2 (8.3)
Role Physical	44.9 (9.7)	43.2 (9.8)	45.4 (10.1)	45.2 (9.2)	43.9 (10.2)
Bodily Pain	48.5 (8.9)	46.5 (10.3)	47.4 (8.8)	48.7 (9.6)	48.3 (9.7)
General Health	49.9 (9.6)	49.8 (8.4)	49.4 (9.2)	48.5 (9.1)	49.5 (8.8)
Vitality	45.2 (8.6)	44.9 (10.4)	45.3 (9.7)	45.3 (8.0)	44.3 (9.8)
Social Functioning	48.2 (9.4)	47.4 (9.0)	48.4 (9.2)	49.0 (8.8)	47.5 (10.1)
Role Emotional	50.7 (8.9)	46.9 (11.6)	48.4 (10.2)	48.9 (9.4)	50.1 (9.0)
Mental Health	51.8 (7.9)	53.1 (7.6)	52.2 (7.5)	51.9 (6.9)	51.9 (7.7)
Physical Component Summary	46.3 (7.8)	44.5 (8.4)	46.9 (8.8)	46.3 (8.5)	45.9 (8.9)
Mental Component Summary	50.7 (9.1)	50.3 (9.4)	49.8 (8.7)	50.3 (8.0)	50.3 (8.5)
EQ-5D-5L, mean (SD)[a]					
VAS	76.8 (15.8)	77.0 (16.4)	77.9 (13.1)	76.8 (14.8)[b]	76.8 (14.9)
Index score	0.85 (0.11)	0.83 (0.13)	0.84 (0.11)	0.84 (0.11)	0.84 (0.10)

[a]mITT population: Placebo, n=114; JZP-110 37.5 mg, n=56; 75 mg, n=58; 150 mg, n=116; 300 mg, n=115; [b]n=115.

BMI, body mass index; CGI-S, Clinical Global Impression of Severity[11]; ESS, Epworth Sleepiness Scale; EQ-5D-5L, 5-dimension, 5-level EuroQoL; mITT, modified intent-to-treat; MWT, Maintenance of Wakefulness Test; SF-36v2, 36-item Short Form Health Survey version 2; SD, standard deviation; VAS, visual analog scale.

- Baseline characteristics were similar among the treatment groups
- The safety population (n=474) was primarily male, white, mid-50 years old, and had a BMI >30 kg/m² (**Table 1**)
  - Patients had ES at baseline (**Table 1**; MWT and ESS)
  - The majority of patients were rated by the clinicians as being moderately or markedly ill
- The mITT population consisted of 459 patients, of whom 404 (88.0%) completed the study
  - The main reason for discontinuation was adverse events and no patients discontinued due to lack of efficacy

Table 2. Observed Values at Week 12 (mITT Population)

Endpoint	Placebo (n=114)	JZP-110 37.5 mg (n=56)	JZP-110 75 mg (n=58)	JZP-110 150 mg (n=116)	JZP-110 300 mg (n=115)
MWT sleep latency, min, mean (SD)[a,b]	13.4 (10.3)	18.6 (12.3)*	21.8 (11.3)†	23.6 (11.0)†	25.3 (11.3)†
ESS score, mean (SD)[c]	12.2 (4.5)	9.7 (5.3)*	10.0 (5.2)*	7.5 (4.7)†	7.1 (4.8)†
PGI-C, % improved[d]	49.1	55.4	72.4*	89.7†	88.7†

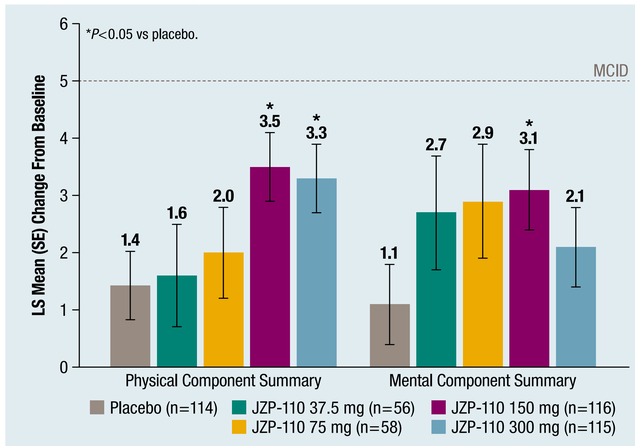
*P<0.05 and †P<0.0001 relative to placebo.

[a]On the first 4 trials of a 5-trial MWT; [b]Placebo, n=100; JZP-110 37.5 mg, n=49; JZP-110 75 mg, n=54; JZP-110 150 mg, n=105; JZP-110 300 mg, n=93. [c]Placebo, n=102; JZP-110 37.5 mg, n=49; JZP-110 75 mg, n=54; JZP-110 150 mg, n=106; JZP-110 300 mg, n=94. [d]Percentage of patients who reported "minimally improved," "much improved," or "very much improved."

ESS, Epworth Sleepiness Scale; mITT, modified intent-to-treat; MWT, Maintenance of Wakefulness Test; PGI-C, Patient Global Impression of Change; SD, standard deviation.

- Complete primary results are presented in an accompanying APSS **Poster #349**[8]
  - Coprimary endpoints (change from baseline to week 12 in MWT and ESS) were significantly different from placebo at all doses of JZP-110 (**Table 2**)
  - Key secondary endpoint, Patient Global Impression of Change, was significantly different from placebo at all doses of JZP-110 except for JZP-110 37.5 mg (**Table 2**)

Figure 1. Change From Baseline at Week 12 on the Physical and Mental Component Summary Scores of the SF-36v2

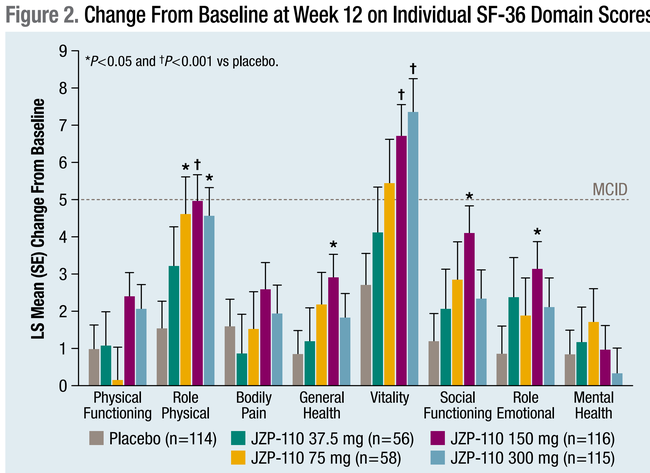


Values are for the modified intent-to-treat population (n=459). Dashed horizontal line represents the MCID for a change in SF-36v2 score.[12]

LS, least squares; MCID, minimal clinically important difference; SE, standard error; SF-36v2, 36-item Short Form Health Survey version 2.

- Dose-dependent increases in the Physical Component Summary Scale were statistically significant at JZP-110 150 and 300 mg (**Figure 1**)
- Mental Component Summary scores were similar among the JZP-110 37.5, 75, and 150 mg doses with only JZP-110 150 mg reaching statistical significance (**Figure 1**)
- The changes on the Physical Component Summary and Mental Component Summary did not exceed the minimal clinically important difference (MCID)

Figure 2. Change From Baseline at Week 12 on Individual SF-36 Domain Scores

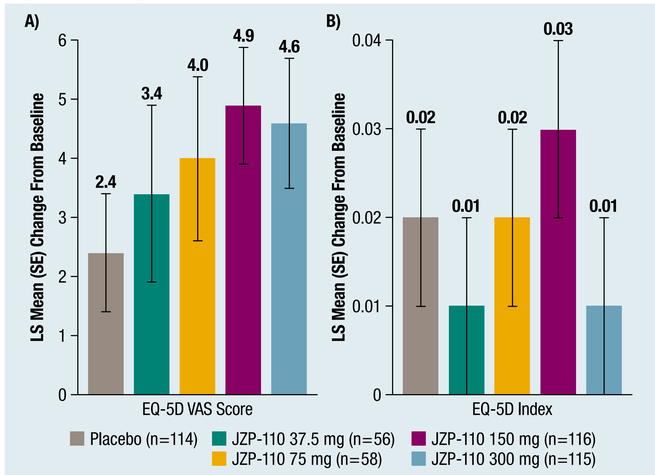


Values are for the modified intent-to-treat population (n=459). Dashed horizontal line represents the MCID for a change in SF-36 score.[12]

LS, least squares; MCID, minimal clinically important difference; SE, standard error; SF-36, 36-item Short Form Health Survey.

- Among the individual SF-36 domains, the largest effects of JZP-110 were observed on Vitality followed by Role Physical (**Figure 2**)
  - These 2 domains showed the greatest impairment at baseline as indicated by having the lowest scores across all treatment groups (**Table 1**)
- There was a dose-dependent response on the Vitality domain that exceeded the MCID at JZP-110 75, 150, and 300 mg (**Figure 2**), and was significantly greater than placebo at the 150 and 300 mg doses
- JZP-110 150 mg also resulted in significantly greater improvement (changes from baseline relative to placebo) on the Role Physical, General Health, Social Functioning, and Role Emotional domains (**Figure 2**)

Figure 3. Change From Baseline at Week 12 on EQ-5D-5L Scores



Values are for the modified intent-to-treat population (n=459).

EQ-5D-5L, 5-dimension, 5-level EuroQol; LS, least squares; SE, standard error; VAS, visual analog scale.

- Effects of JZP-110 on the EQ-5D VAS appeared to be dose dependent, but were not significantly different from placebo (**Figure 3A**)
- There were no significant effects on the EQ-5D-5L index value (**Figure 3B**)

Table 3. Incidence of TEAEs in the Safety Population

TEAE	Placebo (n=119)	JZP-110 37.5 mg (n=58)	JZP-110 75 mg (n=62)	JZP-110 150 mg (n=117)	JZP-110 300 mg (n=118)	JZP-110 All Doses (n=355)
	Incidence, n (%)					
Any TEAE	57 (47.9)	37 (63.8)	30 (48.4)	83 (70.9)	91 (77.1)	241 (67.9)
Serious TEAEs	2 (1.7)	2 (3.4)	0	1 (0.9)	0	3 (0.8)
Discontinuations due to TEAEs	4 (3.4)	3 (5.2)	2 (3.2)	5 (4.3)	15 (12.7)	25 (7.0)
Most common TEAEs[a]						
Headache	10 (8.4)	4 (6.9)	5 (8.1)	10 (8.5)	17 (14.4)	36 (10.1)
Nausea	7 (5.9)	3 (5.2)	3 (4.8)	10 (8.5)	12 (10.2)	28 (7.9)
Decreased appetite	1 (0.8)	1 (1.7)	3 (4.8)	9 (7.7)	14 (11.9)	27 (7.6)
Anxiety	0	1 (1.7)	2 (3.2)	6 (5.1)	16 (13.6)	25 (7.0)
Nasopharyngitis	8 (6.7)	2 (3.4)	1 (1.6)	7 (6.0)	8 (6.8)	18 (5.1)
Diarrhea	1 (0.8)	1 (1.7)	3 (4.8)	5 (4.3)	8 (6.8)	17 (4.8)
Dry mouth	2 (1.7)	1 (1.7)	1 (1.6)	5 (4.3)	9 (7.6)	16 (4.5)
Insomnia	2 (1.7)	1 (1.7)	0	3 (2.6)	11 (9.3)	15 (4.2)
Feeling jittery	0	3 (5.2)	3 (4.8)	1 (0.9)	7 (5.9)	14 (3.9)
Sinusitis	3 (2.5)	1 (1.7)	4 (6.5)	0	3 (2.5)	8 (2.3)
Irritability	0	3 (5.2)	0	4 (3.4)	1 (0.8)	8 (2.3)
Pruritus	0	3 (5.2)	0	1 (0.9)	0	4 (1.1)

[a]≥5% in any treatment group. TEAEs, treatment-emergent adverse events.

- The most common TEAEs (≥5%) were headache, nausea, decreased appetite, anxiety, and nasopharyngitis (combined JZP-110 doses; **Table 3**)
- The incidence of TEAEs and discontinuation due to TEAEs were generally dose dependent
- Seven serious TEAEs were reported in 5 patients: goiter (n=1) and motor vehicle accident, back pain, and sciatica (n=1) in placebo; bile duct obstruction (n=1), and streptococcal endocarditis (n=1) in JZP-110 37.5 mg; and hyperglycemia (n=1) in JZP-110 150 mg
  - There was 1 non–treatment-emergent serious adverse event of coronary artery disease, which began prior to the patient receiving JZP-110 300 mg

Conclusions

- JZP-110 met the co-primary MWT and ESS endpoints of reducing ES at all doses
- The most common TEAEs (≥5%) were headache, nausea, decreased appetite, anxiety, and nasopharyngitis, and were generally consistent with the safety profile of JZP-110 in phase 2 studies in narcolepsy
- Treatment with JZP-110 was associated with improvements in HRQoL as measured on the SF-36v2
  - JZP-110 150 mg had the greatest impact on the SF-36v2 subscales with statistically significant improvements on the Physical and Mental Component Summary Scales, and on the Role Physical, General Health, Vitality, Social Functioning, and Role Emotional domains
  - JZP-110 300 mg showed significantly greater improvements relative to placebo on Role Physical and Vitality domains and on the Physical Component Summary Scale
  - The MCID threshold was exceeded for the Vitality domain for JZP-110 75, 150, and 300 mg, but not for the other rating scales
- Baseline scores on the SF-36v2 and the EQ-5D-5L were close to population norms and did not indicate marked impairment at baseline even though these patients had substantial ES as indicated by their baseline MWT sleep latency times and ESS scores
- No significant changes were observed on the EQ-5D-5L index score or VAS

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Code is not for promotional purposes.

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