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Original Article

Effect of oral JZP-110 (ADX-N05) treatment on wakefulness and sleepiness in adults with narcolepsy

Richard K. Bogan [a,*], Neil Feldman [b], Helene A. Emsellem [c], Russell Rosenberg [d], Yuan Lu [e], Gary Bream [f], Moise Khayrallah [f], D. Alan Lankford [g]

[a] SleepMed, Columbia, SC, USA
[b] Clinical Research Group of St. Petersburg, St. Petersburg, FL, USA
[c] The Center for Sleep and Wake Disorders, Chevy Chase, MD, USA
[d] NeuroTrials Research, Atlanta, GA, USA
[e] Jazz Pharmaceuticals, Palo Alto, CA, USA
[f] Aerial BioPharma, LLC, Morrisville, NC, USA
[g] Sleep Disorders Center of Georgia, Atlanta, GA, USA

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ABSTRACT

Background: JZP-110 is a wake-promoting agent with dopaminergic and noradrenergic activity.
Methods: This double-blind, crossover study, randomized adults with narcolepsy with or without cataplexy ($N = 33$) to placebo or JZP-110 at 150 mg/day (weeks 1 and 3) increased to 300 mg/day (weeks 2 and 4). Patients had to have baseline Epworth Sleepiness Scale (ESS) scores ≥10 and mean sleep latencies ≤10 min on the Maintenance of Wakefulness Test (MWT). Efficacy end points included MWT sleep latency and ESS, and the percentage of patients improved on the Clinical Global Impression of Change.
Results: Patients were primarily male (57.6%) and white (69.7%), with a mean (standard deviation) age of 37.1 (12.4) years. At two weeks, the change in the mean MWT sleep latency was 11.8 min longer with JZP-110 than with placebo ($P = 0.0002$); JZP-110 resulted in greater changes in sleep latency on each MWT trial ($P < 0.001$). For ESS, JZP-110 was more efficacious relative to placebo after 1 ($P < 0.0001$) and two weeks ($P = 0.0002$); final ESS scores were 10.8 with JZP-110 and 15.2 with placebo, changes of –6.7 and –2.4, respectively. JZP-110 was generally well tolerated; the most common adverse events with JZP-110 were nausea (12%), noncardiac chest discomfort (9.1%), and headache (9.1%).
Conclusions: The efficacy of JZP-110 for impaired wakefulness and excessive sleepiness was observed at 150–300 mg/day and as early as one week after initiating treatment (Clinicaltrials.gov identifier NCT01485770).

1. Introduction

Narcolepsy is a chronic, debilitating neurological disorder with an early onset, generally by the second decade of life [1,2], that tends to be under-recognized and underdiagnosed [3]. The prevalence of narcolepsy is low, 0.05% in the United States [4] and from 0.02% to 0.05% in most countries in the world, with extremes in Japan (0.16%) and Israel (0.002%) [5,6]. Narcolepsy is associated with substantial patient and economic burdens resulting from reductions in function and quality of life as well as higher health-care resource utilization and costs relative to those without narcolepsy [7–9].

Narcolepsy is characterized by a pentad of symptoms that include excessive sleepiness, cataplexy, sleep paralysis, hypnagogic hallucinations, and disrupted nighttime sleep. Excessive sleepiness, although not unique to narcolepsy, is present in all patients, and it is an essential component of both the *International Classification of Sleep Disorders, Third Edition,* and the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [10,11] diagnostic criteria. It is often the first presenting symptom at narcolepsy onset [12].

The treatment of narcolepsy focuses on alleviating symptoms as there is currently no cure. Published treatment recommendations reflect practice parameters, society guidelines, and evidence-based review [13–15]. In the United States, these recommendations include drugs that have been approved by the United States Food and Drug Administration for narcolepsy either as a general condition (ie, stimulants such as Dexedrine [dextroamphetamine] and Ritalin [methylphenidate]), to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy (ie, wake-promoting agents such as Provigil [modafinil; Teva Pharmaceuticals, Frazer, PA, USA] and Nuvigil [armodafinil; Teva Pharmaceuticals, Frazer, PA, USA]), or for the treatment of excessive daytime sleepiness

* Corresponding author. SleepMed, Incorporated, 1333 Taylor Street, Suite 6B, Columbia, SC 29201, USA. Tel.: +1 803 251 3093; fax: +1 803 376 1876.
E-mail address: RBogan@sleepmed.md (R.K. Bogan).

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and cataplexy in narcolepsy (Xyrem [sodium oxybate; Jazz Pharmaceuticals Inc., Palo Alto, CA, USA]). In the European Union, drugs approved for narcolepsy by the European Medicines Agency include modafinil, sodium oxybate, and immediate release methylphenidate. These published recommendations also include other drugs that have lower levels of evidence and that are used for narcolepsy off-label for cataplexy (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors, venlafaxine, and reboxetine) [13–15]. In addition to treatment recommendations, practical considerations for patient management in the clinical setting have also been published [16,17]. However, despite this guidance, management remains challenging because some drugs may not be appropriate for particular patients, and patients may not necessarily respond to a particular drug or to any drug currently available, or it may have issues of tolerability. In particular, excessive sleepiness and the inability to maintain wakefulness are reported by patients as having a great impact on daily function [18]. Patients also report that they have difficulty in balancing the benefits and risks of therapies, some of which may result in intolerable side effects, have complex medication regimens, or result in increased tolerance over time [18]. Consequently, there remains a need for new therapeutic options.

JZP-110 ([*R*]-2-amino-3-phenylpropylcarbamate hydrochloride; formerly known as ADX-N05), is a phenylalanine derivative and an atypical wake-promoting drug with a mechanism of action that differs from traditional stimulants such as dextroamphetamine and wake-promoting agents such as modafinil [19]. JZP-110 indirectly enhances dopaminergic and noradrenergic neurotransmission [19], and it does not inhibit serotonin reuptake, release monoamines, or inhibit monoamine oxidase A (MAO-A) enzymatic activity [20].

In nonclinical studies, JZP-110 has been shown to have robust wake-promoting effects without producing pronounced increases in locomotor activity [19]. These effects were in contrast to those of dextroamphetamine, which also delayed sleep onset, but produced pronounced hyperactivity and stereotypic movements [20]. Another observed difference between JZP-110 and dextroamphetamine in preclinical studies was that animals treated with JZP-110 exhibited the recovery of rapid eye movement (REM) and non-REM sleep without rebound hypersomnia, whereas animals treated with dextroamphetamine exhibited overcompensation of non-REM and REM sleep (ie, rebound hypersomnia) [20,21].

The above observations suggest that JZP-110 may have therapeutic potential for the treatment of excessive sleepiness and impaired wakefulness in narcolepsy. This article presents the results of a proof-of-concept study evaluating the efficacy and safety of oral administration of JZP-110 in adults with narcolepsy.

2. Methods

2.1. Study design

This was a randomized, double-blind, placebo-controlled trial of crossover design that consisted of a 2-week treatment with JZP-110 or with placebo followed by immediate crossover to the other treatment (Clinicaltrials.gov identifier NCT01485770). Patients were randomized to one of the two treatment sequences, that is, placebo followed by JZP-110 or the converse sequence (Fig. 1). The study was performed in accordance with the Declaration of Helsinki, and all patients provided written informed consent prior to participation. The study protocol, all protocol amendments, and the informed consent form were reviewed and approved by the central institutional review board prior to study initiation.

2.2. Patients

Adults between 18 and 65 years of age with a diagnosis of narcolepsy with or without cataplexy, defined by the second edition of the *International Classification of Sleep Disorders*, were included in the study [22]. Patients also were required to have a baseline score of ≥10 on the Epworth Sleepiness Scale (ESS) [23] and a baseline sleep latency of ≤10 min for the average of a four-trial Maintenance of Wakefulness Test (MWT), which was performed the day following an overnight stay at the study site.

Participants were excluded if they had a history of significant cardiovascular disease; a medical disorder, other than narcolepsy, that was associated with excessive sleepiness; a history of phenylketonuria or hypersensitivity to phenylalanine-derived products; a body mass index >34; a nicotine dependence that has an effect on sleep; or a history of alcohol or drug abuse within the past two years. Participants were also excluded if they reported excessive caffeine use one week prior to study; the use of any product with stimulating or sedating properties, selective serotonin reuptake inhibitors, or anticonvulsant agents within 14 days prior to dosing; or any investigational drug use within 30 days prior to dosing. Women who were pregnant or lactating were also excluded. Prior use of medications for the treatment of narcolepsy including any over-the-counter sleep aids or stimulants was allowed provided the last use was a minimum of five half-lives of the drug(s) in question; for those previously using sodium oxybate, a return to baseline level of excessive sleepiness was required for enrollment. At the time of screening, five patients were taking modafinil or armodafinil, five patients were taking an amphetamine or methamphetamine product, two patients were taking sodium oxybate, and one patient was taking an antidepressant (fluoxetine) for narcolepsy symptoms.

2.3. Treatment

Patients were randomized in a 1:1 ratio to one of two treatment sequences that included two weeks of placebo, immediately followed by crossover to two weeks of JZP-110 treatment or the converse sequence. During JZP-110 treatment, the drug was administered at a dose of 150 mg/day during the first week, and it was increased to 300 mg/day for the second week, with the doses reflecting the free base of the molecule. Patients were instructed to take their single daily dose of study medication in the morning on an empty stomach within 1 h of awakening; breakfast was allowed after 30 min following dosing. At the end of each treatment week, patients returned to the investigative site to complete

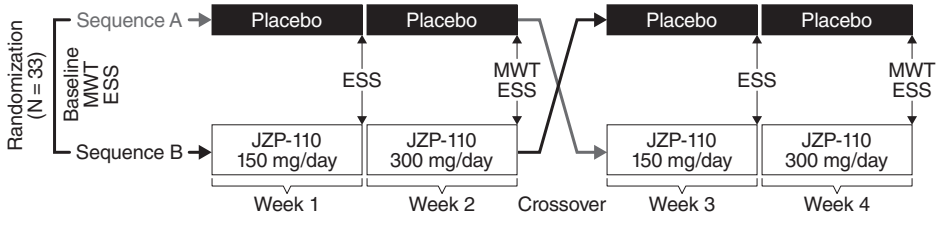

Fig. 1. Study design. ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness Test.