CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211230Orig1s000
211230Orig2s000

SUMMARY REVIEW

Joint Supervisory Review

Date	March 20, 2019
From	Javier A. Muñiz, MD; Tiffany Farchione, MD; Ellis Unger, MD
Subject	Joint Supervisory Review
NDA/BLA #	NDA 211230
Applicant	Jazz Pharmaceuticals
Date of Submission	December 20, 2017
PDUFA Goal Date	December 20, 2018; extended by major amendment to March 20, 2019
Proprietary Name / Non-Proprietary Name	Sunosi solriamfetol
Dosage form(s) / Strength(s)	75-mg, 150-mg
Applicant Proposed Indication(s)/Population(s)	Excessive daytime sleepiness in patients with narcolepsy; excessive daytime sleepiness in patients with obstructive sleep apnea
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Excessive daytime sleepiness in patients with narcolepsy; excessive daytime sleepiness in patients with obstructive sleep apnea

Reference ID: 4406963

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Solriamfetol is a new molecular entity for the treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy and patients with obstructive sleep apnea (OSA). Excessive daytime sleepiness is a prominent symptom of these conditions. Although sleepiness secondary to insufficient sleep occurs in healthy individuals, the EDS occurring in narcolepsy and OSA is more severe and poses significant burdens on patients. Patients with narcolepsy report that daytime sleepiness is the symptom with the most significant impact on daily function. Potential consequences of EDS include reduced attention, cognitive impairment, compromised performance on psychomotor tasks, accidents, decreased productivity, interference with social and occupational function, and overall decreased quality of life. Limitations of existing treatments for EDS include abuse potential, short duration of action, and possible development of tolerance to the wake-promoting effects. Given the significant impact of EDS on the lives of patients with narcolepsy and OSA and the limitations of available treatments, there is a need for additional treatment options.

Importantly, solriamfetol is intended only to treat the sleepiness associated with OSA, and has no effect on the underlying disorder. Labeling will underscore the importance of continuing to treat the underlying OSA, and make it clear that the drug should be initiated only if the patient's daytime sleepiness does not improve following standard-of-care treatment for the underlying OSA.

Three placebo-controlled trials were positive on measures of maintenance of wakefulness and reduction in sleepiness for patients with narcolepsy and patients with OSA. In addition, two placebo-controlled randomized-withdrawal trials with stabilization periods of 6 months and 4 weeks were conducted to assess the longer-term effectiveness in both populations. In both randomized-withdrawal trials, patients who showed initial improvement with solriamfetol and were randomized to remain on solriamfetol continued to benefit whereas subjects randomized to switch to placebo showed a statistically significant mean loss of effect. It is anticipated that the majority of individuals with OSA and narcolepsy will experience *some* reduction in EDS in response to solriamfetol.

Dose-related adverse reactions seem typical for drugs with shared pharmacodynamic properties (e.g., stimulants, bupropion, etc.) and include reversible anorexia, anxiety/nervousness, insomnia, and irritability, as well as dry mouth, nausea, and diarrhea. Patients will be able to perceive whatever benefits they receive from the drug, largely in terms of improved wakefulness, weigh these benefits against the various side effects they might experience, and adjust the dose within a fairly broad range to maximize their benefits and tolerability. None of the aforementioned adverse reactions is likely to cause actual harm.

Solriamfetol's major safety concern, however, is increased blood pressure, which can go undetected. Solriamfetol causes dose-related increases in systolic and diastolic blood pressure, as well as increases in heart rate. Effects are greatest at T_{max}, but largely persist throughout the day. Even small blood pressure increases on the order of those found with solriamfetol can increase the risk of major adverse cardiovascular events (MACE), with greater risk in patients with elevated blood pressure, established cardiovascular disease, and other cardiovascular risk factors. Many patients with OSA and narcolepsy have cardiovascular risk factors, including hypertension, diabetes, hyperlipidemia, and obesity; therefore, the absolute risk of MACE is clinically meaningful in the indicated populations.

Reference ID: 4406963

Despite the availability of numerous antihypertensive medications, hypertension is often underdiagnosed, poorly managed, and poorly controlled in patients in the US. Solriamfetol's effect on blood pressure could be difficult to detect reliably, yet it has significant clinical implications. Labeling will include a Warning/Precaution to mitigate the risk of blood pressure increases, and language to discourage off-label use of doses > 150 mg/d.

The review team agrees unanimously that the benefits of solriamfetol outweigh the risks in the treatment of EDS in patients with OSA and narcolepsy, and all recommend approval, with risk mitigation through labeling, in particular, a warning for hypertension.

Reference ID: 4406963

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Excessive daytime sleepiness is a disabling symptom of narcolepsy and OSA • Although sleepiness secondary to insufficient sleep occurs in healthy individuals, the EDS occurring in narcolepsy and OSA is more severe and poses significant burdens on patients and society • A 2013 survey of patients with narcolepsy indicated that EDS was the narcolepsy symptom that had the most significant impact on their daily lives • Potential consequences of EDS include reduced attention, cognitive impairment, compromised performance on psychomotor tasks, accidents, decreased productivity, interference with social and occupational functioning, and decreased quality of life	EDS associated with narcolepsy and OSA can significantly impact patients' quality of life, and compromise the safety of the patient and other individuals.
Current Treatment Options	• For EDS in narcolepsy: sodium oxybate, modafinil, armodafinil, methylphenidate, amphetamine • For EDS in OSA: modafinil and armodafinil • Methylphenidate and amphetamine: limited by tolerance and abuse potential; Schedule II • Sodium oxybate: limited by abuse potential and possible diversion for use in drug-facilitated sexual assault; Schedule III, with Schedule I penalties for illicit use; requires a REMS • Modafinil and armodafinil are substrates, inducers, and inhibitors of CYP450 isoenzymes, raising the possibility of drug-drug interactions • Modafinil and armodafinil have label warnings for Stevens-Johnson Syndrome, angioedema, anaphylactoid reactions, and multi-organ hypersensitivity reactions • Several off-label treatments for EDS have been evaluated in clinical studies (e.g., methylphenidate, bupropion, fluoxetine, etc.). There is little evidence supporting these approaches.	Limitations of existing treatment options, including tolerance and abuse potential for some agents and short duration of action for others, support the need for additional treatment options.

Reference ID: 4406963

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The Applicant conducted five adequate and well-controlled trials to assess the efficacy of solriamfetol for the treatment of EDS in narcolepsy and OSA. In both indications, wakefulness and sleepiness were assessed using the Maintenance of Wakefulness Test (MWT) and the Epworth Sleepiness Scale (ESS). The MWT measures an individual's ability to remain awake during the daytime in a darkened, quiet environment. Patients were instructed to remain awake for as long as possible during serial 40-minute test sessions, and sleep latency was determined as the mean number of minutes patients could remain awake in the first four test sessions. The ESS is an 8-item questionnaire by which patients rate their perceived likelihood of falling asleep during usual daily life activities. Change in overall symptom severity was assessed using the Patient Global Impression of Change (PGIc) scale. The PGIc is a 7-point patient-reported scale by which patients rate their symptom change since the beginning of the study. Responses range from "very much improved" to "very much worse." • Study ADX-N05-202 (narcolepsy): The co-primary endpoints were the change in MWT and CGIc scores. For both endpoints, the placebo-subtracted differences in mean change from baseline were statistically significant. • Study 14-002 (narcolepsy): The co-primary endpoints were the placebo-corrected changes in MWT and ESS at Week 12. The study was statistically significantly positive for the 150-mg dose group, but not for the 75-mg dose group. • Study 14-003 (OSA): The co-primary endpoints were the placebo-corrected changes in MWT and ESS at Week 12. There were statistically significant treatment effects for all dose groups (37.5-mg, 75-mg, and 150-mg). • Study 14-004 (OSA): The co-primary endpoints were the placebo-corrected changes in MWT and ESS at Week 12. For both endpoints, the difference in mean change compared to placebo during the randomized withdrawal period was statistically significant. • Study 14-005 (narcolepsy, OSA): The primary endpoint for the randomized withdrawal period was the	Solriamfetol demonstrated statistically significant efficacy compared to placebo on all five trials. There is substantial evidence effectiveness to support approval of solriamfetol for the treatment of EDS in narcolepsy and for the treatment of EDS in OSA. Size of Treatment Effect: In studies in both narcolepsy and OSA, the placebo-subtracted change in MWT from Baseline to Week 12 was approximately 10 to 13 minutes (out of 40 possible minutes), a statistically and clinically significant treatment effect. In studies in both narcolepsy and OSA, the placebo-subtracted change in ESS (an 8-item questionnaire to assess the patient's perceived likelihood of falling asleep during usual daily activities) from Baseline to Week 12 was approximately 5 at the high dose, on a scale ranging from 0 (best) to 24 (worst), where the baseline score was ~16. A 5-point change is both statistically and clinically significant.

Reference ID: 4406963

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	change in ESS. For both subjects with narcolepsy and subjects with OSA, the mean ESS score increased significantly more for the placebo group than for the solriamfetol group, indicating better control of daytime sleepiness for subjects who remained on solriamfetol during the randomized withdrawal.	
Risk and Risk Management	• Dose-related adverse reactions are consistent with other drugs with overlapping mechanisms of action (e.g., bupropion, stimulants, etc.) and include reversible anorexia, anxiety/nervousness, insomnia, and irritability, as well as dry mouth, nausea, and diarrhea. Patients should generally be able to perceive whatever benefits they receive from the drug, largely in terms of improved wakefulness, weigh these benefits against the various side effects they might experience, and adjust the dose within a broad range to maximize benefits and tolerability. With the possible exception of blood pressure increases, none of the aforementioned adverse reactions is likely to cause actual harm. • Solriamfetol's major safety concerns are increased blood pressure and lack of compliance with therapy(ies) aimed at improving/managing the underlying OSA. • Solriamfetol causes dose-related increases in systolic and diastolic blood pressure, as well as increases in heart rate. Based on ambulatory blood pressure monitoring, the mean effect of the 300-mg dose was approximately 3-5/2-4 mmHg, with increases in mean heart rate of as much as 10 beats/minute. Effects were greatest at T_{max}, but largely persisted throughout the day. Blood pressure effects were less for lower doses. Blood pressure increases can increase the risk of major adverse cardiovascular events (MACE), especially in patients with cardiovascular risk factors. Many patients with OSA and narcolepsy have such risk factors, including hypertension, diabetes, hyperlipidemia, and obesity; therefore, the absolute risk of MACE is clinically meaningful in the indicated populations. (b) (4) [redacted] the Applicant submitted a major amendment with a proposed maximum dose of	(b) (4) [redacted]. For patients with OSA, the recommended starting dose will be 37.5 mg, to ensure that patients with high pre-existing cardiovascular risk are given a trial on the lowest dose that might be efficacious.

Reference ID: 4406963

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	150 mg per day. • Solriamfetol does not treat the underlying airway obstruction in OSA, and there is concern that some patients will believe that solriamfetol, alone, is adequate to treat their OSA, and abandon treatment for their fundamental disorder. The label will include language strongly encouraging continued treatment of the underlying OSA. • The label will highlight (Section 2) that doses above 150 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.	

2. Background

Solriamfetol (JZP-110, ADX-N05; proposed proprietary name "Sunosi") is a new molecular entity not currently marketed in the US or elsewhere. The Applicant, Jazz Pharmaceuticals, developed solriamfetol for the treatment of excessive daytime sleepiness (EDS) in narcolepsy and in obstructive sleep apnea (OSA). Because solriamfetol does not treat the underlying OSA condition, it will be recommended only for patients who continue to have EDS despite receiving adequate treatment for their illness [e.g., after at a month of continuous positive airway pressure (CPAP), the treatment of choice for OSA]. Patients will be strongly encouraged to continue their treatment modality(ies) for their underlying OSA.

Excessive daytime sleepiness is a prominent symptom of both narcolepsy and OSA. While sleepiness secondary to insufficient sleep occurs in healthy individuals, the EDS occurring in narcolepsy and OSA is of greater magnitude, is disabling, and poses significant burdens on patients and society. Potential consequences of EDS include reduced attention, cognitive impairment, compromised performance on psychomotor tasks, accidents, and decreased quality of life.

Solriamfetol is a derivative of the amino acid phenylalanine. Although its mechanism of action is not known, it is thought to be mediated by dopamine (DA) and norepinephrine (NE) reuptake inhibition in the brainstem arousal systems. The product will be available in 75-mg and 150-mg tablets. (b) (4) The 75-mg tablet will be scored, to allow a 37.5-mg dose for patients (b) (4) The proposed starting dose is 37.5-mg daily for patients with OSA and 75-mg daily for patients with narcolepsy. The Applicant recommends a doubling of the dose at intervals of at least three days, based on clinical response and tolerability. The maximum recommended dose is 150-mg daily.

Reference ID: 4406963

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) review team and their technical lead, David Claffey, PhD, recommend approval.

The Office of Process and Facilities (OPF) review team found each of the manufacturing sites acceptable for the functions listed in this application. The environmental assessment team found the categorical exclusion claim under 21 CFR Part 25.31(b) and provided statement of no extraordinary circumstance to be acceptable. The Biopharmaceutics review team found the proposed dissolution method acceptable for release and stability testing. This application included a BCS-Class 1 biowaiver request supporting the bridge between the Phase 2 to Phase 3 formulation and dosage form changes (from capsules to tablets). Data provided in the application demonstrated similarity between dissolution profiles of the capsules and tablets, which the Biopharmaceutics team found acceptable. In addition, the drug product reviewer, Stephanie Emory, determined that the stability data supported a 30-month product expiry period when stored at USP Controlled Room Temperature.

4. Nonclinical Pharmacology/Toxicology

Jia Yao, PhD, was the primary nonclinical reviewer for this application; he recommends approval.

In dogs and humans, solriamfetol undergoes limited hepatic metabolism. The majority of the drug is excreted unchanged in the urine. Compared to animal species, there are no unique or major human metabolites. Dr. Yao concludes that, at clinically relevant doses, solriamfetol is unlikely to cause significant drug-drug interactions.

Based on data from mice studies, solriamfetol's wake-promoting properties do not appear to be directly dependent on orexin. The Applicant states that solriamfetol's wake-promoting effects are presumed to be through its activity as a dopamine- and norepinephrine-reuptake inhibitor (DNRI). In order of decreasing affinity, solriamfetol has relatively low binding affinities for the norepinephrine transporter (NET) and the dopamine transporter (DAT). At therapeutically relevant levels, solriamfetol appears to have negligible serotonergic activity, and does not stimulate the release of dopamine, norepinephrine, or serotonin.

Although there was some discussion and disagreement within the review team about the appropriate established pharmacologic class for solriamfetol (i.e., amphetamine vs. DNRI), we believe that DNRI best characterizes its mechanism of action; this class includes drugs such as bupropion. Unlike amphetamines, solriamfetol has no known action on the trace amine-associated receptor 1 (TARR1) or on vesicular monoamine transporters (VMAT) 1 and 2, which could explain why solriamfetol does not appear to release DA and NE into the synaptic cleft, as amphetamines do. Solriamfetol's human abuse potential will be discussed later in this review.

Most of the safety pharmacology studies in this NDA were conducted prior to issuance of ICH S7A. Therefore, they were not performed with full GLP (Good Laboratory Practice) compliance. However, Dr. Yao did not identify any significant issues with the quality of the safety

Reference ID: 4406963

pharmacology studies or the interpretability of the data. The safety pharmacology of solriamfetol was evaluated in the cardiovascular, respiratory, and central nervous system (CNS) systems. No adverse effects were identified at clinically-relevant doses. Drug-related effects observed in these studies included slight increases in heart rate (HR) and blood pressure (BP), increases in the locomotor activity, and slight and transient increases in respiratory rate. Dr. Yao states that "these effects are expected, based on the pharmacology of solriamfetol and are not considered to be adverse." Mice studies suggest that the proposed product has a low potential to reduce the seizure threshold. Solriamfetol does not significantly inhibit the hERG (human Ether-à-go-go-Related Gene) channel.

Across all nonclinical species, the CNS was the primary target organ for toxicity. The severity of CNS clinical signs increased in a dose-dependent manner, from hyperactivity at lower doses to tremor, convulsion, and self-injury in rats at higher doses. Solriamfetol also caused dose-dependent decreases in food consumption and body weight gain, particularly during the first few weeks after initiation of treatment. The safety margins relative to the original maximum recommended human dose (MRHD) of 300 mg at the no observed adverse effect levels (NOAELs) in the pivotal general toxicology studies were approximately 1 in the dog and < 1 in the mouse and rat. However, many of the dose-limiting toxicities in animal studies were due to pharmacology-related CNS signs and/or body weight decreases, which are clinically monitorable and were reversible on treatment cessation. Dr. Yao opines that the small safety margins do not impose unacceptable risks for the proposed indication and do not preclude approval of the application.

The proposed product was non-genotoxic in an adequate battery of genotoxicity assays. Solriamfetol was not carcinogenic and did not induce tumors in rats or mice when administered orally at doses up to approximately 3.5 and 9 times the original MRHD of 300 mg/day to rats and mice, respectively, based on AUC. Solriamfetol did not affect fertility or sperm parameters when administered orally to male rats for eight weeks at doses approximately 1 and 3.5 times the original MRHD (based on body-surface area). At approximately 11 times the MRHD, sperm count and sperm concentration were decreased by approximately 10%, without affecting fertility. Solriamfetol did not affect fertility when administered orally to female rats for two weeks premating, during mating, and through gestation day seven at approximately 0.5, 2, and 9.5 times the MRHD. In embryo-fetal developmental studies, oral administration of solriamfetol during organogenesis caused maternal and fetal toxicities in rats and rabbits at doses ≥ 2 and 2.5 times MRHD, respectively, and was teratogenic at doses 9.5 and ≥ 2.5 times the original MRHD, respectively. Dr. Yao concluded that these animal findings do not suggest a need for specific or additional human monitoring recommendations; however, the risk-to-benefit profile should be carefully considered when administering solriamfetol to pregnant or breastfeeding women, as fetal and infant exposure are likely to occur with a small safety margin.

5. Clinical Pharmacology

The review team from the Office of Clinical Pharmacology (OCP) recommends approval of this application.

The following is a summary of the product's clinical PK features:

Reference ID: 4406963

- **Absorption:** Solriamfetol is readily absorbed after oral administration, with peak plasma concentrations occurring at a median T_{max} of 2 hours (range 1.25 to 3.0 hours) under fasted conditions. Solriamfetol has an oral bioavailability of > 90% with negligible first pass metabolism, based on the percentage of dose excreted unchanged in urine. Its absorption is similar in fasted vs. fed states.
- **Distribution:** Solriamfetol has an apparent volume of distribution of approximately 200 L. Plasma protein binding ranged from 13.3% to 19.4% over a drug concentration range of 0.059 to 10.1 mcg/mL in human plasma. The mean blood-to-plasma concentration ratio ranged from 1.16 to 1.29.
- **Metabolism and Elimination:** Solriamfetol does not undergo CYP-mediated phase I metabolism in humans; 1% or less of the administered dose was recovered in urine as the minor inactive metabolite N-acetyl solriamfetol. In a human mass-balance study, approximately 95% of the dose was recovered in urine as unchanged solriamfetol. Renal clearance represented the majority of apparent total clearance and exceeded creatinine clearance by approximately 3-fold, indicating that active renal secretion of the parent drug is the major elimination pathway. Solriamfetol exhibits first-order elimination after oral administration. The apparent mean elimination half-life is about 7.1 hours. The apparent oral clearance of solriamfetol is approximately 19.5 L/h, and renal clearance is about 18.2 L/h.

Two principal review issues are identified for this application from an OCP perspective:

1. **Appropriateness of the dosing instruction in general patients.** (b) (4) Clinical trials in this development program suggest that solriamfetol increases BP in a dose-dependent manner. Our concern (articulated in our 2018 draft Guidance for Industry: Assessment of Pressor Effects of Drugs) is that even small increases in blood pressure over prolonged periods of time may lead to increased risk for major adverse cardiovascular events (MACE), such as stroke, myocardial infarction, and cardiovascular death. To decrease these risks, the OCP team recommends patients with OSA should start with the 37.5-mg dose and patients with narcolepsy should start with the 75-mg dose; we agree with these recommendations. The dose should only be increased when there is inadequate clinical response, and clinically important increases in blood pressure have been corrected.
2. **Recommendations in specific patient populations (i.e., renal impairment).** The OCP team agrees with the Applicant that solriamfetol is not recommended for patients with end-stage renal disease. The Applicant proposed a range of (b) (4) mg for patients with moderate renal impairment, and (b) (4) for patients with severe renal impairment. OCP suggests that, because of the prolonged half-life of solriamfetol in patients with moderate or severe renal impairment, a higher risk for insomnia and sustained increases in blood pressure and heart rate are likely, (b) (4) OCP recommends the addition of language to the label to communicate these risks. For treatment initiation, the starting dose should be 37.5 mg per day for all renal impairment patients, except for patients with end-stage renal disease (for whom solriamfetol is not recommended). The OCP team also recommends a minimum 7-day dose escalation schedule for patients with moderate renal impairment with a

Reference ID: 4406963

maximum daily dose of 75 mg. For patients with severe renal impairment, the maximum recommended daily dose is 37.5 mg. We agree with these recommendations.

Upon review of the thorough QT study, the OCP team concluded that solriamfetol did not induce significant QTc prolongation at a dose of 900 mg, three times the MRHD.

Population pharmacokinetic (PK) analyses suggest that sex and race do not have clinically relevant effects on solriamfetol's PK profile. Dose adjustments were not performed in the clinical studies that enrolled patients age 65 years and above. Although C_{max} in the clinical studies was higher in females than males after solriamfetol administration, either under fasting or fed conditions, C_{14hr} levels were comparable. The OCP team concludes that no dosage adjustment based on age, race, or sex is necessary.

6. Clinical Microbiology

No clinical microbiology data were needed for this application.

7. Clinical/Statistical – Efficacy

David Millis was the primary clinical reviewer and Jinglin Zhong was the primary biostatistics reviewer for this NDA. They both agree the Applicant has provided substantial evidence of efficacy for solriamfetol for the treatment of narcolepsy and OSA; we concur. The Applicant submitted three trials to provide short-term efficacy data (Studies ADX-N05-202, 14-002, and 14-003), a randomized withdrawal trial (Study 14-004) to demonstrate maintenance of effect, and a long-term safety trial (Study 14-005) that incorporated a randomized withdrawal phase to further demonstrate maintenance of efficacy.

Individual Study Results

Study ADX-N05-202 (Indication: Narcolepsy)

Study ADX-N05-202 was a twelve-week, Phase 2, double-blind, placebo-controlled, randomized, parallel-group, multicenter (US only) study of the safety and efficacy of solriamfetol in the treatment of excessive daytime sleepiness in subjects with narcolepsy. Subjects completed a Screening Phase (up to 28 days, including screening assessments and discontinuation of any current narcolepsy treatments) and a Baseline Phase (including an overnight stay for baseline efficacy and safety measurements). Subjects who continued to meet eligibility requirements were randomly assigned to two treatment groups:

- Group #1
  - Weeks 1-4: solriamfetol 150 mg/day
  - Weeks 5-12: solriamfetol 300 mg/day
- Group #2
  - Weeks 1-12: placebo

To be enrolled in the study, subjects must have been 18 to 70 years of age. Subjects must have met ICSD-2 narcolepsy criteria and, if without a clear history of cataplexy, the diagnosis must have been confirmed with polysomnography (PSG) followed by a Multiple Sleep Latency Test

Reference ID: 4406963

(MSLT). Additionally, a baseline Epworth Sleepiness Scale (ESS) score must have been ≥ 10. A baseline mean sleep latency time of ≤ 10 minutes must have also been present, as documented by the average of the first four test sessions of the five-session Maintenance of Wakefulness Test (MWT) during the Baseline Phase. The MWT measures the ability to stay awake under soporific conditions for a defined period of time. The maximum time (best result) is 40 minutes. The assumption is that the volitional ability to stay awake is more important to know in some instances than the tendency to fall asleep. Although the MSLT remains the gold standard for measuring sleepiness, the MWT has been used widely in narcolepsy clinical studies and is an appropriate primary outcome measure.

The primary endpoints were: 1) change from baseline (CFB) in the average sleep latency time (in minutes) as determined by the MWT (average of the first four test sessions) for solriamfetol vs. placebo at last assessment; 2) Clinical Global Impression-Change (CGI-C) scores for solriamfetol vs. placebo at last assessment.

Neither the protocol nor the statistical analysis plan (SAP) were reviewed by our team and the choice of these primary endpoints presents an area of concern. The CGI-C is a 7-point scale that requires the clinician to rate the change of the patient's illness at the time of assessment, relative to the patient's baseline. Because of its subjectivity and need for recall (through an intermediary), it is unlikely we would have accepted the CGI-C as a primary endpoint. There were four secondary endpoints, for which there was no control of the Type-I error rate.

Of the 213 subjects screened, 93 subjects were randomly assigned to a treatment group (44 to solriamfetol and 49 to placebo) and received at least one dose of study medication. Ninety (90) subjects (43 on solriamfetol and 47 on placebo) had at least one post-Baseline efficacy assessment (intent-to-treat or ITT population). Of these subjects, 74 subjects (36 on solriamfetol and 38 on placebo) completed all 12 weeks of treatment and completed an MWT on the same day as their last dose of study drug (per protocol population), and 32 subjects (17 on solriamfetol and 15 on placebo) had cataplexy (cataplexy population).

Most subjects were female (65%) and Caucasian (74%). Mean (SD) age was 38.7 (12.1) years, (range 18 to 70). Mean body weight was 76.1 (16.4) kg. Mean body mass index was 26.6 (4.5) kg/m^2. Dr. Millis concludes that protocol violations identified in the study report were infrequent and would not appear to bias the interpretation of results in favor of solriamfetol treatment. The demographic characteristics of the ITT population (e.g., race, sex, age) seem generalizable to the to-be-marketed population.

The primary and secondary efficacy analyses were conducted on the ITT population (as defined above). Two-sided tests at a 0.05 significance level were used to compare treatment groups. There was no multiplicity adjustment for the primary or secondary endpoints. The primary analysis on the MWT CFB at the last post-baseline assessment used a two-sample test. Two sensitivity analyses were planned by the Applicant: analysis of covariance (ANCOVA) and per-protocol analysis. The primary analysis on CGI-C at the last postbaseline assessment used Fisher's exact test. An additional sensitivity analysis was performed using logistic regression. The Applicant's primary endpoints were assessed at the last post-baseline assessment. The MWT

Reference ID: 4406963

and CGI-C results are summarized in Table 1 and Table 2, respectively. The mean treatment effect was approximately 10 minutes (difference in CFB between solriamfetol and placebo).

Table 1: MWT Change from Baseline (minutes) at the Last Post-Baseline Assessment; Study ADX-N05-202

	Observed Values Mean (SD)	Calculated Change from Baseline Mean (SD)	P-Value[2]
Baseline		-	-
ADX-N05 (N=43)	5.66 (5.89)		
Placebo (N=47)	5.70 (2.83)		
Week 12/Last Assessment[1]			
ADX-N05 (N=40)	17.6 (11.42)	12.8 (10.28)	<0.0001[1]
Placebo (N=45)	7.9 (8.63)	2.1 (7.88)	

[1]Week 12/Last Assessment; missing data imputed using last post-Baseline observation carried forward.
[2]Two-sample t-test
SD=standard deviation
Best possible MWT result is 40 minutes.
[Source: clinical study report (CSR), ADX-N05-202; Table 7, page 60]

Table 2: CGI-C Change from Baseline at the Last Post-Baseline Assessment; Study ADX-N05-202

	Observed Values Mean (SD)	Proportion of Subjects Experiencing Improvement[2] N (%)	P-Value[3]
Baseline			
ADX-N05 (N=43)	5.00 (0.79)		
Placebo (N=47)	5.04 (1.02)		
Week 12/Last Assessment[1]			
ADX-N05 (N=43)	2.2 (1.16)	37 (86.0)	<0.0001
Placebo (N=47)	3.5 (1.10)	18 (38.3)	

Note: Observed values for the Baseline visit are derived from the CGI-Subject assessment. Observed values for Week 12/Last Assessment are derived from the CGI-C. CGI-C scores range from 1 through to 7 (worst result).
[1]Missing data imputed using last post-Baseline observation carried forward.
[2]Two-sample t-test
[3]Fisher's Exact test
SD=standard deviation
[Source: CSR, ADX-N05-202; Table 8, page 61]

Dr. Zhong verified the Applicant's primary findings and one of the two pre-specified sensitivity analyses. Dr. Zhong did not think that the second sensitivity analysis, a per-protocol analysis, was sensible; thus, she did not include it in her review. Dr Zhong also performed analyses like

Reference ID: 4406963

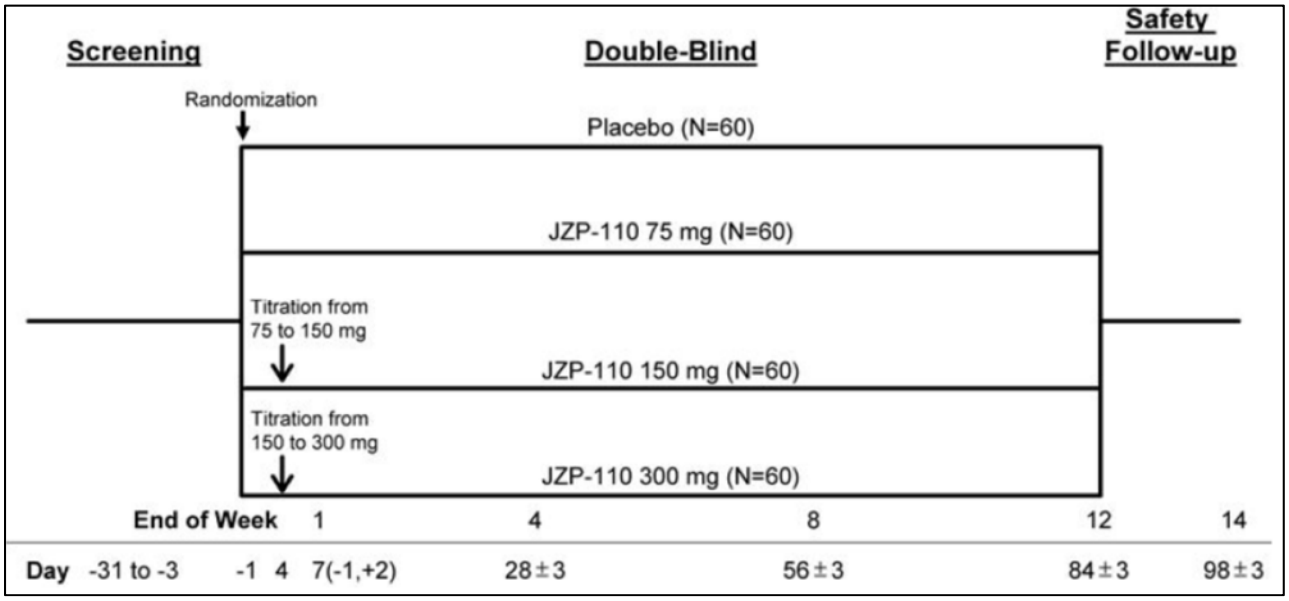
those in the pivotal studies in this application, using a 12-week timepoint in lieu of the last post-baseline assessments; these results support the Applicant's efficacy findings for the primary endpoints.

In summary, Study ADX-N05-202 was a positive trial, per its pre-specified objectives. Although its overall design was appropriate, there are problems with the choice of primary outcomes and the statistical analysis plan that limit the strength of its conclusions.

Study 14-002 (Indication: Narcolepsy)

Study 14-002 (TONES 2) was a 12-week, randomized, double-blind, placebo-controlled, multicenter, four-arm, parallel group study of the safety and efficacy of solriamfetol in the treatment of excessive sleepiness in adult subjects with narcolepsy. Subjects were randomized to one of four treatments: placebo, or solriamfetol 75 mg, 150 mg, or 300 mg per day. Randomization was stratified by the presence or absence of cataplexy. Subjects had to be 18 to 75 years old with a documented diagnosis of narcolepsy according to criteria of either the International Classification of Sleep Disorders, Third Edition (ICSD-3) or Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The study scheme is presented in Figure 1.

Figure 1: Study 14-002



[Source: CSR, Study 14-002; Figure 1, page 36]

There were two co-primary endpoints: MWT CFB at Week 12 and ESS (Epworth Sleepiness Scale) CFB at Week 12. The ESS is a self-administered questionnaire with eight questions. Respondents are asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in eight different activities. The higher the ESS score, the greater the perceived sleep propensity in daily life (0 is best; 24 worst). The ESS is widely used as a screening tool in research and clinical settings; it has also been commonly used as a clinical outcome in clinical trials. Some of the questions in the ESS, however, are non-specific or prone

Reference ID: 4406963

to introduce recall bias, limiting the scale's reliability as a primary outcome measure. The key secondary endpoint for Study 14-002 was the percentage of subjects reported as "improved" (i.e., minimally, much, or very much) at Week 12 as measured by the PGIc (Patient Global Impression of change).

The analysis population was the modified intent-to-treat (mITT) population, defined as subjects who received at least one dose of study medication and had baseline and at least one post-baseline MWT or ESS evaluation. The co-primary endpoints (MWT and ESS) were analyzed using MMRM, with treatment, time, treatment-by-time interaction, and randomization stratification factor (presence or absence of cataplexy at Screening) as fixed effects, and the baseline value of the efficacy endpoint as the covariate. The key secondary endpoint, PGIc, was analyzed using a chi-squared test using last observation carried forward (LOCF) for missing data. A sequential gatekeeping testing procedure was utilized to control the overall type-I error rate at 0.05. The sequence of testing multiple endpoints was:

1. MWT and ESS: 300-mg vs. placebo; proceed to the next test if both are significant at α=0.05
2. PGIc: 300-mg vs. placebo; proceed to the next test if significant at α=0.05
3. MWT and ESS: 150-mg vs. placebo; proceed to the next test if both are significant at α=0.05
4. PGIc: 150-mg vs. placebo; proceed to the next test if significant at α=0.05
5. MWT and ESS: 75-mg vs. placebo; proceed to the next test if both are significant at α=0.05
6. PGIc: 75-mg vs. placebo; use α=0.05

The study was conducted in 50 North American and nine European centers and enrolled 239 subjects. Three subjects were randomized in error but did not receive the study medication. The safety population consisted of the remaining 236 subjects; the mITT population, 231 subjects; the per protocol (PP) population, 195 subjects; and the PK population, 172 subjects.

The most frequent reasons for withdrawal from the study were lack of efficacy and adverse events. Cataplexy was the most frequent treatment-emergent adverse event (TEAE) leading to withdrawal, occurring in one subject in the placebo group and two subjects in the solriamfetol 300-mg group, and was the only TEAE that led to withdrawal of more than one subject. All three subjects had a previous history of cataplexy.

The majority of subjects were white (80%) and female (65%), and 81% were from North America. Median age was 34. Median body mass index was 28 kg/m^2. Demographic characteristics were reasonably balanced across treatment groups. A higher percentage of subjects in the 75-mg treatment group were from European sites compared with the other treatment groups. The demographic characteristics of the study seem generalizable to the to-be-marketed patient population. In general, baseline disease characteristics and important concomitant medications were distributed similarly across all groups. About half of the subjects had cataplexy. Overall, Dr. Millis concludes that protocol violations identified in the study report were infrequent and would not appear to bias the interpretation of results in favor of solriamfetol.

Reference ID: 4406963

The Applicant performed the pre-specified primary analyses on co-primary and key secondary endpoints. Based on the fixed hierarchical testing sequence, solriamfetol doses of 150 and 300 mg achieved statistically significant on the co-primary and key secondary endpoints (Table 3). In all sensitivity analyses, solriamfetol doses of 150 and 300 mg showed statistically significant treatment effects in the MWT and ESS compared with placebo. Dr. Zhong was able to replicate the Applicant's analyses and created a histogram for the MWT CFB (Figure 2), showing greater fractions of solriamfetol-treated patients with improvement on MWT than placebo.

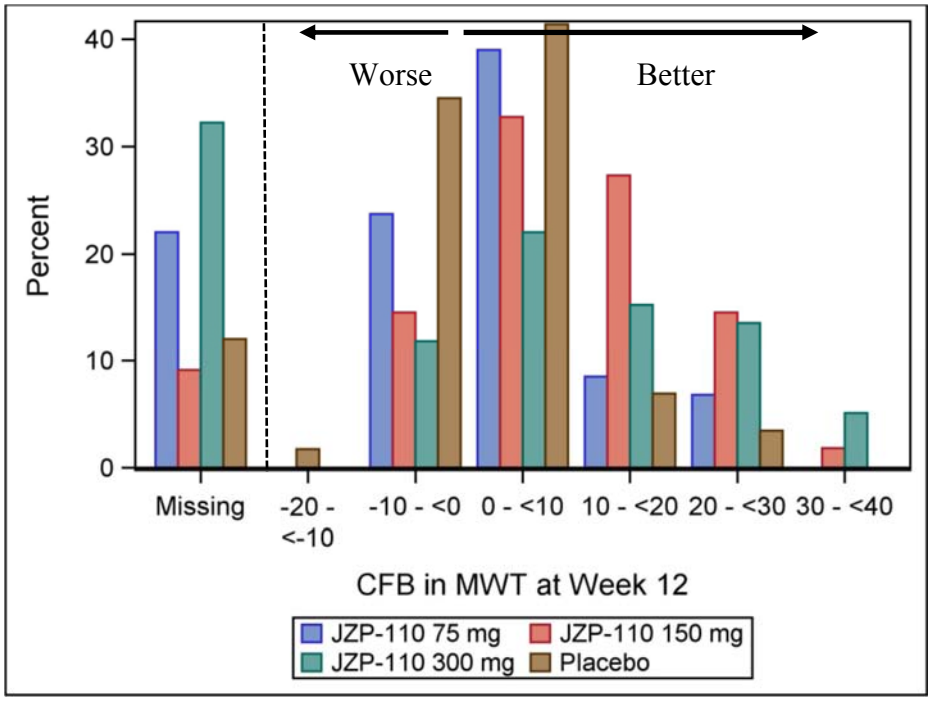
Table 3: Applicant's Primary Analysis Results on Co-Primary and Key Secondary Efficacy Endpoints; Study 14-002

	Placebo	**Solriamfetol**		
	N = 58	**75 mg N = 59**	**150 mg N = 55**	**300 mg N = 59**
Co-Primary Endpoints				
Change in MWT from Baseline to Week 12 (Minutes)				
LS Mean (SE)	2.1 (1.3)	4.7 (1.3)	9.8 (1.3)	12.3 (1.4)
LS Mean Difference vs. Placebo	NA	2.6	7.6	10.1
95% CI	NA	(-1.0, 6.3)	(4.0, 11.3)	(6.4, 13.9)
p-value	NA	0.16	<0.01	<0.01
Change in ESS Score from Baseline to Week 12				
LS Mean (SE)	-1.6 (0.7)	-3.8 (0.7)	-5.4 (0.7)	-6.4 (0.7)
LS Mean Difference vs. Placebo	NA	-2.2	-3.8	-4.7
95% CI	NA	(-4.0, -0.3)	(-5.6, -2.0)	(-6.6, -2.9)
p-value	NA	0.02	<0.01	< 0.01
Key Secondary Endpoint				
PGIc: Subjects Reported Improved at Week 12				
Yes [N (%)]	23 (39.7)	40 (67.8)	43 (78.2)	50 (84.7)
No [N (%)]	35 (60.3)	19 (32.2)	12 (21.8)	9 (15.3)
% Difference (Yes) from Placebo (95% CI)	NA	28.1 (10.8, 45.5)	38.5 (21.9, 55.2)	45.1 (29.1, 60.7)
p-value	NA	<0.01	<0.01	<0.01

[Source: Adapted from CSR, Study 14-002; Table 13, page 95]
Best possible MWT score is 40 minutes; worst = 0 minutes.
ESS scores range from 0 (best) to 24 (worst). A negative change represents improvement.
PGIc scores range from 1 (best) to 7 (worst).

Reference ID: 4406963

Figure 2: MWT Change from Baseline at Week 12 by Treatment; Study 14-002



[Source: Biostatistics Review; Figure 12, page 40]

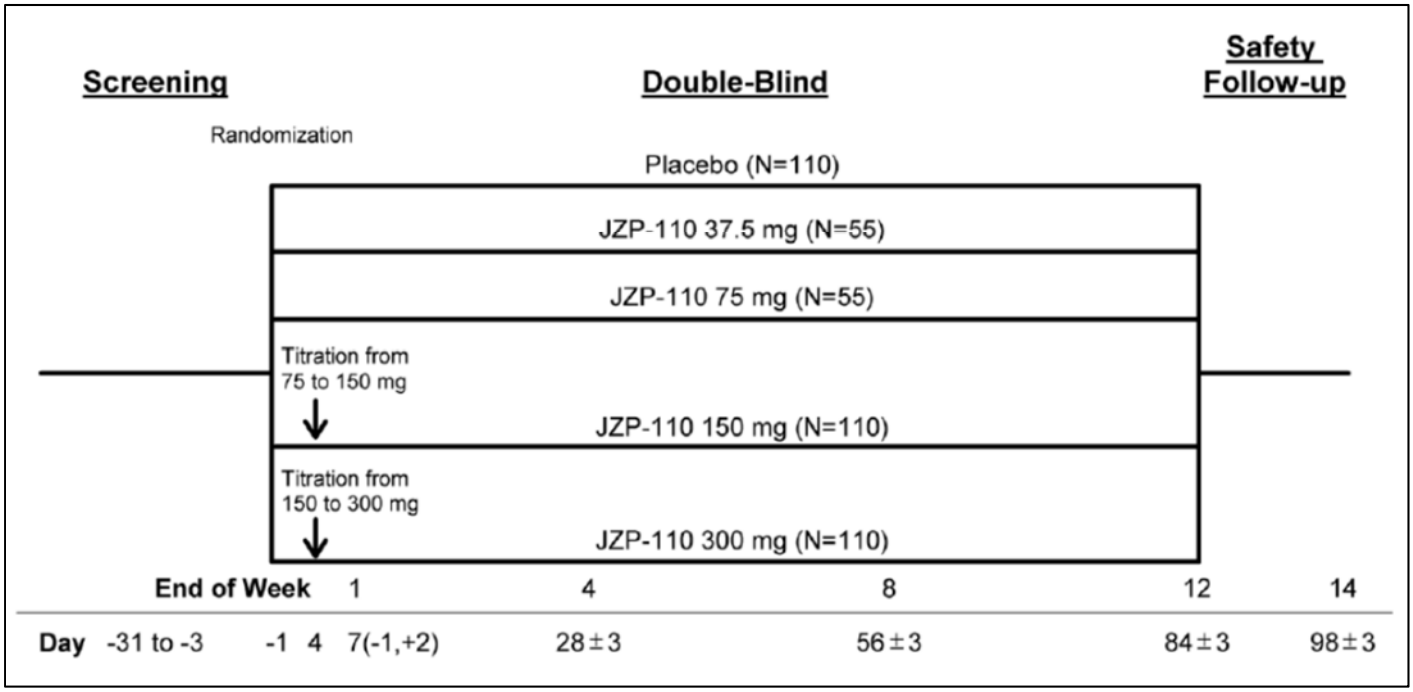
In summary, Study 14-002 was an adequate and well-controlled study with statistically significant results (vs. placebo) at the 150- and 300-mg doses. Although the ESS has some limitations as a primary outcome, we are reassured that both co-primary endpoints and the key secondary endpoint support a conclusion of efficacy for the two higher doses. The 75-mg dose was statistically significant only for ESS score CFB. The LS mean difference from placebo increased with dose on both co-primary endpoints, with the greatest separation at the 300-mg dose. Finally, the presence of cataplexy did not importantly influence solriamfetol's efficacy in patients with narcolepsy (data not shown).

Study 14-003 (Indication: Obstructive Sleep Apnea)

Study 14-003 (TONES 3) was a 12-week, randomized, double-blind, placebo-controlled, multicenter, five-arm, parallel group study of the safety and efficacy of solriamfetol in the treatment of excessive sleepiness in adult subjects with OSA. Subjects were randomized in a 1:1:2:2:2 ratio to receive solriamfetol 37.5 mg, 75 mg, 150 mg, 300 mg, or placebo daily for 12 weeks. Randomization was stratified on the basis of compliance with primary OSA therapy. The study scheme is shown in Figure 3.

Reference ID: 4406963

Figure 3: Study 14-003



[Source: CSR, Study 14-003; Figure 1, page 31]

The endpoints for this trial were the same as in Study 14-002: MWT CFB at Week 12 and ESS score CFB in at Week 12 were the co-primary endpoints; PGIc at Week 12 was the secondary endpoint. The sequential testing procedure was performed as described for Study 14-002. For enrollment, subjects must have been 18-75 years old with a documented diagnosis of OSA according to ICSD-3 criteria.

The trial was conducted at 50 North American and nine in European sites and enrolled 476 subjects. All but two subjects received at least one dose of study medication (safety population). The mITT population consisted of 459 subjects; the per protocol population, 392 subjects; and the PK population, 343 subjects. Overall, 85% of subjects randomized to both solriamfetol and placebo completed the study. A greater percentage of subjects in the 300-mg solriamfetol group (13.6%) relative to all other treatment groups did not complete the study because of adverse events. The majority of subjects were white (76%) and male (63%), and 97% of subjects were enrolled at sites in North America. Demographic characteristics were balanced across treatment groups and fairly representative of the US target population. Median age was 55; median body mass index was 33 kg/m^2. Seventy percent of subjects were reported to be compliant with their primary OSA therapy.

Baseline CGI evaluations categorized most subjects as moderately (43%) or markedly (32%) ill. The baseline incidence of hypertension (HTN) was approximately 50% in all treatment groups. The overlap between OSA, HTN, and its relationship to solriamfetol will be explored in the safety section of this summary review. There were no important protocol violations.

Reference ID: 4406963

There was statistically significant improvement on the co-primary endpoint at all solriamfetol doses, and for the secondary endpoint on all but the lowest dose. Dr. Zhong was able to verify all of the Applicant's analyses. The Applicant's primary analyses are summarized in Table 4. Dr. Zhong created a histogram for the MWT CFB (

Reference ID: 4406963

Figure 4) showing greater fractions of solriamfetol-treated patients with improvement on MWT than placebo.

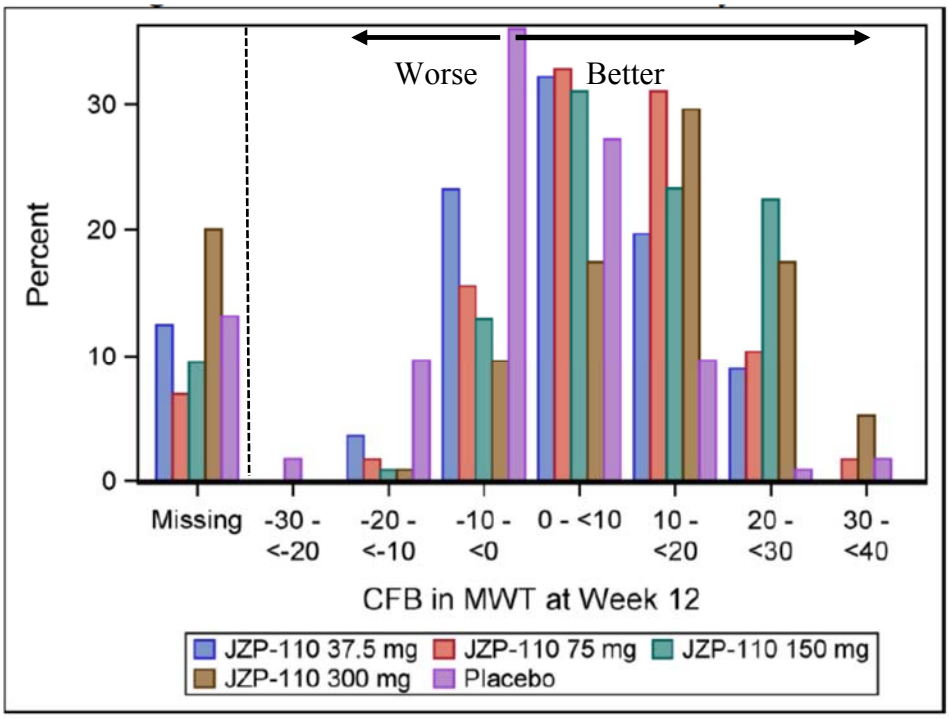
Table 4: Applicant's Primary Analyses; Study 14-003

	Placebo	Solriamfetol			
	N = 114	37.5 mg N = 56	75 mg N = 58	150 mg N = 116	300 mg N = 115
Co-Primary Endpoints					
Change in MWT from Baseline to Week 12 (Minutes)					
LS Mean (SE)	0.2 (1.00)	4.7 (1.42)	9.1 (1.36)	11.0 (0.97)	13.0 (1.04)
LS Mean Difference	NA	4.53	8.87	10.74	12.77
95% CI	NA	(1.16, 7.90)	(5.59, 12.14)	(8.05, 13.44)	(10.00, 15.55)
p-value	NA	0.009	< 0.0001	< 0.0001	< 0.0001
Change in ESS Score from Baseline to Week 12					
LS Mean (SE)	-3.3 (0.45)	-5.1 (0.64)	-5.0 (0.62)	-7.7 (0.44)	-7.9 (0.46)
LS Mean Difference	NA	-1.9	-1.7	-4.5	-4.7
95% CI	NA	(-3.4, -0.3)	(-3.2, -0.2)	(-5.7, -3.2)	(-5.9, -3.4)
p-value	NA	0.0161	0.0233	< 0.0001	< 0.0001
Key Secondary Endpoint					
PGIc: Subjects Reported Improved at Week 12					
Subjects Improved (%)					
Yes	56 (49.1)	31 (55.4)	42 (72.4)	104 (89.7)	102 (88.7)
No	58 (50.9)	25 (44.6)	16 (27.6)	12 (10.3)	13 (11.3)
% Difference from Placebo (95% CI)	NA	6.2 (-9.7, 22.2)	23.3 (8.6, 38.0)	40.5 (29.8, 51.3)	39.6 (28.72, 50.4)
p-value	NA	0.4447	0.0035	< 0.0001	< 0.0001

[Source: Adapted from CSR, Study 14-003; Table 13, page 86]

Reference ID: 4406963

Figure 4: MWT Change from Baseline at Week 12 by Treatment; Study 14-003



[Source: Biostatistics Review; Figure 21, page 49]

As in Study14-002, the Applicant excluded primary outcome observations assessed at unscheduled visits. Dr. Zhong re-coded the unscheduled visits to the nearest visits (within one week) and re-analyzed the data. No important differences were found.

In summary, Study 14-003 was a positive trial of adequate design. The limitations of the ESS as a primary endpoint were briefly discussed in Study 14-002; however, we are reassured that the MWT (co-primary) and the key secondary endpoint support solriamfetol's efficacy claim for OSA patients. All solriamfetol doses reached statistical significance on the primary and key secondary endpoints except the 37.5-mg dose, which failed only on the key secondary endpoint. Nevertheless, the positive results on the co-primary endpoints for the 37.5-mg dose strongly suggest that this dose would be effective for some OSA patients. This is important because the potential for solriamfetol to increase blood pressure and heart rate increases with exposure.

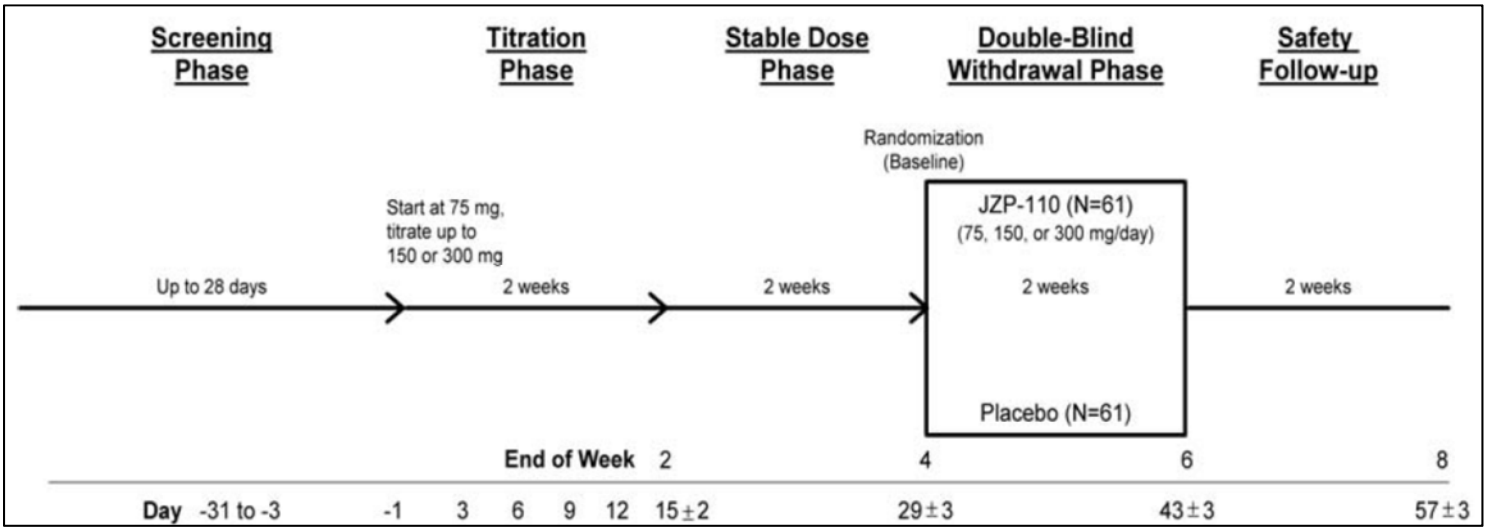
ADDITIONAL STUDIES

Study 14-004 (Indication: Obstructive Sleep Apnea)

Study 14-004 (TONES 4) was a 6-week, double-blind, placebo-controlled, randomized-withdrawal study of the safety and efficacy of solriamfetol for the treatment of EDS in adult subjects with OSA. To be enrolled, subjects must have been 18 to 75 years of age, met the ICSD-3 diagnostic criteria for OSA, had baseline mean sleep latency of < 30 minutes on the MWT, a baseline score of ≥ 10 on the ESS, and were currently using or had a history of an attempt to use an accepted therapy for the primary treatment of OSA. The study design is represented in Figure 5.

Reference ID: 4406963

Figure 5: Study 14-004



[Source: CSR, Study 14-004; Figure 1, page 11]

During a 2-week Titration Phase, subjects were titrated to the maximum dose tolerated. Subjects started at a daily dose of solriamfetol 75-mg and could titrate one dose level (to 150-mg/day or a maximum dose of 300 mg/day) every three days. The dose could be decreased to 75-mg or 150-mg, if necessary, for tolerability. After the completion of the Titration Phase, subjects who had been titrated to a tolerable dose remained on that dose for the next two weeks during an open-label Stable Dose Phase. During the 2-week Stable Dose Phase, subjects received a daily dose of solriamfetol equal to the dose that they received at the end of the Titration Phase. At the end of the Stable Dose Phase (Week 4), subjects who reported "much" or "very much improvement" on the PGIc as compared to the beginning of the Titration Phase underwent additional assessments, which included an overnight stay at the investigational site for a nocturnal PSG followed by a MWT. Subjects who completed the Week 4 Visit and who reported "much" or "very much improvement" on the PGIc and whose mean sleep latency on the MWT and ESS scores also improved were randomized in the Double-blind Withdrawal Phase. Subjects who did not report being "much" or "very much" improved on the PGIc or who did not improve on the MWT and ESS from the beginning of the Titration Phase to Week 4 were discontinued from the study. In the Double-blind Withdrawal Phase, subjects were randomized 1:1 to continue to receive solriamfetol (at the dose received in the Stable Dose Phase) or to switch to placebo for two weeks. Randomization was stratified based on subject's compliance with their primary OSA therapy.

Co-primary endpoints were MWT change and ESS change from the end of the Stable Dose Phase (Week 4) to the end of the Double-blind Withdrawal Phase (Week 6). The key secondary endpoint was the PGIc: percentage of subjects reported as worse (minimally, much, or very much) at the end of the Double-blind Withdrawal Phase (Week 6). The analysis population was the mITT population, defined as subjects who were randomized in the Double-blind Withdrawal Phase, who received at least one dose of study medication in the Double-blind Withdrawal Phase, and who had a Week 4 (end of Stable Dose Phase) and at least one post-Week 4 MWT or ESS assessment. The primary endpoints were analyzed using an ANCOVA model, with treatment and randomization stratification factor as the fixed effects and the value of the efficacy endpoint at

Reference ID: 4406963

the end of the Stable Dose Phase (Week 4) as the covariate. The LOCF method was used for subjects who discontinued early in the Double-Blind Withdrawal Phase. The key secondary endpoint (PGIc) was analyzed using chi-squared test using LOCF for missing data.

This study was conducted in 25 North American and nine European clinical sites, enrolling a total of 174 subjects. Of these, 157 (90.2%) entered the Stable-Dose phase, and 124 (71%) were randomized into the Double-Blind Withdrawal phase. Two of these subjects prematurely discontinued the study and did not have a post-efficacy baseline observation for LOCF. The remaining 122 subjects comprised the mITT population. The most frequent reason for withdrawal from the Titration phase was MWT criteria not met. Overall, the majority of subjects were white (77%), male (62%), and located in North America (81%). Mean age was 56, and mean BMI was approximately 33 kg/m^2. Baseline demographics were similar between the placebo and solriamfetol groups in the Double-Blind Withdrawal Phase. Most subjects were compliant users of a primary OSA therapy (79%). Baseline disease characteristics were also similar between the two groups. The important comorbidities most frequently reported by study subjects were (in decreasing order) hypertension (45%), gastroesophageal reflux disease (~20%), depression (19%), obesity (19%), hyperlipidemia (14%), and diabetes (13%).

The maintenance of treatment effect was statistically significant compared with placebo for the co-primary endpoints (MWT and ESS change from Week 4 to Week 6) and the key secondary endpoint (percent of patients still doing well by PGIc at Week 6), $p<0.05$. The Applicant's efficacy results are summarized in Table 5.

Table 5: Co-Primary and Key Secondary Efficacy Endpoints (Change from Week 4 to Week 6); Study 14-004

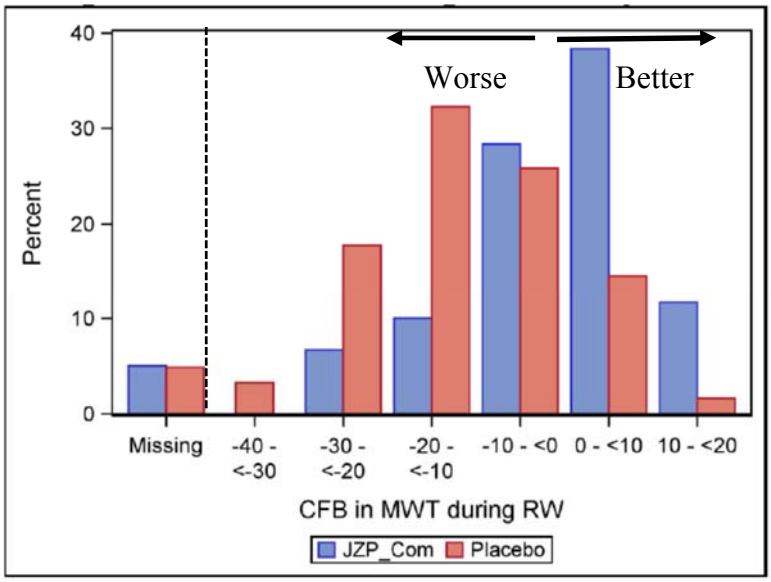
Endpoint	Placebo (N=62)	Combined Solriamfetol (N=60)
Co-Primary Endpoints		
Change in MWT (minutes)		
LS mean (SE)	-12.1 (1.3)	-0.96 (1.3)
LS mean difference (95% CI)		11.2 (7.8, 14.6)
p-value		<0.0001
Change in ESS		
LS mean (SE)	4.5 (0.71)	-0.1 (0.73)
LS mean difference		-4.6 (-6.4, -2.8)
p-value		<0.0001
Secondary Endpoint: Subjects Reported as Minimally, Much, or Very Much Worse on the PGIc		
Yes	31 (50.0)	12 (20.0)
% difference from placebo		-30.0 (-46.0, -1315)
p-value		0.0005

[Source: Adapted from CSR, Study 14-004; Table 14, page 81]

Dr. Zhong was able to verify the results of the Applicant's analyses. Because of the negligible number of subjects with missing values, Dr. Zhong did not include sensitivity analyses in her review. Dr. Zhong created a histogram for the MWT CFB during the Randomized Withdrawal Phase (Figure 6).

Reference ID: 4406963

Figure 6: MWT Change from Baseline During the Randomized Withdrawal Phase by Treatment; Study 14-004



[Source: Biostatistics' Review; Figure 30, page 56]

In summary, Study 14-004 was an adequate and well-controlled trial that showed the persistence of solriamfetol's treatment effect at 6 weeks.

<u>Study 14-005 (Indication: Obstructive Sleep Apnea and Narcolepsy)</u>

Study 14-005 (TONES 5) is an ongoing, long-term, open-label, extension study in subjects with narcolepsy and OSA. The main feature of the study is a 2-week, placebo-controlled, randomized withdrawal after ≥ 6 months of solriamfetol treatment, designed to demonstrate solriamfetol's long-term maintenance of efficacy and to evaluate potential withdrawal effects. An interim data cut was performed on April 21, 2017, to provide safety and maintenance of efficacy data for this application. The interim data cut provides the final data for the randomized withdrawal portion of the study.

Subjects from the 12-week trials (14-002 and 14-003) could roll into this study directly upon completion of their previous study and were designated Group A. As these subjects already had 12 weeks of treatment, their duration in this study was approximately 40 weeks to obtain 52 weeks of treatment. Subjects from the other studies who did not roll over directly from prior studies were designated as Group B; their time in this study was approximately 52 weeks. After 6 months of treatment, subjects were randomized to switch to placebo or continue solriamfetol at the dose they had been taking. Randomization was stratified by diagnosis (narcolepsy or OSA). The primary endpoint was the ESS change from the beginning to the end of the 2-week randomized withdrawal phase. There were two key secondary endpoints, the PGIc and CGIc, as percentage of subjects reported as worse at the end of the 2-week randomized withdrawal phase.

The analysis population was the mITT population, defined as subjects who were randomized, received at least one dose of study medication in the Double-blind Withdrawal Phase, and who

Reference ID: 4406963

had evaluable efficacy data at Week 29 (Group A) or Week 28 (Group B). An ANCOVA model was used for the primary ESS analysis. The response variable was the change from the beginning to the end of Randomized Withdrawal Period. The model included treatment group, randomization stratification factor (narcolepsy vs. OSA), and efficacy baseline as fixed effects. The PGIc and CGIc secondary endpoints were analyzed using a chi-squared test. LOCF was used to impute missing data for subjects who discontinued from the study. To address multiplicity issues in the analysis of the primary and secondary efficacy endpoints, a fixed hierarchical testing sequence (ESS, then PGIc and CGIc) was used. Interim analyses were planned in the protocol and SAP; however, specifics on the interim analyses and adjustment of alpha were missing.

A total of 640 subjects were enrolled: 227 with narcolepsy and 413 with OSA. The majority (521 subjects) had previously completed Studies 14-002 or 14-003 (Group A). Two subjects withdrew from the study prior to receiving study drug, one for "other reasons" and one due to withdrawal of consent. A total of 638 subjects, including 226 with narcolepsy and 412 with OSA, received at least one dose of solriamfetol in the open-label phase and were included in the Safety Population. The safety population for the randomized withdrawal period included 282 subjects: 79 with narcolepsy and 203 with OSA. Approximately half the patients had cataplexy. Mean baseline ESS was 16. The Applicant's results are summarized in Table 6.

Reference ID: 4406963

Table 6: Primary and Key Secondary Efficacy Endpoints; Study 14-005

Endpoint	Overall		OSA		Narcolepsy	
	Placebo (N=141)	Combined Solriamfetol (N=139)	Placebo (N=101)	Combined Solriamfetol (N=101)	Placebo (N=40)	Combined Solriamfetol (N=38)
Primary Endpoints						
Change in ESS						
LS mean (SE)	5.3 (0.4)	1.6 (0.4)	4.9 (0.5)	1.1 (0.5)	4.9 (0.6)	1.1 (0.6)
LS mean difference	NA	-3.7 (-4.8, -2.7)	NA	-3.7 (-5.1, -2.4)	NA	-3.8 (-5.5, -2.2)
p-value	NA	<0.0001	NA	<0.0001	NA	<0.0001
Key Secondary Endpoints:						
Subjects Reported as Worse on PGIc						
Yes	89 (64.5)	37 (28.2)	59 (59.0)	26 (27.7)	30 (78.9)	11 (29.7)
% (difference [Yes]) from placebo	NA	-36.2 [-47.4, -25.2]	NA	-31.3 [-44.6, -18.1]	NA	-49.2 [-68.8, -29.6]
p-value	NA	<0.0001	NA	<0.0001	NA	<0.0001
Subjects Reported as Worse on CGI-C						
Yes	90 (63.8)	39 (28.7)	63 (62.4)	27 (27.0)	27 (67.5)	12 (33.3)
% difference from placebo	NA	-35.2 [-46.1, -24.2]	NA	-35.4 [-48.2, -22.5]	NA	-34.2 [-55.3, -13.0]
p-value	NA	<0.0001	NA	<0.0001	NA	0.0029

[Source: Adapted from CSR, Study 14-005; Table 19, page 113]

In summary, Study 14-005 was an adequate and well-controlled trial with a statistically positive result. In conjunction with the data provided by Study 14-004, the study provides evidence of maintenance of effect for solriamfetol in patients treated for up to 52 weeks.

Integrated Summary of Efficacy

Solriamfetol's efficacy in improving wakefulness and reducing EDS was evaluated in three short-term placebo-controlled studies: two in patients with narcolepsy and one in patients with OSA. Studies 14-002 (narcolepsy) and 14-003 (OSA) had co-primary endpoints of MWT and ESS. We consider MWT to be an adequate efficacy measure. Although ESS has limitations, it has been widely used in sleep medicine trials and can provide useful efficacy information in conjunction with the MWT. Study ADX-N05-202 (narcolepsy) had a co-primary endpoint of MWT and CGI-C. Neither the protocol nor the SAP were considered by the review team in the Division of Psychiatry Products prior to study initiation. There are concerns about the choice of CGI-C as a co-primary endpoint, the lack of control of the Type-I error rate, and the method of imputing missing data, which together limit the strength of the findings. Nevertheless, when

Reference ID: 4406963

these three trials are evaluated collectively, they provide substantial evidence of effectiveness for the treatment of EDS in the narcolepsy and OSA patient populations.
The Applicant also submitted two double-bind, placebo-controlled, randomized withdrawal studies (14-004 and 14-005) to show maintenance of solriamfetol's effect in patients with narcolepsy and OSA. Studies 14-004 and 14-005 showed persistence of treatment effects through 6 weeks and 38 to 50 weeks, respectively.

Overall, the studies show a clear dose-response, and support starting doses of 75 and 37.5 mg for the narcolepsy and OSA populations, respectively, with a maximum dose of 300 mg in both populations. US patients were well-represented in the development program (> 90%). Three-fourths of patients were Caucasian; ~17% were Black. Male and female patients were equally represented. Median age was ~50. Dr. Zhong conducted a number of analyses to examine the treatment effects in important demographic subsets. With small numbers in most subsets, interpretation is difficult; however, the results appeared to be consistent across subsets.

8. Safety

The safety review for this application was completed by Dr. Millis; he did not find any safety signal that would preclude approval of this NDA.

In addition to the five clinical studies described in the efficacy section of this summary review, the Applicant submitted data from Phase 1 safety and PK studies, a thorough QT (TQT) study, two abuse liability studies, and three Phase 2 studies in subjects with major depressive disorder (MDD) ((b) (4) at doses up to 800 mg per day). For these additional studies, only high-level safety information was evaluated (i.e., deaths, serious adverse events, dropouts associated with adverse events) because the lack of a placebo control limits the interpretability of the data. The Applicant pooled studies according to design or diagnosis. Pool 1 consisted of the 12-week, placebo-controlled, parallel group studies in subjects with narcolepsy or OSA (ADX-N05-202, 14-002, and 14-003). Pool 2 consisted of all data from studies in narcolepsy and OSA, including short-term studies and studies with exposures considerably longer than the exposures in the placebo-controlled studies. Although the Applicant pooled the safety data in various groups, the principal group of interest is Pool 1, as it allows comparison of drug-treated and placebo-treated subjects, and of subjects with different drug doses. Because the OSA and narcolepsy populations have different risk factors, comorbidities, and concomitant medications, we focused on indication-specific data within Pool 1, particularly for cardiovascular assessment.

Pool 1 included 328 subjects with narcolepsy and 471 subjects with OSA, for a total of 799 subjects. Of these subjects, 573 received solriamfetol and 226 received placebo. The main comparison is among the five treatment groups, solriamfetol 37.5, 75, 150, and 300 mg, and placebo, and between the combined solriamfetol groups and placebo. Note that all subjects in the solriamfetol 37.5-mg group had OSA.

In Study 14-005 (the long-term, open-label study), 638 subjects were exposed to solriamfetol as of the cutoff date of April 21, 2017. This included 255 subjects with exposure < 6 months, 383 subjects with exposure > 6 months, and 18 subjects with exposure > 12 months. Although the

Reference ID: 4406963

number of subjects with exposures of > 12 months is low, the original study design allowed for exposure to solriamfetol for only up to 12 months. According to the Applicant (Integrated Summary of Safety, Table 15), total exposure was 185,527 person-days for solriamfetol and 26,497 person-days for placebo, which correspond to 508 and 73 person-years, respectively. Overall, Dr. Millis concludes that the size of the safety database is adequate.

Table 7 summarizes the demographics of the subjects participating in all 12-week placebo-controlled studies (Pool 1).

Table 7: Demographics of the Safety Population – 12-Week Placebo-Controlled Studies

Characteristic	Placebo N=226	Combined Solriamfetol N=573	Solriamfetol 37.5 mg N=58	Solriamfetol 75 mg N=120	Solriamfetol 150 mg N=218	Solriamfetol 300 mg N=217
Age (years)						
Mean (SD)	45.6 (15.4)	47.4 (14.1)	57.1 (10.2)	45.5 (15.0)	46.4 (13.4)	45.8 (13.9)
Median	48.0	49.0	59.5	47.0	48.0	46.0
Range	18, 74	18, 75	33, 72	18, 74	19, 75	18, 72
Sex, n (%)						
Male	119 (52.7)	290 (50.6)	39 (67.2)	56 (46.7)	102 (46.8)	106 (48.9)
Female	107 (47.4)	283 (49.4)	19 (32.8)	64 (53.3)	116 (53.2)	111 (51.2)
Race, n (%)						
American Indian or Alaskan Native	1 (0.4)	2 (0.4)	0	0	1 (0.5)	1 (0.5)
Asian	4 (1.8)	20 (3.5)	3 (5.2)	1 (0.8)	7 (3.2)	10 (4.6)
Black or African American	45 (19.9)	95 (16.6)	10 (17.2)	25 (20.8)	34 (15.6)	37 (17.1)
Native Hawaiian or other Pacific Islander	1 (0.4)	3 (0.5)	0	0	2 (0.9)	2 (0.9)
White	173 (76.6)	445 (77.7)	45 (77.6)	92 (76.7)	170 (78.0)	164 (75.6)
Multiple	2 (0.9)	8 (1.4)	0	2 (1.7)	4 (1.8)	3 (1.4)
Region, n (%)						
North America	215 (95.1)	524 (91.5)	55 (94.8)	104 (86.7)	206 (94.5)	199 (91.7)
Europe	11 (4.9)	49 (8.6)	3 (5.2)	16 (13.3)	12 (5.5)	18 (8.3)

[Source: Integrated Summary of Safety (ISS), modified from Table 5.3.5.3.1.2.1, page 520]

Other baseline characteristics (not shown) include mean weight = 90 kg, mean body mass index = 31, mean heart rate = 75, and mean blood pressure = 124/77 mmHg. The groups appear balanced with respect to these characteristics and seem representative of a typical US patient with narcolepsy or OSA.

Reference ID: 4406963

There was one death in the solriamfetol development program – a 70-year-old male with OSA and multiple comorbidities who was enrolled in Study 14-005. The cause of death was sepsis; there is no way to determine whether this death was causally related to solriamfetol.

The proportion of subjects with treatment-emergent adverse events (TEAEs) that led to withdrawal was higher in solriamfetol-treated subjects (6.5%) than in subjects in placebo groups (3.1%), with similar proportions in the two disease populations. These adverse events were similar to drugs that share a similar mechanism of action, such as bupropion (Table 8).

In the 12-week randomized studies in both indications, serious adverse events were reported in 1.0% of solriamfetol-treated subjects and 0.9% of placebo subjects (

Reference ID: 4406963

Table 9). These serious adverse events were isolated (only one serious adverse event per preferred term) and reported across multiple organ systems without a pattern suggestive of a pathophysiologic relationship or causality. Only two serious adverse events were reported in the CNS system-organ-class: conversion reaction and anxiety. In short, the serious adverse events reported in the placebo-controlled database do not suggest drug-related toxicity.

Table 8: Adverse Events Leading to Discontinuation in Placebo-controlled Studies by Preferred Term (≥ 2 Subjects in Combined Solriamfetol)

Preferred Term	Narcolepsy and OSA		Narcolepsy		OSA	
	Placebo N = 226	Combined JZP-110 N = 573	Placebo N = 108	Combined JZP-110 N = 220	Placebo N = 118	Combined JZP-110 N = 353
Any TEAEs Leading to Study Drug / Study Withdrawal	7 (3.1)	37 (6.5)	3 (2.8)	12 (5.5)	4 (3.4)	25 (7.1)
Anxiety	0	5 (0.9)	0	1 (0.5)	0	4 (1.1)
Dizziness	0	4 (0.7)	0	1 (0.5)	0	3 (0.8)
Nausea	0	4 (0.7)	0	1 (0.5)	0	3 (0.8)
Feeling jittery	0	4 (0.7)	0	0	0	4 (1.1)
Chest discomfort	0	3 (0.5)	0	0	0	3 (0.8)
Agitation	0	2 (0.3)	0	0	0	2 (0.6)
Restlessness	0	2 (0.3)	0	0	0	2 (0.6)
Tic	0	2 (0.3)	0	0	0	2 (0.6)
Insomnia	0	2 (0.3)	0	1 (0.5)	0	1 (0.3)
Non-cardiac chest pain	0	2 (0.3)	0	1 (0.5)	0	1 (0.3)
Cataplexy	1 (0.4)	2 (0.3)	1 (0.9)	2 (0.9)	0	0
Palpitations	0	2 (0.3)	0	1 (0.5)	0	1 (0.3)

[Source: Adapted from NDA-211230 ISS, Table 19, page 72]

Reference ID: 4406963

Table 9: Serious Adverse Events in the 12-Week Placebo-controlled Studies in Narcolepsy and OSA

Preferred Term, n (%)	Narcolepsy and OSA		Narcolepsy		OSA	
	Placebo N = 226	Combined solriamfetol N = 573	Placebo N = 108	Combined solriamfetol N = 220	Placebo N = 118	Combined solriamfetol N = 353
Any Serious Adverse Events	2 (0.88)	6 (1.05)	0	3 (1.36)	2 (1.69)	3 (0.85)
Anxiety	0	1 (0.17)	0	1 (0.45)	0	0
Back pain	1 (0.44)	0	0	0	1 (0.85)	0
Bile duct obstruction	0	1 (0.17)			0	1 (0.28)
Cholecystitis acute	0	1 (0.17)	0	1 (0.45)	0	0
Conversion disorder	0	1 (0.17)	0	1 (0.45)	0	0
Goitre	1 (0.44)	0	0	0	1 (0.85)	0
Hyperglycaemia	0	1 (0.17)	0	0	0	1 (0.28)
Non-cardiac chest pain	0	1 (0.17)	0	1 (0.45)	0	0
Road traffic accident	1 (0.44)	0	0	0	1 (0.85)	0
Sciatica	1 (0.44)	0	0	0	1 (0.85)	0
Streptococcal endocarditis	0	1 (0.17)	0	0	0	1 (0.28)

[Source: ISS, modified from Table 17, page 68]

Serious cardiovascular adverse events were reported in six subjects in the development program: all of these were reported in subjects on solriamfetol; none were on placebo, and all had been receiving solriamfetol at higher doses (150 to 300 mg/day).

For a drug that increases blood pressure and heart rate, a 6:0 difference in serious adverse cardiovascular events seems concerning; however, the difference must be considered in light of the marked 7:1 disparity in time of exposure (508 and 73 total person-years of exposure, respectively, for solriamfetol vs. placebo). If even a single serious cardiovascular adverse event had been reported in the placebo group, the numbers of events per person-year would have been essentially equivalent in the two treatment groups. Thus, the 6:0 disparity in serious cardiovascular adverse events, although worrisome on its face, seems likely to represent a chance difference.

Reference ID: 4406963

Table 10: Serious Cardiovascular Adverse Events

Subject ID	Study	Type/Phase of Study	Indication	Solriamfetol Dose	Serious Adverse Event
A	MDD-201	Placebo-controlled study	MDD	100 mg bid	myocardial infarction
B	14-005	Open-label phase of randomized withdrawal study	OSA	150 mg/day	cerebrovascular accident
C	14-005	Open-label phase of randomized withdrawal study	OSA	300 mg/day	atrial fibrillation
D	14-005	Open-label phase of randomized withdrawal study	OSA	300 mg/day	angina pectoris
E	14-005	Open-label phase of randomized withdrawal study	OSA	300 mg/day	myocardial infarction, sepsis, respiratory failure
F	14-003	Placebo-controlled study	OSA	300 mg/day	coronary artery disease

[Source: Modified from Table 57 of the Clinical Review]

Table 11 summarizes the most common TEAEs across all registration studies, in decreasing order of frequency. Dr. Millis noted that the order of frequency of TEAEs is fairly similar across the studies. The TEAE lists for the six-week randomized-withdrawal study (Study 14-004) and the long-term study (Study 14-005) did not reveal TEAEs that were not commonly reported in the 12-week placebo-controlled studies.

Table 11: Most Common Adverse Events Across Registrational Studies

Study	Indication	Most Common TEAEs
ADX-N05-202	narcolepsy	insomnia, headache, nausea, decreased appetite, anxiety, diarrhea
14-002	narcolepsy	headache, nausea, decreased appetite, nasopharyngitis, dry mouth, anxiety, diarrhea
14-003	OSA	headache, nausea, decreased appetite, anxiety, diarrhea, dry mouth, insomnia
14-004	OSA	insomnia, dry mouth, influenza, nasopharyngitis, headache
14-005	narcolepsy	nausea, headache, anxiety, nasopharyngitis, insomnia, decreased appetite, dry mouth
14-005	OSA	insomnia, headache, nasopharyngitis, dry mouth, nausea, feeling jittery, anxiety
Composite TEAE List		**headache, nausea, insomnia, decreased appetite, nasopharyngitis, anxiety, dry mouth, diarrhea, influenza, feeling jittery**

[Source: Clinical Review, Table 70, page 171]

Adverse reactions with an incidence ≥ 5% and reported more frequently with the use of solriamfetol than placebo in either the narcolepsy or OSA populations were headache, nausea, decreased appetite, anxiety, and insomnia, and these will be reported in the Adverse Reactions Section (Section 6) of labelling.

Dr. Millis analyzed effects on laboratory parameters for Studies ADX-N05-202, 14-002, and 14-003, 14-004, and 14-005, and found no clinically significant patterns.

Reference ID: 4406963

Increases in Blood Pressure and Heart Rate

Epidemiological studies have shown that increases in blood pressure increase the risk of major adverse cardiovascular events (MACE): stroke, myocardial infarction, and cardiovascular death. The absolute risk of MACE is a function of the increase in blood pressure and the baseline risk of MACE in the patient population. Although the data are not as compelling, increases in heart rate are also thought to increase the risk of MACE. Many patients for whom solriamfetol may be considered are likely to have pre-existing cardiovascular risk factors that predispose them to MACE. This is particularly true for patients with OSA, a population with high rates of hypertension, hyperlipidemia, diabetes, and obesity. Obesity is also a common co-morbidity in patients with narcolepsy. Because of these pre-existing risk factors and because drugs that increase noradrenergic tone are known to increase blood pressure and heart rate, the effects of solriamfetol on blood pressure were a focus of the review. In addition, cardiovascular adverse events were identified as adverse events of special interest for this application.

As noted above (Table 10), Dr. Millis highlighted serious cardiovascular adverse events reported in six patients in the development program, all in subjects receiving solriamfetol 150 or 300 mg per day.

In studies of both narcolepsy and OSA, the Applicant assessed blood pressure and heart rate during the MWT sessions with measurements pre-dose, and 1, 2, 4, 6, and 8 hours after dosing. Ambulatory blood pressure monitoring was also assessed at one of the visits.

Tables 12 and 13 show the blood pressure changes in narcolepsy and OSA, in Studies 14-002 and 14-003, respectively, reprinted from the Applicant's study reports and the clinical review. Dose-related increases in both systolic and diastolic blood pressure are evident 2 hours post-dose (near peak). In the narcolepsy study, the change from baseline in systolic blood pressure was approximately 5 mmHg for the 150- and 300-mg dose groups; effects were slightly less in the OSA study.

Table 12: Study 14-002 (Narcolepsy), Systolic and Diastolic Blood Pressure on MWT Days, Mean Changes from Baseline to Week 12 at Trough and Peak

Vital Sign Time Point	Parameter	Placebo (N = 59)	Solriamfetol 75 mg (N = 59)	Solriamfetol 150 mg (N = 59)	Solriamfetol 300 mg (N = 59)
Systolic BP (mmHg)					
Trough (pre-dose)	n	49	48	48	43
	Mean (SD)	-0.7 (11.6)	-2.1 (7.7)	-1.7 (11.1)	0.1 (10.8)
Peak (2 hours post-dose)	n	50	48	49	43
	Mean (SD)	-0.1 (10.2)	1.5 (10.6)	4.9 (11.2)	5.0 (9.2)
Diastolic BP (mmHg)					
Trough (pre-dose)	n	49	48	48	43
	Mean (SD)	-1.1 (6.8)	-0.6 (5.9)	-1.4 (9.9)	0.9 (8.1)
Peak (2 hours post-dose)	n	50	48	49	43
	Mean (SD)	-1.8 (8.4)	1.3 (5.7)	4.2 (7.7)	4.0 (6.8)

[Source: Study 14-002 Clinical Study Report, Table 57, page 198.]

Reference ID: 4406963

Table 13: Study 14-003 (OSA), Systolic and Diastolic Blood Pressure on MWT Days, Mean Changes from Baseline to Week 12 at Trough and Peak

Vital Sign Time Point	Parameter	Placebo (N = 119)	Solriamfetol 37.5 mg (N = 58)	Solriamfetol 75 mg (N = 62)	Solriamfetol 150 mg (N = 117)	Solriamfetol 300 mg (N = 118)
Systolic BP (mmHg)	n	99	49	53	103	91
Trough Change (pre-dose)	Mean (SD)	-1.6 (11.7)	0.2 (13.4)	0.0 (11.3)	-0.4 (11.1)	0.0 (11.7)
Peak Change (2 hours post-dose)	Mean (SD)	0.6 (10.2)	1.9 (11.6)	1.1 (10.2)	2.4 (10.3)	4.0 (13.7)
Diastolic BP (mmHg)	n	99	49	53	103	91
Trough Change (pre-dose)	Mean (SD)	-0.1 (8.3)	0.4 (7.3)	-2.1 (7.9)	-0.7 (7.1)	-0.4 (8.2)
Peak Change (2 hours post-dose)	Mean (SD)	0.5 (6.8)	0.1 (6.1)	1.0 (9.2)	1.1 (7.3)	2.1 (8.3)

[Source: Study 14-003 Clinical Study Report, Table 55, page 189.]

(b) (4)

(b) (4) additional analyses were conducted by Dr. Atul Bhattaram (Office of Clinical Pharmacology), Dr. Marc Stone (Deputy Director of Safety, DPP), and Dr. Preston Dunnmon (Division of Cardiovascular and Renal Products). Having independently analyzed the data, all agreed that solriamfetol causes dose-related increases in blood pressure and heart rate; however, for unexplained reasons, the blood pressure changes as measured by ambulatory blood pressure monitoring were inconsistent with respect to the 75- and 150-mg doses. The mean blood pressure increase for the 75-mg dose group was similar to the increase in the 300-mg dose group, whereas the 150-mg dose group showed no mean increase (i.e., it was similar to placebo). The review team reached the conclusion (b) (4) to place a warning in labeling, while expressing the changes in blood pressure and heart rate.

The review team (including consultants from the Division of Cardiovascular and Renal Products) had difficulty finding consistent and reasonable estimates for the effects of solriamfetol on blood pressure and heart rate. In essence, there was a number of ways to consider that data, and some of the data were inconsistent. We opted to place two tables in labeling, in an attempt to summarize these changes.

The first table (Table 4 in labeling) summarizes the data from the MWT sessions. The table shows, by indication (narcolepsy and OSA) and dose (37.5, 75, 150, and 300 mg), the mean

Reference ID: 4406963

changes from baseline for the week (1, 4, or 12) and time point (1, 2, 4, 6, or 8 hours post-dose) with maximal changes in systolic blood pressure, diastolic blood pressure, and heart rate.

The second table (Table 5 in labeling) shows the mean changes from baseline in systolic/diastolic blood pressure and heart rate as determined during 24-hour ambulatory monitoring at Week 8 in the narcolepsy and OSA studies, Studies 14-002 and 14-003, respectively.

The main messages included in Section 5.1 of labeling are: 1) solriamfetol increases blood pressure and heart rate in dose-related fashion; 2) increases in blood pressure increase the risk of MACE, particularly in patients where the background risk of MACE is higher (such as patients with OSA, and, to a lesser extent, narcolepsy); 3) blood pressure should be assessed and controlled before initiating treatment; 4) blood pressure should be monitored (b) (4) during treatment; 5) judicious use is warranted in patients at higher baseline risk of MACE and with concomitant drugs that increase blood pressure; 6) need for treatment should be periodically reassessed; and 7) discontinuation of solriamfetol is recommended if blood pressure cannot be controlled.

9. Advisory Committee Meeting

No advisory committee meeting was held for this application. Although solriamfetol is a new molecular entity, the evaluation of the safety data did not reveal particular safety issues that were unexpected for this class of drugs, the design and results of the efficacy trials did not pose particular concerns or challenges, and the efficacy findings were clear.

10. Pediatrics

This application did not include pediatric data. The narcolepsy indication is exempt from the Pediatric Research Equity Act (PREA) requirement for pediatric studies because the Applicant has been granted orphan drug designation for the indication. In their initial Pediatric Study Plan (iPSP) the Applicant requested an indication-specific waiver for neonates, infants, children, and adolescents, on the basis that clinical studies in these age groups would be highly impracticable or unfeasible. Surgical management is the treatment of choice for pediatric patients with OSA and professional treatment guidelines do not recommend pharmacological interventions. In light of the above, we granted the Applicant's request for a waiver.

11. Other Relevant Regulatory Issues

Good Clinical Practices Audit

Two study sites were inspected by the Office of Scientific Investigations (OSI). These sites were identified for a Good Clinical Practices (GCP) audit based on relative importance of the study to the NDA and the numbers of subjects per site. No special concerns were identified for protocol violations or investigators' conflict of interests. Overall, the data submitted by the Applicant in support of this NDA are acceptable.

Reference ID: 4406963

Human Reproduction and Pregnancy
The Division of Pediatric and Maternal Health (DPMH) conducted a data review regarding solriamfetol's use during pregnancy. The available data are very limited at the time of this writing and are insufficient to assess drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are no data available on the presence of solriamfetol or its metabolites in human milk, the effects on breastfed infants, or the effect of solriamfetol on milk production. Nonclinical studies indicate that solriamfetol is present in rat milk; thus, it is likely for the drug to be present in human milk. DPMH recommends a lactation study (milk only) to characterize the drug in the breast milk and its effects on the breastfed child (see Section 13).

DPMH recommends a pregnancy registry (two studies to be included: A prospective, registry based observational exposure cohort study and an additional study that uses a different study design [for example a retrospective cohort study using claims or electronic medical record data or a case control study]) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age in women exposed to solriamfetol during pregnancy compared to an unexposed control population (see Section 13).

DPMH's recommendations for labeling have been incorporated.

Abuse Potential and Scheduling
Based on the findings of the human abuse liability study, low rate of abuse-related AEs in clinical trials, absence of withdrawal symptoms, and lack of evidence of drug abuse and diversion during the clinical trials, the Controlled Substance Staff (CSS) team concurs with the Applicant and recommends scheduling of solriamfetol as a Schedule IV drug.

12. Labeling

In addition to the labeling recommendations already described in this review, the following section will discuss additional revisions by the review team that were incorporated into the label:

- **Contraindications**: Because of its mechanism of action (i.e., DNRI) and expected increase in the risk of a hypertensive reaction, solriamfetol is contraindicated in patients receiving concomitant treatment with monoamine oxidase (MAO) inhibitors, or within 14 days following discontinuation of monoamine oxidase inhibitor.
- **Warnings and Precautions**. In addition to the warning previously discussed, this section was extensively revised to more accurately describe dose-related blood pressure and heart rate increases associated with solriamfetol treatment. This section now communicates the risks of MACE, particularly in patient with comorbid conditions (e.g., diabetes, obesity, hyperlipidemia, etc.), and potential interventions by prescribing clinicians. The team agrees with the Applicant's warnings to prescribers to ensure that blood pressure is adequately controlled before initiating solriamfetol.
- **Adverse reactions.** This section was also extensively revised as follows:
    - The clinical trial experience section was modified to describe the pooling of the three 12-week placebo-controlled studies used to support the Agency's labeling recommendations.

Reference ID: 4406963

- The adverse reaction table for the pooled was updated with comparisons between solriamfetol and placebo by associated condition (i.e., narcolepsy or OSA). A dose-dependent AE table now describes all doses, including 37.5-mg.
- Tables were added to describe the (b) (4) ambulatory blood pressure and heart rate data.

- **Clinical Studies**. Section 14 has been extensively re-written to more accurately describe the pivotal clinical studies, primary outcomes, and key secondary endpoints (as appropriate).
- A Medication Guide was requested by the Agency and it has been negotiated to an agreement.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
The need for a REMS was evaluated by the Division of Risk Management (DRISK). The DRISK reviewer, Naomi Redd, determined that a REMS was not needed because the risks associated with solriamfetol use could be adequately managed with labeling and the Division agreed with their recommendation. Dr. Redd opines that "AEs such as cardiac events, blood pressure increases, and the potential for psychiatric events are not new or unusual events and are seen in other treatments for these disorders; thus, it would be expected that the prescribing population would be knowledgeable in the management thereof. The abuse potential for solriamfetol is like that of other Schedule IV drugs indicated in the management of wakefulness and narcolepsy."

Postmarketing Requirements (PMRs) and Commitments (PMCs)
The following postmarketing requirements (PMRs) are requested by the review team and will be conveyed to the Applicant in the Approval Letter:

3475-1 A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to solriamfetol during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

Final Protocol Submission:	September 20, 2019
Study/Trial Completion:	September 20, 2029
Final Report Submission:	September 20, 2030

3475-2 An additional pregnancy study that uses a different design from the Pregnancy Registry (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a

Reference ID: 4406963

case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to solriamfetol during pregnancy compared to an unexposed control population.

Final Protocol Submission:	September 20, 2019
Study/Trial Completion:	September 20, 2024
Final Report Submission:	September 20, 2025

3475-3 Perform a lactation study (milk only) in lactating women who have received therapeutic doses of solriamfetol using a validated assay to assess concentrations of solriamfetol in breast milk and the effects on the breastfed infant.

Final Protocol Submission:	September 20, 2019
Study/Trial Completion:	September 20, 2020
Final Report Submission:	September 20, 2021

The Applicant has expressed agreement with these three PMRs and with the proposed timeframes.

Reference ID: 4406963

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JAVIER A MUNIZ
03/20/2019 05:20:54 PM

TIFFANY R FARCHIONE
03/20/2019 05:21:59 PM

ELLIS F UNGER
03/20/2019 05:24:44 PM