EU Risk Management Plan for Sunosi® 75 mg film-coated tablets and Sunosi® 150 mg film-coated tablets (solriamfetol)

RMP Version number: 2.0

Data lock point for this RMP: 19 March 2025

Date of final sign-off: 10 June 2025

Rationale for submitting an updated RMP: This update of the RMP is to align with the Rapporteurs assessment report received on 14 November 2024 for the responses to the Request for supplementary information with respect to the EU PASS study (JZP865-401) and to support the renewal of the marketing authorisation application (EMEA/H/C/004893/R/0023).

Summary of significant changes in this RMP:

- Part II: Module SIII: The cumulative clinical trial exposure data was updated.
- Part II: SVII.1.2: 'Missing information 2: use in lactating women' was re-inserted.
- Part II: SVII.2: SmPC text on breast-feeding was removed as not final yet.
- Part III.1: Safety concern name 'Serious psychiatric events' was added to the follow-up questionnaire for Depression including suicidality.
- Annex 4: Format and the structure of the specific adverse reaction questionnaires were updated in line with the Guideline on specific adverse reaction follow-up questionnaires (EMA/PRAC/490455/2023).

Details of the superseded RMP:

Version number: 1.0

Approved with procedure: EU/1/19/1408/001-010

Date of approval (opinion date): 22 September 2023

QPPV name: Jack O'Reilly

QPPV signature: 

Table of content

Table of Content

LIST OF TABLES

Part I: Product(s) Overview

Table Part I.1: Product Overview

Active substance(s) (INN or common name):	(*R*)-2-amino-3-phenylpropylcarbamate hydrochloride (solriamfetol), also known as JZP-110.
Pharmacotherapeutic group(s) (ATC Code):	Centrally acting sympathomimetics (N06BA14)
Marketing Authorisation Holder:	Atnahs Pharma Netherlands B.V.
Medicinal products to which this RMP refers:	2
Invented name(s) in the European Economic Area (EEA):	Sunosi 75 mg film-coated tablets Sunosi 150 mg film-coated tablets
Marketing authorisation procedure:	Centralised
Brief description of the product:	Chemical class: Phenylalanine derivative
	Summary of mode of action: The mechanism(s) of solriamfetol to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnoea has not been fully characterised. However, its efficacy could be mediated through its activity as a dopamine and norepinephrine reuptake inhibitor (DNRI).
	Important information about its composition: N/A
Hyperlink to the Product Information:	Section 1.3.1 Product Information
Indication(s) in the EEA:	Current: Improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy (with or without cataplexy). Improve wakefulness and reduce excessive daytime sleepiness (EDS) in adult patients with obstructive sleep apnoea (OSA) whose EDS has not been satisfactorily treated by primary OSA therapy, such as continuous positive airway pressure (CPAP).
	Proposed: Not applicable
Dosage in the EEA:	Current: **Narcolepsy** The recommended starting dose is 75 mg once daily, upon awakening. If clinically indicated in patients with more severe levels of sleepiness, a starting dose of 150 mg may be considered. Depending on clinical response, the dose can be titrated to a higher level by doubling the dose at intervals of at least 3 days, with a recommended maximum daily dose of 150 mg once daily.

	OSA The recommended starting dose is 37.5 mg once daily, upon awakening. Depending on clinical response, the dose can be titrated to a higher level by doubling the dose at intervals of at least 3 days, with a recommended maximum daily dose of 150 mg once daily.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths:	Current: Each film-coated tablet contains solriamfetol hydrochloride equivalent to 75 mg or 150 mg of solriamfetol.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Treatment of Excessive Daytime Sleepiness in Patients with Narcolepsy

Incidence and prevalence:

Narcolepsy is a lifelong neurologic disease for which no cure has been identified. It affects approximately 4.7 per 10,000 (0.047%) in the general population of five European countries (United Kingdom (UK), Germany, Italy, Portugal and Spain; Ohayon et al, 2002). Prevalence is estimated at 1 in 2000 individuals in the United States and an estimated 0.02% to 0.067% of the population worldwide (Ohayon, 2007). There is a substantial amount of evidence that there are no differences in the disease pathophysiology and core symptoms as well as co-morbidities and treatment approaches in patients with excessive daytime sleepiness (EDS) associated with narcolepsy between Europe and North America (Billiard et al, 2006; Billiard et al, 2011; Broughton, 1981; Daniels et al, 2001; Khatami et al, 2016; Maski et al, 2017; Morgenthaler et al, 2007; Ohayon, 2013; Ruoff et al, 2017; Vandeputte & Weerd, 2003).

Demographics of the population in the narcolepsy indication and risk factors for the disease:

Narcolepsy affects both males and females and usually begins between the ages of 10 and 20 years with the sudden onset of persistent daytime sleepiness. The aetiological risk factors for narcolepsy are not fully elucidated, but likely include genetic, environmental, and possibly autoimmune-related factors. With respect to genetic/environmental risk factors, narcolepsy with cataplexy is closely associated with certain human leukocyte antigen (HLA) subtypes; the association with HLA subtype DQB1*0602 is well established in the aetiology of narcolepsy with cataplexy.

The main existing treatment options:

Two drugs are authorised in the European Union (EU) for the treatment of narcolepsy in adult patients: sodium oxybate (Xyrem®; indicated only in narcolepsy patients with cataplexy) and pitolisant (Wakix®). Modafinil (Provigil®) is authorised for the treatment of excessive sleepiness in adult patients with narcolepsy (with or without cataplexy).

These available options for treating EDS in narcolepsy are all associated with one or more inadequacies in meeting patient needs with respect to efficacy or safety.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Excessive daytime sleepiness is a defining characteristic of narcolepsy, and the degree of EDS is severe in most patients. The consequences of not treating or inadequately treating EDS include unsafe driving, impaired daytime functioning and cognition, decreased productivity and quality of life. Narcolepsy patients suffer impaired psychosocial functioning, with an associated socioeconomic burden related to reductions in quality of life and work performance (Dodel et al, 2004; Dodel et al, 2007; Ingravallo et al, 2012; Jennum et al, 2012). Because of the impairment related to this chronic disorder, patients also are at substantially increased risk of accidents while driving or when operating heavy equipment, adding marked mortality to this patient population (Philip et al, 2010; Smolensky et al, 2011).

Important co-morbidities:

A general tendency toward overweight and obesity is common in narcolepsy (Okun et al, 2002), and adults with narcolepsy have been shown to have a significantly greater body mass index (BMI) than controls (Ohayon et al, 2005). Narcolepsy has a profound impact on the lives of patients due to psychiatric and medical comorbidities, reduced health-related quality of life issues and increased mortality (Black et al, 2017; Ruoff et al, 2017; Ohayon et al, 2014; Daniels et al, 2001; Dodel et al, 2007; Vignatelli et al, 2004). Patients with narcolepsy have more frequent psychiatric disorders,

specifically higher rates of depression and anxiety disorders (Daniels et al, 2001; Broughton et al, 1981; Vandeputte & Weerd, 2003; Ruoff et al, 2017; Ohayon, 2013), compared to controls. In addition, results from a large population-based study showed that patients with narcolepsy have a higher prevalence for mental illness, diseases of the digestive system, and diseases of the nervous system/sense organs, compared to controls (Black et al, 2017).

Treatment of Excessive Daytime Sleepiness in Patients with Obstructive Sleep Apnoea

Incidence and prevalence:

Prevalence estimates for obstructive sleep apnoea (OSA) are similar between North America and Europe and higher in certain population subsets, including overweight or obese people, males, and older individuals. Based on a systematic review, the prevalence of OSA in adults in the general population is 9% to 38% (Senaratna et al, 2017). The prevalence of EDS associated with OSA is approximately 3% to 7% for adult men and 2% to 5% for adult women in the general population (Punjabi, 2008). There is a substantial amount of evidence that there are no differences in the disease pathophysiology and core symptoms as well as co-morbidities and treatment approaches in patients with EDS associated with OSA between Europe and North America (AASM 2014; Epstein et al, 2009; Fietze et al, 2011; Garvey et al, 2015; Gay et al, 2006; Hedner et al, 2011; Jennum and Riha, 2009; Morgenthaler et al, 2007; Punjabi, 2008; Randerath et al, 2011).

Demographics of the population in the OSA indication and risk factors for the disease:

Several risk factors have been identified for the development of OSA, including obesity (Garvey et al, 2015). Other risk factors include aging, male gender, craniofacial abnormalities, smaller upper airway anatomy, and genetic predisposition (Young et al, 2004).

The main existing treatment options:

Positive airway pressure (PAP) applied through a nasal, oral, or oronasal interface during sleep is considered to be the reference standard treatment for OSA by the European Respiratory Society (ERS) (Fietze et al, 2011, Randerath et al, 2011). When PAP is not accepted by the patient or when it is not tolerable or effective, alternative therapies used for the primary treatment of OSA may include behavioural therapy, use of an oral appliance, or surgical intervention (Epstein et al, 2009).

Even with successful stabilisation of the airway, EDS can continue to be a problem for patients with OSA. The prevalence of residual EDS in OSA patients with compliant use of PAP has been estimated to be 6% based on data from a multicentre study in France (Pépin et al, 2009) and 13% based on data from the French National Sleep Registry (Gasa et al, 2013). In addition, although primary OSA therapy can be highly successful in treating the underlying airway obstruction, some patients who have EDS are unable to use these primary therapies or are inadequately compliant with their use (for review, Vanderveken 2010).

In 2021, Ozawade® (pitolisant) was approved for OSA patients in the EU. Modafinil was previously authorised in this population, but the indication was withdrawn on recommendation of the Committee for Medicinal Products for Human Use (CHMP) during an Article 31 review of Directive 2001/83/EC in 2011 on the grounds that its benefit-risk balance continued to be negative. Other prescription drugs are also used off-label for the treatment of EDS in OSA, including traditional stimulants (e.g., amphetamines); however, there is little clinical evidence to support their use in OSA. These agents are not ideal as many of them carry substantial abuse liability and may induce adverse effects.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Patients often complain of EDS, non-restorative (unrefreshing) sleep or fatigue and may also report nocturnal breathing disturbance such as snoring, gasping, choking, or pauses in breathing. During the day, their sleepiness is most evident during relaxing or inactive situations; however, with extreme sleepiness, sleep may occur while actively conversing, eating, walking, or driving (AASM, 2014). This pathological sleepiness often continues despite primary treatment of the airway obstruction with PAP or other therapies (AASM 2014; Gay et al, 2006; Fietze et al, 2011; Randerath et al, 2011).

The adverse consequences of EDS in OSA include decreased productivity, impaired daytime functioning and cognition, and poor quality of life (Nena et al, 2010; Omachi et al, 2009; Silva et al, 2009). Impairments in motivation and mood, and increases in depression and anxiety are also associated with EDS in OSA (Bixler et al, 2005; Gasa et al, 2013; Lee et al, 2015; Vernet et al, 2011). Furthermore, patients with untreated OSA are at greater risk for automobile accidents compared to healthy subjects without OSA because of an inability to maintain alertness or to stay awake behind the wheel, adding marked morbidity and mortality to this patient population (Barbé et al, 1998; Findley et al, 1999; Sassani et al, 2004; Smolensky et al, 2011; Philip et al, 2013).

Important co-morbidities:

Cardiovascular (CV) comorbidities, such as hypertension, coronary artery disease, and cerebrovascular disease, are associated with OSA (Garvey et al, 2015, Lee et al, 2008). Among 11,900 participants in the multi-national European Sleep Apnoea Cohort (ESADA) study, OSA severity indices, and in particular the oxyhaemoglobin desaturation index, were strong independent predictors of hypertension (Tkacova et al, 2014). There are also co-morbid relationships between OSA, obesity, and metabolic disease (Garvey et al, 2015; Lee et al, 2008). In a large European Sleep Apnoea Cohort study with over 6,000 subjects, severe OSA was associated with an increased likelihood (approximately a 2-fold increase) of concomitant Type 2 diabetes compared to controls (Kent et al, 2014).

Part II: Module SII - Non-clinical part of the safety specification

No significant safety concerns for the clinical use of solriamfetol arose from toxicology studies. The principal toxicities noted at high doses of solriamfetol in animal studies were consistent with the compound's mechanism of action as a dopamine and norepinephrine reuptake inhibitor (Baladi et al, 2018).

Key safety findings from nonclinical studies and relevance to human usage are summarised below.

Table Part II: Module SII.1: Key Safety Findings from Nonclinical Studies

Key Safety Findings (from Nonclinical Studies)	**Relevance to Human Usage**
Toxicity	
Repeat Dose Toxicity Studies	
In rats, repeated daily oral doses of ≥253 mg/kg of solriamfetol for 6 months (≤19 times the human exposure [AUC] at a daily MRHD of 150 mg) were associated with dose-related decreases in body weight and body weight gains and reductions in food consumption.	Adverse drug reactions of decreased appetite and decreased weight were observed in the 12-week placebo-controlled trials; these events were mild to moderate in nature and did not lead to discontinuation from the study for the majority of subjects.

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Reproductive and Developmental Toxicity	
Fertility Solriamfetol did not affect fertility or sperm parameters when administered orally to male rats for 8 weeks at doses of 35 and 110 mg/kg/day, which are approximately 2 and 7 times the maximum recommended human dose (MRHD), based on mg/m^2 body surface area. At 350 mg/kg/day, which is approximately 22 times the MRHD based on mg/m^2 body surface area, solriamfetol decreased sperm count and sperm concentration without affecting fertility. Solriamfetol did not affect fertility when administered orally to female rats for 2 weeks premating, during mating, and through gestation day 7 at 15, 67, and 295 mg/kg/day, which are approximately 1, 4, and 19 times the MRHD, based on mg/m^2 body surface area. *Developmental Toxicity* In pregnant rats, oral administration of Sunosi drug substance at ≥67 mg/kg/d (approximately 4 times the MRHD on a body surface area [mg/m^2] basis) during the period of organogenesis was associated with maternal toxicity and embryofoetal toxicity in the form of increased early and total resorptions, post-implantation losses, total implantation losses, and decreased foetal weights. Solriamfetol at 19 times the MHRD increased the incidence of foetal anomalies that included severe stern brae malalignment, hindlimb rotation, bent limb bones, and situs inversus. In rats, the exposure margins at the maternal and development no observed adverse effect level (NOAEL) were below the human exposure (0.6 – 0.7 based on area under the curve (AUC)) at the MRHD. In pregnant rabbits, oral administration of solriamfetol during the period of organogenesis caused maternal toxicity of body weight loss and decreased food consumption, slight to moderate foetal stern brae malalignment, and embryofoetal toxicity in the form of decreased foetal weights. In rabbits, the NOAEL for maternal and foetal toxicity is approximately 5 times the MRHD (based on mg/m^2 body surface area).	There are limited data on the use of solriamfetol in pregnant women. The effects of solriamfetol on fertility and embryofoetal development in humans are unknown.

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Pre- and Post-natal Development: Rats In rats exposure levels (AUC) of above 0.6 – 0.7 the human exposure (AUC) at the MRHD during pregnancy and lactation resulted in maternal toxicity and adverse effects on growth and development in the offspring. At exposure levels (AUC) 8 to 12 times the human exposure (AUC) at the MRHD no long-term effects on learning and memory were observed but mating and pregnancy indices of the offspring were decreased.	
Lactation	
Solriamfetol was present in the milk of female rats that received daily oral doses of Sunosi ranging from approximately 2 to 22 times the MRHD on a body surface area (mg/m^2) basis from day 6 of presumed gestation to Day 20 postpartum or Day 24 of presumed gestation. Mean solriamfetol concentrations in rat plasma and milk increased with dose in an approximately proportional manner. The mean solriamfetol milk to plasma ratio was similar between groups: 3.86 for 35 mg/kg/d, 4.25 for 110 mg/kg/d, and 3.30 for 350 mg/kg/d.	Completed study JZP110-401 confirmed that solriamfetol is excreted in human milk and the exposure is approximately 2-fold higher on average in milk, than in plasma.
Genotoxicity	
Solriamfetol was negative for genotoxic potential in a battery of bacterial and mammalian in vitro assays and an in vivo mouse bone marrow micronucleus assay.	Non-clinical data reveal no special hazard for humans based on conventional studies of genotoxicity.
Carcinogenicity	
Solriamfetol was not tumorigenic in mice or rats. Daily oral administration of solriamfetol to male and female mice for up to 104 weeks at dose levels that produced up to about 7 times the plasma exposure (AUC) in humans at the MRHD was not associated with drug-induced neoplasms. Daily oral administration of Sunosi drug substance to male and female rats for up to 101 weeks at dose levels that produced up to about 18 times the plasma exposure (AUC) in humans at the MRHD was not associated with drug-induced neoplasms.	The carcinogenic potential of solriamfetol in humans is unknown.

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Safety Pharmacology	
Central Nervous System	
In repeated dose studies in mice (duration 3 months), rats (duration 6 months with a 3-month recovery period) and dogs (duration 12 months with a 3-month recovery period) with daily oral application, safety factors for solriamfetol (based on animal to human AUC exposure ratios at the respective NOAEL and the maximum recommended human dose of 150 mg/day) were approximately 1, mainly due to exaggerated pharmacological effects on central nervous system (CNS) activity.	Adverse drug reactions of irritability, agitation, and feeling jittery were reported in the 12-week placebo-controlled trials. These events were generally mild to moderate in severity and did not lead to discontinuation from the study for the majority of subjects.
Cardiovascular System	
Slight effects on blood pressure (BP) and heart rate (HR) in laboratory animals given oral doses of solriamfetol. *Cardiac Electrophysiology* In vitro and in vivo safety pharmacology evaluations indicated solriamfetol had minimal effects on CV function. Concentrations of solriamfetol up to 10 µM had no effect on rapid delayed rectifier potassium current (I_{Kr}) in the human ether-a-go-go-related gene (hERG) assay. Solriamfetol had no notable effects on cardiac contractility in isolated guinea pig atria. Solriamfetol had no relevant effects on electrophysiological parameters or early after-depolarizations in isolated rabbit Purkinje fibres. Solriamfetol treatment did not result in prolongation of the electrocardiogram (ECG) QTc interval in anesthetized guinea pigs or beagle dogs.	In the 12-week placebo-controlled trials, dose-dependent increases in BP and HR were observed with solriamfetol treatment. The effect of solriamfetol on the QT/QTcF interval was investigated in a single-centre, randomised placebo and positive controlled double-blind, 4-period crossover thorough QT study in 60 healthy patients (CSR 15-002). At a supratherapeutic dose of 900 mg (6 times the maximum recommended dosage), solriamfetol did not prolong the QTcF interval to a clinically relevant extent. The upper bounds of the 2-sided 90% CIs for ddQTcF between the 900 mg dose and placebo were < 10 msec at all post-dose time points. This finding was supported in 12-week randomised, placebo-controlled studies in patients with narcolepsy or OSA, where solriamfetol at doses up to 300 mg did not have an effect on QTcF prolongation.

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Renal System	
In rats, repeated daily oral doses of 379 mg/kg/d for 3 weeks resulted in no substantial adverse effects on clinical chemistry and urinalysis parameters (decreased urine pH, increased urine volume), and no changes in kidney weight or gross pathologic findings except swelling and vacuolation were noted with light and electron microscopy in papilla, collecting ducts and thin loop of Henle, and/or pelvic epithelium. No changes in plasma or urinary parameters indicative of kidney injury and no changes in mRNA levels of 4 genes in kidney tissue that are regarded as nephrotoxicity biomarkers (kidney injury molecule-1 [KIM-1], lipocalin-2 [LCN2], clusterin (Clu), and SPP1 [osteopontin]) were noted.	The absence of degenerative/necrotic findings in this study, as confirmed by histopathology, electron microscopy, and the absence of obvious adverse effects on biochemical markers for structural damage suggested kidney findings obtained in solriamfetol repeat-dose toxicity studies were of a reactive/adaptive nature and do not suggest that there will be any adverse reactions in humans related to solriamfetol excretion in urine.
Hypothalamus-Pituitary-Adrenal (HPA) Axis	
Assessments of main components of the HPA axis, limited to the measurement of plasma corticosterone levels and plasma/urine levels of vasopressin in a single repeat-dose study in rats, were not sufficient to draw definitive conclusions concerning HPA axis activation by solriamfetol. Though animals in the solriamfetol repeat-dose toxicity studies variously showed clinical signs of stress, on the basis of the available data, these clinical signs were not considered related to chronic overdrive of the HPA axis.	No treatment-emergent adverse events indicative of immunotoxicity were reported in the solriamfetol clinical programme.
Abuse and Dependence	
Solriamfetol was not intravenously self-administered by rats across a range of doses, including doses larger than those of the positive control (cocaine), and did not produce significant conditioned place preference. Solriamfetol fully and partially generalized to cocaine and amphetamine discriminative stimulus effects, respectively.	In a dedicated human abuse liability study (14-001) conducted in recreational drug users, ratings of momentary and overall "drug liking" and ratings of desire to "take again" were significantly lower than doses of phentermine, which is a weak stimulant drug. In addition, there were no indicators of drug abuse or misuse observed in the target populations across any of the Phase 2 and Phase 3 clinical trials. There were also no signs or symptoms of physical dependence observed after abrupt cessation of treatment in patients who received placebo during the 2-week randomized withdrawal periods in studies 14-004 and 14-005 (after 4 weeks and at least 6 months of treatment, respectively).

Table Part II: Module SII.2 summarises updated exposure margins extrapolated from no observed adverse effect level (NOAELs) in pivotal repeat-dose studies (additions italicized).

Table Part II: Module SII.2: Safety Ratios Comparing Exposures in Mice, Rats, Dogs, and Humans Following Administration of solriamfetol

Species	Study No.	Duration, ROA	NOAEL (mg/kg)	AUC_{0-24h} (or $0-\infty$) (ng·h/mL)	Safety Ratio Based on AUC
Mouse	JNJ-TOX-6128	3 months, PO	17	2955	0.17
Rat	JNJ-5651	2 weeks, PO	*29 (F)*	*11,330*	*0.66*
Rat	Pharmakon 0470RY01-001	90 days, PO	*29 (F)*	*7060*	*0.41*
Rat	JNJ-TOX-5705	6 months, PO	*29* [a]	*12,189*	*0.71*
Rat	JNJ-6677	2 weeks, IV	*29*	*11,560*	*0.68*
Dog	Pharmakon 0470DY01-002	90 days, PO	*23*	*79,125*	*4.6*
Dog	JNJ-TOX-5706	52 weeks, PO	8	14,600	0.85
Dog	JNJ-TOX-6574	2 weeks, IV	ND	–	–
Human	15-002 and 5-009	-	5 [b]	17,096 [c]	NA

[a] Findings observed at 29 mg/kg/d (waste of water, agitation, salivation, serum chemistry variances) were considered non-adverse because they were isolated, not associated with related pathology, and/or below levels of toxicological concern.

[b] Based on maximum daily dose of 300 mg and 60 kg body weight.

[c] Human $AUC_{0-\infty}$ derivation based on the PK data averaged from two solriamfetol single-dose 300-mg clinical studies in healthy human volunteers (CSR 15-002 and CSR 15-009).

CSR=clinical study report; F=female; NA=not applicable; ND=not determined; NOAEL=no observed adverse effect level; ROA=route of administration

Part II: Module SIII - Clinical trial exposure

No clinical trials have been performed by Atnahs. Legacy clinical trial data is available from clinical trials sponsored by the previous MAH Jazz Pharmaceuticals and Axsome Therapeutics Inc.
The estimates of overall cumulative subject exposure since the Development International Birth Date (DIBD) to 19 March 2025 by duration of exposure, age group and gender and ethnic group are provided in the tables below.

Table SIII.1: Duration of exposure

Indication	**Study**	**Solriamfetol**	**Blinded Study Drug**	**Placebo**	**Active Control**
Healthy Subjects	YUCIC-9603-01	24		24	
	R228060-P01-101	4			
	YUKIC-9702-01	40		10	
	R228060-NED-1	93		30	
	R228060-SAB-101	18		18	18
	14-001	43		41	40
	15-001	31			
	15-002	60		59	58
	15-009	32			
	JZP110-401	6			
	IGN-B0301-01	15			
	Total	**366**		**182**	**116**
MDD	SOL-MDD-301[a]		345		
	SKUP-9801	27		8	
	R228060-USA-10	61		16	
	R228060-MDD-201	245		121	122
	Total	**333**	**345**	**145**	**122**
ADHD	SOL-ADHD-301	344		172	
	Total	**344**		**172**	
BED	SOL-BED-301[a,b]		168		
	SOL-BED-303[a]	26			
	Total	**26**	**168**		
OSA	15-004	34		34	
	14-003	355		119	
	14-004	174		62	
	JZP110-405	59		59	
	IGN-B0301-03	102		102	
	Total	**724**		**376**	
Narcolepsy	15-005	24		24	

Indication	Study	Solriamfetol	Blinded Study Drug	Placebo	Active Control
	ADX-N05-201	33		33	
	ADX-N05-202	44		49	
	14-002	177		59	
	Total	**278**		**165**	
Narcolepsy + OSA	14-005	131[c]		142	
	Total	**131[d]**		**142**	
Paediatric Narcolepsy	JZP865-101	12		0	
	Total	**12**		**0**	
Parkinson's Disease	JZP166-201	56		10	
	Total	**56**		**10**	
SWD	SOL-SWD-301[a]		17		
	Total		**17**		
Total		**2,270**	**530**	**1,192**	**238**

ADHD = attention deficit hyperactivity disorder; BED = binge eating disorder; MDD = major depressive disorder; OSA = obstructive sleep apnoea; SWD = shift work disorder

[a] Study is ongoing. Cutoff date is 19Mar2025.

[b] Study SOL-BED-301 is blinded. Completers from the blinded study are rolled over into SOL-BED-303 and dosed with open-label study drug. Thus, this subject count does not include subjects that have rolled over into the open-label study.

[c] Since Study 14-005 enrolled subjects that rolled over from previous studies in OSA or narcolepsy, only those subjects on placebo during the parent study were included in the cumulative exposure estimate.

Table SIII.2: Age group and gender

Indication	Study	Age	Number of Subjects Exposed to Solriamfetol			
		Mean (Range)	Male	Female	Unknown	Total
Healthy Subjects	YUCIC-9603-01	35.0 (22-47)	24	0	0	24
	R228060-P01-101	48.8 (41-59)	4	0	0	4
	YUKIC-9702-01	35.2 (22-50)	40	0	0	40
	R228060-NED-1	31.4 (18-55)	47	46	0	93
	R228060-SAB-101	43.1 (34-51)	12	6	0	18
	14-001	29.3 (19-52)	32	11	0	43
	15-001	58.5 (29-80)	18	13	0	31
	15-002	36.9 (18-53)	26	34	0	60
	15-009	35.6 (19-54)	16	16	0	32
	JZP110-401	28.7 (21-35)	0	6	0	6
	IGN-B0301-01	30.7 (26-40)	13	2	0	15
	Total		**232**	**134**	**0**	**366**
MDD	SKUP-9801	37.7 (19-60)	12	15	0	27

Indication	Study	Age	Number of Subjects Exposed to Solriamfetol			
		Mean (Range)	Male	Female	Unknown	Total
	R228060-USA-10	38.3 (22-60)	46	15	0	61
	R228060-MDD-201	39.1 (18-65)	102	143	0	245
	Total		**160**	**173**	**0**	**333**
ADHD	SOL-ADHD-301	35.3 (18-55)	158	186	0	344
	Total		**158**	**186**	**0**	**344**
BED	SOL-BED-303	38.5 (24-55)	4	19	3	26
	Total		**4**	**19**	**3**	**26**
OSA	15-004	51.6 (25-68)	30	4	0	34
	14-003	53.9 (21-75)	220	135	0	355
	14-004	54.8 (24-74)	107	67	0	174
	JZP110-405	52.2 (21-65)	38	21	0	59
	IGN-B0301-03	45.7 (23-74)	94	8	0	102
	Total		**489**	**235**	**0**	**724**
Narcolepsy	15-005	40.4 (21-62)	13	11	0	24
	ADX-N05-201	37.1 (18-59)	19	14	0	33
	ADX-N05-202	41.0 (19-70)	14	30	0	44
	14-002	36.3 (18-68)	58	119	0	177
	Total		**104**	**174**	**0**	**278**
Narcolepsy +OSA	14-005*	48.4 (18-75)	68	63	0	131
	Total		**68**	**63**	**0**	**131**
Paediatric Narcolepsy	JZP865-101	12.8 (7-17)	5	7	0	12
	Total		**5**	**7**	**0**	**12**
Parkinson's Disease	JZP166-201	65.0 (45-78)	40	16	0	56
	Total		**40**	**16**	**0**	**56**
Total			**1,260**	**1,007**	**3**	**2,270**

*Since Study 14-005 enrolled subjects from parent studies in OSA or narcolepsy, only those subjects on placebo during the parent study were included in the cumulative exposure estimate.
Ongoing studies SOL-MDD-301, SOL-SWD-301, and SOL-BED-301 are not included at this time as treatment assignment remains blinded.
ADHD = attention deficit hyperactivity disorder; BED = binge eating disorder; MDD = major depressive disorder; OSA = obstructive sleep apnoea; SWD = shift work disorder

Table SIII.3: Dose

For the dose, only legacy clinical trial data was available from clinical trials sponsored by the previous MAH Jazz Pharmaceuticals. The cumulative exposure to solriamfetol hydrochloride was obtained from Jazz Clinical Study Reports, clinical study database, and the Integrated Summary of Safety. Exposure was based on actual treatment for unblinded studies.

Narcolepsy and OSA (person time)		
Dose of exposure	**Patients**	**Person time (Days)**

37.5 mg	33	2654
75 mg	114	17570
150 mg	288	62359
300 mg	500	121607
Total	**935**	**204190**
Narcolepsy		
37.5 mg	0	0
75 mg	32	4053
150mg	90	16159
300 mg	199	47837
Total	**321**	**68049**
OSA		
37.5 mg	33	2654
75 mg	82	13517
150mg	198	46200
300 mg	301	73770
Total	**614**	**136141**

Table SIII.4: Ethnic origin

Indication	**Study**	**Number of Subjects Exposed to Solriamfetol**						
		American Indian or Alaska Native	**Asian**	**Black**	**Caucasian**	**Native Hawaiian or Other Pacific Islander**	**Unknown**	**Other**
Healthy Subjects	YUCIC-9603-01	0	0	15	9	0	0	0
	R228060-P01-101	0	0	0	4	0	0	0
	YUKIC-9702-01	0	0	20	10	0	0	10
	R228060-NED-1	0	3	3	86	0	0	1
	R228060-SAB-101	0	0	16	2	0	0	0
	14-001	0	0	29	14	0	0	0
	15-001	0	0	11	20	0	0	0
	15-002	0	0	4	55	1	0	0
	15-009	0	0	17	15	0	0	0

Indication	Study	Number of Subjects Exposed to Solriamfetol						
		American Indian or Alaska Native	Asian	Black	Caucasian	Native Hawaiian or Other Pacific Islander	Unknown	Other
	JZP110-401	0	0	3	3	0	0	0
	IGN-B0301-01	0	15	0	0	0	0	0
	Total	**0**	**18**	**118**	**218**	**1**	**0**	**11**
ADHD	SOL-ADHD-301	3	10	52	253	1	1	24
	Total	**3**	**10**	**52**	**253**	**1**	**1**	**24**
BED	SOL-BED-303	0	1	7	13	0	3	2
	Total	**0**	**1**	**7**	**13**	**0**	**3**	**2**
MDD	SKUP-9801	0	0	2	25	0	0	0
	R228060-USA-10	0	2	22	37	0	0	0
	R228060-MDD-201	0	1	40	176	0	0	28
	Total	**0**	**3**	**64**	**238**	**0**	**0**	**28**
OSA	15-004	0	0	0	34	0	0	0
	14-003	0	13	63	274	1	0	4
	14-004	0	2	34	137	0	0	1
	JZP110-405	0	3	12	43	0	1	0
	IGN-B0301-03	0	102	0	0	0	0	0
	Total	**0**	**120**	**109**	**488**	**1**	**1**	**5**
Narcolepsy	15-005	0	0	2	21	0	0	1
	ADX-N05-201	0	0	10	23	0	0	0
	ADX-N05-202	0	1	12	30	1	0	0
	14-002	2	6	23	142	1	0	3
	Total	**2**	**7**	**47**	**216**	**2**	**0**	**4**
Narcolepsy + OSA	14-005*	1	2	28	98	1	0	1
	Total	**1**	**2**	**28**	**98**	**1**	**0**	**1**
Paediatric Narcolepsy	JZP865-101	0	0	2	10	0	0	0
	Total	**0**	**0**	**2**	**10**	**0**	**0**	**0**
Parkinson's Disease	JZP166-201	1	0	3	51	0	1	0
	Total	**1**	**0**	**3**	**51**	**0**	**1**	**0**
Total		**7**	**161**	**430**	**1,585**	**6**	**6**	**75**

*Since Study 14-005 enrolled subjects from parent studies in OSA or narcolepsy, only those subjects on placebo during the parent study were included in the cumulative exposure estimate.

Ongoing studies SOL-MDD-301, SOL-SWD-301, and SOL-BED-301 are not included at this time as treatment assignment remains blinded.

ADHD = attention deficit hyperactivity disorder; BED = binge eating disorder; MDD = major depressive disorder; OSA = obstructive sleep apnoea; SWD = shift work disorder

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria	
Criteria	**Reason for exclusion**
Paediatric population (< 18 years old)	Paediatric patients may have age-related physiologic changes that may alter pharmacokinetic (PK) and pharmacodynamic (PD) effects of drugs. A Paediatric Investigation Plan (PIP) has been approved. Phase IIa study was completed, and the clinical study report was issued in 2022. Two other trials are being planned. Not included as missing information as the product is not intended to be used by paediatric patients.
Patients > 75 years old	Patients > 75 years old may have age-related physiologic changes that may alter PK and PD of drugs. Not included as missing information because the clinical data did not suggest that the safety profile in elderly patients will be different than that of younger patients.
Pregnant and lactating women	Reproductive toxicity studies performed in pregnant rats and rabbits showed embryofoetal toxicity in the presence of maternal toxicity. There is insufficient data on effects of solriamfetol in human foetal development. Solriamfetol was excreted in rat milk. Solriamfetol is excreted in human milk and the exposure is approximately 2-fold higher, on average, in milk than plasma. Use in pregnant women is not included as missing information as "Reproductive toxicity" is listed as an important potential risk.
Any clinical relevant medical, behavioural, or psychiatric disorder (other than narcolepsy or OSA) that is associated with excessive sleepiness (ES).	Primary and secondary aetiologies of ES other than narcolepsy or OSA were excluded. Not included as missing information as the exclusion criteria was in place to allow for interpretation of the clinical trial results.
History or presence of any acutely unstable medical condition, behavioural or psychiatric disorder (including active suicidal ideation), that could affect the safety of the subject or interfere with study efficacy, safety, or PK assessments.	Stimulants (i.e., amphetamines, methylphenidate) and wake-promoting agents have the potential to exacerbate underlying conditions such as mania and psychotic disorders. Not included as missing information because serious psychiatric disorders are an important potential risk and psychiatric symptoms are adequately addressed in the Warnings and Precautions section of the SmPC.
History of bariatric surgery within the past year or a history of any gastric bypass procedure.	Bariatric or gastric bypass surgery could alter the absorption of the drug, affect the safety of the subject, or interfere with study efficacy, safety, or PK assessments. Not included as missing information as the exclusion criteria was in place to allow for appropriate interpretation of the clinical trial results.

Exclusion criteria	
Criteria	**Reason for exclusion**
Presence of renal impairment or calculated creatinine clearance (CrCL) < 60 mL/min.	Solriamfetol is primarily excreted unchanged in the urine (≥ 90%); therefore, moderate-to-severe renal impairment was expected to impact solriamfetol exposure and elimination half-life. The subsequent PK study in subjects with renal impairment (CSR 15-001) showed that the half-life (t½) and area under the curve (AUC) increased and urinary recovery of solriamfetol decreased with increasing levels of renal impairment, while Cmax was essentially unchanged. Not included as missing information because the exclusion criteria was in place to avoid subjecting patients with CrCL < 60 mL/min to higher exposures of solriamfetol compared to patients with CrCL > 60 mL/min at equivalent doses. The Summary of Product Characteristics (SmPC) contains dosing recommendations for patients with moderate or severe renal impairment. Solriamfetol is not recommended for use in patients with end stage renal disease.
Presence of significant CV disease including but not limited to: myocardial infarction within the past year, unstable angina pectoris, symptomatic congestive heart failure, revascularization procedures within the past year, ventricular cardiac arrhythmias requiring automatic implantable cardioverter defibrillator or medication therapy.	Patients with significant underlying CV disease or an acutely unstable medical condition were excluded for safety reasons. Sunosi can result in dose-dependent increases in BP and HR. These effects may increase the risk of serious CV events. Not included as missing information because serious CV events are an important identified risk. Sunosi therapy is contraindicated in patients with a history of a myocardial infarction within the past year, patients with unstable angina pectoris, patients with uncontrolled hypertension, patients with serious cardiac arrhythmias, and patients with other serious heart problems in the SmPC.
Presence of uncontrolled hypertension (systolic BP ≥ 155 mm Hg, diastolic BP ≥ 95 mm Hg)	Sunosi can result in dose-dependent increases in BP and HR. Pre-existing hypertension should be controlled before starting treatment with Sunosi. Not included as missing information because increases in BP and HR are adequately addressed in the Warnings and Precautions section of the SmPC. Sunosi therapy is contraindicated in patients with uncontrolled hypertension in the SmPC.
Current or past (within the past 2 years) diagnosis of a moderate or severe substance use disorder according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria. Current, past (within the past 2 years), or seeking treatment for a substance related disorder. Urine drug screen positive for an illicit drug of abuse (including cannabinoids) at screening or at any point throughout the duration of the study, except for a prescribed drug (e.g., amphetamine) at screening.	Preclinical and clinical studies have indicated that solriamfetol has low potential for abuse relative to stimulant drugs. Not included as missing information because potential for abuse, misuse and diversion is an important potential risk, and abuse is adequately addressed in the in the Warnings and Precautions section of the SmPC.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions (≥ 1/10,000 to < 1/1,000), adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of Special Population	**Exposure**
Pregnant and lactating women	Six (6) healthy adult females, postpartum, were exposed to Sunosi in a study on pharmacokinetics in breast milk and plasma. There was no pregnant women exposure.
Paediatric patients	12 paediatric patients with the diagnosis of Narcolepsy were exposed to Sunosi within the PIP program.
Geriatric patients	190 patients aged ≥ 65 years were exposed to Sunosi in the clinical development programme. Most of the geriatric subjects were OSA patients. Subjects greater than 75 years of age were prohibited from enrolling in clinical studies with Sunosi.
Patients with relevant comorbidities:	
Patients with increased ocular pressure or risk of angle closure glaucoma	Patients with angle closure glaucoma were not investigated in the clinical development programme.
Patients with hepatic impairment	Hepatic impairment studies were not included in the clinical development programme because Sunosi undergoes minimal hepatic metabolism.
Patients with renal impairment	A Phase 1 renal impairment study included 25 subjects: six (6) exposed patients had mild renal impairment, six (6) patients had moderate renal impairment, six (6) patients had severe renal impairment, and seven (7) patients had end-stage renal disease and were receiving dialysis.
Subpopulations carrying relevant genetic polymorphisms	Subpopulations carrying relevant genetic polymorphisms were not investigated in the clinical development programme.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The cumulative worldwide patient exposure to solriamfetol has been calculated from available sales data between March 2023 to October 2024 and is provided below. The exposure data includes the sales figures from Axsome Malta Ltd for the period March 2023 to October 2024.

SV.1.2 Exposure

The MAH does not have access to the gender and age information for patients, who have taken solriamfetol across various geographies.

For narcolepsy the recommended starting dose is 75 mg once daily, upon awakening with a recommended maximum daily dose of 150 mg once daily and for OSA the recommended starting dose is 37.5 mg once daily, upon awakening with a recommended maximum daily dose of 150 mg once daily. Due to the trending patterns of use, the average daily dose for solriamfetol is estimated to be 75 mg. The patient years was derived by dividing the total milligram quantity of solriamfetol sold by the average daily dose and then dividing by 365 days per year.

The estimate of patient exposure to solriamfetol is based on the number of blisters and bottles sold. The total cumulative sales represent a total of 1,358,869 patient years. The patient exposure between March 2023 to October 2024 from marketing experience by product strength has been presented in the table below.

Table SV.1: Cumulative Exposure from Marketing Experience by Product Strength

Formulation	**Pack Size**	**Quantity sold**	**Quantity sold (milligram)**	**Patient Years**
Sunosi Tablet Blister 75 mg	28	3,130,037	6,573,077,700	240,112
Sunosi Tablet Blister 150 mg	28	7,291,897	30,625,967,400	1,118,757
Total			**37,199,045,100**	**1,358,869**

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

There is some potential for solriamfetol to be abused or misused in the post authorisation period, due to its pharmacological mechanism of action. However, preclinical and clinical studies have indicated that solriamfetol has low potential for abuse relative to stimulant drugs. In a dedicated human abuse liability study (14-001) conducted in recreational drug users, ratings of momentary and overall "drug liking" and ratings of desire to "take again" were significantly lower than doses of phentermine, which is a weak stimulant drug. In addition, there were no indicators of drug abuse or misuse observed in the target populations across any of the Phase 2 and Phase 3 clinical trials. There were also no signs or symptoms of physical dependence observed after abrupt cessation of treatment in patients who received placebo during the 2-week randomized withdrawal periods in studies 14-004 and 14-005 (after 4 weeks and at least 6 months of treatment, respectively). Based on the pharmacological properties of the drug, there is no meaningful risk of solriamfetol being misused for facilitation of sexual assault.

"Abuse, misuse and diversion" is an important potential risk in the RMP. In addition, the description of this risk is appropriately described in the Warnings and Precautions section of the SmPC, emphasizing caution when treating patients with a history of substance of alcohol abuse, who may be at greater risk for abuse or misuse of drugs in general.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Risks related to the nervous and gastrointestinal system can be detected, monitored, and managed with routine measures and treatments used in clinical practice; addressed through dose reduction or drug discontinuation, if necessary; and are appropriately described in the label.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- None

Known risks that require no further characterisation and are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers:

- In pre-clinical investigations, solriamfetol had low micromolar affinity for alpha-2A and 2B adrenoceptors in in vitro binding studies; however, solriamfetol had no functional agonist or antagonist activity at human alpha 2A, 2B, or 2C receptors recombinantly expressed in mammalian cell lines. Because alpha-2 adrenergic agonists are used to lower intraocular pressure in glaucoma patients and high levels of solriamfetol-related radioactivity were present in the eye of pigmented rats after parenteral administration of [^{14}C] solriamfetol, there may be a possibility of a pharmacodynamics (PD) interaction of solriamfetol and ophthalmic solutions containing alpha-2 agonists, but this is unknown at present. In the clinical studies, patients with a history of glaucoma were not excluded and medications used to treat glaucoma were not prohibited. In all studies in narcolepsy and OSA (N=935), no treatment emergent adverse events (TEAEs) of acute angle-closure glaucoma were observed in any subject who received solriamfetol. Due to the pharmacological actions of Sunosi (dopamine and norepinephrine re-uptake inhibitor) there is a risk of precipitating

acute angle close glaucoma in predisposed patients. In section 4.4 of the SmPC, prescribers are advised to use Sunosi with caution in patients with increased ocular pressure or at risk of acute angle closure glaucoma.

Known risks that do not impact the risk-benefit profile:

- In populations not studied/underrepresented in the Sunosi clinical development programme, namely, paediatric patients and elderly patients, risks to these populations will be mitigated through language in the SmPC (in section 4.2). The MAH commits to proactively reviewing/monitoring data regarding these populations via routine PV activities and in future PBRERs as topics kept under close surveillance.

Other reasons for considering the risks not important:

- None

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk 1: Serious Cardiovascular Events

Risk-benefit impact: Stimulants and wake-promoting agents have been associated with increases in heart rate and blood pressure. Sunosi can result in dose-dependent increases in blood pressure and heart rate. These effects may increase the risk of serious CV events. The clinical trials that were the evidence source for this risk were: double-blinded, placebo-controlled trials in narcolepsy and OSA including ADX-N05-201, ADX-N05-202, 14-002, 14-003, 14-004 and open-label long-term extension trial 14-005. Serious CV events occurred uncommonly (≥ 1/1,000 to < 1/100) in Sunosi-treated subjects participating in both the double blinded, placebo- controlled trials and in the open-label long term extension trial (0.5%; 5/935). All five (5) treatment- emergent SAEs (acute myocardial infarction, atrial fibrillation [2], Angina pectoris, and Deep vein thrombosis) occurred in OSA subjects at a modal dose of 300 mg, and all five (5) subjects had underlying CV risk factors, including coronary artery disease, hypertension, obesity, diabetes mellitus and hyperlipidaemia. In addition, one (1) Sunosi-treated subject (1/935; 0.11%) experienced an SAE of cerebrovascular accident in a subject with OSA receiving a modal dose of 150 mg and who had concomitant cerebrovascular risk factors. Based on the CV co-morbidities in this population and depending on the CV risk profile, these events are anticipated to occur in this population. There was no clear evidence to support a causal relationship to Sunosi. In addition to routine risk minimisation measures such as patient selection, dosage recommendations, contraindications and warnings in the SmPC, corresponding patient information leaflet (PIL) sections, and ongoing pharmacovigilance (PV) monitoring, serious CV events occurring in the Sunosi-exposed OSA population will be collected and analysed during an observational post- authorisation safety study as supplementary PV activities.

Based on Sunosi's pharmacological mechanism of action, patients taking antihypertensive medication before initiating treatment with Sunosi may need to have their antihypertension medication adjusted during treatment. With respect to the use of antihypertensive medications in the placebo-controlled 12-week Phase 3 studies in narcolepsy and OSA (doses of 37.5 mg to 150 mg), minimal changes were observed in concomitant anti-hypertensive medication use, with small percentages of subjects in the placebo and combined solriamfetol groups demonstrating any adjustment (1.33% and 2.02%, respectively). Among subjects with narcolepsy, a similar percentage of subjects initiated de novo antihypertension medication for blood pressure control during the study in the placebo and solriamfetol groups (0.93% vs. 0.62%, respectively); no subjects with OSA initiated de novo antihypertension medication during the study. In addition, the number of subjects who discontinued due to adverse events of BP increased/hypertension was low (one (1) subject in the 12-week, placebo-controlled studies who was receiving a dose of 150 mg). In section 4.2 of the SmPC, prescribers are advised that blood pressure should be assessed before initiating treatment with Sunosi and should be monitored after dosage increases and periodically during treatment, especially after increasing the dose. Prescribers are further advised that if a patient is experiencing increased blood pressure during treatment that cannot be managed with Sunosi dosage reduction or appropriate medical intervention, then discontinuation of Sunosi should be considered.

Important Potential Risk 1: Serious psychiatric events

Risk-benefit impact: Stimulants and wake-promoting agents have been associated with exacerbations of underlying serious psychiatric disorders. The clinical trials that were the evidence source for this risk were: double-blinded, placebo-controlled trials in narcolepsy and OSA including ADX-N05-201, ADX-N05-202, 14-002, 14-003, 14-004 and open-label long- term extension trial 14-

005. Five (5) subjects (5/935; 0.5%) experienced five (5) treatment-emergent serious psychiatric events (Agitation and Hallucination auditory [in one (1) subject, at a dose of 150 mg], Anxiety [in one (1) subject, at a dose of 150 mg], Bipolar disorder [in one (1) subject, at a dose of 300 mg], Conversion disorder [in one (1) subject, at a dose of 150 mg], and Depression and Suicide attempt [in one (1) subject, at a dose of 300 mg]). The frequency of the SAEs was uncommon (≥ 1/1,000 to < 1/100). Four (4) of the five (5) subjects who experienced serious psychiatric disorders were participating in narcolepsy clinical trials. There was no clear evidence to support a causal relationship to Sunosi. In section 4.4 of the SmPC physicians are advised to carefully monitor patients for adverse reactions such as anxiety, insomnia and irritability, which were commonly observed during treatment initiation but tended to resolve with continued treatment and discontinue or reduce the dose if these persisted or worsened. In addition to routine PV monitoring, psychiatric AEs will be collected and analysed as part of the long term, non-interventional observation safety study.

Important Potential Risk 2: Potential for abuse, misuse and diversion

Risk-benefit impact: Nonclinical studies using Sunosi showed low potential for abuse. In a dedicated human abuse liability study (14-001) conducted in recreational drug users, ratings of momentary and overall "drug liking" and ratings of desire to "take again" were higher than placebo and significantly lower than doses of phentermine, which is a weak stimulant drug. Data from the clinical studies revealed no signal of drug misuse, abuse or dependence, or diversion, and no evidence of withdrawal-related effects in the target population. Risk minimisation using the SmPC (a warning is included in section 4.4 of the SmPC for caution to be exercised when treating patients with a history of stimulant (e.g. methylphenidate, amphetamine) or alcohol abuse, and monitoring for signs of misuse or abuse of solriamfetol) and routine pharmacovigilance monitoring are expected to maintain a positive risk-benefit balance.

Additional sensitivity analyses in the long term, non-interventional observational safety study could explore the possible influence of aberrant drug-related behaviours.

Important Potential Risk 3: Reproductive toxicity

Risk-benefit impact: There was limited data on the use of Sunosi in pregnant women during the clinical trials. Animal studies have demonstrated that there are embryofoetal toxicity effects at maternally toxic doses in pregnant rats and rabbits. Sunosi is not recommended during pregnancy and in women of childbearing potential who are not using effective contraception. In addition to routine risk minimisation measures such as warnings in the SmPC, corresponding PIL sections (women of childbearing potential or their male partners must use effective method of contraception while taking solriamfetol) and ongoing PV monitoring, data on risk of reproductive toxicity and teratogenicity will be collected and analysed in two (2) post-marketing US- based pregnancy registries (JZP110-402 and JZP110-403) as additional PV activities. Interim and final results will be reported to the European Medicines Agency (EMA), when available.

Missing information 1: Potential for Pharmacodynamic (PD) interactions

Risk-benefit impact: Although no PD interactions studies with Sunosi were performed, based on the current understanding of Sunosi's mechanism of action, PD interactions resulting from the use of concomitant medications which interfere with the central dopaminergic and noradrenergic neuronal system cannot be excluded. Three (3) classes of drugs with the potential for PD interactions that have to be considered for the safe clinical use of Sunosi are monoamine oxidase inhibitors (MAOIs), drugs that increased heart rate and/or blood pressure, and medicinal products that increase levels of dopamine or that bind directly to dopamine receptors. In section 4.3 the SmPC contraindicates concomitant use of MAOIs or within 14 days after MAOI treatment has been discontinued (see section 4.5). In section 4.2, the SmPC states, "Caution should be exercised when using other medicinal products that increase blood pressure and heart rate (see section 4.5)". The SmPC advises prescribers in section 4.5 (Interaction with other medicinal products and other forms of interaction) that solriamfetol must not be administered concomitantly with MAOIs or within 14 days after MAOI treatment has been discontinued because it may increase the risk of a hypertensive reaction. Additional advisements in section 4.5 include, "Concomitant use of medicinal products that increase blood pressure and heart rate should be used with caution (see section 4.4); and "Medicinal products that increase levels of dopamine or that bind directly to dopamine receptors might result in pharmacodynamic interactions with solriamfetol. Concomitant use of such medicinal products should be used with caution." In addition to routine PV monitoring, data collection of concomitant medications in the long term, non-interventional observational safety study and analysis of events of interest can be assessed for possible pharmacodynamics interactions.

Missing information 2: Use in lactating women

Risk-benefit impact: No studies have been conducted in lactating women. There are no data on the presence of Sunosi in human milk, the effects on the breastfed infant, or the effect of this drug on milk production. Sunosi is present in rat milk. In addition to routine risk minimisation measures such as labelling in the SmPC and ongoing PV monitoring, data on the secretion of Sunosi into breast milk will be collected and analysed in a US post-marketing study of lactating women as additional PV activities. Final study results will be reported to the EMA.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Use in lactating women previously classified as missing information is removed from the list of safety concerns.

Based on pre-clinical studies, Sunosi is present in rat milk. In addition to routine risk minimisation measures such as labelling in the SmPC and ongoing PV monitoring, data on the secretion of Sunosi into breast milk were collected and analysed in a US post-marketing study of lactating women as additional PV activities. A study JZP110-401 was conducted in six (6) healthy adult lactating women who were between 15 and 37 weeks postpartum and were administered a single oral dose of Sunosi 150 mg. Solriamfetol Tmax for both plasma and breast milk were similar and ranged between 1 to 3 hours and followed a parallel monoexponential decline after reached the peak. Solriamfetol breast milk exposure was approximately 2-fold higher than plasma (geometric mean milk:plasma ratio of 2.047). T1/2 appeared similar in plasma and breast milk at approximately 5.0 hours. The average amount that would be passed to the infant was estimated to be 0.59 mg over 24 hours, which is about 4.0% of the maternal dose on a weight-adjusted basis. Solriamfetol was safe and well tolerated in healthy postpartum women. Since a relative infant dose (RID) in the region of 4% (i.e. less than 10%) is in the acceptable range for breast milk drug level via maternal exposure, this information was not re-classified as important risk.

The effects of solriamfetol on breastfed new-born/infants and its effects on milk production will be monitored in the upcoming Periodic Safety Update Reports (PSURs).

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risks:

Identified Risk 1: Serious Cardiovascular (CV) Events		
Potential mechanisms	Sunosi is a selective dopamine and norepinephrine reuptake inhibitor. Medications that indirectly increase dopamine and norepinephrine levels can lead to increased HR and BP. These effects may increase the risk of serious CV events in the narcolepsy and OSA population.	
Evidence source and strength of evidence	The general patient population with narcolepsy or OSA may be at risk for serious CV events due to certain intrinsic factors such as age, obesity, and comorbid cardiovascular and metabolic conditions, as well as underlying disease pathophysiology. CV adverse events were of interest because of observations of modest, reversible increases in HR and BP.	
Characteristics of the risk	**Subjects with Serious CV events** (Narcolepsy and OSA studies; N=935)	**Frequency (%) (Confidence Interval [CI])** 5 (0.53%) CI (0.17, 1.24)
	Subjects with Serious CV events (Narcolepsy studies; N=321)	*0 (0.0%) CI (--, --)*

Identified Risk 1: Serious Cardiovascular (CV) Events		
	Subjects with Serious CV events (OSA studies; N=614)	*5 (0.81%)* *(0.26, 1.89)*
	Serious CV events by MedDRA PT (Cardiac Disorders and Vascular Disorders SOCs) Acute myocardial infarction Angina pectoris Atrial fibrillation Deep vein thrombosis	 1 (0.11%) 1 (0.11%) 2 (0.22%) 1 (0.11%)
	Of the five (5) CV SAEs, the majority of the SAEs were considered severe in nature, the majority resolved with or without sequelae, and the majority resulted in the drug being withdrawn or interrupted. In addition, one (1) Sunosi-treated subject (1/935; 0.11%) was identified in the SMQ for central nervous system haemorrhages and cerebrovascular conditions. This was an SAE of cerebrovascular accident in a subject with OSA and concomitant cerebrovascular risk factors.	
Risk groups or risk factors	Patients with narcolepsy and OSA may be at risk for CV events due to certain intrinsic risk factors, such as increasing age, obesity, concurrent diabetes mellitus, concurrent CV disease, and smoking. Patients with pre-existing hypertension, cardiovascular or cerebrovascular conditions that might be compromised by increases in blood pressure. Other risk groups include patients using high doses (> 150 mg) of Sunosi or who use concomitant medications that increase heart rate and blood pressure.	
Preventability	Patients with narcolepsy or OSA often have co-morbid conditions that increase the risk of CV disease. Sunosi is contraindicated in patients with a history of a myocardial infarction within the past year, unstable angina pectoris, uncontrolled hypertension, serious cardiac arrhythmias, and other serious heart problems. Patients should be advised to immediately report any symptoms of these events. Sunosi can result in dose-dependent increases in blood pressure and heart rate. Patients' vital signs should be assessed before treatment begins and monitored after dosage increases and periodically throughout treatment. Pre-existing hypertension should be controlled before initiating treatment with Sunosi, and caution should be exercised in treating patients with pre-existing hypertension or CV or cerebrovascular conditions that might be compromised by increases in BP. If patients experience a sustained increase in BP or HR that cannot be managed with dose reduction of Sunosi or other appropriate medical intervention, discontinuation of Sunosi should be considered. Concomitant use of Sunosi with drugs that increase BP and HR has not been evaluated, and such combinations should be used with caution.	
Impact on the risk-benefit balance of the product	The SmPC informs prescribers of CV risks and provides guidance with respect to patient selection, dose recommendations, and monitoring. Risk minimisation using the SmPC and routine pharmacovigilance are expected to maintain a positive risk-benefit balance. Additional pharmacovigilance activities include the conduct of a long term, non-interventional observational post-authorisation safety study (PASS) to collect and analyse data on major CV adverse events, and other safety concerns, that occur in Sunosi-exposed patients with OSA.	
Public health impact	Serious CV events have been reported in clinical trials with Sunosi and have predominantly occurred in patients with OSA. In addition, the OSA population comprised the largest portion of the safety database including long-term exposures and observation periods. Based on the CV co-morbidities in this population and depending on the CV risk profile, these events are anticipated to occur in this population. Risk mitigation through the SmPC and pharmacovigilance activities is sufficient to minimise the impact to public health.	

Important Potential Risks:

Potential Risk 1: Serious Psychiatric Events		
Potential mechanisms	Sunosi is a selective dopamine and norepinephrine reuptake inhibitor.	
Evidence source and strength of evidence	Psychiatric adverse events were of interest because psychiatric comorbidities are common in narcolepsy and OSA, and stimulants and wake-promoting agents have the potential to exacerbate underlying psychiatric conditions.	
Characteristics of the risk	**Subjects with Serious Psychiatric Events** (Narcolepsy and OSA studies; N=935)	**Frequency (%)** **(Confidence Interval [CI])** 5 (0.53%) CI (0.17, 1.24)
	Subjects with Serious Psychiatric Events *(Narcolepsy studies; N=321)*	*4 (1.25%)* *(0.34, 3.16)*
	Subjects with Serious Psychiatric Events *(OSA studies; N=614)*	*1 (0.16%)* *(0.00, 0.90)*
	Serious Psychiatric Events by MedDRA PT (Psychiatric Disorders SOC) Agitation* Anxiety Bipolar disorder Conversion disorder Hallucination auditory* Suicide attempt* Depression* *2 subjects experienced 2 SAEs each	 1 (0.11%) 1 (0.11%) 1 (0.11% 1 (0.11% 1 (0.11%) 1 (0.11%) 1 (0.11%)
	Five (5) subjects experienced SAEs of which two (2) subjects experienced two (2) SAEs each for a total of seven (7) SAEs. Of the seven (7) serious psychiatric SAEs, four (4) of the psychiatric SAEs were severe in nature, while two (2) were moderate and one (1) was mild. The majority of SAEs resolved after treatment was discontinues and the majority resulted in the drug being withdrawn or interrupted.	
Risk groups or risk factors	Psychiatric disorders are a frequent comorbidity in patients with narcolepsy (Daniels et al, 2001; Broughton, 1981; Vandeputte & Weerd, 2003; Ohayon, 2013; Ruoff et al. 2017). In OSA patients, observational studies have found a nearly 2-fold higher incidence of depression in patients with OSA when matched to controls without OSA (Strohl, 2017). In the Sunosi clinical development programme, serious psychiatric symptoms occurred more commonly in the narcolepsy population than the OSA population.	
Preventability	Sunosi has not been evaluated in patients with a history of or concurrent psychosis or bipolar disorders. Caution should be exercised when treating these patients due to psychiatric adverse reactions that could exacerbate symptoms (e.g. manic episodes) of pre-existing psychiatric disorders. Patients treated with Sunosi should be carefully monitored for adverse reactions such as anxiety, insomnia, irritability and agitation. These adverse reactions were commonly observed during treatment initiation but tended to resolve with continued treatment. If these symptoms persist or worsen, dose reduction or discontinuation should be considered. Early detection of symptoms can potentially mitigate psychiatric events from becoming serious.	

Impact on the risk- benefit balance of the product	The Sunosi SmPC contains guidance for prescribers regarding monitoring for the emergence or exacerbation of psychiatric symptoms, recommendations for dose reduction or discontinuation of the product and patient selection. Risk minimisation using the SmPC and routine pharmacovigilance (including specific adverse reaction follow-up questionnaire for depression including suicidality) are expected to maintain a positive risk-benefit balance. Additional pharmacovigilance activities include collection and analysis of data on psychiatric AEs in the long term, non-interventional observational PASS.
Public health impact	Serious psychiatric events have been reported in clinical trials with Sunosi and have predominantly occurred in patients with narcolepsy. Based on the psychiatric co-morbidities in this population and depending on the psychiatric risk profile, these events are anticipated to occur in this population. The SmPC informs prescribers of these risks and provides guidance with respect to patient selection, dose recommendations, and monitoring. Risk mitigation through the SmPC and pharmacovigilance activities is sufficient to minimise the impact to public health.

Potential Risk 2: Potential for Abuse, Misuse and Diversion	
Potential mechanisms	Sunosi is a selective dopamine and norepinephrine reuptake inhibitor. It has lower binding affinity to the dopamine active transporter and the norepinephrine transporter than traditional stimulants such as cocaine, and it lacks the characteristic norepinephrine releasing effects of amphetamine.
Evidence source	Sunosi meets the criteria for assessment of abuse potential as a new molecular entity that affects the CNS. In addition, abuse, misuse and diversion potential are associated with other medications used in the treatment of ES that are pharmacologically similar to Sunosi.
Characterisation of the risk	The potential for abuse was directly assessed with a valid human abuse liability (HAL) study (CSR 14-001), designed to be consistent with regulatory guidance and current expert opinion on the design and characteristics of HAL studies. This study compared single supratherapeutic (2, 4, and 8 times the maximum recommended dose) doses of Sunosi to placebo and phentermine (45 and 90 mg). Consistent with the nonclinical data that are suggestive of low abuse potential, ratings on the primary (Peak Liking at the Moment) and key secondary endpoints (Next Day Liking and Next Day Take Again) for the high dose of Sunosi (1008 mg) were higher than placebo and statistically lower ($p < 0.05$) than those for the high dose of phentermine (90 mg). The conclusion was that Sunosi has an abuse potential similar to, or lower than, phentermine (a weak stimulant drug). In addition, a broad search of terms potentially representing drug abuse, dependence, and misuse across clinical studies and both indications revealed no signal of drug misuse, abuse or dependence in subjects with narcolepsy or OSA. With regard to drug accountability and potential misuse or diversion, medication compliance has not been suggestive of a signal of misuse or diversion. There was no pattern of withdrawal signs or symptoms based on analysis of AEs that occurred after discontinuation of short- or long-term exposure to Sunosi, and no evidence to suggest rebound hypersomnia after discontinuation of Sunosi.
Risk groups or risk factors	Patients with a history of substance abuse (alcohol and/or drugs).
Preventability	Patients treated with Sunosi should be observed for signs or symptoms of abuse misuse, or diversion.

Impact on the risk- benefit balance of the product	The Sunosi SmPC contains guidance for prescribers regarding potential for abuse of Sunosi. Risk minimisation using the SmPC and routine pharmacovigilance are expected to maintain a positive risk-benefit balance. Additional pharmacovigilance activities include collection of data on supratherapeutic doses and sensitivity analyses assessing possible aberrant drug-related behaviours in the long term, non-interventional observational PASS.
Public health impact	The SmPC informs prescribers of the risk and provides guidance with respect to patient selection and monitoring. Risk mitigation through SmPC and routine pharmacovigilance is sufficient to minimise the impact to public health.

Potential Risk 3: Reproductive Toxicity	
Potential mechanisms	Unknown
Evidence source	Preclinical reproductive toxicity studies in pregnant rats and rabbits showed evidence of embryofoetal toxicity.
Characterisation of the risk	In both species, embryofoetal toxicity (increased postimplantation loss in rats, increased incidence of skeletal alterations that included sternebrae malalignment in rats and rabbits, hindlimb rotation and bent bones in rats, and decreased foetal weights in both species) and situs inversus in rats was only evident in the presence of maternal toxicity (decreased body weights). Whether embryotoxicity was a consequence of maternal toxicity or a direct effect of solriamfetol cannot be determined. In a distribution study in pregnant rats ^{14}C-solriamfetol was detected in foetal membrane (around twice as high as in blood), placenta and whole foetus (nearly similar to blood concentration) and thus a direct toxic effect on the foetus cannot be excluded. In rats the exposure margins at the maternal and developmental NOAEL are below the human exposure (0.6 – 0.7 based on AUC) at the MRHD, while in rabbits the exposure margins at the maternal and developmental NOAEL is < 6 (based on mg/m^2 body surface area).
Risk groups or risk factors	Pregnant women and their offspring
Preventability	Women of childbearing potential and their partners must use effective contraception before initiating treatment with Sunosi. Pregnant women must not initiate treatment with Sunosi.
Impact on the risk- benefit balance of the product	The Sunosi SmPC contains guidance for prescribers and patients regarding the use of Sunosi in women of childbearing potential and their partners, and in pregnant women. Risk minimisation using the SmPC and routine pharmacovigilance is expected to maintain a positive risk-benefit balance. Additional pharmacovigilance activities include conducting two (2) post-marketing US-based pregnancy registries to collect and analyse data regarding the safety of Sunosi in exposed pregnant women and their offspring.
Public health impact	The SmPC informs prescribers of the risk and provides guidance with respect to patient selection. Risk mitigation through the SmPC and pharmacovigilance activities is sufficient to minimise the impact to public health.

SVII.3.2. Presentation of the missing information

Missing Information 1	
Potential for Pharmacodynamics interactions	Evidence source: Lack of data in the clinical programme
	Population in need of further characterisation: Those using concomitant medications which interferes with the central dopaminergic and noradrenergic neuronal system. Three (3) classes of drugs with the potential for PD interactions that have to be considered for the safe clinical use of Sunosi are monoamine oxidase inhibitors (MAOIs), drugs that increased heart rate and/or blood pressure, and medicinal products that increase levels of dopamine or that bind directly to dopamine receptors.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Serious Cardiovascular Events
Important potential risks	• Serious Psychiatric Events • Potential for Abuse, Misuse and Diversion • Reproductive Toxicity
Missing information	• Potential for Pharmacodynamics Interactions

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

The MAH will explore the feasibility of looking for signals of abuse and misuse using existing sentinel and database systems such as the European Drug Emergencies Network (Euro-DEN Plus), which monitors drug-related emergency presentations across Europe to provide unique insight into acute health harms related to drug use.

Specific adverse reaction follow-up questionnaires:

- For the important potential risk of "Serious psychiatric events": Follow-up questionnaire on Depression including suicidality

Follow-up questionnaire in relation to depression including suicidality will be provided to the healthcare professionals and patients allowing for detailed data collection on the possible exacerbation of psychiatric symptoms in patients with existing psychiatric disease and concomitant or co-suspect medications. Please refer to Annex 4 for the specific adverse drug reaction follow-up questionnaires.

Other forms of routine pharmacovigilance activities: None proposed

III.2 Additional pharmacovigilance activities

Study name and title:

JZP865-401 'A post-authorisation safety study (PASS) to evaluate cardiovascular events in adult patients with obstructive sleep apnoea (OSA) treated with solriamfetol'.

Rationale and study objectives:

Patients with OSA have greater frequency of cardiovascular (CV) risk factors and comorbidities such as obesity, hypertension, type 2 diabetes, coronary artery disease than non-OSA patients and are at a greater risk for CV events. Therefore, the PASS (JZP865-401) to evaluate CV events in adult patients with OSA treated with solriamfetol is being conducted in Europe to assess the safety of the treatment and to evaluate major adverse cardiovascular events (MACE) and other potential safety outcomes in adult patients.

As per the PASS Protocol version 4.0, dated 26 May 2023, due to variability in data availability across the study countries, i.e., France and Germany, the study objectives differ slightly between two approaches (descriptive and prevalent new user designs). Utilising claims and administrative data that capture data on patients with OSA and excessive daytime sleepiness (EDS) managed according to routine clinical practice the following study objectives will be fulfilled:

Primary objectives:

1. To estimate and compare the incidence rate of major adverse cardiovascular events (MACE), as a composite endpoint of non-fatal acute myocardial infarction (MI), non-fatal stroke, and all-cause mortality, in adults newly exposed to solriamfetol plus positive airway pressure (PAP) vs patients exposed only to PAP (France).
2. To estimate the incidence rate of MACE, as a composite endpoint of (fatal or non-fatal) acute MI, (fatal or non-fatal) stroke, and all-cause mortality, in adults newly exposed to solriamfetol irrespective of PAP use (France and Germany).

Secondary objectives:

1. To describe the demographics, clinical characteristics, and treatment patterns (dose, duration of treatment, number of prescriptions) of patients newly exposed to solriamfetol plus PAP (France), patients exposed only to PAP (France) and patients newly exposed to solriamfetol irrespective of PAP use (France and Germany).
2. a. To estimate and compare the incidence rate of individual MACE components and additional CV events (e.g., unstable angina and arrhythmic events) in patients newly exposed to solriamfetol plus PAP (France) vs patients exposed only to PAP (France).

b. To estimate the incidence rate of individual MACE components and additional CV events (e.g., unstable angina and arrhythmic events) in patients newly exposed to solriamfetol irrespective of PAP use (France and Germany).

3. To estimate the incidence rate of MACE and individual MACE components in patients newly exposed to solriamfetol plus PAP (France), patients exposed only to PAP (France) and patients newly exposed to solriamfetol irrespective of PAP use (France and Germany), by subgroups defined by:
    a. Patient demographics (i.e., age, sex)
    b. CV risk factors (e.g., obesity, hypertension, diabetes, etc.)
    c. Population with CV risk factors mentioned as contraindications in the Summary of Product Characteristics (SmPC) (patients that experienced acute MI one year before study entry or have any history of unstable angina pectoris or serious cardiac arrhythmias)
4. To estimate the incidence rate of serious psychiatric events in patients newly exposed to solriamfetol irrespective of PAP use (France and Germany), in patients newly exposed to solriamfetol on PAP treatment, and in patients exposed only to PAP (France).

Exploratory Objectives:

1. To assess any effect modification (modification of hazard ratio (HR) of MACE by co-medications) indicating potential pharmacodynamic interactions in patients newly exposed to solriamfetol plus PAP (France).
2. To estimate the incidence rate of MACE and individual MACE components in patients newly exposed to solriamfetol with PAP use any time prior to index date (Germany).

Study design:

The study involves the use of secondary data sources (claims) to evaluate the effect of solriamfetol in patients diagnosed with OSA (with or without narcolepsy) and EDS. The source population will be comprised of patients in France and Germany. Due to variability in data availability two different approaches will be used:

1. A prevalent new user design applied only to France, which permits the inclusion of patients who may switch from use of other centrally acting stimulants onto solriamfetol as well as those who were treated only with PAP for a longer time and then have solriamfetol as an add-on drug. This approach will compare patients newly exposed to solriamfetol plus PAP with patients exposed to PAP alone, adjusting for disease severity and for CV risk factors. Time-based exposure sets will be created to produce a counterfactual group of PAP comparator patients for each patient who initiated solriamfetol on top of PAP.
2. A descriptive design applied to France and Germany, will provide a descriptive overview of solriamfetol use in these countries. The study population will consist of patients with OSA newly exposed to solriamfetol irrespective of PAP use. The index date for start of follow-up will be considered as the first solriamfetol prescription. Descriptive analyses will be run on both countries. This will enable to assess similarities in patient characteristics between countries.

Due to the low numbers of patients with OSA treated with W-PA or stimulants and a single additional drug (pitolisant), approved for this indication in the EU, an active comparator cohort on W-PA with OSA is not feasible. Time-based exposure sets provide equivalent time points in the disease course at which confounders can be measured. The German database cannot accurately capture PAP exposure, and therefore, the prevalent new user design will only be conducted in France. Overall, the study aims to evaluate the safety of solriamfetol in patients with OSA and EDS using different study approaches.

Study population:

The study population for this non-interventional observational study will include patients with a diagnosis of OSA (with or without narcolepsy) who are 18 years or older at the index date. The minimal inclusion and exclusion criteria aim to minimize potential selection bias and represent real clinical practice.

Milestones:

Study start date is the reimbursement approval date for OSA in each country. The study was initiated in January 2023.

Study end date will be 5 years from market launch date and 4 years from reimbursement approval for OSA.

Progress reports will be every 6 months for the first 2 years after launch in the EU and then will be annually thereafter. Interim reports will be 42-45 months after reimbursement approval for OSA.

The protocol was registered in September 2022 under the EU PAS register (EUPAS45651) before data extraction.

The final due date for the report is December 2026.

FDA Post-Marketing Requirements

Study 1 (JZP110-402):
Study name and title: SUNOSI (solriamfetol) Pregnancy Registry: an observational study on the safety of solriamfetol exposure in pregnant women and their offspring

Rationale and study objectives:

The Sunosi (solriamfetol) Pregnancy Registry will add to the current body of knowledge regarding the safety of solriamfetol exposure during pregnancy. Currently, there are no clinical studies of solriamfetol in pregnant women, and available human data on solriamfetol exposure during pregnancy are insufficient to inform risk analysis. Data from the registry will supplement data from animal toxicology studies and human exposure data.

The objective of the Sunosi (solriamfetol) Pregnancy Registry is to compare the maternal, fetal, and infant outcomes of pregnant women with a diagnosis of narcolepsy or obstructive sleep apnoea (OSA) who are exposed to solriamfetol during pregnancy with outcomes in 2 concurrent internal comparison cohorts composed of pregnant women with narcolepsy or OSA unexposed to solriamfetol during pregnancy and: (1) unexposed to other prescription wake-promoting medications or stimulants or (2) exposed to other prescription wake-promoting medications or stimulants.

The final protocol was accepted by FDA on 24 August 2021.

Study design:

The Sunosi Pregnancy Registry is a prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to solriamfetol during pregnancy with outcomes in an unexposed comparator 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 at 4 and 12 months of infant age. The study is strictly observational; the schedule of office visits and all treatment regimens will be determined by the treating health care provider (HCP). HCPs will report data to the registry that are routinely documented in the patient's medical record in the course of usual care.

Study population:

The study population will include pregnant women of any age who reside in a country where solriamfetol is available for the treatment of excessive daytime sleepiness (EDS) associated with narcolepsy or OSA, provide consent to participate as well as medical releases for their HCPs to provide data to the registry, and meet the criteria for inclusion into 1 of the cohorts described below.

Milestones:

As has been communicated with the FDA, enrolment of solriamfetol-exposed pregnant women in the registry commenced on 31 July 2019, after submission of the original protocol to the FDA and approval by a central institutional review board (IRB). After FDA and IRB approval of the updated protocol, enrolment of women in the comparator cohorts will commence. The study is planned to end in September 2029, and a final report will be submitted to the FDA by September 2030.

Study 2 (JZP110-403):

Study name and title:

A retrospective cohort study to assess major congenital malformations, spontaneous abortions, stillbirths, small for gestational age and preterm birth in women exposed to solriamfetol during pregnancy compared to unexposed control populations using electronic healthcare databases in the United States.

Rationale and study objectives:

This study will add to the current body of knowledge regarding the safety of solriamfetol exposure during pregnancy. Currently, there are no clinical studies of solriamfetol in pregnant women, and available human data on solriamfetol exposure during pregnancy are insufficient to inform clinical risk-benefit decision-making.

Data from this non-interventional retrospective cohort study will supplement data from animal toxicology studies and human exposure data.

The primary objective of the study is to evaluate whether the percentage of live births with a MCM is statistically higher in women treated with solriamfetol during pregnancy compared to a 1:3 matched active treatment reference group of solriamfetol-unexposed pregnant women from the same patient population (narcolepsy, OSA, or unspecified). This study also seeks to evaluate the following secondary pregnancy outcomes of interest:

- Preterm birth: a live birth occurring at less than 37 weeks of gestation (< 37 weeks of gestation)
- Small for gestational age (SGA): a live birth with a birth weight less than the tenth percentile for the gestational age
- Low birthweight (LBW): a live birth with a birthweight < 2,500 g
- Stillbirth: an involuntary foetal loss occurring at 20 weeks of gestation or greater (≥ 20 weeks of gestation),
- Spontaneous abortion: an involuntary foetal loss or expulsion of products of conception occurring at less than 20 weeks of gestation. The spontaneous abortion operational case definition excludes ectopic pregnancies, molar pregnancies and elective terminations.

Study design:

Non-interventional retrospective cohort study will be conducted as a secondary use of de-identified electronic healthcare data (EHD) that originally were collected for the purposes of health insurance billing and/or routine patient care from the Department of Defense (DoD) and HealthVerity databases.

Study population:

All women with at least one prescription for a stimulant or non-stimulant wake-promoting drug (solriamfetol, modafinil, armodafinil, pitolisant, sodium oxybate, amphetamines or methylphenidate), or a coded diagnosis for narcolepsy, or a coded diagnosis for OSA, or a CPAP device claim (as a surrogate for a coded OSA diagnosis) recorded prior to the service date of any pregnancy-related healthcare encounter between 08-July-2019 and 19-March-2025 will be selected from each database.

Pregnancy database study revised protocol was conditionally accepted by the FDA on 26 January 2022. Final protocol was submitted to FDA on 03 March 2022. The statistical analysis plan is currently under review.

Milestones:

The cohort selection period will start from the US launch date of solriamfetol (08-July-2019). The data cut-off date for patient follow-up is 19-March-2025 (end of study observational period).

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
N/A				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A				
Category 3 - Required additional pharmacovigilance activities				
A post-authorisation safety study (PASS) to evaluate cardiovascular events in adult patients with obstructive sleep apnoea (OSA) treated with solriamfetol. (JZP865-401) On-going	Primary objectives: 1. To estimate and compare the incidence rate of major adverse cardiovascular events (MACE), as a composite endpoint of non-fatal acute myocardial infarction (MI), non-fatal stroke, and all-cause mortality, in adults newly exposed to solriamfetol plus positive airway pressure (PAP) vs patients exposed only to PAP (France). 2. To estimate the incidence rate of MACE, as a composite endpoint of (fatal or non-fatal) acute MI, (fatal or non-fatal) stroke, and all-cause mortality, in adults newly exposed to solriamfetol irrespective of PAP use (France and Germany).	• Serious Cardiovascular Events • Serious Psychiatric Events • Potential for Abuse, Misuse and Diversion • Potential for Pharmacodynamics Interactions	Study start date Progress reports Final report	Study start date is the reimbursement approval date for OSA in each country. The study was initiated in January 2023. Every 6 months for the first 2 years and then annually December 2026

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	Secondary objectives: 1. To describe the demographics, clinical characteristics, and treatment patterns (dose, duration of treatment, number of prescriptions) of patients newly exposed to solriamfetol plus PAP (France), patients exposed only to PAP (France) and patients newly exposed to solriamfetol irrespective of PAP use (France and Germany). 2. a. To estimate and compare the incidence rate of individual MACE components and additional CV events (e.g., unstable angina and arrhythmic events) in patients newly exposed to solriamfetol plus PAP (France) vs patients exposed only to PAP (France). b. To estimate the incidence rate of individual MACE components and additional CV events (e.g., unstable angina and arrhythmic events) in patients newly exposed to solriamfetol irrespective of PAP use (France and Germany). 3. To estimate the incidence rate of MACE and individual MACE components in patients newly exposed to solriamfetol plus PAP (France), patients exposed only to PAP (France) and patients			

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	newly exposed to solriamfetol irrespective of PAP use (France and Germany), by subgroups defined by: a. Patient demographics (i.e., age, sex) b. CV risk factors (e.g., obesity, hypertension, diabetes, etc.) c. Population with CV risk factors mentioned as contraindications in the Summary of Product Characteristics (SmPC) (patients that experienced acute MI one year before study entry or have any history of unstable angina pectoris or serious cardiac arrhythmias) 4. To estimate the incidence rate of serious psychiatric events in patients newly exposed to solriamfetol irrespective of PAP use (France and Germany), in patients newly exposed to solriamfetol on PAP treatment, and in patients exposed only to PAP (France). Exploratory Objectives: 1. To assess any effect modification (modification of hazard ratio (HR) of MACE by co-medications) indicating potential pharmacodynamic interactions in patients newly exposed to solriamfetol plus PAP (France). 2. To estimate the incidence rate of MACE and individual MACE			

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	components in patients newly exposed to solriamfetol with PAP use any time prior to index date (Germany).			
Post-marketing pregnancy registry (prospective, observational) FDA (JZP110-402) On-going	The objective of the SUNOSI (solriamfetol) Pregnancy Registry is to compare the maternal, foetal, and infant outcomes of women exposed to solriamfetol during pregnancy with outcomes in an unexposed comparator population.	• Reproductive toxicity	Annual update Final report	Updates will be provided in the Periodic Safety Update Reports. 2030
Post-marketing pregnancy registry (retrospective database study) FDA (JZP110-403) On-going	The primary objective of the study is to estimate the incidence of major congenital malformations in the offspring of included women. Secondary objectives will be to estimate frequencies of the following: • Pregnancy outcomes (e.g., live birth, spontaneous abortion, foetal death/stillbirth and induced abortion) • Low birth weight • Minor congenital malformations	• Reproductive toxicity	Final report	To be determined

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Serious Cardiovascular Events	Routine risk communication: • SmPC sections 4.2, 4.3, 4.4 and 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.2 and corresponding PIL sections – Blood pressure and heart rate should be assessed before initiating treatment with solriamfetol and should be monitored periodically during treatment, especially when increasing the dose. • SmPC section 4.3 – Contraindication in patients with myocardial infarction within the past year, unstable angina pectoris, uncontrolled hypertension, serious cardiac arrhythmias and other serious heart problems. Other routine risk minimisation measures beyond the product information: Legal status: • Restricted Medical Prescription
Serious Psychiatric Events	Routine risk communication: • SmPC sections 4.4 and 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4 and corresponding PIL sections – Patients treated with solriamfetol should be carefully monitored for adverse reactions such as anxiety, insomnia and irritability. – These adverse reactions were commonly observed during treatment initiation but tended to resolve with continued treatment. If these symptoms persist or worsen, dose reduction or discontinuation should be considered. Other routine risk minimisation measures beyond the product information: Legal status: • Restricted Medical Prescription

Safety concern	Routine risk minimisation activities
Potential for Abuse, Misuse and Diversion	Routine risk communication: • SmPC section 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4 and corresponding PIL sections – Caution should be exercised when treating patients with a history of stimulant (e.g. methylphenidate, amphetamine) or alcohol abuse, and these patients should be monitored for signs of misuse or abuse of solriamfetol. Other routine risk minimisation measures beyond the product information: Legal status: • Restricted Medical Prescription
Reproductive Toxicity	Routine risk communication: • SmPC section 4.4, 4.6 and 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4 and corresponding PIL sections – Women of childbearing potential or their male partners must use effective method of contraception while taking solriamfetol (see section 4.6). • SmPC section 4.6 – Sunosi is not recommended during pregnancy and in women of childbearing potential not using contraception. Other routine risk minimisation measures beyond the product information: Legal status: • Restricted Medical Prescription
Potential for Pharmacodynamics interactions	Routine risk communication: • SmPC section 4.2, 4.3 and 4.5 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.3 and corresponding PIL sections – Contraindication in patients with concomitant use of monoamine oxidase inhibitors (MAOIs) or within 14 days after MAOI treatment has been discontinued (see section 4.5). Other routine risk minimisation measures beyond the product information: Legal status: • Restricted Medical Prescription

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Serious Cardiovascular Events	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4 and 4.8 and corresponding PIL sections Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Long-term safety PASS for OSA patients
Serious Psychiatric Events	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 and corresponding PIL sections Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Follow-up questionnaire for depression including suicidality. Additional pharmacovigilance activities: Long-term safety PASS for OSA patients
Potential for abuse, misuse and diversion	Routine risk minimisation measures: SmPC section 4.4 and corresponding PIL sections Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Explore the feasibility of looking for signals of abuse and misuse using existing sentinel and database systems such as the Euro-DEN Plus. Additional pharmacovigilance activities: Long-term safety PASS for OSA patients
Reproductive toxicity	Routine risk minimisation measures: SmPC sections 4.4, 4.6 and 5.3 and corresponding PIL sections Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: • Post-marketing pregnancy registry (prospective, observational) FDA (JZP110-402) • Post-marketing pregnancy registry (retrospective database study) FDA

		(JZP110-403)
Potential for Pharmacodynamics interactions	Routine risk minimisation measures: SmPC sections 4.2, 4.3 and 4.5 and corresponding PIL sections Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Long-term safety PASS for OSA patients

Part VI: Summary of the risk management plan

Summary of risk management plan for Sunosi 75 mg film-coated tablets and Sunosi 150 mg film-coated tablets (Solriamfetol)

This is a summary of the risk management plan (RMP) for Sunosi 75 mg film-coated tablets and Sunosi 150 mg film-coated tablets. The RMP details important risks of Sunosi 75 mg film-coated tablets and Sunosi 150 mg film-coated tablets, how these risks can be minimised, and how more information will be obtained about Sunosi 75 mg film-coated tablets and Sunosi 150 mg film-coated tablets' risks and uncertainties (missing information).

Sunosi 75 mg film-coated tablets and Sunosi 150 mg film-coated tablets' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Sunosi 75 mg film-coated tablets and Sunosi 150 mg film-coated tablets should be used.

This summary of the RMP for Sunosi 75 mg film-coated tablets and Sunosi 150 mg film-coated tablets should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Sunosi 75 mg film-coated tablets and Sunosi 150 mg film-coated tablets' RMP.

I. The medicine and what it is used for

Sunosi 75 mg film-coated tablets and Sunosi 150 mg film-coated tablets is authorised for improving wakefulness and reducing excessive daytime sleepiness in adult patients with narcolepsy (with or without cataplexy) or obstructive sleep apnoea whose EDS has not been satisfactorily treated by primary OSA therapy, such as continuous positive airway pressure (CPAP) (see SmPC for the full indication). It contains solriamfetol as the active substance and it is given orally.

Further information about the evaluation of Sunosi 75 mg film-coated tablets and Sunosi 150 mg film-coated tablets's benefits can be found in Sunosi 75 mg film-coated tablets and Sunosi 150 mg film-coated tablets' EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/sunosi.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Sunosi 75 mg film-coated tablets and Sunosi 150 mg film-coated tablets, together with measures to minimise such risks and the proposed studies for learning more about Sunosi 75 mg film-coated tablets and Sunosi 150 mg film-coated tablets 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Sunosi 75 mg film-coated tablets and Sunosi 150 mg film-coated tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Sunosi 75 mg film-coated tablets and Sunosi 150 mg film-coated tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Sunosi 75 mg film-coated tablets and Sunosi 150 mg film-coated tablets. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

List of Important Risks and Missing Information	
Important identified risks	• Serious cardiovascular events
Important potential risks	• Serious psychiatric events • Potential for abuse, misuse and diversion • Reproductive toxicity
Missing information	• Potential for pharmacodynamic interactions

II.B Summary of important risks

Important Identified Risk 1: Serious Cardiovascular (CV) Events	
Evidence for linking the risk to the medicine	The general patient population with narcolepsy or OSA may be at risk for serious CV events due to certain intrinsic factors such as age, obesity, and comorbid cardiovascular and metabolic conditions, as well as underlying disease pathophysiology. CV adverse events were of interest because of observations of modest, reversible increases in HR and BP.
Risk factors and risk groups	Patients with narcolepsy and OSA may be at risk for CV events due to certain intrinsic risk factors, such as increasing age, obesity, concurrent diabetes mellitus, concurrent CV disease, and smoking. Patients with pre-existing hypertension, cardiovascular or cerebrovascular conditions that might be compromised by increases in blood pressure. Other risk groups include patients using concomitant medications that increase heart rate and blood pressure.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4 and 4.8 and corresponding PIL sections Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Long-term safety PASS for OSA patients. See section II. C of this summary for an overview of the post- authorisation development plan.

Important Potential Risk 1: Serious Psychiatric Events	
Evidence for linking the risk to the medicine	Psychiatric adverse events were of interest because psychiatric comorbidities are common in narcolepsy and OSA, and stimulants and wake-promoting agents have the potential to exacerbate underlying psychiatric conditions.
Risk factors and risk groups	Psychiatric disorders are a frequent comorbidity in patients with narcolepsy. In OSA patients, observational studies have found a nearly 2-fold higher incidence of depression in patients with OSA when matched to controls without OSA. In the Sunosi clinical development programme, serious psychiatric symptoms occurred more commonly in the narcolepsy population than the OSA population.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 and corresponding PIL sections Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Long-term safety PASS for OSA patients. See section II. C of this summary for an overview of the post- authorisation development plan.

Important Potential Risk 2: Potential for Abuse, Misuse and Diversion	
Evidence for linking the risk to the medicine	Sunosi meets the criteria for assessment of abuse potential as a new molecular entity that affects the CNS. In addition, abuse, misuse and diversion potential are associated with other medications used in the treatment of ES that are pharmacologically similar to Sunosi.
Risk factors and risk groups	Patients with a history of substance abuse (alcohol and /or drugs)
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and corresponding PIL sections Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Long-term safety PASS for OSA patients See section II. C of this summary for an overview of the post- authorisation development plan.

Important Potential Risk 3: Reproductive Toxicity	
Evidence for linking the risk to the medicine	Preclinical reproductive toxicity studies in pregnant rats and rabbits showed evidence of embryofoetal toxicity.
Risk factors and risk groups	Pregnant women and their offspring.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.6 and 5.3 and corresponding PIL sections Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Post-marketing pregnancy registry (prospective, observational) FDA (JZP110-402) • Post-marketing pregnancy registry (retrospective database study) FDA (JZP110-

	403) See section II. C of this summary for an overview of the post- authorisation development plan.

Missing Information 1: Potential for Pharmacodynamics Interactions	
Risk minimization measures	Routine risk minimisation measures: SmPC section 4.2, 4.3 and 4.5 and corresponding PIL sections Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Long-term safety PASS for OSA patients. See section II. C of this summary for an overview of the post- authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Sunosi 75 mg film-coated tablets and Sunosi 150 mg film-coated tablets.

II.C.2 Other studies in post-authorisation development plan

JZP865-401: A post-authorisation safety study (PASS) to evaluate cardiovascular events in adult patients with obstructive sleep apnoea (OSA) treated with solriamfetol.

Purpose of the study:

Patients with OSA have greater frequency of cardiovascular (CV) risk factors and comorbidities such as obesity, hypertension, type 2 diabetes, coronary artery disease than non-OSA patients and are at a greater risk for CV events. Therefore, the PASS to evaluate cardiovascular events in adult patients with OSA treated with solriamfetol is being conducted in Europe to assess the safety of the treatment and to evaluate major adverse cardiovascular events (MACE) and other potential safety outcomes in adult patients.

Due to variability in data availability across the study countries, i.e., France and Germany, the study objectives differ slightly between two approaches (descriptive and prevalent new user designs). Utilising claims and administrative data that capture data on patients with OSA and excessive daytime sleepiness (EDS) managed according to routine clinical practice the following study objectives will be fulfilled:

Primary objectives:

1. To estimate and compare the incidence rate of major adverse cardiovascular events (MACE), as a composite endpoint of non-fatal acute myocardial infarction (MI), non-fatal stroke, and all-cause mortality, in adults newly exposed to solriamfetol plus positive airway pressure (PAP) vs patients exposed only to PAP (France).
2. To estimate the incidence rate of MACE, as a composite endpoint of (fatal or non-fatal) acute MI, (fatal or non-fatal) stroke, and all-cause mortality, in adults newly exposed to solriamfetol irrespective of PAP use (France and Germany).

Secondary objectives:

1. To describe the demographics, clinical characteristics, and treatment patterns (dose, duration of treatment, number of prescriptions) of patients newly exposed to solriamfetol plus PAP (France), patients exposed only to PAP (France) and patients newly exposed to

solriamfetol irrespective of PAP use (France and Germany).

2. a. To estimate and compare the incidence rate of individual MACE components and additional CV events (e.g., unstable angina and arrhythmic events) in patients newly exposed to solriamfetol plus PAP (France) vs patients exposed only to PAP (France).

   b. To estimate the incidence rate of individual MACE components and additional CV events (e.g., unstable angina and arrhythmic events) in patients newly exposed to solriamfetol irrespective of PAP use (France and Germany).

3. To estimate the incidence rate of MACE and individual MACE components in patients newly exposed to solriamfetol plus PAP (France), patients exposed only to PAP (France) and patients newly exposed to solriamfetol irrespective of PAP use (France and Germany), by subgroups defined by:
   a. Patient demographics (i.e., age, sex)
   b. CV risk factors (e.g., obesity, hypertension, diabetes, etc.)
   c. Population with CV risk factors mentioned as contraindications in the Summary of Product Characteristics (SmPC) (patients that experienced acute MI one year before study entry or have any history of unstable angina pectoris or serious cardiac arrhythmias)

4. To estimate the incidence rate of serious psychiatric events in patients newly exposed to solriamfetol irrespective of PAP use (France and Germany), in patients newly exposed to solriamfetol on PAP treatment, and in patients exposed only to PAP (France).

Exploratory Objectives:

1. To assess any effect modification (modification of hazard ratio (HR) of MACE by co-medications) indicating potential pharmacodynamic interactions in patients newly exposed to solriamfetol plus PAP (France).
2. To estimate the incidence rate of MACE and individual MACE components in patients newly exposed to solriamfetol with PAP use any time prior to index date (Germany).

JZP110-402: SUNOSI (solriamfetol) Pregnancy Registry: an observational study on the safety of solriamfetol exposure in pregnant women and their offspring.

Purpose of the study:

The Sunosi (solriamfetol) Pregnancy Registry will add to the current body of knowledge regarding the safety of solriamfetol exposure during pregnancy. Currently, there are no clinical studies of solriamfetol in pregnant women, and available human data on solriamfetol exposure during pregnancy are insufficient to inform risk analysis. Data from the registry will supplement data from animal toxicology studies and human exposure data.

The objective of the Sunosi (solriamfetol) Pregnancy Registry is to compare the maternal, fetal, and infant outcomes of pregnant women with a diagnosis of narcolepsy or obstructive sleep apnoea (OSA) who are exposed to solriamfetol during pregnancy with outcomes in 2 concurrent internal comparison cohorts composed of pregnant women with narcolepsy or OSA unexposed to solriamfetol during pregnancy and: (1) unexposed to other prescription wake-promoting medications or stimulants or (2) exposed to other prescription wake-promoting medications or stimulants.

JZP110-403: A retrospective cohort study to assess major congenital malformations, spontaneous abortions, stillbirths, small for gestational age and preterm birth in women exposed to solriamfetol during pregnancy compared to unexposed control populations using electronic healthcare databases in the United States.

Purpose of the study:

This study will add to the current body of knowledge regarding the safety of solriamfetol exposure during pregnancy. Currently, there are no clinical studies of solriamfetol in pregnant women, and available human data on solriamfetol exposure during pregnancy are insufficient to inform clinical

risk-benefit decision-making.

Data from this non-interventional retrospective cohort study will supplement data from animal toxicology studies and human exposure data.

The primary objective of the study is to evaluate whether the percentage of live births with a MCM is statistically higher in women treated with solriamfetol during pregnancy compared to a 1:3 matched active treatment reference group of solriamfetol-unexposed pregnant women from the same patient population (narcolepsy, OSA, or unspecified). This study also seeks to evaluate the following secondary pregnancy outcomes of interest:

- Preterm birth: a live birth occurring at less than 37 weeks of gestation (< 37 weeks of gestation)
- Small for gestational age (SGA): a live birth with a birth weight less than the tenth percentile for the gestational age
- Low birthweight (LBW): a live birth with a birthweight < 2,500 g
- Stillbirth: an involuntary foetal loss occurring at 20 weeks of gestation or greater (≥ 20 weeks of gestation),
- Spontaneous abortion: an involuntary foetal loss or expulsion of products of conception occurring at less than 20 weeks of gestation. The spontaneous abortion operational case definition excludes ectopic pregnancies, molar pregnancies and elective terminations.

Part VII: Annexes

Table of contents

Annex 4 - Specific adverse drug reaction follow-up forms

Specific adverse reaction follow-up questionnaire for the important potential risk of "serious psychiatric events": Depression including suicidality

Follow up questionnaire for Depression (HCP)

PREFACE:

You are receiving this questionnaire because you have reported adverse event possibly related to **Depression including suicidality related with SUNOSI film-coated tablets (Solriamfetol)**. We kindly request your assistance in providing additional information to better understand the nature and impact of this event. Your responses contribute to the ongoing drug safety efforts and support patient safety and appropriate product use.

PRIVACY STATEMENT:

All personal data will be handled in accordance with applicable data protection regulations. Patient identifiers should not be included unless already anonymised.

A. PATIENT & CASE INFORMATION

(If not previously provided)

1. **Patient Initials / Reference ID (anonymised):** _____

2. **Patient gender:** ☐ Male ☐ Female ☐ Other ☐ Unknown

3. **Age (at time of reaction):** _____ years / _____ months

4. **Weight:** _____ kg (if known)

5. **Start date of SUNOSI administration:** ____ / ____ / _____

6. **Date and time of depression including suicidality related adverse event onset:**
____ / ____ / _____ at _____

7. **Date of resolution (if applicable):** ____ / ____ / _____

8. **Please confirm if the patient has any medical history or concurrent condition of depression, suicidal ideation, suicidal attempt, or any other psychiatric condition? If yes, please provide onset date and treatment received. In addition, is there any impact on the respective condition (frequency or severity) increased or decreased after starting therapy with SUNOSI?**
☐ Yes ☐ No
☐ If yes, please provide details: _____

9. **Concomitant medications (name, indication, dose, start/stop dates) [if relevant]:**

10. **Please confirm if SUNOSI is added to any pre-existing drug regimen for treating the same condition and any suspected potential drug interaction.**
☐ Yes ☐ No
☐ If yes, please provide details and its current status: _____

B. MEDICINAL PRODUCT INFORMATION

11. **Exact indication for use:**
☐ Excessive daytime sleepiness with Narcolepsy
☐ Excessive daytime sleepiness with Obstructive Sleep Apnoea (OSA)
☐ Other: _____

12. **Prescribed dose of SUNOSI:**
☐ 37.5 mg ☐ 75 mg ☐ 150 mg

13. **Prescribed frequency of taking SUNOSI:**
☐ Once daily
☐ Other: _____

14. **If the patient started SUNOSI at lower dose 37.5 mg or 75 mg, then please confirm whether up-titration was performed up to 150 mg or any other dose, along with details.**
☐ Yes ☐ No
If yes, Details and reason for starting at lower dose of 37.5 mg: _____

C. ADVERSE REACTION DESCRIPTION

15. **Please confirm if the patient has a diagnosis of depression.**
☐ Yes ☐ No
☐ If yes, please provide details including any tests/assessment performed to diagnose it:
_____

16. **Has the patient ever experienced <Event verbatim for depression> before taking SUNOSI?**
☐ Yes ☐ No
☐ If yes, please provide the start date of the condition: _____

Please also confirm if there was any worsening of the condition:
☐ Yes ☐ No
☐ If yes, please provide the details including timelines: _____

17. **Please confirm if the patient has any familial history of depression, suicidal thoughts/attempt, or any other psychiatric condition?**
☐ Yes ☐ No

☐ If yes, please provide details: _____

18. **Please confirm if the patient has any history of substance use. If yes, please provide details on duration (onset date, if available) and chemical substance/product of abuse.**
☐ Yes ☐ No
☐ If yes, please provide details: _____

19. **Please provide details if patient had any acute life events (e.g., post-traumatic stress disorder, etc.) after starting therapy with SUNOSI.**
☐ Yes ☐ No
☐ If yes, please provide details: _____

H. ADDITIONAL COMMENTS

20. **Please provide any other comments, relevant context, or documentation (e.g., incident report):**

Thank you for your collaboration.

Follow up questionnaire for Depression (Patient)

PREFACE:

You are receiving this questionnaire because you have reported adverse event possibly related to **Depression including suicidality related with SUNOSI film-coated tablets (Solriamfetol)**. We kindly request your assistance in providing additional information to better understand the nature and impact of this event. Your responses contribute to the ongoing drug safety efforts and support patient safety and appropriate product use.

PRIVACY STATEMENT:

All personal data will be handled in accordance with applicable data protection regulations. Patient identifiers should not be included unless already anonymised.

A. PATIENT & CASE INFORMATION

(If not previously provided)

1. **Patient Initials / Reference ID (anonymised):** _____

2. **Patient gender:** ☐ Male ☐ Female ☐ Other ☐ Unknown

3. **Age (at time of reaction):** _____ years / _____ months

4. **Weight:** _____ kg (if known)

5. **Start date of SUNOSI administration:** ____ / ____ / _____

6. **Date and time of depression including suicidality related adverse event onset:**
____ / ____ / _____ at _____

7. **Date of adverse event resolution (if applicable):** ____ / ____ / _____

8. Are you currently taking or did you take any other medications? **(please include name, reason, dose, start/stop dates) [if relevant]:**

9. **Do you have a history of depression, suicidal thoughts or attempt, or any other mental health condition? If yes, please confirm when it started, and any treatment received. Also, did the condition improved or worsened after starting therapy with SUNOSI?**
☐ Yes ☐ No
Details: _____

B. MEDICINAL PRODUCT INFORMATION

10. **Exact indication for use:**
☐ Excessive daytime sleepiness with Narcolepsy
☐ Excessive daytime sleepiness with Obstructive Sleep Apnoea (OSA)
☐ Other: _____

11. **Prescribed dose of SUNOSI:**
☐ 37.5 mg ☐ 75 mg ☐ 150 mg

12. **Prescribed frequency of taking SUNOSI:**
☐ Once daily ☐ Other: _____

13. **If you started with a lower dose (e.g., 37.5 mg), was your dose increased later?**
☐ Yes ☐ No
Please provide details and reason if known: _____

14. **Please provide the total duration of SUNOSI therapy**:

C. ADVERSE REACTION DESCRIPTION

15. **Please confirm if there is any condition (any adverse event) or underlying depression that got changed or worsened due to the change in the dosage of SUNOSI.**
☐ Yes ☐ No
☐ If yes, please provide details: _____

16. **Please confirm any family history of depression, suicidal thoughts/attempt, or any other psychiatric condition?**
☐ Yes ☐ No
☐ If yes, please provide details: _____

17. **Please confirm if any acute life events (e.g., post-traumatic stress disorder, etc.) happened after starting therapy with SUNOSI.**
☐ Yes ☐ No
☐ If yes, please provide details: _____

H. ADDITIONAL COMMENTS

18. **Please provide any other comments, relevant context, or documentation (e.g., incident report):**

Thank you for your collaboration.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 - Other supporting data (including referenced material)

American Academy of Sleep Medicine (AASM) (2014). International Classification of Sleep Disorders-Third Edition (ICSD-3), Darien, IL. American Academy of Sleep Medicine;53- 62,143-155.

Baladi MG, Forster MJ, Gatch MB, et al. (2018). Characterization of the neurochemical and behavioral effects of solriamfetol (JZP-110), a selective dopamine and norepinephrine reuptake inhibitor. J Pharmacol Exp Ther. 366:367–376.

Barbé F, Pericás J, Muñoz A, et al. (1998). Automobile accidents in patients with sleep apnea syndrome: an epidemiological and mechanistic study. Am J Respir Crit Care Med;158:18–22.

Billiard M1, Bassetti C, Dauvilliers Y, et al, and the EFNS Task Force. (2006) EFNS guidelines on management of narcolepsy. Eur J Neurol;13(10):1035-1048.

Billiard M, Jaussent I, Dauvilliers Y, et al. (2011). Recurrent hypersomnia: a review of 339 cases. Sleep Med Rev;15:247-257.

Bixler EO, Vgontzas AN, Lin HM, et al. (2005). Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. J Clin Endocrinol Metab Aug 1;90(8):4510-4515.

Black J, Reaven NL, Funk SE, et al. (2017). Medical comorbidity in narcolepsy: findings from the Burden of Narcolepsy Disease (BOND) study. Sleep Med. May;33:13-18.

Broughton R, Ghanem Q, Hishikawa Y, et al. (1981). Life effects of narcolepsy in 180 patients from North America, Asia and Europe compared to matched controls. Can J Neurol Sci. 8(4):299–304.

Daniels E, King MA, Smith IE, et al. (2001). Health-related quality of life in narcolepsy. J Sleep Res;10:75-81.

Dodel R, Peter H, Walbert T, et al. (2004). The socioeconomic impact of narcolepsy. Sleep; 27:1123-1128.

Dodel R, Peter H, Spottke A, et al. (2007). Health-related quality of life in patients with narcolepsy. Sleep Med;8:733-41.

Epstein LJ, Kristo D, Strollo PJ, et al. (2009). Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med;5(3):263–276.

Fietze I, Penzel T, Alonderis A, et al. (2011). COST Action B26 Group. Management of obstructive sleep apnea in Europe. Sleep Med;12:190-197.

Findley LJ, Suratt PM, Dinges DF. (1999). Time-on-task decrements in "steer clear" performance of patients with sleep apnea and narcolepsy. Sleep;22:804-809.

Garvey JF, Pengo MF, Drakatos P, et al. (2015). Epidemiological aspects of obstructive sleep apnea. J Thorac Dis;7(5):920-929.

Gasa M, Tamisier R, Launois SH, et al. (2013). Scientific Council of the Sleep Registry of the French Federation of Pneumology-FFP. Residual sleepiness in sleep apnea patients treated by continuous positive airway pressure. J Sleep Res;22:389-397.

Gay P, Weaver T, Loube D, et al. (2006). Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults: A review by the Positive Airway Pressure Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep;29:381-401.

Hedner J, Grote L, Bonsignore M, et al. (2011). The European sleep apnoea database (ESADA): report from 22 European sleep laboratories. Eur Respir J;38:635-642.

Ingravallo F, Gnucci V, Pizza F, et al. (2012). The burden of narcolepsy with cataplexy: How disease history and clinical features influence socio-economic outcomes. Sleep Med;13:1293- 1300.

Jennum P, Riha R. (2009). Epidemiology of sleep apnoea/hypopnoea syndrome and sleep-disordered breathing. Eur Respir;33:907-914

Jennum P, Ibsen R, Petersen ER, et al. (2012). Health, social, and economic consequences of narcolepsy: A controlled national study evaluating the societal effect on patients and their partners. Sleep Med;13:1086-1093.

Kent BD, Grote L, Ryan S, et al. (2014). Diabetes mellitus prevalence and control in sleep-disordered breathing: the European Sleep Apnea Cohort (ESADA) study. Chest;146:982-990.

Khatami R, Luca, G, Baumann CR, et al. (2016). The European Narcolepsy Network (EU-NN) database. J Sleep Res. 25:356–364

Lee W, Nagubadi S, Kryger MH, et al. (2008). Epidemiology of obstructive sleep apnea: a population-based perspective. Expert Rev Respir Med;2(3):349–364.

Lee SA, Han SH, Ryu HU. (2015). Anxiety and its relationship to quality of life independent of depression in patients with obstructive sleep apnea. J Psychosom Res;79(1):32-36.

Maski K, Steinhart E, Williams D, et al. (2017). Listening to the patient voice in narcolepsy: Diagnostic delay, disease burden, and treatment efficacy. J Clin Sleep Med;13(3): 419-425.

Morgenthaler TI, Kapur VK, Brown TM, et al. (2007). Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep;30:1705-1711.

Nena E, Steiropoulos P, Constantinidis TC, et al. (2010). Work productivity in obstructive sleep apnea patients. J Occup Environ Med;52(6):622-625.

Ohayon MM, Priest RG, Zulley J, et al. (2002). Prevalence of narcolepsy symptomatology and diagnosis in the European general population. Neurology;58:1826–1833.

Ohayon MM, Ferini-Strambi L, Plazzi G, et al. (2005). Frequency of narcolepsy symptoms and other sleep disorders in narcoleptic patients and their first-degree relatives. J. Sleep Res. 14, 437– 445.

Ohayon MM. (2007). Epidemiology of narcolepsy. In Narcolepsy and Hypersomnia. C Bassetti, M Billiard, E Mignot, eds. New York: Informa Healthcare: pp 125-132.

Ohayon MM. (2013). Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population. Sleep Med; 14(6):488-492.

Ohayon MM, Black J, Lai C, et al. (2014). Increased mortality in narcolepsy. Sleep. Mar 1;37(3):439-444.

Okun ML, Lin L, Pelin Z, et al. (2002). Clinical aspects of narcolepsy-cataplexy across ethnic groups. Sleep;25:27-35.

Omachi TA, Claman DM, Blanc PD, et al. (2009). Obstructive sleep apnea: a risk factor for work disability. Sleep;32(6):791-798.

Pépin J-L, Viot-Blanc V, Escourrou P, et al. (2009). Prevalence of residual excessive sleepiness in CPAP-treated sleep apnoea patients: the French multicentre study. Eur Respir J;33:1062– 1067.

Philip P, Sagaspe P, Lagarde E, et al. (2010). Sleep disorders and accidental risk in a large group of regular registered highway drivers. Sleep Med;11:973-979.

Philip P, Chaufton C, Taillard J, et al. (2013). Maintenance of Wakefulness Test scores and driving performance in sleep disorder patients and controls. Int J Psychophysiol;89:195-202.

Provigil® (modafanil) tablets. Summary of Product Characteristics (20 Jun 2018). Teva Pharma B.V.

Punjabi NM. (2008). The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc. 5:136-143.

Randerath WJ, Verbraecken J, Andreas S, et al. (2011). Non-CPAP therapies in obstructive sleep apnoea. European Respiratory Society task force on non-CPAP therapies in sleep apnoea. Eur Respir J;37:1000-1028.

Ruoff CM, Reaven NL, Funk SE, et al. (2017). High rates of psychiatric comorbidity in narcolepsy: Findings from the Burden of Narcolepsy Disease (BOND) study of 9,312 patients in the United States. J Clin Psychiatry. Feb;78(2):171-176.

Sassani A, Findley LJ, Kryger M, et al. (2004). Reducing motor-vehicle collisions, costs, and fatalities by treating obstructive sleep apnea syndrome. Sleep;27(3):453-458.

Senaratna CV, Perret JL, Lodge CJ, et al. (2017). Prevalence of obstructive sleep apnea in the general population: A systematic review. Sleep Med Rev. Aug;34:70-81.

Silva GE, An MW, Goodwin JL, et al. (2009). Longitudinal evaluation of sleep-disordered breathing and sleep symptoms with change in quality of life: the Sleep Heart Health Study (SHHS). Sleep;32(8):1049-1057.

Smolensky MH, Di Milia L, Ohayon MM, et al. (2011). Sleep disorders, medical conditions, and road accident risk. Accid Anal Prev;43(2):533-548.

Strohl KP. (2017). Overview of obstructive sleep apnea in adults. www.uptodate.com ©2018

Tkacova R, McNicholas WT, Javorsky M, et al. (2014). Nocturnal intermittent hypoxia predicts prevalent hypertension in the European Sleep Apnoea Database cohort study. Eur Respir J;44:931-941.

Vandeputte M, and de Weerd A. (2003). Sleep disorders and depressive feelings: a global survey with the Beck depression scale. Sleep Med. Jul;4(4):343-345.

Vernet C, Redolfi S, Attali V, et al. (2011). Residual sleepiness in obstructive sleep apnoea: phenotype and related symptoms. Eur Respir J;38(1):98-105.

Vignatelli L, D'Alessandro R, Mosconi P, et al. (2004). Health-related quality of life in Italian patients with narcolepsy: the SF-36 health survey. Sleep Med. Sep;5(5):467-475.

Wakix® (pitolisant hydrochloride) film coated tablets. Summary of Product Characteristics (30 Sep 2016). Lincoln Medical Limited.

Xyrem® (sodium oxybate) oral solution. EU Prescribing Information (2017). Jazz Pharmaceuticals.

Young T, Skatrud J, Peppard PE. (2004). Risk factors for obstructive sleep apnea in adults. JAMA. 291(16):2013–2016.