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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sunosi

International non-proprietary name: solriamfetol

Procedure No. EMEA/H/C/004893/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

5-HT	5-Hydroxytryptophan, serotonin
AASM	American Academy of Sleep Medicine
AE	Adverse event
AEOI	Adverse event of interest
AHQ	Ad hoc query
ANOVA	analysis of variance
AUC	Area under the concentration-time curve
AUC_{0-inf}	Area under the concentration-time curve from time 0 to infinity
AUC_{0-t}	Area under the concentration-time curve from time 0 to time of last quantifiable concentration
AUCtau	Area under the concentration-time curve during one dosing interval at steady state
AUC50	Effective AUC associated with 50% of the placebo-subtracted drug effect
AUC80	Effective AUC associated with 80% of the placebo-subtracted drug effect
BCS	Biopharmaceutics Classification System
BP	Blood pressure
bpm	Beats per minute
CGIc	Clinical Global Impression of Change
CGIs	Clinical Global Impression of Severity
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CL/F	Apparent oral clearance
CLR	Renal clearance
Cmax	Maximum plasma concentration
CPAP	Continuous positive airway pressure
CQA	Critical quality attribute
CrCl	Creatinine clearance
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DA	Dopamine
DAT	Dopamine reuptake transporter
DBP	Diastolic blood pressure
DNRI	Dopamine and norepinephrine reuptake inhibitor
DPA	D-Phenylalaninol
D-Phe	D-Phenylalanine
DSC	Differential Scanning Calorimetry
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DVS	Dynamic vapour sorption
EC	European Commission
ECG	Electrocardiogram
Emax	Maximum effect
EOP2	End-of-Phase-2
EDS	Excessive daytime sleepiness
ESRD	End stage renal disease
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
HDPE	High density polyethylene

HPC	Hydroxypropylcellulose
HR	Heart rate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
ICSD	International Classification of Sleep Disorders
IND	Investigational New Drug
IP	Intraperitoneal
IPC	In-process control
IR	Infrared
IV	Intravenous
JZP-110	Previously known as ADX-N05, R228060, BZ 10A000-301, CTDP 31,827, and JNJ 16253887-AAC
Ka	Absorption rate constant
LOAEL	Lowest observed adverse effect level
LS mean	Least squares mean
MAA	Marketing Authorization Application
MDRD	Modification in Diet in Renal Disease
MP	Medicinal product
MRHD	Maximal recommended human dose
MWT	Maintenance of Wakefulness Test
NDA	New drug application
NE	Norepinephrine
NET	Norepinephrine reuptake transporter
NMR	Nuclear Magnetic Resonance
NOAEL	No observed adverse effect level
OSA	Obstructive sleep apnoea
PAP	Positive airway pressure
PC	Placebo controlled
PCTFE	Polychlorotrifluoroethylene
PD	Pharmacodynamic
PDE	Permitted daily exposure
PGIc	Patient Global Impression of Change
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
PK/PD	Pharmacokinetic / pharmacodynamic
PO	Peroral
PP	Polypropylene
PSG	Polysomnography
PVC	Polyvinyl chloride
QD	Once daily
QTPP	Quality target product profile
Rand	Randomized
RH	Relative humidity
RW	Randomized withdrawal
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SERT	Serotonin reuptake transporter
SF-36v2	36-Item Short Form Health Survey Version 2
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA Query
TEAE	Treatment emergent adverse event
t½	Elimination Half-life
TGA	Thermogravimetric analysis
tmax	Time to maximum concentration
US	United States

UV	Ultraviolet
V/F	Apparent volume of distribution
Vz/F	Apparent volume of distribution based on terminal phase
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Jazz Pharmaceuticals Ireland Limited submitted on 8 November 2018 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Sunosi, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 September 2017.

The applicant applied for the following indication: indicated to improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy (with or without cataplexy) or obstructive sleep apnoea (OSA).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0207/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0207/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance solriamfetol contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific Advice on the development relevant for the approved indication from the CHMP on 09 November 2017. The Scientific Advice pertained to the following quality, preclinical and clinical aspects of the dossier.

To summarise, in the advices on JZP-110 in the indication treatment of excessive daytime sleepiness associated with narcolepsy and obstructive sleep apnoea (OSA), the applicant asked for advice concerning:

- use of bioequivalence data to support the evolution of drug product formulation (quality),
- the scope of nonclinical data package to support MAA (nonclinical),
- the scope of clinical pharmacology data, the adequacy of the clinical development program including the need for an active comparator-controlled trial, the submission strategy concerning possible separate indications of excessive sleepiness in the OSA and narcolepsy populations, the projected safety database size and composition, and the nature of cardiovascular safety assessments (clinical).

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig Co-Rapporteur: Daniela Melchiorri

The application was received by the EMA on	8 November 2018
The procedure started on	29 November 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 February 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	25 February 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	4 March 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 March 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 May 2019
The following GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at 2 investigational sites in the United States and Germany between February and May 2019. The outcome of the inspection carried out was issued on.	20 May 2019

The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	01 July 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2019
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	25 July 2019
The applicant requested a clock stop extension	02 August 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	18 September 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	02 October 2019
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	16 October 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Sunosi on	14 November 2019
The CHMP adopted a report on similarity on	16 October 2019; re-adopted on 21 November 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Narcolepsy is a chronic sleep disorder which affects the ability to regulate sleep-wake cycles producing excessive daytime sleepiness (EDS), typically associated with cataplexy and other Rapid Eye Movement (REM) sleep conditions such as sleep paralysis and hypnagogic and hypnopompic hallucinations. The presence of EDS is a defining characteristic of narcolepsy and a major diagnostic criterion. The degree of ES is severe in most patients (Khatami et al, 2016). Cataplexy is the second most common symptom of narcolepsy and the most specific one. In fact, narcolepsy can be subclassified depending on the presence (type I) or absence (type II) of this symptom. Cataplexy is defined as a sudden loss of voluntary muscle tone with preserved consciousness triggered by emotion. Its frequency is extremely variable from one or less per year to several per day. Other symptoms, referred to as auxiliary symptoms, are less specific and not essential for diagnosis. They include hypnagogic and hypnopompic hallucinations, visual perceptual experiences occurring at sleep onset or awakening, sleep paralysis and others (Billiard et al. 2006).

Obstructive sleep apnoea (OSA) is a serious disorder characterized by sleep fragmentation caused by repeated arousals secondary to partial or complete obstruction of the upper airway during sleep. Persistent EDS is a major presenting complaint in many patients, and most patients with OSA awaken in the morning feeling tired and unrefreshed regardless of the duration of their time in bed (American Academy of Sleep Medicine [AASM] 2014). As with narcolepsy, the persistent sleepiness in patients with OSA occurs at inappropriate times, for instance while actively conversing, eating, working, and driving (AASM 2014). This pathological sleepiness often continues despite primary treatment of the airway obstruction with positive airway pressure or other therapies (Gay et al. 2006; Fietze et al. 2011; and Randerath et al. 2011).

2.1.2. Epidemiology

Narcolepsy is a rare, underdiagnosed and lifelong disease for which no cure has been identified. In adults, narcolepsy affects an estimated 0.02% to 0.067% of the population worldwide and approximately 4.7 per 10,000 (0.047%) in the general population of 5 European countries (UK, Germany, Italy, Portugal and Spain) (Ohayon et al 2002; Ohayon 2007; Majid and Hirshkowitz 2010).

Prevalence estimates of OSA worldwide range from 9% to 38% (Senaratna et al. 2017). Prevalence estimates of ES associated with OSA range from 2% to 7% (Garvey et al. 2015).

2.1.3. Biologic features

Features of narcolepsy include dysregulation of arousal state boundaries as well as autonomic and metabolic disturbances. Disruption of neurotransmission through the hypocretin / orexin (HCRT) system, usually by degeneration of the HCRT-producing neurons in the posterior hypothalamus, results in narcolepsy. The cause of HCRT neurodegeneration is unknown but thought to be related to autoimmune processes (Black et al. 2017).

In OSA, abnormalities in the anatomy of the pharynx, the physiology of the upper airway muscle dilator, and the stability of the ventilator control are important causes of repetitive pharyngeal collapse during sleep (Malhotra et al. 2002).

2.1.4. Clinical presentation, diagnosis

Both narcolepsy and OSA diagnosis was established according to the International Classification of Sleep Disorders 3rd ed. (ICSD-3) to be eligible for participation in the solriamfetol clinical trial programme.

Diagnostic criteria for narcolepsy include the presence of EDS. According to ICSD-3, narcolepsy type I additionally requires either the presence of definitive cataplexy with positive result in the Mean Sleep Latency Time (MSLT) or low hypocretin concentration in the cerebrospinal fluid (CSF). Narcolepsy type II requires the absence of cataplexy, a positive result in MSLT and normal or unperformed CSF hypocretin levels.

Obstructive sleep apnoea can be diagnosed on the basis of characteristic history (snoring, daytime sleepiness) and physical examination (increased neck circumference), but overnight polysomnography is needed to confirm presence of the predominantly obstructive respiratory events (Malhotra et al. 2002).

2.1.5. Management

Narcolepsy has no cure, but drug therapies and lifestyle changes can often help improve symptoms and quality of life. Three drugs are authorized in the EU for the "treatment of narcolepsy" in adult patients: sodium oxybate (Xyrem®) for narcolepsy type I, pitolisant (Wakix®) for narcolepsy types I and II and modafinil (Provigil®) considered the first line pharmacological treatment of EDS adult patients with narcolepsy types I or II.

Currently there are no available pharmacological therapies for treating EDS in patients with OSA in the EU. Traditional stimulants, such as amphetamines, prescribed off-label for their wake promoting effects, are limited by unwanted side effects like tachyphylaxis and carry substantial abuse liability. In OSA, positive airway pressure (PAP) applied through a nasal, oral, or oronasal interface during sleep is considered to be the reference standard treatment by the European Respiratory Society (Fietze et al, 2011; Randerath et al, 2011) with the aim to stabilize the upper airway. 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, or surgical intervention (Epstein et al, 2009; Randerath et al, 2011).

About the product

Solriamfetol is a dopamine and norepinephrine reuptake inhibitor (DNRI; Baladi et al, 2018). *In vitro* results indicate that solriamfetol has dual reuptake inhibition activity at dopamine (DA) and norepinephrine (NE) transporters and that this activity is associated in vivo with an increase in extracellular concentration of DA in the striatum and of NE in the prefrontal cortex as measured by microdialysis in rats (Baladi et al. 2018). The role of DA transporters in sleep regulation was described in the literature (Wisor et al. 2001) and is supported by the specific dopaminergic wake-promoting action of amphetamines and modafinil.

The clinical development of solriamfetol follows a symptom-oriented approach, intended to improve wakefulness and reduce EDS. Sunosi film-coated tablets are proposed to improve wakefulness and reduce EDS in adult patients with narcolepsy (with or without cataplexy) (75-150 mg) or obstructive sleep apnoea (OSA)

(37.5 – 150 mg). During clinical trials solriamfetol was used in OSA patients with previous or current use of cPAP. As a wake-promoting agent solriamfetol is not suitable to treat underlying airway obstruction in OSA. Sunosi is not designed as a substitute, but an addition of primary CPAP therapy.

Therefore, solriamfetol could potentially add to the array of available treatment options in narcoleptic patients (oxybate, pitolisant, modafinil) and could constitute the first medication approved to reduce EDS in OSA patients.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 75, 150 or 300 mg of solriamfetol. The product contains the hydrochloride salt.

Other ingredients are: hydroxypropyl cellulose, magnesium stearate, poly(vinyl alcohol) macrogol, talc, titanium dioxide (E 171), iron oxide yellow (E 172).

The product is available in PVC/PCTFE/aluminium blisters and high density polyethylene (HDPE) bottles with polypropylene (PP) child-resistant caps with integrated silica gel desiccant as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of solriamfetol hydrochloride is (*R*)-2-amino-3-phenylpropylcarbamate hydrochloride corresponding to the molecular formula $C_{10}H_{14}N_2O_2$.HCl. It has a relative molecular mass of 230.69 g/mol and the following structure:

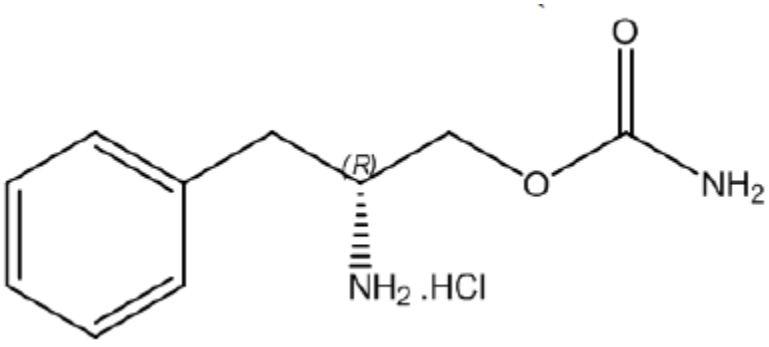


Figure 1: active substance structure

The chemical structure of solriamfetol hydrochloride was elucidated by a combination of ^{1}H and ^{13}C NMR spectroscopy, elemental analysis, mass spectrometry, Fourier transform infrared spectroscopy and ultraviolet-visible spectroscopy. The solid state properties of the active substance were measured by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), dynamic vapour sorption (DVS) and x-ray powder diffraction (XRPD).

The active substance is a white to off-white crystalline solid, not hygroscopic below 75% relative humidity (RH) but slightly hygroscopic above 75% RH, and freely soluble in aqueous media across the physiological pH range. Due to the high solubility, particle size is not critical and is not controlled in the specification.

Solriamfetol exhibits stereoisomerism due to the presence of a single chiral centre.

Manufacture, characterisation and process controls

Solriamfetol hydrochloride is synthesized in two synthetic steps and salt formations using a well-defined starting material with acceptable specifications.

During the procedure, the starting material was re-defined to ensure that enough of the process is defined in the dossier. Prior to this, only one chemical transformation step was included in the proposed manufacturing process. As a result, an additional manufacturer, responsible for the extra step, was added to the dossier. All requirements related to these changes including analytical method validation and process validation were successfully addressed during the procedure.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced to improve the process have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is doubly packaged in tightly-closed polyethylene bags which comply with the EC directive 2002/72/EC and EC 10/2011 as amended. The bags are subsequently stored within fibre drums.

Specification

The active substance specification includes tests for appearance (visual), identity (IR, HPLC), identity of chloride (Ph. Eur.), assay (HPLC), related substances (HPLC), chiral purity (chiral HPLC), water content (Ph. Eur.), residual solvents (GC), residue on ignition (Ph. Eur.) and microbial enumeration (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from development and commercial scale batches were provided. The results were within the specifications were met at each phase or development and commercial scale production and the batch data were consistent from batch to batch.

Stability

Stability data from seven batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (25 ºC / 60% RH) and from 3 batches stored for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were

provided. The following parameters were tested: appearance, assay, related substances, chiral purity, water content and microbial enumeration. The analytical methods used were the same as for release and were stability indicating. No significant trends were observed for the measured attributes.

Photostability testing following the ICH guideline Q1B was performed on one batch. No degradation was observed, so solriamfetol is not considered photosensitive. Data on stress conditions were also provided.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months when stored in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as immediate-release film-coated tablets in three strengths: 75 mg, 150 mg and 300 mg. The compositions of the tablet cores are proportionate in terms of excipients and the tablets are distinguished by size and colour (different shades of yellow), with different film-coating compositions being used for each strength. In addition, the tablets are debossed on one side with 75, 150 or 300 respectively.

Initial clinical studies were conducted using a simple "drug in capsule" formulation.

The aim of pharmaceutical development was to develop a pharmaceutical form for commercialisation; a stable, immediate release solid dosage form with visual differentiation of different dosage strengths with equivalent stability and dissolution properties.

A Quality Target Product Profile (QTPP) was established from which the Critical Quality Attributes (CQAs) were determined and justified.

The active substance, solriamfetol hydrochloride, is a chemically stable compound, highly soluble in water and highly permeable. These factors were informative to the designing of the final pharmaceutical form.

A granulation approach was adopted during manufacturing development to facilitate subsequent blending and compression. Further studies were performed to optimise the relative quantities of excipients. Opadry was selected as a cosmetic coat.

Compatibility with the various excipients was demonstrated during high humidity and high temperature studies on binary compressed mixtures. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

A discriminatory dissolution test has been validated and has been used to support comparability of the development and commercial presentations.

Testing in line with Ph. Eur. 0478 on sub-division of tablets was conducted. The tablets are shown to split consistently in half.

The primary packaging is PVC/PCTFE/Aluminium blisters or HDPE bottles with PP child-resistant caps and integrated silica gel desiccant. The materials comply with Ph. Eur. and EC requirements. The choice of the

container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: wet granulation and drying; blending and compression; film-coating; packaging. The process is considered to be a standard manufacturing process.

Critical steps of the process have been identified and appropriate process controls are in place.

An acceptable process validation protocol has been submitted with the dossier.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance (visual), identification (HPLC, UV), assay (HPLC), degradation products (HPLC), content uniformity (Ph. Eur.), dissolution (Ph. Eur.), water content (Ph. Eur.) and microbial enumeration (Ph. Eur.). The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Any degradation products or process related impurities are adequately controlled. Elemental impurities in the finished product has been assessed in line with the ICH Q3D Guideline for Elemental Impurities.

Batch analysis results are provided for three 75 mg batches, one 150 mg batch, and three 300 mg batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

The applicant used a bracketing approach in stability studies to cover the three strengths in line with ICH Q1D. Primary stability studies were conducted on 3 batches of unscored 75 mg tablets, 1 batch of scored 150 mg tablets, and 3 batches of scored tablets. Following a change in proposed posology and a change of manufacturing site, additional studies were started on 1 batch each of scored 75 mg tablets, unscored 75 mg tablets, unscored 150 mg tablets and unscored 300 mg, all from the commercial manufacturing site. The bracketing approach is considered acceptable, and the scored tablets and unscored tablets are considered representative of each other. Samples were stored in both proposed packaging formats – blisters and HDPE bottles.

Stability data was generated on batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines. Samples were tested for the stability indicating attributes listed in "Product Specification". The analytical procedures used are stability indicating (see below). No significant trends were observed for any of the measured parameters, other than an increase in water content under accelerated conditions in the HDPE bottle. No increase in water was observed under long term conditions. As a precautionary measure, instructions will be included in the SmPC (section 6.4) to keep the bottle tightly closed.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results indicate that the product is not photosensitive.

Additional forced degradation studies were conducted under stressed conditions to demonstrate the stability indicating nature of the analytical methods. In-use stability studies were conducted on multiple batches of 75 and 150 mg tablets, both intact and split in half. No significant changes were observed for any of the measured parameters. The oldest batch used in these studies was 11 months old. According to the *Note for guidance on in-use stability testing of human medicinal products (CPMP/QWP/2934/99)*, at least one batch out of a minimum of two batches should be chosen towards the end of its shelf-life. Therefore, the applicant has made a commitment to conduct an in-use stability study on a batch of 75 mg tablets following completion of the long term stability studies (planned for 48 months).

Bulk stability studies were conducted on finished product intermediates (granulate, tablet cores, and unpacked film-coated tablets). All intermediates were sufficiently stable over the time periods studied and the bulk storage times have been assigned

Based on available stability data, the proposed shelf-life of 36 months without special storage conditions for the blister packs, or kept tightly closed in the HDPE bottles in order to protect from moisture as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- To conduct an in-use stability study on a batch of 75 mg tablets following completion of the long term stability studies (planned for 48 months).

2.3. Non-clinical aspects

2.3.1. Introduction

Nonclinical studies have been performed to characterize the pharmacodynamics, pharmacokinetics and toxicology of solriamfetol.

Scientific advice on non-clinical aspects has been provided for solriamfetol by the EMA in 2017 (EMA/CHMP/SAWP/716502/2017).

All pivotal toxicological studies were conducted in accordance with GLP regulations.

2.3.2. Pharmacology

Primary pharmacodynamics

The following *in vitro* primary pharmacodynamic studies were conducted to evaluate the mechanism of action of solriamfetol compared with conventional stimulants (e.g. cocaine or amphetamine) or other monoamine reuptake inhibitors (e.g. bupropion) (Table 1).

Table 1: Nonclinical Primary Pharmacodynamic Studies with Solriamfetol – in vitro

Study No.	Study Type	Species or Cell Type	Route	Dose or Concentration	GLP Compliance
JNJ-Y1-DA-5007-03-B	Binding and uptake assay	HEK293 cells expressing cDNA for the hDAT, hNET, or hSERT	In vitro	**Binding:** hDAT 21.6 nM-100 µM hSERT 21.6 nM-100 µM hNET 21.6 nM-10 µM **Uptake:** hDAT 31.6 nM-10 µM hSERT 31.6 nM-100 µM hNET 31.6 nM-100 µM	Non-GLP
JNJ-Y1-DA-5007-03-A	Monoamine release assay	HEK293 cells expressing cDNA for the hDAT, hNET, or hSERT	In vitro	1 nM to 10 µM for hNET and hSERT, 1 nM to 100 µM for hDAT	Non-GLP
JNJ-96-2389	Binding assay	Guinea pig synaptosomes	In vitro	10^{-7} to 10^{-4} M	Non-GLP
JNJ-8470	Binding assay	Membrane extracts; cell lines expressing transfected receptors	In vitro	10^{-9} to 10^{-5} M (Up to 10^{-4} M in the case of $hA_{\alpha 2A}$, $hA_{\alpha 2B}$, $hA_{\alpha 2C}$ and DAT)	Non-GLP
UNC 5318	Binding, uptake, and release assay	Rat brain synaptosomes and clonal cell lines	In vitro	0 to 100 µM	Non-GLP
JNJ-9072	Binding and uptake assay	HEK293 cells expressing cDNA for the hVMAT-2	In vitro	$3x10^{-6}$ M to 10^{-3} M	Non-GLP
NovaScreen 870 & 871	Binding assay	Bovine cerebral membranes; guinea pig striatal membranes	In vitro	10^{-9} to 10^{-5} M	Non-GLP
DD06604	Binding assay at histamine 3 receptor	Transfected SK-N-MC cells	In vitro	0.5 to 65 nM	Non-GLP
JNJ-6605	Functional assay at orexin receptor 2	PFSK-1 cells	In vitro	Up to 10 µM	Non-GLP
JNJ-16253887-22457057	Binding assay at various GPCRs	Human receptors recombinantly expressed in COS-7 cells	In vitro	20,000 cpm per sample	Non-GLP

In vivo primary pharmacodynamics studies were conducted in mice (wild-type and genetically modified strains) and rats to evaluate the behavioural and wake-promoting mechanism of action of solriamfetol in comparison to conventional stimulants or other wake-promoting agents (e.g. modafinil).

Table 2: Nonclinical Primary Pharmacodynamics Studies with Solriamfetol – in vivo/ex vivo

Study No.	Study Type	Species or Cell Type	Route	Dose or Concentration	GLP Compliance
JNJ-0893	Ex vivo binding assay at monoamine receptors	Male Wistar rats	SC, ex vivo	40 mg/kg	Non-GLP
UNC 5318	Neurochemical assay (mono-amine levels)	Male Sprague-Dawley rats; mouse caudate slices	IP	15 and 30 mg/kg	Non-GLP
JNJ-8880	Neurochemical assay (mono-amine levels)	Male Sprague-Dawley rats	SC	10 and 30 mg/kg	Non-GLP
PCOL 95-12	Behavioral effects	Male CD-1 mice	IP	60 mg/kg	Non-GLP
JNJ-1783	Behavioral effects	Male Wistar rats and NMRI mice	SC or IP	Several doses	Non-GLP
JNJ-3946	Behavioral effects	Male and female DAT knockout and wild-type mice	SC	10, 30, 100 mg/kg	Non-GLP
PCOL 96-3	Behavioral effects	CD-1 mice	PO	30 and 60 mg/kg	Non-GLP
Yukong 1833	Behavioral effects	Male Sprague-Dawley rats	IP	30, 60, 90 mg/kg	Non-GLP
SU-001	Wake-promoting profile of effects	Hypocretin cell-ablated narcoleptic mice and their littermate wild-type mice	PO	50, 100, 150 mg/kg	Non-GLP
Hasan et al. 2009	Wake-promoting profile of effects	Male mice from 3 inbred strains (DBA/2J, C57BL/6J, AKR/J)	IP	150 mg/kg	Non-GLP
JNJ-1485	Wake-promoting profile of effects	Male Sprague-Dawley rats	IP	3, 10, 30 mg/kg	Non-GLP

***In vitro* studies**

Studies to characterize effects on uptake and release of monoamines (dopamine, noradrenaline, serotonin)

Cells transfected with cDNA of human monoamine transporters

Binding studies: In an *in vitro* study with HEK293 cells transfected with cDNA for human DAT, NET and SERT, solriamfetol bound to human DAT and human NET, however, with a potency (K_i-values 14,200 nM and 3,700 nM, respectively) clearly lower than cocaine (K_i-values 236 and 505 nM, respectively). Whereas cocaine bound also to the SERT with high potency (Ki 361 nM), affinity of solriamfetol for the SERT was very low (K_i 81,500 nM).

In a study with CHO cells transfected with cDNA for the human monoamine transporters, binding of solriamfetol (but not of the solriamfetol metabolite N-acetyl solriamfetol) to the hDAT could be confirmed, however, solriamfetol failed to show binding to the human hNET and hSERT at a concentration of 10 µM. Solriamfetol also failed to show binding to the hNET in a receptor screening assay when applied at a concentration of 1 µM.

Inhibition of monoamine reuptake: Solriamfetol inhibited uptake of dopamine and noradrenalin by the transfected HEK293 cells with IC_{50}-values of 2,900 nM and 4,400 nM, respectively (corresponding values for cocaine were 385 nM and 194 nM). Whereas cocaine also inhibited serotonin uptake with high potency (IC_{50} 355 nM), solriamfetol was practically ineffective (IC_{50} > 100µM) (JNJ-Y1-DA-5005-03-B).

Stimulation of monoamine release: Solriamfetol had no effect on the release of preloaded ^{3}H-dopamine, ^{3}H-noradrenaline and ^{3}H-5-HT from the HEK293 cells, whereas methamphetamine stimulated the release of radiolabelled dopamine (EC50 721 nM) and noradrenaline (EC_{50} 103 nM) and, less potent, serotonin (EC_{50} 22,800 nM) (JNJ-Y1-DA-5005-03-A).

Rat (brain tissue and recombinant transporters)

Binding studies

- In rat brain tissue, solriamfetol (but not its stereoisomer) bound to the DAT (K_i about 10,000 nM), but not to the SERT (UNC 5318).
- Binding studies conducted in rat striatal synaptosomes confirmed that solriamfetol inhibited binding to the rDAT (IC_{50} 2,600 nM), however, with a lower binding affinity than the known monoamine reuptake inhibitors cocaine and mazindol (JNJ-8470).
- In a screening assay, solriamfetol inhibited binding to the rDAT with a Ki-value of 5,158 nM, however, failed to show binding to the rNET (and to the hSERT) in concentrations up to 10 µM (JNJ 8470).
- Solriamfetol also failed to show binding to the rNET and rSERT in another assay when tested at concentrations up to 10 µM.
- The weak interaction of the DAT inhibitor mazindol with ^{3}H-solriamfetol binding to rat striatal synaptosomes argues for a weak interaction of solriamfetol with the rat DAT and suggests other non-specific cellular binding sites for solriamfetol. A high-degree of non-specific binding of radiolabelled solriamfetol to rat striatal membranes is also suggested by the fact that radiolabelled solriamfetol could only slightly displaced by an excess concentration of "cold" solriamfetol (JNJ-8470).

Inhibition of monoamine reuptake

In rat brain synaptosomes, solriamfetol inhibited dopamin reuptake (striatal) and noradrenalin reuptake (hypothalamic) with IC_{50}-values of 21,000 nM and 6,500 nM, respectively. Compared with the reference ligands GBR-12909, bupropion, and desipramine, solriamfetol displayed low potency. For example, the Ki of solriamfetol for inhibition of dopamine uptake was 22-fold higher than the Ki of bupropion for this parameter (UNC 5318).

Stimulation of monoamine release

In a study with rat brain synaptosomes, the highest concentration of solriamfetol tested (30 µM) resulted in dopamine and 5-HT release (approximately 70% and 30% of that of the respective high potency reference compounds amphetamine and MMAI). Release of norepinephrine was not stimulated (UNC 5318).

Guinea pig brain tissue

Binding studies: Solriamfetol inhibited radioligand binding to the guinea pig DAT with a Ki of 3,410 nM (JNJ-96-2389.

***In vitro* studies to detect potential interactions of solriamfetol with other pharmacological targets**

Solriamfetol completely displaced ^{3}H-cocaine from its binding sites on rat striatal synaptosomes (IC_{50} 4,100 nM) (JNJ-8470).

In HEK293 cells transfected with cDNA for the human vesicular monoamine transporter, solriamfetol showed very low binding affinitiy (K_i > 250,000 nM), however, inhibited ^{3}H-serotonin uptake with an IC_{50} of 6,300 nM (JNJ-9072). Solriamfetol, in concentrations up to 10 µM, did also not show binding affinity for the rat vesicular monoamine transporter (Eurofins 66491).

Solriamfetol, in concentrations up to 10 µM, was devoid of binding affinity for dopamine (UNC 5318) and histamine receptors (H1, H2, and H3) in rat brain tissue (NovaScreen 870 and 871), in SK-N-MC cells transfected with cDNA for human histamine receptors (DD06604) and in PFSK-cells expressing the orexin receptor 2 (JNJ 6605).

In a screening assay with transfected human receptors, binding affinity of solriamfetol to adrenergic alpha 2-receptors type A (Ki 10,470 nM) and B (Ki 2,684 nM) was observed (JNJ-8470). However, in vitro functional assays showed that solriamfetol in concentrations up to 100 µM has no agonist or antagonist activity in cells expressing human recombinant alpha 2A, 2B or 2C receptors.

In additional screening assays (CEREP 870189, JNJ-8470) investigating a wide variety of receptors, transporters and enzymes no relevant binding of solriamfetol was observed. However, the tested solriamfetol concentrations of 1 µM, respectively 10 µM, appear to be too low to allow for a definite conclusion whether the evaluated targets are potential candidates for interaction with solriamfetol (JNJ-8470).

***In vivo* studies**

Studies to characterize effects on uptake and release of monoamines (dopamine, noradrenaline, serotonin)

Binding studies

Binding studies conducted in rats following a single SC dose of 40 mg/kg solriamfetol did not demonstrate any significant occupancy at several receptors (dopamine D2, adrenergic alpha 2A and 2B) and transporters (DAT, NET, and SERT) as measured by autoradiography (JNJ-0893).

Effects on brain levels of monoamines (dopamine, noradrenaline, serotonin)

Striatal dopamine and prefrontal cortical norepinephrine extracellular levels in freely moving conscious rats were measured via *in vivo* brain microdialysis. At a SC dose of 30 mg/kg (but not 10 mg/kg), if normalized to a starting (t=0 min) level of 100% per treatment group, striatal dopamine and prefrontal noradrenaline tissue levels appeared to be increased by solriamfetol in a time-dependent manner during an evaluation period of 550 min. However, if calculated on basis of the absolute tissue levels measured, a significant increase could not be demonstrated (which may, at least in part, be due to the large individual differences in monoamine tissue levels). No consistent effects of solriamfetol (at doses of 10 and 30 mg/kg) on serotonin levels were detected in either region (JNJ-8880).

In a second *in vivo* microdialysis study in rats, no significant increases were observed in levels of dopamine, dopamine metabolites (DOPAC, HVA) or the serotonin metabolite 5-H1AA after IP administration of 15 and 30 mg/kg solriamfetol (UNC 5318).

Studies on behavioural effects of solriamfetol

General behavioural effects in healthy animals

In a general observation test, IP solriamfetol induced sniffing (ED_{50} 16 mg/kg), mydriasis (ED_{50} 21 mg/kg), excitation (ED_{50} 25 mg/kg), rearing (ED_{50} 25 mg/kg), exophthalmos (ED_{50} 32 mg/kg), and hyperthermia (ED_{50} 37 mg/kg) in rats, thereby mimicking amphetamine in profile (JNJ-1783).

However, in contrast to the effects of amphetamine, solriamfetol did not reverse hypomotility and miosis induced by Ro-4-1284 (a vesicular monoamine transport [VMAT-2] inhibitor that depletes secretory vesicles), did not induce stereotyped behaviour, did not block the tail-pinch response, and did not potentiate the behavioral effects of 5-HT in mice and rats (JNJ-1783).

Solriamfetol does not appear to have relevant *in vivo* functional activity at the SERT and monoamine oxidase type A and B. In contrast to the effects of the selective serotonin reuptake inhibitor (SSRI) fluoxetine, solriamfetol (30 and 60 mg/kg PO) decreased the sensitivity of mice to 5-HT-induced head twitches, indicating that solriamfetol does not likely function as an SSRI (PCOL 96-3).

Further evidence that solriamfetol does not exhibit behavioural effects consistent with those of SSRIs as well as directly-acting 5-HT agonists, is that unlike the ability of these compounds to increase haloperidol-induced catalepsy, solriamfetol (30, 60 and 90 mg/kg IP) decreased the cataleptic effects of haloperidol (Yukong 1833).

Behavioral effects in DAT knock-out mice

In wild-type mice, solriamfetol (10, 30, 100 mg/kg SC) had no effect on spontaneous or stereotypic activity while amphetamine (2 mg/kg SC) induced robust increases in spontaneous and stereotypic activity. Solriamfetol demonstrated a dose-dependent reduction in locomotor, rearing, and stereotypy activities in DAT knockout mice, suggesting that, *in vivo*, the effects of solriamfetol are not solely mediated by DAT (JNJ-3946).

Wake-promoting profile of solriamfetol

Effects of Solriamfetol on Sleep in Narcoleptic and Wild-Type Mice

Effects of solriamfetol (50, 100 and 150 mg/kg PO) on various sleep parameters were evaluated in hypocretin/ataxin-3 transgenic mice (mouse model of narcolepsy) and their littermate wild-type mice, with modafinil (50 and 200 mg/kg PO) as a reference compound (SU-001).

During the light (resting) period, solriamfetol dose-dependently induced continuous wakefulness in most wild-type and narcoleptic mice for up to 5 hours. During this period, REM and non-REM sleep were completely suppressed. No abnormal EEG patterns were detected after solriamfetol administration and the sleep that occurred after the prolonged wakefulness was normal by polygraphic assessments.

During the dark (active) period (when narcoleptic mice spend more time sleeping than wild-type mice), solriamfetol dose-dependently increased wakefulness in both wild-type and narcoleptic mice. The wake-promoting effects in wild-type mice were less robust due to the high amount of wakefulness naturally present during the dark period. Importantly, the wake amounts observed in narcoleptic mice after 100 and 150 mg/kg of solriamfetol were similar to those of wild-type mice, suggesting that solriamfetol normalized the sleep/wake activity of narcoleptic animals. Non-REM and REM sleep were reduced in narcoleptic mice by solriamfetol to the levels observed in wild-type mice. Suppression of the DREM phase by solriamfetol suggests that this compound may have therapeutic effects on catalepsy.

No abnormal EEG patterns were detected after solriamfetol administration and sleep time that occurred after the prolonged wakefulness was normal (no rebound hypersomnia). The wake-promoting effects of solriamfetol in mice were not consistently accompanied by locomotor and stereotypic effects.

In this study, modafinil was not as potent for inducing wakefulness, and the magnitude of effects was not as robust, compared with solriamfetol. Moreover, an increased sensitivity to modafinil in hypocretin-deficient, compared with wild-type, mice was observed, suggesting that the availability of hypocretin might change the sensitivity to modafinil.

Wake-Promoting Activities of Solriamfetol in 3 Inbred Strains of Mice

Solriamfetol was found to be a wake-promoting agent without behavioural side effects that can be characteristic of D-amphetamine (i.e. locomotor and stereotypic effects). Wakefulness induced by solriamfetol was followed by a compensatory rebound in both the duration and intensity (i.e. EEG delta power) of sleep but no evidence of rebound hypersomnolence (i.e. over-compensation for sleep lost). The wake duration induced by solriamfetol (150 mg/kg IP) and D-amphetamine (6 mg/kg IP) was similar among genotypes, whereas differences among the 3 mouse strains were observed after modafinil (150 mg/kg IP) treatment. Brain transcriptome and clustering analyses indicated that the various pathways activated pharmacologically to maintain an awake brain by solriamfetol differ from those of D-amphetamine and modafinil (Hasan et al. 2009).

Effects of Solriamfetol on Sleep-Wake Organization in Rats

Effects of solriamfetol (3, 10, 30 mg/kg IP), cocaine (1, 3, 10 mg/kg IP), amphetamine (1, 3, 10 mg/kg IP), on sleep-wake organization in rats were investigated following the acrophase of sleep (i.e. drugs were administered at the beginning of the light period when most sleep would be expected to occur in rodents). Sleep polygraphic variables were measured for 16 hours following administration of drug (JNJ-1485).

Minor changes in vigilance states were observed following administration of solriamfetol 3 and 10 mg/kg. However, treatment with solriamfetol at 30 mg/kg strongly increased active wakefulness at the expense of time spent in light sleep, deep sleep and REM sleep during the first 3 to 4 hours after the administration. A rebound effect was seen between 4-10 hours following administration of the compound, as an increase in time spent in deep sleep occurred that gradually decreased in the hours thereafter. Moreover, solriamfetol affected other sleep-wake parameters: it increased significantly the number of shifts from light sleep and REM sleep into wakefulness and lengthened the latency of REM sleep onset.

Cocaine 1 and 3 mg/kg only slightly affected the sleepwake organization. In contrast, cocaine at 10 mg/kg significantly enhanced active wakefulness and reduced slow wave sleep and REM sleep during the first 3 to 4 hours following injection of the compound. All sleep latencies were increased.

Amphetamine dose-dependently increased wakefulness and reduced all sleep states during 3 to 8 hours following administration. A clear dose-dependent rebound effect was observed for deep sleep. Additionally, the latencies of all sleep states were significantly increased.

Secondary pharmacodynamics

In *in vitro* screening assays (CEREP 870189, JNJ-8470) binding of solriamfetol to a wide variety of receptors, transporters and enzymes was evaluated (see above, no relevant binding of solriamfetol was observed. However, the tested solriamfenol concentrations of 1 µM, respectively 10 µM, appear to be too low to allow for a definite conclusion whether the evaluated targets are potential candidates for interaction with solriamfetol (JNJ-8470).

In vivo studies conducted to characterize potential secondary pharmacodynamic effects related to safety pharmaology are summarized below

Safety pharmacology

***In vitro* studies**

Non-GLP *in vitro* safety pharmacology studies were conducted to evaluate solriamfetol effects on the cardiovascular system.

Concentrations of solriamfetol up to 10 µM did not block the rapid component of the delayed rectifier potassium current, IKr in the human ether-a-go-go-related gene (hERG) assay (JNJ-CPF-924), had no notable effects on cardiac contractility in isolated guinea pig atria (JNJ-5899), and had no relevant effects on electrophysiological parameters or early after-depolarizations in isolated rabbit Purkinje fibers (JNJ-CPF-922).

***In vivo* studies**

Solriamfetol has been studied in central nervous, cardiovascular, respiratory, and renal systems to assess the safety pharmacology profile.

Central Nervous System

Alertness, activity, and coordination

Motor activity: Solriamfetol (30, 60 and 100 mg/kg PO) numerically increased motor activity (statistically non significant) in mice (imipramine, used as comparator, significantly reduced motor activity).

Solriamfetol (30 and 60 mg/kg PO) did not increase motor activity in rats (Yukong PCOL 95-9).

In a GLP study in telemetered male dogs, locomotor activity was increased by solriamfetol (4, 13 and 42 mg/kg PO) at all doses tested in a dose-dependent manner (measured (Cmax)-values correspond to 0.6×, 1.8×, and 6.3× the human expected steady-state Cmax of 1,880 ng/mL for a daily solriamfetol dose of 300 mg) (JNJ-TOX-6188).

Rotarod performance: Solriamfetol produced a dose-dependent reduction of rotarod performance in mice with a half-maximal toxic dose of 1,618 mg/kg (Imipramine 116 mg/kg)(Yukong 1868)

Hexobarbital-induced hypnosis: Solriamfetol (30 and 100 mg/kg PO) did not potentiate the depressant effects of hexobarbital but reduced the mean sleeping time duration (Imipramine 100 mg/kg PO increased the duration of sleeping time) (Yukong PCOL-95-7).

Antidepressant and anxiolytic properties

Anxiogenic liability: Metrazol (40 mg/kg PO), a known anxiogenic, produced an anxiogenic response as indicated by a significant reduction in percentage open-arm time compared with the vehicle-treated group in a rat elevated-plus maze and spontaneous motor activity test. Solriamfetol (5, 10 and 35 mg/kg PO) produced responses similar to vehicle at all doses tested (JNJ-15756).

Reserpine-induced hypothermia: Solriamfetol antagonized reserpine-induced hypothermia in mice in a dose-dependent manner, with an ED_{50} of 37.8 mg/kg (imipramine ED_{50} 40,3 mg/kg) (Yukong PCOL 95-5).

Tetrabenazine (VMAT-2 inhibitor)-induced ptosis: Solriamfetol (10, 30 and 60 mg/kg PO) inhibited tetrabenazine-induced ptosis in mice with an ED_{50} of 33.2 mg/kg (imipramine ED_{50} 1.6 mg/kg) (Yukong PCOL 95-3).

Fighting behaviour: Solriamfetol (15, 22 and 30 mg/kg PO) antagonized isolation-induced aggressive behavior of mice with an ED_{50} of 25.9 mg/kg (imipramine ED_{50} 30 mg/kg) (Yukong PCOL 95-4).

Differential reinforcement of low-rate 72-second (DRL-72) procedure: Solriamfetol (10, 30 and 55 mg/kg PO) produced a statistically significant dose-related increase in response rates and a decrease in rewards (similar to bupropion) (Vukong PCOL 96-1).

Tail suspension test: Solriamfetol (3, 10, 30 mg/kg IP) decreased immobility in mice at 30 mg/kg (antidepressant effect) (JNJ-5550).

Shock avoidance (Vogel) test: Solriamfetol (30 mg/kg IP) had no significant effect. Diazepam (positive control)-treated animals took significantly more shocks than vehicle. The results indicate that solriamfetol does not possess anxiolytic properties (Yukong PCOL 96-2).

Forced Swim (Behavioral Despair): Solriamfetol produced a reduction in the duration of immobility in mice (ED_{50} 16.6 mg/kg single applcation, ED_{50} 5.5 mg/kg multipe-dose) and rats (ED_{50} 18.5 mg/kg single dose) as a measure of antidepressant activity (Yukong PCOL 95-1).

A significant reduction in the duration of immobility in mice by solriamfetol was also observed in another study, whereas the enatiomer of solriamfetol was inactive (Yukong PCOL 96-6).

Solriamfetol produced a reduction in the duration of immobility in mice (ED_{50} 13.6 mg/kg) and rats (ED_{50} 7.4 mg/kg) following a 6-minute preliminary swimming session 1 day before experimentation (Yukong PCOL 95-2).

A linear correlation (r^2=0.96) was observed between reduction of immobility and peak plasma concentration in Wistar rats for doses between 5 and 35 mg/kg (Yukong 96-05).

Anticholinergic activity

Oxotremorine-induced tremors: Neither solriamfetol (100 mg PO) nor its enantiomer antagonized the tremors induced by oxotremorine, suggesting that neither compound has the potential to produce anticholinergic side effects (Yukong PCOL 95-8).

Cognitive Performance

Water maze test: Solriamfetol (3, 10, 30 mg/kg SC) had no effect on memory storage and retention in the water maze test in mice (JNJ-6751).

Acquisition of visual discrimination: Animals treated with 3 or 30 mg/kg of solriamfetol or with D-amphetamine 1 mg/kg needed fewer trials to reach criterion levels of performance and had better accuracy scores relative to vehicle-treated rats. It was concluded that solriamfetol enhanced behavioral performance in this task similar to D-amphetamine (JNJ-4015).

5-choice serial reaction time task: Solriamfetol did not affect the attentional measures in this task (response accuracy and number of omissions), but the highest dose of solriamfetol increased the number of premature and perseverative responses (JNJ-2397).

Seizure Potential

Maximal electroshock test: Solriamfetol (50, 75 and 100 mg/kg PO) displayed protective effects in the maximal electroshock test in mice (ED_{50} 81.6 mg) (Yukong PCOL 95-13).

Comparative toxicity of solriamfetol and bupropion: Solriamfetol produced ataxia, hypermotility, prostration, fore and hind limb extension, tremors, and loss of righting reflex at doses of 200 to 600 mg/kg IP. Doses of 800 and 1,000 mg/kg produced loss of the righting reflex, dyspnea, and death. Solriamfetol did not elicit seizures at any time. Bupropion produced ataxia, prostration, and fore- and hind-limb extension at 100 mg/kg, clonic seizures, spasms, and loss of righting reflex at 200 mg/kg, and clonic seizures, dyspnea, and death at 300 mg/kg (Yukong 7316).

Pentylenetetrazole test: Solriamfetol 30 mg/kg PO was not pro-convulsant in the pentylenetetrauole test in mice (JNJ-8742).

Coadministration with biphenylacetic acid: Solriamfetol (30 or 100 mg/kg PO) does not exhibit convulsant effects when co-administered with biphenylacetic acid, an active metabolite ($GABA_A$-receptor antagonist) of the NSAID fenbufen (JNJ-8742).

Effects on food intake

Food intake in rats: Like amphetamine, solriamfetol lowered treated-feed consumption and lowered body weights during the treated-feed periods (Yukong 95-4a).

Animals treated with vehicle or solriamfetol ingested more food than those treated with amphetamine (control agent). When solriamfetol was combined with amphetamine, food intake was not reduced any further suggesting that solriamfetol does not potentiate the effects of amphetamine (Yukong PCOL 95-10).

Food intake in food deprived and non-food deprived mice: It was concluded that solriamfetol induced clear anorexic effects in mice at dosages ≥60 mg/kg SC (JNJ-7006).

In non-deprived animals treated at the beginning of the light phase, solriamfetol (60 and 120 mg/kg SC) induced a significant decrease in food intake.

Functional observational battery (FOB)

As requested in the EMA scientific advice given in 2017 (EMA/CHMP/SAWP/716502/2017), a FOB study was conducted. Juvenile Sprague-Dawley rats were given solriamfetol (35, 110, 200, 300 mg/kg) or control (0.9% saline) once daily PO from postnatal day (PND) 21 through PND 111, followed by a recovery phase of 10 weeks (GLP study 20091367) A full conventional FOB was performed on PND 87 (± 2 days) and on PND 145 (± 2 days), that included evaluation of a brought spectrum of CNS/neurological effects (e.g. home cage behaviour, reaction to removing and handling, defecation and urination in "open" field, gait pattern and abnormalities, abnormal respiration, tactile/auditory/tail-pinch reaction, extensor thrust reflex, forelimb and hindlimb grip test). No relevant solriamfetol-related effects on FOB variables were evident at PND 87 and during the recovery phase at PND 145. Toxicokinetic data have not been provided, however, it can be expected that the applied dose range has covered and clearly exceeded the clinical exposure range of solriamfetol. Overall, these data do not give cause for concern concerning adverse CNS/neurological effects of solriamfetol

Cardiovascular system

In *in vivo* cardiovascular safety pharmacology studies with anesthetized rats, guinea pigs, dogs or in conscious, unrestrained telemeterized Beagle dogs, solriamfetol did not result in prolonged QT interval corrected for heart rate (QTc) but demonstrated transient effects on blood pressure parameters and cardiac output.

Anesthetized rats: Solriamfetol (10, 30 and 100 mg/kg IV) produced a dose-dependent reduction in systolic blood pressure and a decrease in heart rate over a 10-minute experimental period. Solriamfetol had no apparent effect on the ECG.

Solriamfetol did not potentiate the pressor effects of tyramine, and, in fact, appeared to antagonize them, suggesting that solriamfetol is not a MAO inhibitor (Yukong PCOL 95-14).

Anaesthetized guinea pigs: Increasing doses of solriamfetol (0.16 to 5 mg/kg IV; total dose 9.85 mg/kg IV) had no statistically significant effect on heart rate, mean arterial blood pressure, and PQ, QRS, QT, and corrected QTc (by Bazett formula) ECG intervals. No changes in ECG morphology were noted during the postdosing period. C_{max} at the highest dose was 2.7× the human expected steady-state C_{max} of 1,88 ng/mL based on a daily solriamfetol dose of 300 mg PO (JNJ-CPF-533).

Open-chest anesthetized dogs: Solriamfetol (3.5 and 10 mg/kg IV) produced no biologically relevant effects on cardiac output, left ventricular pressure, left ventricular end diastolic pressure, intraventricular pressure, systemic blood pressure, and ECG variables. A slight decrease in cardiac output and increases in blood pressure (systolic, diastolic and mean) and left ventricular end diastolic pressure were observed for solriamfetol 35 mg/kg IV. The values returned to baseline by 60 minutes after dosing.

Instrumented, conscious dogs: Solriamfetol (5 mg/kg PO) had no effect on heart rate, blood pressure, cardiac contractility, cardiac relaxation, pressure rate product, cardiac output, stroke volume, systemic vascular resistance, QRS and QT intervals, QT dispersion, and ECG morphology. Solriamfetol tended to increase the duration of the PQ interval and tended to decrease slightly the duration of the QTc (Bazett, Fridericia, and Van de Water corrections). Peak solriamfetol plasma concentration was 2,138 ng/mL 60 minutes after dosing, which is 1.1× the human expected steady-state C_{max} of 1,880 ng/mL based on a daily solriamfetol dose of 300 mg PO (JNJ-CPF-536).

Telemetered male dogs: Effects of solriamfetol on cardiovascular function were evaluated in a GLP study in telemetered, conscious, unrestrained male beagle dogs. Solriamfetol (4 mg/kg PO) had no marked effects on blood pressure and heart rate. For solriamfetol (13 mg/kg PO), a slight, transient increase in blood pressure was evident 2 hours after dosing that was accompanied by an increase in respiratory rate over 2 to 4 hours, a slight decrease in respiratory tidal volume 2 hours after treatment, and an increase in locomotor activity for up to 11 hours after dosing. A slight increase in heart rate was considered possibly related to the increase in locomotor activity. Solriamfetol (42 mg/kg PO) resulted in significant increases in systolic blood pressure (versus control values) and percentage changes of diastolic blood pressure and mean blood pressure (versus control values) at 30 minutes after dosing. Respiratory rate was markedly increased and tidal volume slightly decreased over a period of 2 to 4 hours after dosing. Locomotor activity was increased over a 10-hour period starting 2 hours after dosing. Mean plasma concentrations in samples taken approximately 70 minutes ($\approx t_{max}$) after doses of 4, 13 and 42 mg/kg solriamfetol represented multiples of 0.6×, 1.8× and 6.3× the human expected steady-state C_{max} for a daily solriamfetol dose of 300 mg PO (JNJ-TOX-6188).

Dogs, in repeated-dose toxicity studies: In a 3-month study where solriamfetol was administered at 8, 15 and 23 mg/kg/day PO, no treatment-related ECG findings were observed during the fourth and last weeks of treatment (Pharmakon-0470DY01-002).

In a 1-year study with a 3 month recovery period, in which dogs were given daily doses of 8, 21 and 42 mg/kg/day PO solriamfetol, cardiovascular examinations were performed pretest and during Weeks 1, 4, 13, 26, 39, 52 and 65. Slight variations in heart rate, cardiac conduction, cardiac rhythm, and wave forms were not considered treatment related and were of no toxicological relevance.

In male and female Beagle dogs dosed once daily with a slow bolus IV injection with 4, 8 and 13 mg/kg/day solriamfetol for 2 consecutive weeks, ECGs and heart rates were measured prior to the start of dosing and on Day 14 (30 minutes after dosing). No solriamfetol-related arrhythmias were noted in any dog (JNJ-TOX-6574).

Respiratory System

Telemetered male dogs: Effects of solriamfetol on cardiovascular function were evaluated in a GLP study in telemetered, conscious, unrestrained male beagle dogs. Single increasing doses of 4, 13 or 42 mg/kg PO solriamfetol produced vomiting, restlessness, transient dose-dependent increase in respiratory rates and decreased tidal volumes. At 13 mg/kg solriamfetol, respiratory rate was increased from 2 to 4 hours postdose with a slight decrease in tidal volume 2 hours postdose. At 42 mg/kg solriamfetol, respiratory rate was markedly increased, and tidal volume was slightly decreased from 2 to 4 hours postdose. Increased locomotion may explain the increased respiratory rate (JNJ-TOX-6574).

Renal System

Study in rats**:** As part of a non-GLP mechanistic study, rats were given a high daily dose of solriamfetol (379 mg/kg PO) for 3 weeks. No substantial adverse effects were noted in clinical chemistry and urinalysis parameters (decreased urine pH, increased urine volume), and no changes in kidney weight or gross pathologic findings, however, 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, identified in the literature as being implicated in kidney toxicity (KIM-1, LCN2, Clu, and SPP1/osteopontin), were noted.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies with solriamfetol have been conducted.

2.3.3. Pharmacokinetics

The nonclinical pharmacokinetics (PK) of solriamfetol was evaluated *in vitro* and in single- and repeat-dose *in vivo* studies. The majority of studies in mice, rats, and dogs evaluated solriamfetol formulated in saline or water as a solution for PO or IV administration. In several studies in dogs, solriamfetol was formulated as powder in a capsule. In studies with high-dose administration, solriamfetol was occasionally formulated as an aqueous methylcellulose suspension.

Absorption

After oral dosing with ^{14}C-solriamfetol, based on percentage recovery of radioactivity in the 0-96 hour or 0-168-hour urine samples, the absorption of radioactivity across the gastrointestinal tract was estimated to be at least 63% to 73% in rats, 85% in dogs, and 96% in humans.

The absorption of solriamfetol across gut epithelial membranes is predominantly governed by a passive transcellular mechanism and absorptive transport (apical to basolateral) increased with an increasing pH (6 to 7.4) where greater concentrations of solriamfetol exist in the non-ionized state more suitable for passive diffusion across epithelial membranes.

Generally, no marked sex differences in solriamfetol exposure were noted in the species evaluated.

Systemic exposures to solriamfetol (C_{max}, AUC)) were approximately dose proportional or slightly supra-proportional following single and repeated dosing.

In rats and dogs, exposure to solriamfetol after repeated dosing was similar to that after a single dose, although slight accumulation was detected in rats, especially at higher doses.

Distribution

Solriamfetol plasma protein binding in animals and humans was low, ranging from 8.4% in rabbit and dog to 19.4% in human, and concentration independent.

In rats and dogs, the blood-to-plasma concentration ratio for ^{14}C-solriamfetol-derived radioactivity was approximately 1, indicating a small extent of binding and/or distribution into blood cells.

The apparent volume of distribution of solriamfetol (2.08 to 9.35 L/kg) in animals exceeded total blood volume, indicating extensive tissue distribution beyond the vascular compartment.

Solriamfetol distributed rapidly to systemic tissues in the rat with high concentrations in the excretory organs, liver and kidney, consistent with its route of elimination.

Following oral administration of ^{14}C-solriamfetol to pigmented rats, total radioactivity peaked at 5 hours post dose and declined rapidly thereafter with similar rates of decline in blood and non-pigmented tissues.

Among non-pigmented tissues, a substantially higher tissue-to-blood AUC ratio was found in the kidney and liver, which is consistent with the kidney and liver being excretory organs for solriamfetol in the rat.

^{14}C-solriamfetol-related radioactivity appeared to bind to melanin and distribution of total radioactivity was highest in the eye, especially the ciliary body and choroid. The decline of radioactivity in pigmented structures was slower than in other tissues; however, no undue retention of radioactivity was observed with residual concentrations at the last time point representing only 1% to 2% of peak total radioactivity.

Although solriamfetol is a basic, charged, hydrophilic molecule, it crosses the blood-brain barrier with radioactivity concentrations in whole brain similar to blood. The duration of exposure to solriamfetol in brain ECF was longer than the duration observed in plasma, which may contribute to a longer pharmacological effect relative to its short elimination half-life.

^{14}C-solriamfetol-related radioactivity crossed the placenta in pregnant rats. The AUC for total radioactivity in the whole fetus was slightly lower than in maternal blood (0.80-fold), while the AUC for total radioactivity in the fetal membrane was 2.61-fold higher than maternal blood.

^{14}C-solriamfetol-related radioactivity distributed into the mammary gland; the AUC for total radioactivity in the mammary gland was 1.56-fold higher than in maternal blood.

Solriamfetol binds to melanin; however, based on UV absorbance maximum of 258 nm, solriamfetol is not considered sufficiently photoreactive to result in direct phototoxicity.

Metabolism

The overall metabolic pathway of solriamfetol in the liver includes aliphatic hydroxylation (M7), aromatic hydroxylation (M5), carbamate hydrolysis (M8), glucuronidation (M1), alcohol oxidation (M4), *N*-acetylation (M11), glutathione conjugation (M2), and premercapturic acid formation (M13/M14).

Solriamfetol exhibits interspecies differences in metabolism. While solriamfetol undergoes significant hepatic metabolism in rats, very limited hepatic metabolism was observed in dogs and humans, both *in vitro* and *in vivo*. There are no unique human metabolites. Minor inactive metabolite, M11 (*N*-acetyl solriamfetol), observed in human urine, is also present in the toxicology species. Therefore, safety risks for solriamfetol and its metabolites are fully evaluated in the toxicology program.

Excretion recovery of ^{14}C-solriamfetol-related radioactivity in rats, dogs, and human was complete (≥93%), which suggests that no significant reactive metabolites are formed *in vivo*.

In rat, dog, and human plasma, unchanged solriamfetol was the major radioactive component. The major metabolite in rat plasma was the glucuronide conjugate of the p-hydroxy metabolite (M1); no major metabolite was observed in dog and human plasma. The minor inactive metabolite M11 (*N*-acetyl solriamfetol), identified in human urine, was also detected in rat plasma. Overall, no clear sex differences in the metabolism of solriamfetol were observed in rats.

No chiral inversion of solriamfetol to its *S*-enantiomer was observed in any species.

Apart from a low inhibitory potential toward cytochrome P450 (CYP) 2D6, solriamfetol was not found to be a substrate or inhibitor for any of the major human cytochrome P450 (CYP) enzymes in vitro.

Weak, reversible induction of CYP3A and CYP2B activity was observed in rats in vivo. No effect on uridine 5'-diphospho (UDP)-glucuronosyltransferase activity was observed and solriamfetol was not a peroxisome proliferator.

Excretion

Elimination was relatively rapid with half-life values following oral administration of 1 to 2 hours in mice, 2 to 4 hours in rats (longer in chronic studies at high doses), and 4 to 5 hours in dogs, with no unexpected accumulation with repeated administration.

Solriamfetol clearance in rats was about 4 L/h/kg, approximately equivalent to hepatic blood flow in this species (3.3 L/h/kg). By contrast, lower clearance was observed in dogs, about 0.35 L/h/kg, compared with hepatic blood flow of 1.86 L/h/kg (Davies and Morris 1993).

Significant excretion of solriamfetol was found in milk following oral administration in rats, with concentrations higher than those in plasma. Solriamfetol is not excreted in expired air and may undergo minor biliary or transepithelial elimination in rats.

In humans, solriamfetol is excreted almost entirely in urine and nearly all as unchanged drug (≥95%), with a minor metabolite (N-acetyl solriamfetol) accounting for ≤1% of the dose excreted in urine (CSR R228060-P01-101). Feces accounted for a negligible amount of unabsorbed solriamfetol and as a result, a metabolic profile in feces was not determined.

Pharmacokinetic drug interactions

Comprehensive *in vitro* CYP and uptake/efflux transporter studies using human biomaterials with solriamfetol were conducted. According to the presented data, PK interactions through drug-metabolizing enzymes or drug transporters are unlikely to occur in patients taking solriamfetol.

2.3.4. Toxicology

Single dose toxicity

Single oral doses of solriamfetol were well tolerated by mice, rats, and dogs up to 600, 750, and 140 mg/kg, respectively. Clinical signs were mainly related to CNS stimulation in all species. In addition to these signs, dogs also exhibited salivation, mydriasis, panting, and/or marked transient elevation of body temperature that abated by 24 hours post dose.

Repeat dose toxicity

Repeat-dose toxicity studies of durations up to 3 months in mice, 6 months in rats, and 12 months in dogs resulted in dose-related CNS effects similar to those observed after single doses.

Mice: In a pivotal 3-month repeat-dose toxicity study, daily oral doses of 17, 168 and 505 mg/kg solriamfetol caused dose-related CNS effects. In addition, lower body weight gain with reduced hepatocellular glycogen and subcutaneous fat, centrilobular hepatocellular hypertrophy, and increased protein casts and regenerating epithelium in renal tubules were observed. The NOAEL was considered to be 17 mg/kg.

Toxicokinetics: The 17 mg/kg/day dose resulted in mean C_{max}-values of 3.07 µg/ml (males 3.03 µg/ml, females 3.11 µg/ml) and a mean $AUC_{0\text{-}24h}$ of 2.96 µg•h/mL (males 3.06 µg•h/mL, females 2.85 µg•h/mL) at day 86 of the dosing phase, which corresponds to about 0.35-fold the predicted steady-state human solriamfetol exposure at 150 mg/day (estimated human $AUC_{0\text{-}24h}$ = 8.548 µg•h/mL).

Rats: In a pivotal 6-month repeat-dose toxicity study with a 3-month recovery period, daily oral doses of 29, 253 and 505 (reduced to 379 at study day 93 because of overt toxicity) mg/kg solriamfetol produced CNS-related clinical signs. Mortality and early death were seen at 505/379 mg/kg. Hepatocellular hypertrophy and increased incidence of foamy macrophages in the lungs (consistent with phospholipidosis) were observed at all dose levels. In kidneys, solriamfetol caused diuresis and vacuolation of renal epithelium in distal tubules and collecting ducts.

Other effects observed at ≥253 mg/kg/day were: swelling of zona fasciculata cells in adrenal glands of females, swollen/vacuolated tubular cells in the renal papilla and/or medulla in both sexes and renal cortical tubular hypertrophy in females, increased eosinophilic corpora lutea and presence of cystic follicles in ovary, increased hemosiderin in the spleen of males, increased thymic involution in males, atrophic changes in adipose tissue, and fibrinous material within alveoli and bronchi in females. Additional other effects at 505/379 mg/kg/day were: more prominent granulopoiesis in the sternal bone marrow of females, multifocal vacuolation of the cerebral cortex and presence of shrunken, dark-staining neurons in the hippocampus with perivascular edema in females that died or were euthanized early, hepatocellular necrosis in females that died or were euthanized early, hypotrichosis in the skin of females, increase in tertiary follicles in the ovary, and dilated urinary bladder in males.

The observed changes were not all completely reversible. At the end of a 3-month recovery period, effects in adrenal glands, lungs (females), and skin (males) showed partial recovery, all other effects had resolved completely (JNJ-TOX-5705). A NOAEL could not be determined in this study.

Toxicokinetics: The 29 mg/kg/day dose (LOAEL) resulted in mean C_{max}-values of 4.30 µg/ml (males 4.87 µg/ml, females 3.72 µg/ml) and a mean $AUC_{0\text{-}24h}$ of 12.15 µg•h/mL (males 10.6 µg•h/mL, females 13.7 µg•h/mL) at day 177 of the dosing phase, which corresponds to about 1.42-fold the predicted steady-state human solriamfetol exposure at the MRHD of 150 mg/day (estimated human $AUC_{0\text{-}24h}$ =8.548 µg•h/mL).

The lowest dose with only partially reversible changes (253 mg/kg/day) resulted in mean C_{max}-values of 21.7 µg/mL (males 17.1 µg/mL, females, 25.2 µg/mL) and a mean exposures of $AUC_{0\text{-}24h}$ of 161.370 µg•h/mL (males 127.4 µg•h/mL, females 195.4 µg•h/mL) on day 177 of the dosing phase that corresponds to about 18.9-fold the predicted steady-state human solriamfetol exposure at the MRHD.

Dogs: In a pivotal 12-month repeat-dose toxicity study with a 13-week recovery period, solriamfetol given in two divided daily oral doses of (total) 8, 21, or 42 mg/kg caused hyperactivity/agitation and transient weight loss at all dose levels (JNJ-TOX-5706). At doses ≥21 mg/kg/day panting, salivation, unsteady gait, subdued behavior/reduced activity, weakness of hindquarters, crawling, barking, or stereotypical movements were noted along with slightly increased heart rate. At 42 mg/kg/day, there was a trend toward slightly decreased (generally <10%) RBC parameters and serum calcium concentration tended to be lower. Effects on lungs, adrenal glands and skin were only partially reversible during a 3-month recovery period. The NOAEL was considered by the Applicant to be 8 mg/kg/day, which is not agreed since adverse effects (decreased body weight and food consumption compared with controls in female dogs; hyperactivity/agitation, panting, salivation) were already observed at this dose.

Toxicokinetics: The dose of 8 mg/kg/day (LOAEL) resulted in mean C_{max}-values of 1.39/1.61 µg/mL (males 1.39/1.44 µg/mL, females 1.39/1.77 µg/mL) and mean $AUC_{0\text{-}24h}$ values of 14.6 µg•h/mL (males 15.1 µg•h/mL, females 14.1 µg•h/mL) at Week 52 of the dosing phase, which corresponds to about 1.70-fold the predicted steady-state human solriamfetol exposure at the MRHD of 150 mg/day (estimated human $AUC_{0\text{-}24h}$ =8.548 µg•h/mL).

In summary, animal-to-human exposure ratios (calculated on basis of clinical exposure at the MRHD of 150 mg/day), were <1 for mice (based on NOAEL) and <2 for rats and dogs (based on LOAEL).

Genotoxicity

Solriamfetol was tested in standard *in vitro* and *in vivo* genotoxicity studies. While solriamfetol was negative in all *in vitro* tests, it was slightly positive in an IP mouse micronucleus test. However, these findings were not dose-related and within the historical control ranges of the testing facility. Reassuringly, solriamfetol was negative in a second oral mouse micronucleus test at sufficient exposure. Taken together, solriamfetol can be considered as not genotoxic.

Carcinogenicity

Long-term oral carcinogenicity studies have been performed in mice, treated with daily solriamfetol doses of 20, 65 and 200 mg/kg for up to 104 weeks, and in rats, treated with daily solriamfetol doses of 35, 80 and 200 mg/kg for up to 101 weeks. Solriamfetol did not increase the incidence of neoplastic findings in these lifetime carcinogenicity assays. AUC-based safety margins at the high dose to the maximal recommended human dose (MRHD, 150 mg/day) were about 7.8 in mice and about 20.7 in rats. In the light of negative genotoxicity and no

increase of tumor incidence in both carcinogenicity studies, it can be concluded that solriamfetol does not pose a carcinogenic risk to humans.

Compared to controls, cumulative survival rates in week 104 were (numerically) decreased in solriamfetol-treated mice, maximal at a dose of 65 mg/kg/day (AUC-based safety margin to MRHD about 2.9) from 70% (control) to 48% (p-value 0.0074) in male mice and from 63% to 45% (p-value 0.0923) in female mice. A decrease in survival rate in the solriamfetol-treated groups was not observed in the rat study.

In general, the identified causes of premature death were of the types commonly seen in studies using mice of the tested strain and age. However, the decreased survival rates in the mid and high dose solriamfetol-treated groups appeared to be associated with an increased incidence of premature death of undetermined cause (i.e. for which no histologic/macroscopic reason could be identified), amounting to 18.3% and 16.7% versus 6.6% (control) for male mice and 11.7% and 13.3% versus 6.6% for female mice.

Reproduction Toxicity

Sexual behaviour and fertility

In a non GLP compliant study it was shown that treatment of female rats with solriamfetol did not suppress female sexual behaviour.

Possible solriamfetol related effects on male and female fertility were evaluated in separate studies.

Neither male nor female fertility was negatively influenced up to the highest doses tested, despite clinical signs and body weight reductions, which had to be expected, based on the pharmacodynamic properties of the substance.

Although lower fertility indices were noted for males in the mid and high dose groups, this was not considered relevant as the values were in the range of the historical control data. In addition, the significantly reduced sperm count and sperm concentration observed in high dose males, apparently had no impact on male reproductive capacity. Accordingly, the NOAEL for male fertility is 350 mg/kg/d, the highest dose tested.

Likewise, female fertility was not affected, and again despite of clinical signs and adverse effects on body weights in the mid and high dose groups. In the study report, no NOAEL for female fertility was proposed due to the non-dosage related increase in the numbers of corpora lutea in the groups receiving solriamfetol. Whilst still being within the normal control ranges, in view of the findings in the 90-day rat study, where necropsy and subsequent histopathology showed an increase in ovarian weight, prominent corpora lutea and para-ovarian cysts, the involvement of solriamfetol in this finding was not excluded. According to the pathology report of the 90-day study, there was no clear evidence of any substance related impairment of female fertility. Furthermore, prolactin levels were not adversely affected by chronic solriamfetol treatment for 6 months in rats. But anyway, even if a drug-related effect on the ovars cannot be dispelled totally, this had no impact on female fertility in the current study. Thus, the NOAEL for female fertility is 350 mg/kg/d, the highest dose tested.

Embryofoetal development

Possible effects on embryofoetal development were investigated in rats and rabbits, respectively. In both species, developmental toxicity (significantly increased post implantation loss in rats and significantly decreased foetal weights in both species) was obvious at maternal toxic doses only. In addition, in rat foetuses an increased number of skeletal anomalies were observed.

Whether developmental toxicity was a consequence of maternal toxicity or a direct effect of solriamfetol cannot be determined. In a distribution study in pregnant ^{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. No malformations were noted in any species.

In rats the NOAEL for both maternal and developmental toxicity is 18 mg/kg/d based on significantly decreased maternal body weights and significantly increased postimplantation loss at higher dosages. In rabbits, the NOAEL for prenatal development set at 90 mg/kg/d (high dose) in the study report is not accepted, as foetal body weights were significantly decreased in high dose foetuses. Based on significantly decreased maternal and foetal body weights in the high dose group, the NOAEL for maternal and developmental toxicity is 45 mg/kg/d.

Prenatal and postnatal development

When pregnant rats were dosed from gestation day 6 to lactation day 21 with increasing doses of solriamfetol, effects (clinical signs and significantly decreased body weights) correlated with those effects observed in other toxicity studies performed in rats. Based on significant body weight reduction at doses ≥ 110 mg/kg/d, the NOAEL for maternal toxicity has to be set at 35 mg/kg/d.

With respect to the F1 generation, the NOAEL for viability, growth and development is 35 mg/kg/d, too, as an increase in pup mortality, decreased pup body weights and as a consequence of lower body weights delayed sexual maturation were noted at higher doses (≥ 110 mg/kg/d). Learning and memory functions were not impaired up to the highest dose tested (350 mg/kg/d). Regarding the NOAEL for F1-reproduction, the dosage proposed in the study report, is not agreed, as the number of males that mated as well as the number of females that became pregnant was reduced. Hence, the NOAEL for reproduction for the F1 generation should be set at 110 mg/kg/d. Toxicokinetic investigations performed on lactation day 15 revealed a mean solriamfetol milk-to-plasma ratios of approximately 3 to 4 among all groups at 0.75 hours postdose.

Safety margins related to adverse findings in reproductive toxicity studies

Unfortunately, toxicokinetic (TK) investigations have not been performed in any of the reproductive toxicity studies except for C_{max} concentrations in milk and plasma samples on lactation day 15 in the prenatal and postnatal development study.

Calculation of the safety margins for parameters of reproduction (fertility, prenatal and postnatal development) in rats was therefore based on TK data obtained in the 90-day toxicity study in rats. While the exposure at the NOAELs for male and female fertility were 2 and 19 times the human exposure (AUC) at the MRHD, there was apparently no safety margin at all with regard to embryofoetal and postnatal development (0.6 – 0.7 times).

For rabbits no TK data are available. Using the HED concept the safety margin for maternal and developmental toxicity is approximately 5, when calculated as multiples of the maximum human dose based on mg/m2 body surface area. Due to the insufficient exposure at the NOAELs especially in the prenatal and postnatal development studies in rats, which resulted in no safety margins at all, reproductive toxicity should be included as a potential important risk in the RMP.

Other toxicity studies

Immunotoxicity

No specific studies conducted.

Mechanistic studies

A high oral dose of solriamfetol (379 mg/kg) was administered once daily to rats for a period of 3 consecutive weeks to determine biomarkers for the effects of solriamfetol on kidney and fat tissue/lipid metabolism noted in the general toxicity studies and to get insight into the underlying mechanism of action for solriamfetol-induced renal effects. The results substantiated the conclusion that solriamfetol-induced kidney effects can be considered to be of a reactive nature.

During a three-week toxicity study in male rats (Study JNJ-TOX-6895) with a high dose (450 mg/kg/day) of solriamfetol, a (numerical) increase in corticosterone plasma levels (corticosterone is the main glucocorticoid in rats) and of vasopressin recovered in urine was observed.

Dependence

In a rat self-administration model used to test reinforcing properties, solriamfetol showed no clear abuse potential. Solriamfetol decreased cocaine self-administration in rats and monkeys. In rats, solriamfetol showed no significant rewarding properties in the place-preference model, except a trend toward an increased place preference at the highest dose tested (90 mg/kg). In drug discrimination procedures, solriamfetol partially generalized to the discriminative stimulus effects of amphetamine in rats and completely generalized to the discriminative stimulus effects of cocaine in rats and monkeys. Effects of solriamfetol on locomotion in various rodent studies were not definitively established, with effects ranging from no to little effect, an increase in locomotion that was about 60% of that observed with the cocaine control, to effects similar to those of modafinil and amphetamine.

Impurities

Solriamfetol and seven related specified impurities (NMT 0.15%) were tested *in silico* (statistical based and expert rule-based systems) for potential mutagenicity according to ICH M7(R1). None of the compounds was predicted to be genotoxic. Furthermore, seven potentially genotoxic impurities have been identified in the manufacturing process. All of them will be controlled below the TTC of 1.5 µg/day according to ICH M7(R1), resulting in a limit of NMT 10 ppm based on the MRHD of 150 mg solriamfetol.

Other studies

Phototoxicity: As solriamfetol did not absorb light at wavelengths between 290 and 700 nm and its molar extinction coefficient was <1,000 L/mol/cm (Jazz PD Memo 585-00), it meets the ICH S10 guidance criteria (which supplements the ICH M3(R2) guideline) for compounds that are not considered sufficiently photoreactive to result in direct phototoxicity.

2.3.5. Ecotoxicity/environmental risk assessment

A complete Phase II risk assessment of solriamfetol, conducted in accordance with the EMEA/CHMP/SWP/4447/00 corr 2* guideline, is currently underway and will be submitted by the second quarter of 2020.

Summary of main study results

Substance (INN/Invented Name): Solriamfetol hydrochloride			
CAS-number (if available): 178429-65-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	pH metric method	1.2	Potential PBT N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined with prevalence	0.51	µg/L	> 0.01 threshold Y

The available data do not allow to conclude definitively on the potential risk of solriamfetol hydrochloride to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacology

Primary pharmacodynamics

***In vitro* studies**

Studies to characterize effects of solriamfetol on uptake and release of monoamines (dopamine, noradrenaline, serotonin)

Data concerning interaction of solriamfetol with cloned human DAT, NET and SERT

In radioligand-binding experiments with cells expressing cloned human receptors/transporters, solriamfetol showed affinity for the dopamine (replicate K_i=6.3 and 14.2 µM) and norepinephrine transporter (replicate K_i= 3.7 and >10 µM) but no appreciable affinity to the serotonin transporter. Solriamfetol inhibited the reuptake of dopamine (replicate IC_{50}=2.9 and 6.4 µM) and norepinephrine (IC_{50}= 4.4 µM) but not of serotonin by these cells. This information has been included n SmPC section 5.1.

Although the calculated Hill coefficients were in most cases different from 1, overall, a visual investigation of the graphs presented for the binding studies and for the functional assays did not suggest the presence of more than one binding site for solriamfetol per monoamine transporter.

Potential species differences concerning effects of solriamfetol on uptake and release of dopamine and norepinephrine

Mice, dogs and rabbits have been widely used in pharmacological and toxicological studies with solriamfetol. However, no specific data concerning interaction of solriamfetol with mouse, dog and rabbit DAT or NET have been provided by the Applicant. Human and rat *in vitro* data (IC_{50} for inhibition of dopamine uptake 2.9/6.4 µM versus 21 µM; stimulation of dopamine and serotonin release only in rat brain tissue) as well as *in vivo* data from different species (differences in effects on body temperature and sensitivity to stimulation of locomotion and sterotype movements) raised the question of species differences concerning the effects of solriamfetol on uptake and release of monoamines. However, based on a literature review provided by the Applicant, it can be agreed that an extrapolation of the animal safety data obtained with solriamfetol to the human situation is considered acceptable.

Studies to detect potential interactions of solriamfetol with other pharmacological targets

In screening assays that evaluated the binding of solriamfetol to a wide variety of cloned human receptors, enzymes and transporters, no other relevant binding affinity of solriamfetol in concentrations of 1 µM respectively 10 µM was detected. However, taking into account that a Ki as high as 14.2 µM was observed for the human DAT and the fact that *in vivo* solriamfetol concentrations in some tissues (e.g. kidneys and eyes) may well reach the 100 µM range, the solriamfetol concentrations tested in the screening assays appear to be too low to allow for definite conclusions. The fact that the potential mechanism(s) of action of solriamfetol has/have not been fully characterized is expressed in SmPC section 5.1.

***In vivo* studies**

Studies to characterize effects on uptake of monoamines (dopamine, noradrenaline, serotonin)

Monoamine brain tissue levels: In proof of concept studies, a stimulatory effect of solriamfetol on striatal dopamine and prefrontal norepinephrine tissue levels of rats could be evidenced if tissue levels were normalized to a starting (t=0 min) level of 100% per treated animal (wheras serotonin levels were not stimulatied in either tissue). This information has been included in SmPC section 5.1. It may however be mentioned that measured absolute tissue levels of dopamine and norepinephrine were not significantly higher in the solriamfetol-treated groups than in the control groups.

Binding studies: Following a single SC dose of 40 mg/kg to rats, a dose that results in clear wake-promoting effects in rats, no significant binding of solriamfetol to brain monoamine transporters (DAT, NET, and SERT) could be evidenced by autoradiography. This information has been included in SmPC section 5.1

Studies on behavioural effects of solriamfetol

Solriamfetol induced stimulatory CNS effects in rats, which, however, differed in several aspects from the effects induced by amphetamine, SSRIs or MAO inhibitors.

In DAT knockout mice, solriamfetol demonstrated clear effects on CNS (e.g. locomotor, rearing, and stereotypy) activities, suggesting that the *in vivo* effects of solriamfetol are not solely mediated by DAT inhibition.

In a proof of concept study in hypocretin/ataxin-3 transgenic mice (mouse model of narcolepsy), solriamfetol dose-dependently induced continuous wakefulness during the resting (light) and active (dark) phase. The wake amounts observed in narcoleptic mice in the active phase after solriamfetol administration were similar to those of wild-type mice, suggesting that solriamfetol normalized the sleep/wake activity of narcoleptic animals. Non-REM and REM sleep were reduced in narcoleptic mice by solriamfetol to the levels observed in wild-type mice. No abnormal EEG patterns were detected after solriamfetol administration and sleep time that occurred after the prolonged wakefulness was normal (no rebound hypersomnia). These results confirm a potential effectiveness in treating EDS in narcolepsy.

In three inbred strains of mice, wakefulness induced by solriamfetol was followed by a compensatory rebound in both the duration and intensity (i.e., EEG delta power) of sleep but no evidence of rebound hypersomnolence (i.e., over-compensation for sleep lost). Brain transcriptome and clustering analyses indicated that the pharmacological pathways involved in the wake-promoting effects of solriamfetol may differ from those of amphetamine and modafinil.

In rats, when administered at the acrophase of sleep (i.e at the beginning of the light period when most sleep would be expected to occur in rodents), treatment with solriamfetol at 30 mg/kg strongly influenced sleep-wake organization, increasing active wakefulness at the expense of time spent in light sleep, deep sleep and REM sleep during the first 3 to 4 hours after the administration. A rebound effect was seen between 4-10 hours

following administration of the compound, as an increase in time spent in deep sleep that gradually decreased in the hours thereafter. Effects of solriamfetol differed in several aspects from the wake-promoting effects of cocaine and amphetamine.

Safety pharmacology

A large number of non-GLP and GLP *in vitro* and *in vivo* safety pharmacology studies have been performed for solriamfetol to characterize effects on CNS and cardiovascular, respiratory and renal systems, which overall, have not raised major serious safety concerns.

With regard to the scientific advice given by the EMA in 2017 (EMA/CHMP/SAWP/716502/2017) on safety pharmacology evaluation of solriamfetol

- the Applicant points to the fact that cardiovascular safety of solriamfetol has been evaluated in nonclinical *in vitro* and *in vivo* studies (including a GLP-conform safety pharmacology study in conscious, unrestrained telemetered beagle dogs), as well as in clinical studies (including the thorough QT study 15-002) Since the QTc-prolonging potential of solriamfetol has been qualitatively and quantitatively characterized on basis of the aforementioned studies, the position of the Applicant not to repeat *in vitro* hERG and isolated cardiac tissue studies under formally GLP-compliant conditions appears acceptable.
- concerning CNS safety pharmacology, the Applicant has submitted the requested FOB study (conducted in juvenile rats) that showed no relevant no relevant solriamfetol-related effects on FOB variables.

Pharmacodynamic drug interactions

Pharmacodynamic drug interactions have not been evaluated for solriamfetol on the non-clinical level. Since knowledge about the pharmacodynamic interaction potential is considered import for a safe clinical use of solriamfetol, the applicant was asked to discuss the pharmacodynamic interaction potential of solriamfetol on basis of the currenty proposed mechanism of action (inhibition of dopamine and norepinephrine uptake in the CNS) and make proposals for inclusion of such information in the SmPC.

In response the Applicant proposed to contraindicate the concomitant use of monoamine oxidase inhibitors (MAOI) or use of solriamfetol within 14 days after MAOI treatment has been discontinued because this may increase the risk of a hypertensive reaction. This proposal of the Applicant is supported and has been included in SmPC section 4.3 and 4.5.

Pharmacokinetics

The nonclinical PK of solriamfetol has been evaluated in a comprehensive battery of studies. Since the primary rodent and nonrodent toxicology species were rats and dogs, the majority of PK evaluations were performed in these species, either *in vivo* or *in vitro* using prepared tissues of interest. Consistent with its classification as a BCS Class 1 drug, solriamfetol was rapidly and well absorbed after oral administration in the toxicology species and in humans. Single-dose PK of solriamfetol in nonclinical species was characterized by moderate to high oral bioavailability, rapid t_{max}, short half-life, moderate apparent volume of distribution, and low (dog) to high (mouse and rat) systemic clearance.

With regard to distribution, high enrichment factors have been observed for several tissues, including the kidneys and the eye (and here in particular melanin-containing structures).

The metabolisation rate was very low in humans and in the evaluated animal species, with the exception of the rat, where metabolisation contributes relevantly to solriamfetol elimination.

Excretion of (mainly unchanged) drug via the kidneys was observed in humans and in the evaluated animal species, with the exception of the rat, where faecal excretion contributed relevantly to drug elimination.

Overall, the absorption, distribution, metabolism, and excretion of solriamfetol have been sufficiently characterized in non-clinical species to support the use of solfriamfetol for the intended indication.

Toxicology

Single dose toxicity

Single oral doses of solriamfetol were well tolerated by mice, rats, and dogs up to 600, 750, and 140 mg/kg, respectively. Clinical signs were mainly related to CNS stimulation in all species.

Repeat-dose toxicity

Pivotal repeat-dose toxicity studies have been performed in mice (up to 3 months), rats (up to 6 months with a 3-month recovery period) and dogs (up to 12 months with a 13 weeks recovery period).

Main target organs were the CNS (in connection with the primary pharmacological effect), liver, kidneys, adrenals and thymus. In the 6-month rat study and in the 12-month dog study a NOAEL could not be established (LOAELs were 29 mg/kg/day and 8 mg/kg/day, respectively). For the 3-month mouse study a NOAEL of 17 mg/kg/day could be established. Some adverse effects were only partially reversible during the recovery period in the 6-month rat study (e.g. histopathological findings in adrenals and lungs) and the 12-month dog study (e.g. decrease in serum calcium). In summary, AUC-based safety factors for solriamfetol derived from these studies (based on comparison with clinical AUC at the maximum recommended human dose of 150 mg/day) were <1 for mice (based on NOAEL) and <2 for rats and dogs (based on LOAEL), mainly due to exaggerated pharmacological effects of solriamfetol on CNS activity. This information has been included in SmPC section 5.3

Genotoxicity

In view of the results obtained the battery of submitted *in vitro* and *in vivo* genotoxicity studies, solriamfetol can be regarded as being not gentoxic. This information has been included in SmPC section 5.3

Carcinogenicity

In the light of negative genotoxicity and no increase of tumour incidence in the long-term mouse and rat carcinogenicity studies, [with AUC-based safety margins at the high solriamfetol dose to the MRHD (150 mg/day) of about 7.8 in mice and about 20.7 in rats], it can be concluded that solriamfetol does not pose a carcinogenic risk to humans. This information has been included in SmPC section 5.3

Compared to controls, cumulative survival rates were (numerically) decreased in solriamfetol-treated mice, maximal at a dose of 65 mg/kg/day (AUC-based safety margin to MRHD about 2.9), with survival rates of 70% (controls) versus 48% (p-value 0.0074) for male and 63% (controls) versus 45% (p-value 0.0923) for female mice. No decrease in cumulative survival rates was observed in the rat carcinogenicity study. Related information has been included in SmPC section 5.3

In general, the identified causes of premature death in the mouse study were of the types commonly seen in studies using mice of the tested strain and age. However, the decreased survival rates in the mid and high dose solriamfetol-treated groups appeared to be associated with an increased incidence of premature death of undetermined cause (i.e. for which no histologic/macroscopic reason could be identified).

Taking into account that cumulative survival rates were not decreased in rats and that no "classical" dose-response relationship was observed in mice, the potential clinical relevance of the mouse findings remains unknown.

Reproduction and developmental toxicity

For rabbits no TK data are available. Using the HED concept the safety margin for maternal and developmental toxicity is <3, when calculated as multiples of the maximum human dose based on mg/m2 body surface area. Possible effects on embryofoetal development were investigated in pregnant rats and rabbits. 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).

In rats exposure levels (AUC) above 0.6 – 0.7 times 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.

A respective wording has been included in SmPC section 5.3.

Due to the insufficient exposure at the NOAELs especially in the prenatal and postnatal development studies in rats, which resulted in no safety margins at all, reproductive toxicity should be included as a potential important risk in the RMP.

Ecotoxicity/environmental risk assessment

The available data do not allow to conclude definitively on the potential risk of solriamfetol hydrochloride to the environment. The applicant is asked to submit the announced data as soon as possible.

Other Toxicity Studies

Immunotoxicity

According to ICH S8 "Immunotoxicity studies for human pharmaceuticals", all new human pharmaceuticals should be evaluated for the potential to produce immunotoxicity. Therefore, the Applicant was asked to follow a weight of evidence approach to discuss whether additional immunotoxicity testing is necessary for solriamfetol

In his response, the Applicant considered that the immune system findings observed in the general toxicity studies were consistent with those caused by (chronic) stress.

According to the ICH S8 guideline, immunotoxicity is defined as unintended immunosuppression or enhancement. It is well known that a chronic "stress" response, e.g. related to a chronic overstimulation of the hypothalamic–pituitary–adrenal axis, can result in immunosuppression and other adverse effects, including hypertension.

It has been reported that other CNS stimulating drugs with effects on CNS dopamine and/or norepinephrine levels, like e.g. amphetamines or cocaine can result in changes in the activity of the hypothalamic–pituitary–adrenal axis and may also have immunosuppressive properties.

The Applicant pointed out that clinical data concerning effects of solriamfetol on main components of the HPA axis (i.e. CRH, vasopressin, ACTH and cortisol plasma levels) are not available.

Non-clinical data concerning effects of solriamfetol on CRH and ACTH plasma levels are also not available. During a three-week toxicity study in male rats (Study JNJ-TOX-6895) with a high dose (450 mg/kg/day) of solriamfetol, a (numerical) increase in corticosterone plasma levels (corticosterone is the main glucocorticoid in rats) and of vasopressin recovered in urine was observed.

With regard to potential functional consequences of an activation of the HPA axis, effects of solriamfetol on the cardiovascular system (heart rate and blood pressure, as measured in dogs) appeared to be relatively small and transient. Concerning the immune system, dose-dependent effects of solriamfetol on numbers of immune cells and morphology/weight of immune-system related organs (most prominent in rat studies) were observed.

Chronic overstimulation of the HPA axis, as observed for other inhibitors of the dopamine and noradrenaline reuptake (like cocaine and amphetamines), has been related to an increased mortality rate. In this respect, equivocal results have been obtained for solriamfetol in the conducted carcinogenicity studies. While an increased mortality rate was observed in (male) mice, no increase was observed in rats (see Discussion on Carcinogenicity).

Overall, the available nonclinical data are not considered sufficient to allow for definite conclusions concerning an activation of the HPA axis by solriamfetol. However, taking into account the claimed mechanism of action of solriamfetol (inhibition of dopamine and noradrenaline reuptake), they raise sufficient concern to justify a critical discussion of this issue and therefore a respective paragraph has been included in Section 5.5: "Uncertainties and limitations about unfavourable effects" of this AR.

Dependence

With regard to dependence and abuse liability, the CHMP has provided scientific advice in 2017 (EMA/CHMP/SAWP/716502/2017).

According to the information provided by the Applicant, although no formal GLP self-administration (reinforcing properties) study was conducted, both non-clinical and clinical data are deemed sufficient to describe the abuse potential of solriamfetol.

Other studies

On basis of the ICH S10 criteria, solriamfetol is considered to be not sufficiently photoreactive to result in direct phototoxicity.

2.3.7. Conclusion on the non-clinical aspects

A large battery of nonclinical studies has been submitted for solriamfetol. Overall, the non-clinical data is considered sufficient to support Marketing Authorisation for solriamfetol. On basis of these non-clinical data, relevant information has been included in SmPC sections 4.6, 5.1 and 5.3.

The available data do not allow to conclude definitively on the potential risk of solriamfetol to the environment. The applicant is asked to submit the announced data as soon as possible.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Module 5.3.3.3					
15-001 Complete Full CSR	Impact of renal impairment on PK and Safety	Phase 1; OL, Single-dose	To evaluate the effect of renal impairment and hemodialysis on the pharmacokinetics of JZP-110 in comparison to subjects with normal renal function	Single oral doses of JZP-110 75 mg (Subjects with ESRD had 2 single doses ≥ 7 days apart)	18 male and 13 female subjects with normal or impaired renal function 58.5 (29 to 80)
Module 5.3.3.4					
15-009 Complete Full CSR	Food effect	Phase 1; OL, Rand, SC, 2 period, Crossover	To assess the effect of food on the PK and bioavailability of JZP-110 in healthy adult subjects (food effect).	Single oral doses of JZP-110 300 mg	16 male and 16 female healthy adult subjects 35.6 (19 to 54)
Module 5.3.4.1					
15-002 Complete Full CSR	Thorough QT Study	Phase 1; TQT DB, Rand, SC, 4 period crossover, Placebo- and positive-controlled (moxifloxacin)	To assess whether JZP-110 had a clinically significant effect on the QT / QTc interval in healthy adult male and female subjects	Single oral doses of Placebo, JZP-110 300 or 900 mg, or Moxifloxacin 400 mg	26 male and 34 female healthy adult subjects 36.9 (18 to 53)

Study/ Protocol No. (Country) (Section)	**Study Phase/ Study Design**	**Product ID/ Batch/Lot No.**	**Study Objective**	**No. Subjects Entered/ Completed (M/F)**	**Healthy/Patients (Age: mean, range)**	**Dosage Form, Route, Frequency Dose (mg)**	**PK Sampling Schedule**	**Study Report Location**
YUKIC 9603-01 (USA) (2.2.1)	Phase 1 double-blind, randomized, SAD, placebo-controlled	21 mg capsules Lot 188I0896. 84 mg capsules Lot 189I0896.	Safety, tolerance, and PK	24/ (24M)	Healthy adults (35, 22-47 years)	Drug substance powder in capsules, oral, single dose Dose [a]: 42, 84, 168, 336, 504, 672, 840, 1008	Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, and 48 hours postdose	Mod5.3.3.1
YUKIC 9702-01 (USA) (2.2.2)	Phase 1 Double-blind, randomized, MAD, placebo-controlled (BID)	84 mg capsules Lot 189IO896	Safety, tolerance, and PK	50/ (49M)	Healthy adults (35, 19-50 years)	Drug substance powder in capsules, oral, BID for 14 days Dose [a]: 84, 168, 252, 336, 420 BID	Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 12 hours after each dose on Days 1 and 14	Mod5.3.3.1
R228060-P01-101 (Belgium) (2.2.3)	Phase 1 Single-dose, open-label mass balance and bio-transformation	Unlabeled solriamfetol: R228060PFA051 ^{14}C-solriamfetol: 1770	Safety, tolerance, and PK	4/(4M)	Healthy adults (49, 41-59 years)	Radio-labeled oral solution, single dose Dose: 200	Predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours postdose Urine was collected as pooled samples during the following time intervals: 0-4, 4-8, 8-16, 16-24, 24-36, 36-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours postdose. Feces were collected per stool.	Mod5.3.3.1

Table 3: Phase II studies (narcolepsy

Placebo-Controlled Studies in Narcolepsy and OSA						
ADX-N05 201 Complete	Safety and Efficacy	Phase 2; Rand, DB, Placebo-controlled, MC, Crossover	To evaluate the efficacy and safety of solriamfetol administered as a once-daily regimen compared to placebo in the treatment of EDS.	Solriamfetol: 33 Placebo: 33	Solriamfetol QD 4 weeks of treatment in 1 of 2 treatment sequences: *Sequence. 1:* Placebo x 2 weeks 150 mg x 1 week 300 mg 1 week *Sequence 2:* 150 mg x 1 week 300 mg 1 week Placebo x 2 weeks	United States (10)
ADX-N05 202 (TONES 1) Complete	Safety and Efficacy	Phase 2; Rand, DB, Placebo-controlled, MC, Parallel-group	To evaluate the efficacy of solriamfetol administered once-daily in a dose range of 150 to 300 mg compared with placebo in the treatment of EDS in adult subjects with narcolepsy.	Solriamfetol: 44 Placebo: 49	Solriamfetol QD 12 weeks *Group 1:* Solriamfetol 150 mg QD x 4 weeks, then 300 mg QD x 8 weeks *Group 2:* Placebo weeks 1 to 12	United States (28)

Table 4: Phase III pivotal studies (narcolepsy, OSA separate)

Study Number, Status	**Type of Study**	**Phase; Study Design**	**Primary Objective(s)**	**Number of Treated Subjects**	**Treatment; Route of Administration, Dose, and Duration of Treatment**	**Number and Location of Study Centers (n)**
14-002 (TONES 2) Complete	Safety and Efficacy	Phase 3; Rand, DB, Placebo-controlled, MC, 4-treatment Parallel-group	To evaluate the efficacy of solriamfetol administered QD for up to 12 weeks in doses of 75, 150, and 300 mg compared to placebo in the treatment of excessive sleepiness in adult subjects with narcolepsy	Solriamfetol: 177 Placebo: 59	Placebo or solriamfetol 75, 150, or 300 mg QD, 12 weeks	Canada (6) Finland (1) France (5) Germany (5) Italy (1) United States (46)
14-003 (TONES 3) Complete	Safety and Efficacy	Phase 3; Rand, DB, Placebo-controlled, MC, 5-treatment Parallel-group	To evaluate the efficacy of solriamfetol administered once daily (QD) for up to 12 weeks in doses of 37.5, 75, 150, and 300 mg compared to placebo in subjects with OSA	Solriamfetol: 355 Placebo: 119	Placebo or solriamfetol 37.5, 75, 150, or 300 mg QD, 12 weeks	Canada (5) France (3) Germany (5) Netherlands (1) United States (46)

Table 5: Randomized withdrawal 6-wk study, phase III (OSA)

Study Number, Status	Type of Study	Phase; Study Design	Primary Objective(s)	Number of Treated Subjects	Treatment; Route of Administration, Dose, and Duration of Treatment	Number and Location of Study Centers (n)
14-004 (TONES 4) Complete	Safety and Efficacy	Phase 3; DB, Placebo-controlled, Randomized-withdrawal	To evaluate the efficacy of solriamfetol administered once daily compared to placebo in the treatment of EDS in adult subjects with OSA.	Total treated: 174 *Titration phase* Solriamfetol: 174 *Stable dose phase* Solriamfetol: 157 *Double-blind randomized withdrawal phase* Solriamfetol: 62 Placebo: 62	*OL period:* Solriamfetol 75, 150, or 300 mg QD, 4 weeks *Randomized withdrawal period:* Placebo or solriamfetol 75, 150 or 300 mg QD, 2 weeks	Finland (3) France (3) Germany (2) Sweden (1) United States (25)

Table 6: Long term safety extension study

Open-label Studies in Narcolepsy and OSA						
14-005 (TONES 5) Complete	Safety and maintenance of Efficacy	Phase 3; OL and 2-week DB, Placebo-controlled, Randomized-withdrawal	To evaluate the safety and tolerability of solriamfetol administered QD for up to 52 weeks in doses of 75, 150, and 300 mg	Total treated: 643 *Open-label phase:* 643 *Double-blind randomized withdrawal phase:* Solriamfetol: 140 Placebo: 142	Solriamfetol 75, 150, or 300 mg QD, 52 weeks *Randomized withdrawal period:* Placebo or solriamfetol 75, 150, or 300 mg QD, 2 weeks	Canada (7) Finland (3) France (6) Germany (6) Italy (1) Netherlands (2) United States (68)

2.4.2. Pharmacokinetics

Mass balance

The absorption, metabolism, and excretion of [^{14}C]-R228060 after a single oral doses of 200 mg base equivalents of R228060 in four healthy male subjects (41-59 years of age, 76-85 kg, BMI 25-27) were examined in single-arm mass balance study R228060-P01-101.

R228060 was rapidly absorbed from an oral solution, reaching maximal plasma concentrations within 30 minutes. The elimination half-life was between 5 and 7 hours for both TR and UD. Key pharmacokinetic parameters including maximum plasma concentration (Cmax), Tmax, t1/2 and area under the concentration-time curve (AUC)and plasma concentration-time profiles were nearly super-imposable for TR and UD, indicating negligible metabolism.

The urinary route constituted the major route of elimination with a negligible amount of TR recovered in the feces. At least 90% of TR was excreted in the urine within the first 48 hours of R228060 administration. As renal clearance represented the majority of apparent total clearance and was greater than CrCL, an estimate of glomerular filtration rate, it appears that renal secretion is involved in the elimination of R228060 by the kidney. Mean (SD) TR recovered in faeces was approximately 0.19% (0.16).

Single dose administration

PK data for the characterisation of SD administration of 300 mg and 900 mg (6 x fold supra-therapeutic dose) of JZP-110 in healthy volunteers were obtained from study 15-002, principally designed to examine the effects of JZP-110 on the QT/QTc interval.

JZP-110 was rapidly absorbed, with median Tmax of 2 and 3 hours following oral administration of 300 and 900 mg doses, respectively. An approximately 3-fold greater JZP-110 Cmax (mean: 5290 versus 1774 ng/mL) and 3.5-fold higher AUC0-inf (mean: 59,190 versus 16,970 ng•h/mL) were observed following the 900 mg dose than following the 300 mg dose. Regressions between log-transformed PK parameters and log-transformed dose had slopes close to 1 for Cmax and AUC between 300 and 900 mg doses, confirming dose-proportional PK.

Food effect study

Study 15-009 examined the food effect of JZP-110 in 32 healthy adult subjects comparing the PK of JZP-110 (300 mg SD) under fasting and fed conditions.

An analysis of variance for PK parameters showed that the 90% confidence intervals of the Geometric Mean Ratios (GMR) for both Cmax and AUC0-inf between fed and fasted treatments (fed/fasted) were contained within the window of 80% to 125% (90% CIs: 89.2-98.8 and 93.8-101.5), respectively.

Dose proportionality

Single ascending dose study YUCIC9603-01 in 24 healthy male volunteers examined the PK profile after SD administration of eight escalating doses of YKP10A (50, 100, 200, 400, 600, 800, 1000 and 1200 mg).

Cmax and AUCO-inf for YKP10A have increased in linear dose-dependent fashion over the dose range 50 to 1200 mg. The compound had moderate dose-independent clearance with a mean terminal half-life of 4.99 to 6.67 hour. Mean Tmax varied between 1.64 and 2.50 hours, with no apparent relationship to dose.

Multiple ascending dose study

In the multiple ascending dose study YUKIC9702-1 the safety, tolerance and PK profile of five dose groups (200 mg, 400 mg, 600 mg, 800 mg, and 1000 mg as total daily dose [YKP10A as HCl salt]). At each dose level, groups of 10 subjects each received an oral dose of either YKP10A (n=8) or placebo (n=2) once every 12 hours for 14 days.

Linear regression of Cmax and AUC against dose demonstrated dose-proportional increases in these 2 parameters. Median Tmax ranged from 1 to 2.5 hours, and mean t½ ranged from 6 to 7.6 hours.

Special populations

Renal impairment study 15-001 examined the pharmacokinetics and safety of JZP-110 (as a 75 mg SD) in subjects with normal or impaired renal function (mild, moderate, severe), and in subjects with end-stage renal disease requiring haemodialysis.

Solriamfetol t½ and AUC increased and urinary recovery of solriamfetol decreased with increasing levels of renal impairment. Based on GMR, solriamfetol AUC0-inf was higher by approximately 53% (1.53-fold), 129% (2.29-fold), and 339% (4.39-fold), and mean t½ increased by approximately 1.2-, 1.9- and 3.9-fold in subjects with mild, moderate, or severe renal impairment, respectively, compared with subjects with normal renal function. In general, mean Cmax and median tmax were not substantially affected by renal impairment.

Based on GMRs, solriamfetol AUC0-t was higher (approximately 518% [6.18-fold] and 357% [4.57-fold], respectively) and Cmax ratios was slightly lower (approximately 3% and 19%, respectively) in End stage renal disease (ESRD) subjects without hemodialysis and ESRD subjects undergoing hemodialysis compared with

subjects with normal renal function. Mean t½ increased >13-fold in ESRD subjects compared with subjects with normal renal function.

Pharmacokinetic interaction studies

DDI Involving CYP and UGT Enzymes: Five in vitro studies using human microsomes, Supersomes, and primary cultured human hepatocyte experimental systems evaluated the potential of solriamfetol to inhibit or induce CYP450 or UGT enzyme activity (JNJ-FK4801, JNJ-0796, Covance 8322976, Covance 8322977, and XT165105). In accordance with the SA received from the CHMP (EMA/CHMP/SAWP/716502/2017) in November 2017, further investigation of the potential of DDI through CYP2D6 was carried out using other exploratory in silico tools such as the mechanistic static model for DDI prediction. In summary, solriamfetol is not a substrate for any of the major drug metabolizing CYP enzymes and does not induce CYP1A2, 2B6, 3A4, or UGT1A1 enzymes. CYP enzyme inhibition results were uniformly associated with insignificant risk factors using basic or mechanistic static models. Taken together, these results show that PK interactions through drug metabolizing enzymes are unlikely to occur.

DDI Involving Transporters: Three in vitro studies were completed to investigate the interaction of solriamfetol with major membrane and renal transporters (Covance 8304273; Covance 8335453; XT168124). Overall, solriamfetol appears to be a low-affinity, non-selective substrate for multiple renal cation transporters. Transporter inhibition results with solriamfetol as the perpetrator were considered insignificant based on the in vitro threshold values or based on PBPK modelling.

2.4.3. Pharmacodynamics

Mechanism of action

The mechanism(s) of solriamfetol to improve wakefulness in patients with EDS associated with narcolepsy or OSA has not been fully characterised. Its efficacy could be mediated through its activity as a dopamine and norepinephrine reuptake inhibitor (Baladi et al, 2018). The dysfunction of the dopaminergic and norepinephrine pathways originating from the brainstem have been observed in animal models of sleep apnoea and narcolepsy (Li et al. 2014; Tsujino et al. 2013; Zhu et al. 2015). The wake-promoting effects of solriamfetol is claimed to be likely due to activity at dopamine and norepinephrine transporters. The role of dopamine transporters in sleep regulation was described in the literature (Wisor et al. 2001) and is supported by the specific dopaminergic wake-promoting action of amphetamines and modafinil.

Primary and Secondary pharmacology

Apart from the human abuse liability study 14-001 (incl. phentermine as positive control, not approved in Europe), no active comparator trials were presented in the clinical data package.

Human abuse liability (HAL) Study 14-001

A Randomized Double-Blind, Placebo-Controlled, Crossover, Human Abuse Liability Study of JZP-110 in Recreational Polydrug Users with Recent Histories of Stimulant Use

The primary objective of this study is to evaluate the abuse potential of JZP-110 as compared to phentermine and placebo in 30 recreational polydrug users with recent histories of stimulant use.

This study involved three phases: a Screening Phase, a Qualification Phase, and a Test Phase. Eligibility of subjects to proceed to the Qualification Phase was determined in the Screening Phase.

Eligible subjects entered a 6-day Qualification Phase and were randomized in a 1:1 ratio to receive either a sequence of placebo on Day 1 and phentermine 60 mg on Day 4 or a sequence of phentermine 60 mg on Day 1 and placebo on Day 4 under double-blind conditions.

Only subjects who tolerated phentermine and who reported greater liking for phentermine versus placebo (peak liking at least 15 points higher on a bipolar liking-disliking visual analog scale [VAS], and neutral liking for placebo (within 40 to 60 points on a bipolar liking-disliking VAS) were eligible for the Test Phase of the study. Of the 92 subjects completing the Qualification Phase about every third (n=33) did not meet the qualification criteria, i.e did not differentiate between the positive control phentermine and placebo in terms of drug liking. In those subjects reporting a difference between phentermine and placebo, peak liking was observed about 2 hours post-administration.

Primary Endpoint

Drug Liking at the Moment was rated on a 0-100 VAS (strong disliking to strong liking) at multiple time points. Peak (Emax) Drug Liking at the Moment across 12 hours was the primary endpoint.

The HAL study was considered valid since both doses (45 mg and 90 mg) of the positive control, phentermine, produced statistically higher ratings than placebo on the primary endpoint, peak (Emax) Liking at the Moment ($p<0.001$).

Table 7: Peak (Emax) Drug Liking at the Moment VAS Across 12 Hours, PP Population (N=37)

	Placebo	JZP-110 300 mg	JZP-110 600 mg	JZP-110 1200 mg	PTN 45 mg	PTN 90 mg
Mean (SD)	52.7 (6.10)	65.3 (16.96)	70.9 (14.69)	79.6 (15.86)	74.9 (16.59)	86.3 (11.94)
Median	50.0	57.0	68.0	79.0	76.0	87.0
Range	50-81	50-97	50-98	50-100	50-100	60-100
95% CI	50.7-54.7	59.6-70.9	66.0-75.8	74.3-84.9	69.3-80.4	82.3-90.3

VAS allowed ratings from 0 (strong disliking) to 100 (strong liking). The 95% CIs are based on the t-distribution.

E_{max}=maximum effect score; PP=per protocol; PTN = phentermine; VAS=visual analog scale

Table 8: Drug Liking at the Moment VAS Emax Across 12 Hours: Pairwise Comparisons, PP Population (N=37)

Pairwise Comparison	Median of Intra-Subject Difference	Inter-Quartile Range for Difference	P-value[a]
Overall Treatment Effect	NA	NA	<0.001
PTN 45 mg - Placebo	23.0	7.0, 34.0	<0.001
PTN 90 mg - Placebo	35.0	25.0, 48.0	<0.001
JZP-110 300 mg - PTN 45 mg	-4.0	-24.0, 1.0	0.005
JZP-110 600 mg - PTN 45 mg	0.0	-16.0, 4.0	0.276
JZP-110 1200 mg - PTN 45 mg	5.0	0.0, 12.0	0.067
JZP-110 300 mg - PTN 90 mg	-18.0	-33.0, -7.0	<0.001
JZP-110 600 mg - PTN 90 mg	-13.0	-23.0, -7.0	<0.001
JZP-110 1200 mg - PTN 90 mg	0.0	-14.0, 3.0	0.031
JZP-110 300 mg - Placebo	4.0	0.0, 28.0	<0.001
JZP-110 600 mg - Placebo	16.0	7.0, 28.0	<0.001
JZP-110 1200 mg - Placebo	28.0	17.0, 40.0	<0.001

VAS allowed ratings from 0 (strong disliking) to 100 (strong liking).

[a] Overall treatment effect was assessed using the Friedman test. Pairwise treatment comparisons were assessed using the Wilcoxon Sign-Rank test on the within-subject differences.

E_{max}=maximum effect score; NA=not applicable; PP=per protocol; PTN = phentermine; VAS=visual analog scale

For all doses of JZP-110, ratings of Drug Liking at the Moment (VAS Emax) were statistically higher than those for placebo ($p<0.001$).

QTcF

Study 15-002 was a randomized, double-blind, placebo- and positive-controlled, 4-period crossover thorough QT study to evaluate the effect of solriamfetol on the QT/QTc intervals in healthy subjects. Each subject received single doses of 300 mg solriamfetol, 900 mg solriamfetol, 400 mg moxifloxacin (positive control), and placebo in separate treatment periods according to a Latin square crossover study design.

Solriamfetol (300 or 900 mg) did not meet the threshold of ICH E14 for prolongation of QTcF. The upper bounds of the 2-sided 90% CIs for the mean difference in least square means for QTcF between the therapeutic (300 mg) or supratherapeutic (900 mg) doses and placebo were <10 msec at all postdose time points.

Increases from baseline in HR were observed in the solriamfetol (300 and 900 mg) groups compared with the placebo group from 2 (around the time of Cmax) through 12 hours after dosing. The peak increase in mean HR from baseline occurred at 6 hours after dosing in the solriamfetol groups (mean change from baseline in HR of 20.8 and 27.3 bpm in the 300 and 900 mg solriamfetol groups compared with 7.9 bpm in the placebo group).

Consistent with the increase in HR observed in the solriamfetol groups compared with the placebo group, treatment-emergent sinus tachycardia (ECG morphological finding) occurred in 6 subjects after receiving 300 mg solriamfetol and 15 subjects after receiving 900 mg solriamfetol compared with no subjects after receiving placebo.

No clinically significant changes in the mean QRS interval were observed via Holter monitoring. Shortening of mean RR, PR, and QT intervals corresponding to the increase in HR were observed after the solriamfetol treatment compared with the placebo treatment.

2.4.4. Discussion on clinical pharmacology

The results of ^{14}C mass balance study R228060-P01-101 in four healthy volunteers are indicative of high gastrointestinal absorption (Ae,u >95% for the unchanged drug). JZP-110 was rapidly and almost completely absorbed. More than 96% of TR was excreted in the urine (Ae,u), with negligible amounts of TR recovered in the faeces (0.19% Ae,f). Estimated renal clearance of the AS was about 3 times higher than GFR, hence JZP is assumed to be actively secreted in the kidney.

The effect of food on the PK of solriamfetol was explored in Study 15-009 and showed that the Cmax and AUC were bioequivalent under fed (after a standardized high-fat, high-calorie meal) and fasted conditions. The Cmax was achieved about one hour later under fed conditions, AUC values were about 6% lower. Intra-subject variability was low, around 10%. The slight differences in plasma levels observed between the fasted vs fed state are not considered to be clinically relevant. Hence, JZP-110 fc tablets may be taken with or without meal.

Ascending multiple dose study YUCIC9702-1 investigated daily doses administered in divided doses twice daily. JZP showed overall linear pharmacokinetics at levels of 200 mg to 1000 mg per day. The minimum plasma concentration (Cmin) values for the 600 mg, 800 mg, 1000 mg (HCl salt) dose groups after twelve days of twice daily administration were slightly increasing, which could not be explained. This is considered of minor relevance, since the effect was observed for supra-therapeutic doses only. Based on the plot of Cmin values, steady state appeared to be achieved by the third day. For the twice daily dosing schedule the accumulation ratio was 1.43, indicating 43% accumulation at steady state compared with the first day. Given the apparent elimination half-life of about 7 hours and the proposed 24 hours dosing interval, accumulation is of no concern in the present case.

After the high portion of renal elimination was shown in the mass balance study, a comprehensive study (15-001) examining the effect of renal impairment was conducted after 75 mg SD administration. AUC0-inf values increased with increasing degree of renal impairment (1.53-fold-, 2.29-fold-, and 4.39-fold in subjects with mild, moderate and severe renal impairment as compared with healthy control). In parallel, elimination of JZP-110 slows down. Mean t½ increased by approximately 1.2-, 1.9- and 3.9-fold in subjects with mild, moderate and severely impaired renal function. Cmax values are only slightly affected by renal function.

In end-stage renal disease patients, AUC0-t values are 6.18-fold increased (without haemodialysis), resp. 4.57-fold higher in subjects undergoing haemodialysis. In these patients, elimination of JZP-110 is markedly slowed down ($t_{1/2}$ values > 13-fold increased). Comparing plasma levels of ESRD subjects with or without haemodialysis, it can be concluded that haemodialysis does not largely impact on solriamfetol's elimination profile after 75 mg single dose administration. The dosing recommendations as proposed in the SmPC are considered to take due account of the results of study 15-001. For subjects with severe renal impairment (creatinine clearance of 15-29 mL/min) the recommended starting dose is 37.5 mg once daily. The 37.5 mg dose can be achieved by splitting the scored 75 mg tablet into equal halves.

Solriamfetol is primarily eliminated unchanged in the urine (≥ 95%), with minimal hepatic metabolism: ≤1% of dose was recovered in urine as the minor inactive metabolite N-acetyl solriamfetol. In view of the low level of hepatic metabolism and the high level of urinary elimination as unchanged drug, a PK study in hepatically impaired subjects is not required.

Results from *in vitro* studies and subsequent mechanistic static and PBPK modelling indicate that solriamfetol is unlikely to be an inhibitor or inducer of any of the major drug metabolizing enzymes or inhibitor of drug transporters. Furthermore, solriamfetol is not a substrate for P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or MATE2-K.

Moreover, in vitro study was performed in order to investigate the potential of solriamfetol to be a substrate of OCT2 and MATE1 transporters. Results seem to indicate that solriamfetol may be a substrate of OCT2 and MATE1 transporters as its uptake was reduced by the presence of inhibitors (quinidine and cimetidine). The same result on OCT2 has been observed in CHO cells.

Study results indicate that solriamfetol is a low-affinity non-selective substrate of multiple cationic renal drug transporters, and most likely undergoes active renal tubular secretion by multiple transporters working in concert. Given the lack of substrate specificity to particular transporters, an increase or decrease in the activity of any given transporter is unlikely to affect the pharmacokinetics of solriamfetol.

Abuse liability

In Human Abuse Liability (HAL) study 14-001 JZP doses of 300 mg, 600 mg and 1200 mg were tested. In terms of the primary endpoint "Drug Liking at the Moment" all three JZP doses achieved highly significant higher sores than placebo. If compared with the positive control phentermine (a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamphetamine, not approved in Europe) the score was equal for both substances, if administered at the highest dose each (phentermine 90 mg, JZP 1200 mg). An abuse potential similar or lower as compared to phentermine can be concluded.

QTcF

The effect of solriamfetol on the QT/QTcF interval was investigated in a single-center, randomized placebo and positive controlled double-blind, 4-period crossover thorough QT study in 60 healthy subjects (Study 15-002). Solriamfetol (300 or 900 mg) did not meet the threshold of ICH E14 for prolongation of QTcF. The upper bounds of the 2-sided 90% CIs for the mean difference in least square means for QTcF between the therapeutic (300 mg) or supra-therapeutic (900 mg) doses and placebo were < 10 msec at all post-dose time points. No subject had a maximum post-dose QTcF interval > 480 milliseconds or an increase in QTcF > 60 milliseconds from baseline following any treatment. These findings were also supported in the 12-week randomized, placebo-controlled clinical studies in patients with narcolepsy or OSA, where solriamfetol at doses up to 300 mg did not have an effect on QTcF prolongation.

2.4.5. Conclusions on clinical pharmacology

Solriamfetol is proposed to be administered in single daily doses of 75 mg, 150 mg, and 300 mg. The 75 mg tablet contains a scoring line and can be halved to enable 37.5 mg dose administration in subjects with OSA and/or renal impairment. Dose proportionality was shown across the therapeutic range. The tablet can be taken irrespective of meals. More than 95% of the drug substance was found unchanged in the urine. Therefore, renal function plays a crucial role. The influence of various degrees of renal impairment (incl. haemodialysis) was adequately characterized.

Based on the presented *in vitro* data as well as mechanistic static and PBPK modeling, PK interactions through drug metabolizing enzymes, drug transporters, or urinary pH modulators are unlikely to occur in patients taking solriamfetol.

At a supra-therapeutic dose of 900 mg (6 times the maximum recommended dosage), solriamfetol did not prolong the QTcF interval to a clinically relevant extent.

As could be expected from the molecular mode of action, liability for abuse of solriamfetol was shown in recreational drug users at about the same level as phentermine, a stimulant, indirect sympathomimetic substance.

The clinical pharmacology characterization of solriamfetol is considered acceptable.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

ADX-N05 201 as proof of concept study

Phase IIa study ADX-N05 201 was conducted in narcolepsy patients to provide proof of concept and inform the design of subsequent phase III studies in the target population. This was a 4-week (28 days), double-blind, placebo-controlled, multicentre, randomized, cross-over study of the safety and efficacy of ADX-N05 in the treatment of EDS in adult subjects (18 to 65 years) with narcolepsy as defined by ICSD-2. Subjects were assigned to two treatment sequences (Sequence #1: 1st and 2nd wk placebo, 3rd wk 150 mg, 4th wk 300 mg; Sequence #2: 1st wk 150 mg, 2nd wk 300 mg, 3rd and 4th week placebo). No dose finding study for the use of solriamfetol in the treatment of EDS was conducted.

Given the limitations of a randomized, cross-over design with subjects acting as their own control, small-scale study ADX-N05 201 is not further discussed here. Nonetheless, early proof of concept study ADX-N05-201 is considered to provide useful information for consecutive phase III studies in terms of endpoints (Maintenance of Wakefulness Test (MWT), Epworth Sleepiness Scale (ESS), Clinical Global Impressions - Change (CGIc), study population and doses.

ADX-N05-202 as phase IIb study

This 12-week, randomized, double-blind, placebo-controlled, multicentre, parallel-group study was designed to evaluate the safety and efficacy of solriamfetol for the treatment of EDS in adult subjects with narcolepsy (ICSD-2). Eligible subjects had a baseline mean sleep latency of < 10 minutes on the MWT, and a baseline score of ≥ 10 on the ESS. The primary objective of this study was to evaluate the efficacy of solriamfetol, administered once-daily in a dose range of 150 to 300 mg, compared with placebo in the treatment of ES. Subjects were randomly assigned to one of two treatment groups (Group #1: Weeks 1-4: ADX-N05 150 mg/day; Weeks 5-12: ADX-N05 300 mg/day; Group #2: Weeks 1-12: Placebo).

The significance of phase II study ADX-N05-202 is given by the fact that it provides the first parallel group, placebo controlled data for solriamfetol in narcolepsy patients although subjects in the active arm underwent forced dose increase. Therefore, phase IIb study ADX-N05-202 does not provide dose finding data in the literal sense. Fixed dose arms were not compared following a parallel group design. Instead, subjects allocated to the ADX arm received 150 mg ADX o.d. for the first four weeks of treatment and dosing then was increased to 300 mg o.d. for the following eight weeks. The ADX arm was compared with placebo. For the main efficacy parameters (MWT, CGI-C, and ESS) efficacy increased over time when the scores of the 4-wk visit are compared with the last assessment after 12 weeks. Superiority over placebo could be shown for all three efficacy endpoints. Therefore, study ADX-N05 202 justifies to further explore the 150 mg resp. 300 mg o.d. dosing regimen over a 12-week treatment period in narcoleptic patients.

2.5.2. Main study(ies)

Two pivotal phase III studies, essentially similar in design (fixed dose arms)/ duration / endpoints, were conducted, one in narcolepsy and one in OSA.

14-002; A 12-week, prospective, randomized, double-blind, placebo-controlled, parallel group study of solriamfetol 75, 150, and 300 mg vs. placebo in subjects with narcolepsy.

Study Participants

Male or female between 18 and 75 years of age, inclusive.

Study 14-002 (Narcolepsy)

Each subject had to meet all of the following criteria to be enrolled in the study:

1. Diagnosis of narcolepsy according to ICSD-3 or DSM-5.
2. Baseline mean sleep latency <25 minutes as documented by the mean of the first 4 trials of the Baseline 5-trial MWT.
3. Baseline Epworth Sleepiness Scale (ESS) score ≥10.
4. Usual nightly total sleep time of at least 6 hours.

Subjects were excluded if presenting with

1. Moderate or severe obstructive sleep apnoea on the baseline PSG
2. Daily caffeine use at the Screening Phase >600 mg/day of caffeine or >6 cups of coffee/day
3. History or presence of any clinically significant or unstable medical condition, behavioural or psychiatric disorder (including suicidal ideation and excluding mild or moderate substance use disorders), or surgical history that could affect the safety of the subject or interfere with study assessments per the judgment of the investigator
4. Presence or history of significant cardiovascular disease including myocardial infarction, hypertension (defined as consistent systolic blood pressure ≥140 mmHg or consistent diastolic blood pressure ≥90 mmHg), angina pectoris, clinically significant arrhythmias, clinically significant valvular heart disease, history of any revascularization procedures or second- or third-degree heart block with/without a pacemaker, or heart failure

Patients were required to discontinue the use of psychostimulants prior to starting on the study drug (washout period of at least 5 half-lives of the drug) for at least 7 days prior to baseline assessment. Concomitant use of psychostimulants was prohibited during the study

Treatments

The main studies are placebo-controlled. JZP-110 37.5 mg (in study 14-003), 75, 150, and 300 mg was administered QD, by mouth as 37.5, 75, 150, and 300 mg tablets (based on the free base of the molecule) that were over-encapsulated in an opaque gelatin capsule. The 37.5 mg tablet used in study 14-003 is not part of the present MAA. Instead, the 75 mg tablet contains a score line and can be divided into equal doses.

Subjects were instructed to take their daily dose of study drug in the morning on an empty stomach within 1 hour of awakening, and to abstain from eating or drinking (except for water) for 30 minutes after taking the study drug. If a subject failed to take the study drug within an hour of awakening, the subject was instructed to take the drug at least 12 hours before bedtime. If this was not possible, the subject was instructed not to take study drug for that day.

Objectives/Outcomes/endpoints

In both pivotal studies the identical set of efficacy co-primary and secondary endpoints was chosen:

Co-primary Efficacy Endpoints:

- MWT: Change in the mean sleep latency time (in minutes) as determined from the first 4 trials of a 40-minute MWT from Baseline to Week 12
- ESS: Change in ESS score from Baseline to Week 12

Key Secondary Efficacy Endpoint:

- PGIc: Percentage of subjects reported as improved (minimally, much, or very much) on the PGIc at Week 12

Post-hoc analyses

Based on feedback from the CHMP, the applicant conducted the following post-hoc efficacy analyses of the data from the individual studies.

- Post-hoc sensitivity analyses of the results for the PGIc in which improvement was defined using only the categories of "much improved" and "very much improved" (for the 12-week Phase 3 Study 14-002 and Study 14-003) or "much worsened" and "very much worsened" (for Phase 3 randomized withdrawal for Study 14-004 and Study 14-005).
- Post-hoc correlation analyses for PGIc and ESS in the 12-week Phase 3 studies to evaluate whether the effect observed on the PGIc is related to the effect on excessive sleepiness.
- Post-hoc analyses of ESS in the 12-week Phase 3 studies to evaluate the percentage of subjects with ESS values below 10 and with their percentage change from baseline.

Randomization

Stratified randomization on the basis of the presence or absence of cataplexy was used to assign subjects in a 1:1:1:1 ratio to receive JZP-110 75, 150, or 300 mg or placebo over the 12-week Treatment phase.

Blinding

A double-blind approach was used during the Treatment Phase. All study drugs were prepared in identical opaque gelatin capsules to ensure adequate blinding, and all study personnel were blinded to the study treatments

Statistical methods

The modified Intent-to-Treat (mITT) Population was used to evaluate the co-primary endpoints and other efficacy endpoints (unless otherwise indicated). It consisted of subjects who received at least one dose of study medication and had baseline and at least one post-baseline evaluation of MWT or ESS. If a subject in the mITT Population did not have an assessment for a particular secondary efficacy endpoint, that subject was excluded from the analysis of that endpoint.

Efficacy analyses were performed for the mITT Analysis Population. For the analysis of the co-primary efficacy endpoints, a mixed-effect repeated measures (MMRM) model was used as the primary method of analysis. This model includes factors for treatment, time as a discrete factor, treatment-by-time interaction, the baseline value of the endpoint and the stratification factor (presence or absence of cataplexy for 14-002 and subjects' compliant or noncompliant use of their primary OSA therapy for 14-003) used for randomisation. All available data was included in the model.

In addition to the MMRM model, an analysis of covariance (ANCOVA) model was used to analyse MWT and ESS to provide sensitivity analyses. This ANCOVA model includes the effect for treatment as a fixed effect and baseline value of the efficacy endpoint as the covariate. The chi-squared test was used to test hypotheses associated with the analysis of the key secondary efficacy endpoint of PGIc and the secondary efficacy endpoint of CGIc at Week 12. For the analysis of the co-primary efficacy parameters of MWT and the total ESS score, missing data was handled by the MMRM methods for the primary analysis.

For sensitivity analyses, the following missing data approaches were used to impute the missing data to assess the potential impact of missing data: two single imputation (SI) approaches using last observation carried forward (LOCF) and mean imputation, and two multiple imputation (MI) approaches, using a Markov Chain Monte Carlo (MCMC) method with regression and a Pattern Mixture Model approach with different dropout patterns.

Results

Participant flow

Of the 364 screened subjects, 125 failed screening. The primary reasons for screen failure were failing to meet inclusion criteria (50.4%) or meeting exclusion criteria (26.4%).

The remaining 239 subjects were randomized in a 1:1:1:1 ratio to receive placebo, 75 mg, 150 mg, or 300 mg JZP-110. Of these, 236 subjects received at least 1 dose of study medication and comprised the Safety Population; the remaining 3 subjects were randomized in error (did not receive study medication) and were excluded from the Safety Population.

The majority of subjects completed the study, 88.1% in the placebo group, and 83.1%, 86.4%, and 72.9% in the 75 mg, 150 mg, and 300 mg JZP-110 groups, respectively.

The most frequent reasons for withdrawal from the study were lack of efficacy and AEs. Withdrawal due to lack of efficacy in the placebo, 75 mg, 150 mg, and 300 mg JZP-110 dose groups was 1.7%, 6.8%, 1.7%, and 10.2%, respectively, and withdrawal due to AEs was 1.7%, 3.4%, 6.8%, and 8.5%, respectively.

Baseline data

As concerns baseline demographics, about two thirds of recruited subjects were female (67.2% in interventional arms and 59.3% in Placebo arm). The mean age of included subjects was around 36 years (range 18-70) reflecting the predominantly young target population. Baseline MWT sleep latency times and baseline ESS scores were similar across treatment groups. Approximately 50% of subjects across all treatment groups had a medical history of cataplexy, reflecting the presence or absence of cataplexy used as a stratification factor for the study. Baseline CGIs evaluation categorized most subjects in each treatment group as markedly ill, with a similar percentage of subjects across all groups classified as moderately or severely ill.

The majority of subjects received concomitant medications during the study being anti-inflammatory/antirheumatic products the most frequently reported. The use of antihistamines for systemic usage (placebo: 8.5% and JZP-110 15.3 %) and antidepressants (placebo: 8.5% and JZP-110 12.4 %) was also reported during the study conduction. Around 25% of subjects presented with a history of depression. The portion of included subjects with mild OSAS was similar across dose arms: 9/59 (15.3%) in the placebo arm, 11/59 (18.6%) for 75 mg, 15/59 (25.4%) for 150 mg and 7/59 (11.9%) in the 300 mg arm.

Table 9: Baseline Disease Characteristics (Safety Population)

Characteristic	Placebo N = 59	75 mg JZP-110 N = 59	150mg JZP-110 N = 59	300 mg JZP-110 N = 59	Combined JZP-110 N = 177
Baseline Mean Sleep Latency Time (min), n	58	58	57	59	174
Mean (SD)	6.14 (5.628)	7.50 (5.386)	7.70 (5.574)	8.73 (6.153)	7.98 (5.710)
Median	4.63	6.13	6.00	6.75	6.44
Range	0.3, 25.4	0.3, 21.9	0.0, 22.4	0.3, 22.6	0.0, 22.6
Baseline ESS Total Score, n	59	59	59	59	177
Mean (SD)	17.3 (2.83)	17.3 (3.53)	16.9 (3.66)	17.2 (2.81)	17.1 (3.34)
Median	17.0	18.0	17.0	17.0	17.0
Range	11, 24	10, 24	10, 24	11, 24	10, 24
Randomization Stratification Factor, n (%)					
Presence of Cataplexy	29 (49.2)	31 (52.5)	30 (50.8)	30 (50.8)	91 (51.4)
Absence of Cataplexy	30 (50.8)	28 (47.5)	29 (49.2)	29 (49.2)	86 (48.6)
Baseline CGIs, n (%)					
1=Normal, not at all ill	0	0	0	0	0
2=Borderline ill	0	0	0	0	0
3=Mildly ill	1 (1.7)	3 (5.1)	3 (5.1)	1 (1.7)	7 (4.0)
4=Moderately ill	14 (23.7)	14 (23.7)	16 (27.1)	17 (28.8)	47 (26.6)
5=Markedly ill	26 (44.1)	20 (33.9)	24 (40.7)	21 (35.6)	65 (36.7)
6=Severely ill	13 (22.0)	17 (28.8)	13 (22.0)	12 (20.3)	42 (23.7)
7=Among the most extremely ill patients	4 (6.8)	5 (8.5)	3 (5.1)	8 (13.6)	16 (9.0)
Missing	1 (1.7)	0	0	0	0

Note: Percentages are based on N, number of subjects within each treatment group. Mean sleep latency is the average sleep latency of the first 4 trials of the MWT, or 3 of the first 4 trials if 1 is missing. Higher latencies indicate greater ability to stay awake; ESS Total Score is defined as the sum of 8 item scores, if 6 or more of them are non-missing. If 1 or 2 ESS items are missing at specific time point, the mean of the remaining 7 or 6 non-missing ESS items at that time point will be used to impute the missing ESS items. Higher scores indicate greater chance of dozing.
CGIs=Clinical Global Impression of Severity; ESS=Epworth Sleepiness Scale; min = minutes; MWT=Maintenance of Wakefulness Test; SD = standard deviation.

Numbers analysed

Table 10: Number of Subjects in Each Analysis Population (All Enrolled Subjects)

Population, n (%)	Placebo N = 60	75 mg JZP-110 N = 59	150 mg JZP-110 N = 60	300 mg JZP-110 N = 60	Combined JZP-110 N = 179	Total N = 239
Randomized Subjects	60	59	60	60	179	239
Safety Population, n (%)	59 (98.3)	59 (100)	59 (98.3)	59 (98.3)	177 (98.9)	236 (98.7)
mITT Population, n (%)	58 (96.7)	59 (100)	55 (91.7)	59 (98.3)	173 (96.6)	231 (96.7)
If Excluded, Reason:						
Not in Safety Population	1 (1.7)	0	1 (1.7)	1 (1.7)	2 (1.1)	3 (1.3)
Did not have baseline and at least one post-baseline evaluation of MWT and ESS	1 (1.7)	0	4 (6.7)	0	4 (2.2)	5 (2.1)
PP Population, n (%)[a]	52 (86.7)	49 (83.1)	51 (85.0)	43 (71.7)	143 (79.9)	195 (81.6)
Did Not Complete the Study	8 (13.3)	10 (16.9)	9 (15.0)	17 (28.3)	36 (20.1)	44 (18.4)
Had a Major Protocol Violation	2 (3.3)	2 (3.4)	1 (1.7)	4 (6.7)	7 (3.9)	9 (3.8)
PK Population, n (%)	0	59 (100)	56 (93.3)	57 (95.0)	172 (96.1)	172 (72.0)

Note: Percentages are based on N, number of randomized subjects within each treatment group. The mITT Population exclusion reasons are mutually exclusive. Subjects could have had both Per-Protocol Population exclusion reasons and were counted in both rows.

[a] Prior to database lock, major violations (or per protocol deviations) were flagged among all major deviations and subjects with any major violation from the protocol were identified for exclusion from the PP Population.

ESS=Epworth Sleepiness Scale, mITT = modified Intent-to-Treat, MWT=Maintenance of Wakefulness Test, PP = Per Protocol, PK = Pharmacokinetic.

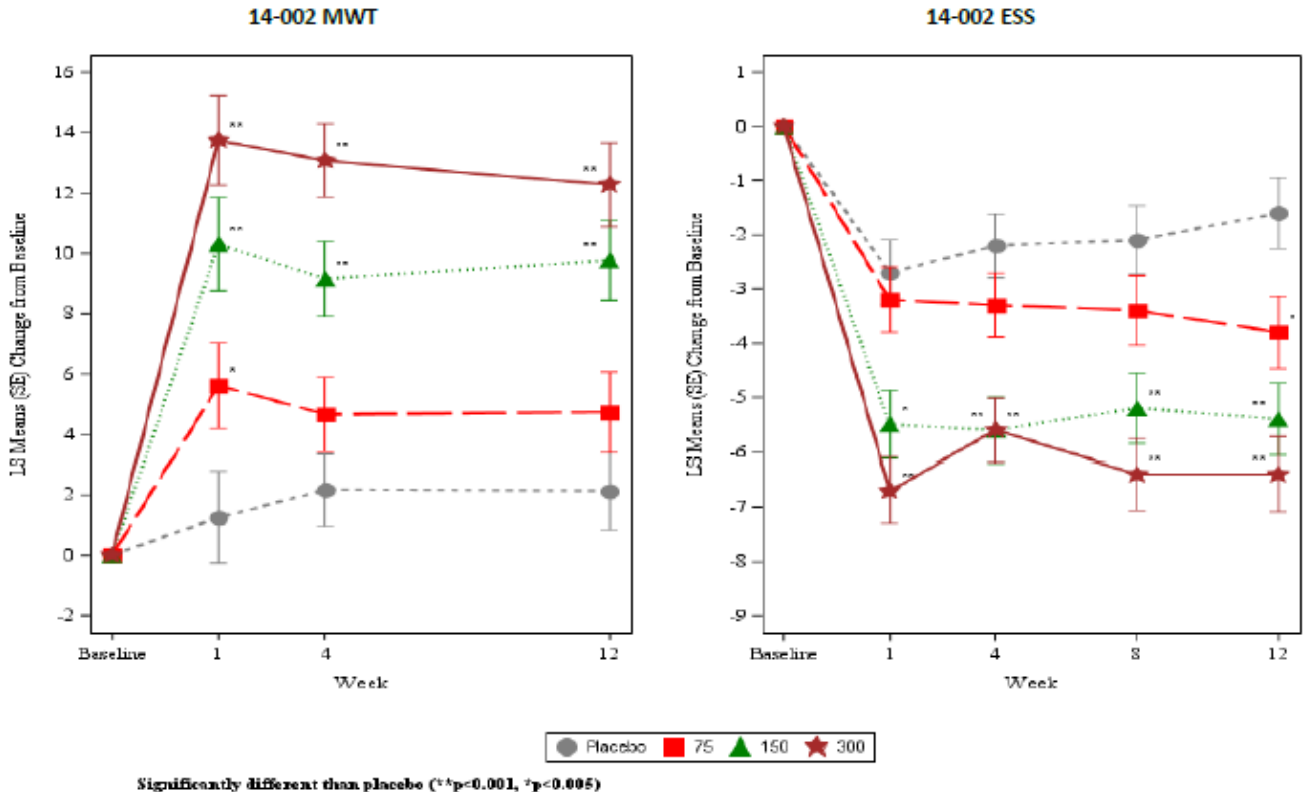
Outcomes and estimation

Co-primary and key secondary endpoints

Subjects who received solriamfetol demonstrated improvement in wakefulness, as measured on the MWT, and a reduction in EDS based on ESS scores (co-primary endpoints). At Week 12, subjects randomized to 150 mg and 300 mg of solriamfetol demonstrated a statistically significant improvement based on the MWT, ESS, and PGIc compared with placebo. Subjects randomized to 75 mg showed statistically significant improvement on the ESS but not on the MWT or PGIc (Please refer to tabulated summary of efficacy results).

The magnitude of effect was dose-dependent, was observed by Week 1, and was maintained over the 12 weeks of treatment on both the MWT and ESS.

Figure 2: 14-002 Study: MWT and ESS Change from Baseline by Study Visit (Week) in Subjects with Narcolepsy



Sensitivity analyses: Co-primary endpoints

Four sensitivity analyses of the co-primary endpoints of change from baseline to Week 12 in MWT mean sleep latency and ESS scores were performed.

Sensitivity analysis 1 and sensitivity analysis 2 utilized an ANCOVA model, with change from baseline as the response variable, and fixed-effect model terms of treatment, baseline, and randomization stratification factor (presence or absence of cataplexy). Missing data was imputed using an LOCF approach in sensitivity analysis 1 and the corresponding treatment group mean in sensitivity analysis 2.

Sensitivity analysis 3 utilized an MMRM, with change from baseline as the response variable and fixed-effect of treatment, visit, treatment by visit, randomization stratification factor (presence or absence of cataplexy), covariate of baseline, and unstructured variance-covariance structure. Missing data was imputed using multiple imputation method by MCMC for non-monotone missing and regression method for monotone missing data within each treatment group.

The results of sensitivity analyses 1, 2, and 3 were generally consistent with and supported the primary analyses, with a statistically significant increase relative to placebo observed at the 300 and 150 mg JZP-110 doses but not at the 75 mg JZP-110 for change in MWT mean sleep latency at Week 12. An exception was at the 75 mg JZP-110 dose in sensitivity analysis 2, in which statistical significance compared with placebo for MWT mean sleep latency was observed (p = 0.0413). In all 3 sensitivity analyses, a statistically significant improvement compared with placebo was observed for change in ESS score at Week 12 at the 75, 150, and 300 mg JZP-110 doses.

Table 11: Summary of Sensitivity Analyses of Change in MWT Mean Sleep Latency and ESS Total Score from Baseline to Week 12 (mITT Population)

Analysis	Endpoint	P-value		
		75 mg JZP-110 N = 59	150 mg JZP-110 N = 55	300 mg JZP-110 N = 59
Sensitivity Analysis 1[a]	MWT Mean Sleep Latency	0.2014	< 0.0001	< 0.0001
	ESS Score	0.0261	<0.0001	< 0.0001
Sensitivity Analysis 2[b]	MWT Mean Sleep Latency	0.0413	< 0.0001	< 0.0001
	ESS Score	0.0197	< 0.0001	< 0.0001
Sensitivity Analysis 3[c]	MWT Mean Sleep Latency	0.1313	< 0.0001	< 0.0001
	ESS Score	0.0283	< 0.0001	< 0.0001

[a] Missing data were imputed using LOCF.
[b] Missing data were imputed using the corresponding treatment group mean.
[c] Missing data were imputed using multiple imputation method by MCMC for non-monotone missing and regression method for monotone missing data within each treatment group.

For sensitivity analysis 4, the robustness of the JZP-110 response for improving wakefulness as measured by MWT mean sleep latency and ESS score was evaluated using the missing not at random method and applying progressively more stringent analysis criteria by subtracting an increasingly greater percentage of the treatment effect (K) which accounted for dropouts due to AE, lack of efficacy (LOE), and AE and LOE. For the change in MWT mean sleep latency, for all adjustments for treatment effect, treatment differences in the response and significance compared with placebo were maintained for the 150 and 300 mg JZP-110 groups. For ESS score, treatment differences in the response and significance compared with placebo were maintained after all adjustments for the 75, 150, and 300 mg JZP-110 dose groups.

Clinical Global Impression of Change (CGIc): Percentage of Subjects Improved

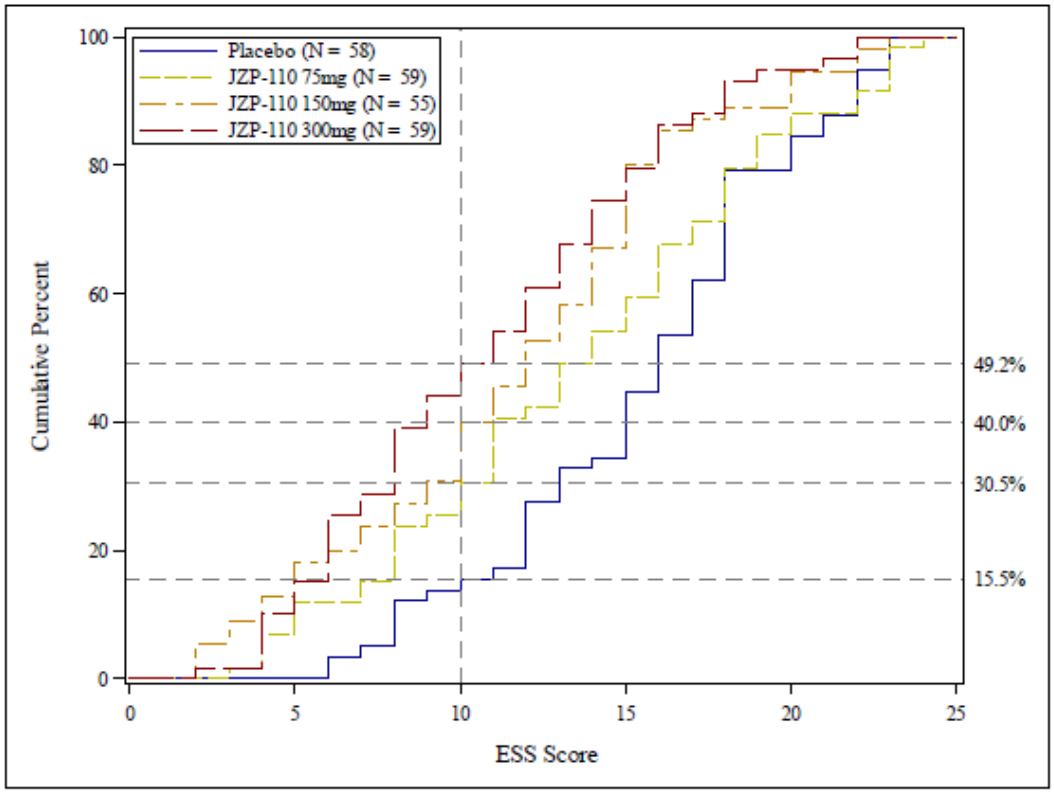
Numerical increases in the percentage of subjects with improvement from baseline on the CGIc at Weeks 1, 4, 8, and 12 were observed in the placebo group and in JZP-110 dose groups. At Week 12, subjects in all 4 treatment groups were improved on the CGIc, with 41.4% (less than half) of subjects in the placebo group reported to have overall improvement on the CGIc compared with 69.5%, 83.6%, and 83.1% in the 75, 150, and 300 mg JZP-110 groups, respectively. At Week 12, percentage differences of 28.1% (p = 0.0022), 42.3% (p <0.0001), and 41.7% (p <0.0001) were observed for the 75, 150, and 300 mg JZP-110 dose groups, respectively.

Post-hoc analysis

Magnitude of change on ESS

Additional post-hoc analyses evaluated the magnitude of change on the ESS to estimate the percentage of subjects with an ESS score ≤10 and the percentage of subjects with at least a 25% decrease from baseline in ESS score. At Week 12, results showed that treatment with solriamfetol increased the percentage of subjects who had an ESS score ≤ 10 in a dose-dependent manner; 15.5% of the subjects in the placebo group had an ESS score ≤ 10 vs. 30.5%, 40.0%, and 49.2% of subjects in the 75 mg, 150 mg, and 300 mg solriamfetol groups, respectively.

Figure 3: Cumulative Distribution for ESS at Week 12, Last Observation Carried Forward Approach (mITT Population)



Missing data are imputed using last observation carried forward approach (LOCF).

14-003: A 12-week, prospective, randomized, double-blind, placebo-controlled, parallel group study of solriamfetol 37.5, 75, 150, and 300 mg vs. placebo in subjects with OSA.

Methods

Study Participants

To be eligible for enrolment, subjects had to meet the following criteria:

1. Diagnosis of OSA according to ICSD-3 criteria.
2. Subject report (with clinician concurrence) of at least minimal use of a primary therapy for OSA or an attempt to use a primary therapy for OSA.
3. Subject report (with clinician concurrence) of a stable level of compliance with a primary OSA therapy for at least 1 month prior to Baseline.
4. Baseline ESS score ≥10.
5. Baseline mean sleep latency <30 minutes as documented by the mean of the first 4 trials of the MWT.
6. Usual nightly total sleep time of at least 6 hours.

7. Body mass index (BMI) from 18 to <45 kg/m^2.

Subjects were excluded if occupation required variable shift work, or the usual bedtime was later than 1 A.M. Further exclusion criteria in both studies were:

1. Excessive caffeine use 1 week prior to the Titration Phase or anticipated excessive use during the study defined as >600 mg/day of caffeine.
2. Use of any over-the-counter (OTC) or prescription medications that could affect the evaluation of excessive sleepiness within a time period prior to the Baseline Visit corresponding to at least 5 half-lives of the drug(s) or planned use of such drug(s) at some point throughout the duration of the study. Examples of excluded medications included OTC sleep aids or stimulants (e.g., pseudoephedrine), methylphenidate, amphetamines, modafinil, armodafinil, sodium oxybate, pemoline, trazodone, hypnotics, benzodiazepines, barbiturates, and opioids. Medications were to be discontinued such that the subject returned to his/her baseline level of daytime sleepiness at least 7 days prior to the Baseline visit, in the opinion of the Investigator.
3. History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria.
4. History or presence of any acutely unstable medical condition, behavioural or psychiatric disorder (including suicidal ideation).
5. Presence of significant cardiovascular disease including but not limited to: myocardial infarction within the past year, unstable angina pectoris, symptomatic congestive heart failure (American College of Cardiology/American Heart Association stage C or D), revascularization procedures within the past year, ventricular cardiac arrhythmias requiring an automatic implantable cardioverter defibrillator (AICD) or medication therapy, uncontrolled hypertension, systolic blood pressure ≥155 mmHg or diastolic blood pressure ≥95 mmHg (at screening, or consistently across Baseline measures according to protocol specifications), or any history of cardiovascular disease or any significant cardiovascular condition that in the investigator's opinion could jeopardize subject safety in the study.

Treatments; Outcomes/endpoints

The treatments, endpoints and statistical analyses were the same as for study 14-002. Stratification factor was different for 14-003.

Randomization

Stratified randomization on the basis of subjects' compliant or noncompliant use of their primary OSA therapy was used to assign subjects in a 1:1:2:2:2 ratio to receive JZP-110 37.5, 75, 150, or 300 mg or placebo over the 12-week Treatment phase.

Blinding

A double-blind approach was used during the Treatment Phase. All study drugs were prepared in identical opaque gelatin capsules to ensure adequate blinding, and all study personnel were blinded to the study treatments

Results

Participant flow

A total of 476 subjects were enrolled in the study and were randomized to receive 37.5, 75, 150, or 300 mg JZP-110 or placebo in a 1:1:2:2:2 ratio. Of these, 474 subjects received at least 1 dose of study medication and comprised the Safety Population; the majority of subjects randomized to receive placebo (84.9%) or a dose of JZP-110 (85.4%) completed the study.

Reasons for subject withdrawal from the study for the placebo group included: "other" (5.0%), adverse event (3.4%), withdrawal of consent (3.4%), and noncompliance with treatment (1.7%). For subjects randomized to a dose of JZP-110, reasons for subject withdrawal from study included: adverse event (7.3%), "other" (3.1%), withdrawal of consent (2.5%), lost to follow-up (0.8%), protocol violation (0.6%), and noncompliance with treatment (0.3%). Overall, a greater number and percentage of subjects in the 300 mg JZP-110 group (13.6%) relative to all other treatment groups did not complete the study due to 1 or more adverse events.

Baseline data

As concerns baseline demographics, about two thirds of recruited subjects were male (62.0% in interventional arms and 64.7% in Placebo arm) and the mean age of included subjects was between 52.7 to 57.1 years (range 20-75). Regarding BMI as a measure of obesity status, the mean BMI of recruited subjects ranged from 32.92 to 34.07 kg/m^2 across treatment arms. The portion of subjects compliant with primary OSA therapy is consistent across treatment arms (68.4-72.9% across treatment arms, 70.5% of overall safety population). Baseline CGIs evaluation categorized most subjects as moderately (~40%) or markedly ill (~30%). Overall, baseline disease characteristics were balanced between placebo and JZP-110 dose groups both in terms of disease severity (CGI-S, MWT, ESS) and primary OSA therapy use. Other co-morbidities related to OSA reported for at least 10% of patients included hypertension (48.7%), hyperlipidaemia (47.9%), gastroesophageal reflux disease (26.8%), diabetes mellitus (29.6%), depression (23.1%), obesity (12.7%), and anxiety (11.8%).

Table 12: Baseline Disease Characteristics (Safety Population)

Characteristic	Placebo N = 119	37.5 mg JZP-110 N = 58	75 mg JZP-110 N = 62	150 mg JZP-110 N = 117	300 mg JZP-110 N = 118	Combined JZP-110 N = 355
Baseline Mean MWT Sleep Latency Time (min), n	114	55	61	116	116	348
Mean (SD)	12.40 (7.193)	13.64 (8.085)	13.08 (7.240)	12.50 (7.165)	12.00 (7.347)	12.61 (7.381)
Median	10.81	12.88	12.25	11.63	10.63	11.50
Range	0.6, 29.5	1.4, 40.0	1.9, 29.4	1.1, 37.0	1.0, 29.6	1.0, 40.0
Baseline ESS Total Score, n	119	58	62	117	118	355
Mean (SD)	15.6 (3.30)	15.1 (3.48)	14.8 (3.53)	15.1 (3.37)	15.2 (3.13)	15.1 (3.33)
Median	15.0	15.0	14.0	15.0	15.0	15.0
Range	10, 24	10, 24	10, 23	10, 24	10, 23	10, 24
Primary OSA Therapy Use, n%						
Compliant	83 (69.7)	40 (69.0)	45 (72.6)	80 (68.4)	86 (72.9)	251 (70.7)
Noncompliant	36 (30.3)	18 (31.0)	17 (27.4)	37 (31.6)	32 (27.1)	104 (29.3)
Baseline CGIs, n (%)						
1 = Normal, not at all ill	0	0	0	0	0	0
2 = Borderline ill	3 (2.5)	1 (1.7)	1 (1.6)	2 (1.7)	1 (0.8)	5 (1.4)
3 = Mildly ill	8 (6.7)	5 (8.6)	4 (6.5)	7 (6.0)	10 (8.5)	26 (7.3)
4 = Moderately ill	48 (40.3)	28 (48.3)	31 (50.0)	53 (45.3)	44 (37.3)	156 (43.9)
5 = Markedly ill	39 (32.8)	14 (24.1)	15 (24.2)	41 (35.0)	44 (37.3)	114 (32.1)
6 = Severely ill	15 (12.6)	9 (15.5)	7 (11.3)	14 (12.0)	17 (14.4)	47 (13.2)
7 = Among the most extremely ill patients	4 (3.4)	1 (1.7)	3 (4.8)	0	2 (1.7)	6 (1.7)
Missing	2 (1.7)	0	1 (1.6)	0	0	1 (0.3)

Note: Percentages are based on N, number of subjects within each treatment group.
Mean sleep latency is the average sleep latency of the first 4 trials, or 3 of the first 4 trials if 1was missing. Higher scores indicate greater ability to stay awake.
ESS Total Score was defined as the sum of 8 item scores, if 6 or more of them were nonmissing. If 1 or 2 ESS items were missing at specific time point, the mean of the remaining 7 or 6 nonmissing ESS items at that time point was used to impute the missing ESS items. Higher scores indicate greater chance of dozing.
CGIs = Clinical Global Impression of Severity; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; OSA = Obstructive Sleep Apnea; SD = standard deviation.

Numbers analysed

Table 13: Number of Subjects in Each Analysis Population (All Enrolled Subjects)

Population, n (%)	Placebo N = 119	37.5 mg JZP-110 N = 59	75 mg JZP-110 N = 61	150 mg JZP-110 N = 118	300 mg JZP-110 N = 119	Combined JZP-110 N = 357	Total N = 476
Randomized Subjects	119	59	61	118	119	357	476
Safety Population	119 (100)	58 (98.3)[a]	62(101.6)[b]	117 (99.2)	118 (99.2)	355 (99.4)	474 (99.6)
mITT Population	114 (95.8)	56 (94.9)	58 (95.1)	116 (98.3)	115 (96.6)	345 (96.6)	459 (96.4)
If Excluded, Reason:							
Not in Safety Population	0	1 (1.7)	1 (1.6)	0	0	2 (0.6)	2 (0.4)
Did not have baseline or at least 1 post-baseline evaluation of MWT and ESS	5 (4.2)	2 (3.4)	2 (3.3)	2 (1.7)	4 (3.4)	10 (2.8)	15 (3.2)
PP Population	98 (82.4)	48 (81.4)	52 (85.2)	103 (87.3)	91 (76.5)	294 (82.4)	392 (82.4)
Did Not Complete the Study	18 (15.1)	10 (16.9)	7 (11.5)	12 (10.2)	25 (21.0)	54 (15.1)	72 (15.1)
Had a Major Protocol Violation	8 (6.7)	3 (5.1)	3 (4.9)	4 (3.4)	7 (5.9)	17 (4.8)	25 (5.3)
PK Population	0	56 (94.9)	57 (93.4)	115 (97.5)	115 (96.6)	343 (96.1)	343 (72.1)

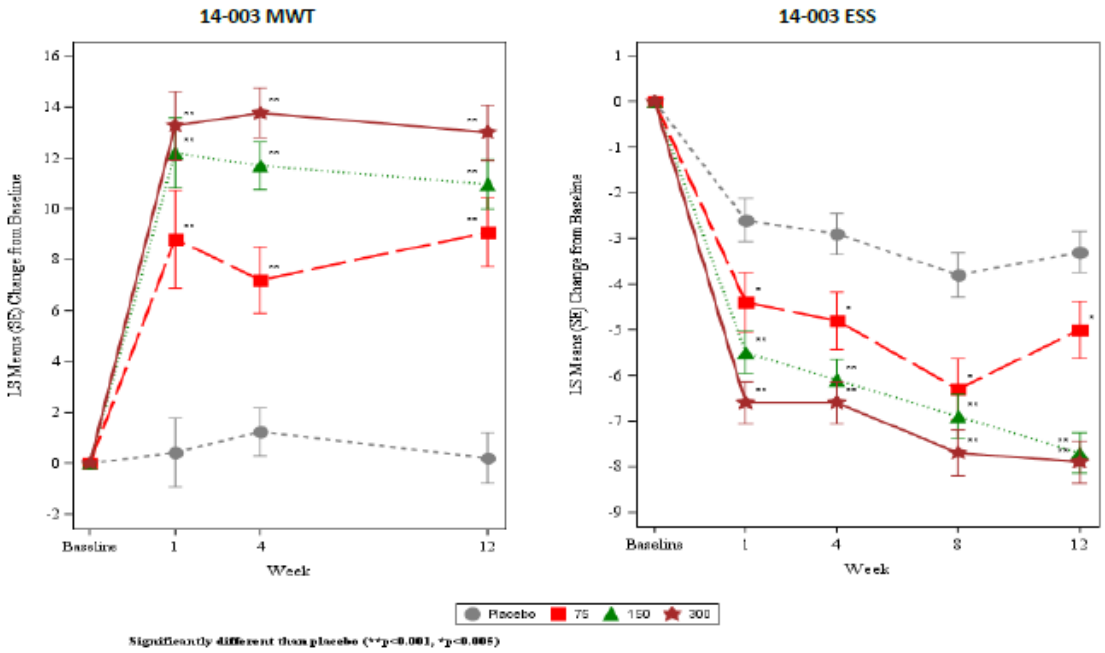
Outcomes and estimation

Co-primary and key secondary endpoints

Subjects who received solriamfetol demonstrated improvement in wakefulness, as measured by the MWT, and a reduction in EDS based on ESS scores (co-primary endpoints). At Week 12, subjects randomized to 75 mg, 150 mg, and 300 mg of solriamfetol demonstrated statistically significant improvement on the MWT, ESS, and PGIc scores compared with placebo. Subjects randomized to 37.5 mg solriamfetol showed significant improvement based on the MWT and ESS, but not on the PGIc. (Please refer to tabulated summary of efficacy results).

The magnitude of effect was dose-dependent, observed by Week 1, and maintained over the 12 weeks of treatment on both the MWT and ESS.

Figure 4: 14-003 Study: MWT and ESS Change from Baseline by Study Visit (Week) in Subjects with OSA



Source: CSR 14-003\Table 14.2.1.1.1; Table 14.2.2.1.1

Sensitivity analyses: Co-primary endpoints

The same set of sensitivity analyses as already undertaken for study 14-002 was also used in study 14-003. The results of sensitivity analyses 1, 2, and 3 were consistent with and supported the primary analyses, with increases observed from Baseline to Week 12 in MWT mean sleep latency (in minutes) and reductions in mean ESS Score for all JZP-110 dose groups compared with placebo.

Sensitivity analysis 4 assessed the robustness of the JZP-110 response for improving wakefulness as measured by the MWT mean sleep latency and mean ESS score using the missing not at random method and applying progressively more stringent analysis criteria by subtracting an increasingly greater percentage of the treatment effect (K) which accounted for dropouts due to AEs, lack of efficacy (LOE), and AEs or LOE. For the change in MWT mean sleep latency and for mean ESS score, treatment differences in the response were maintained compared with placebo after all adjustments were made for all 4 JZP-110 dose groups

Clinical Global Impression of Change (CGIc): Percentage of Subjects Improved

Consistent dose-related increases in the percentage of subjects with overall improvement on the CGIc were observed with JZP-110 treatment. At Week 12, approximately one half of placebo subjects (49.1%) were reported to have an overall improvement in their condition, whereas 58.9%, 70.7%, 90.5%, and 88.7% of subjects in each of the 37.5, 75, 150, and 300 mg JZP-110 dose groups, respectively, were reported with overall improvement on the CGIc.

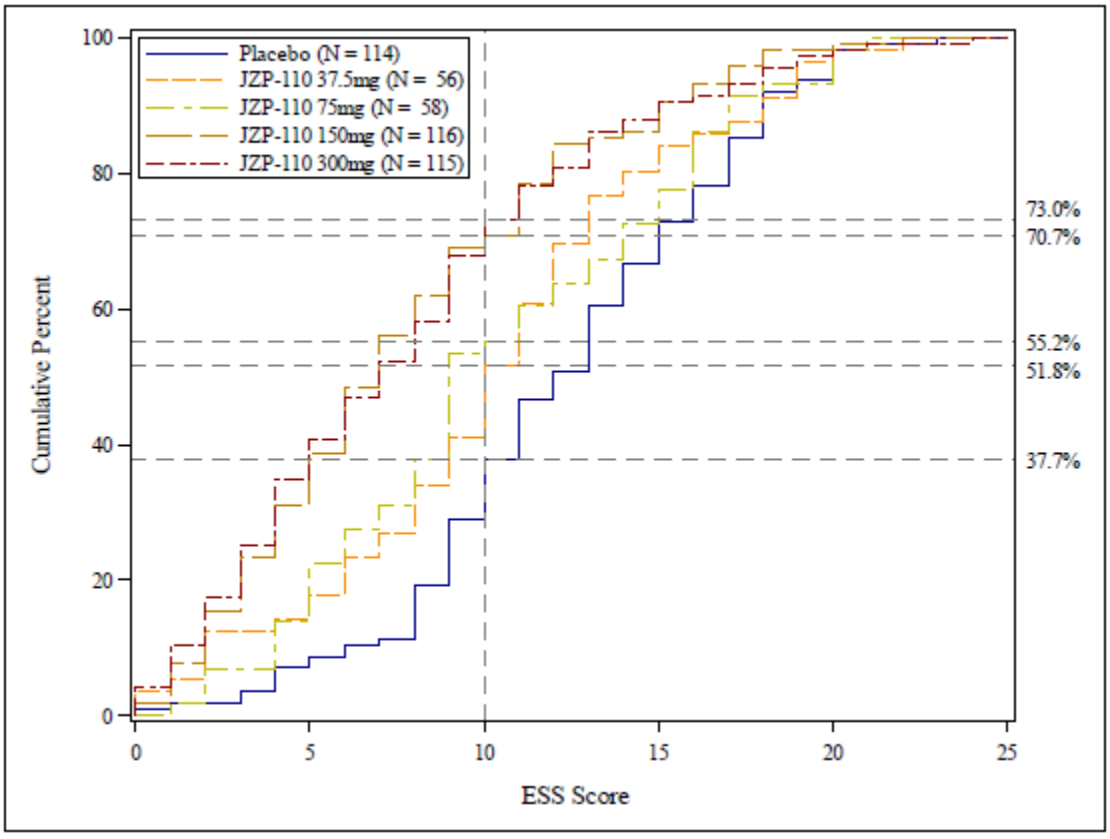
Percentage differences relative to placebo of 9.8% (p=0.2289), 21.6% (p=0.0070), 41.4% (p<0.0001), and 39.6% (p<0.0001) were observed for each of the 37.5, 75, 150, and 300 mg JZP-110 dose groups, respectively.

Post-hoc analysis

Magnitude of change on ESS

At Week 12, treatment with solriamfetol increased the percentage of subjects who reached an ESS score <10 in a dose-dependent manner (ie, 37.7% of the subjects in the placebo group vs. 51.8%, 55.2%, 70.7%, and 73.0% of subjects in the 37.5 mg, 75 mg, 150 mg, and 300 mg solriamfetol groups, respectively.

Figure 5: Cumulative Distribution for ESS at Week 12, Last Observation Carried Forward Approach (mITT Population)



Missing data are imputed using last observation carried forward approach (LOCF).

Of note, at Week 12 the mean ESS scores across all solriamfetol dose groups (37.5 mg: 9.7, 75 mg: 10.0, 150 mg: 7.5, 300 mg: 7.1) decreased to the commonly accepted definition of normal sleepiness (ie, ESS scores ≤ 10; Johns and Hocking, 1997).

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 14 Summary of Efficacy for trial 14-002

Title: A Twelve-Week, Double-Blind, Placebo-Controlled, Randomized, Parallel-Group, Multicentre Study of the Safety and Efficacy of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the Treatment of Excessive Sleepiness in Subjects with Narcolepsy			
Study identifier	14-002		
Design	Phase III, prospective, randomized, double-blind, 3 fixed dose arms of test drug, placebo-controlled, parallel group, pivotal, multicentre		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks of db treatment No run-in; screening within 1 month prior to randomization Option to enter 52-wk open label long term safety study 14-005; if not continuing, subjects returned at the end of wk-14 for a safety follow-up
Hypothesis	Superiority over placebo The primary objective of the study was to evaluate the efficacy of JZP-110 administered QD for up to 12 weeks in doses of 75, 150, and 300 mg compared with placebo in the treatment of EDS in adult subjects with narcolepsy. To address this objective, pairwise treatment differences between each of the 3 doses and placebo were tested.		
Treatments groups	JZP-110 75 mg QD		p.o. tablet over-encapsulated, 12-wk, n=59
	JZP-110 150 mg QD		p.o. tablet over-encapsulated, 12-wk, n=55
	JZP-110 300 mg QD		p.o. tablet over-encapsulated, 12-wk, n=59
	Placebo		p.o. capsules, identical to the test product, 12-wk, n=58
Endpoints and definitions	Co-Primary endpoints	MWT	Change in the mean sleep latency time (in minutes) as determined from the first 4 trials of a 40-minute MWT from Baseline to Week 12
		ESS	Change in ESS score from Baseline to Week 12
	Key Secondary endpoint	PGIc	Patient Global Impression of change (PGIc): Percentage of subjects reported as improved (minimally, much, or very much) on the PGIc at Week 12
	Other Secondary endpoints	Time course of efficacy on the MWT	Change in sleep latency time (in minutes) on each of the 5 MWT trials at Week 4 and Week 12
		CGIc	Clinical Global Impression of change: Percentage of subjects reported as improved (minimally, much, or very much) at Week 12
		MWT	Change in the mean sleep latency time (in minutes) as determined from the first 4 trials of a 40-minute MWT from Baseline to Week 4

		ESS	Change in ESS score from Baseline to Week 1, Week 4, and Week 8
		PGIc	Percentage of subjects reported as improved at Week 1, Week 4, and Week 8
		CGIc	Percentage of subjects reported as improved at Week 1, Week 4, and Week 8
Database lock	13 April 2017		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Co-primary endpoints were calculated as change from baseline to week 12 in the modified Intention-to-treat population (mITT) consisting of subjects who received at least 1 dose of study medication and had baseline and at least 1 post-baseline evaluation of MWT or ESS (total rand. N=239; mITT N=231)				
Descriptive statistics and effect estimate per comparison vs placebo Co-primary endpoints	Treatment group	Placebo	JZP-110 75 mg	JZP-110 150 mg	JZP-110 300 mg
	Number of subject	N=58	N=59	N=55	N=59
	Change in **MWT** from baseline to week 12 LS Mean (SE)	2.12 (1.289)	4.74 (1.335)	9.77 (1.327)	12.27 (1.389)
	LS Mean Difference	N/A	2.62	7.65	10.14
	95% CI	N/A	-1.04, 6.28	3.99, 11.31	6.39, 13.90
	P-value	N/A	0.1595	**<0.0001**	**<0.0001**
	Change in **ESS** score from baseline to week 12 LS Mean (SE)	-1.6 (0.65)	-3.8 (0.67)	-5.4 (0.66)	-6.4 (0.68)
	LS Mean Difference	N/A	-2.2	-3.8	-4.7
	95% CI	N/A	-4.0, -0.3	-5.6, -2.0	-6.6, -2.9
	p-value	N/A	**0.0211**	**<0.0001**	**<0.0001**
Key secondary endpoint					
	PGIc: Subjects reported improved at week 12				

	Yes (%)	23 (39.7)	40 (67.8)	43 (78.2)	50 (84.7)
	No (%)	35 (60.3)	19 (32.2)	12 (21.8)	9 (15.3)
	Percentage Difference (Yes) from placebo	N/A	28.1	38.5	45.1
	95% CI	N/A	10.80, 45,48	21.86, 55.19	29.51, 60.67
	p-value	N/A	0.0023[a]	**<0.0001**	**<0.0001**
Notes	Note: P-value for MWT and ESS are based on MMRM with change from baseline as response variable and fixed effect of treatment, visit, treatment by visit, randomization factor, and covariate of baseline value. P-value of PGIc is based on Chi-square test. Percentage of subjects reported improved on PGIc is based on n, the number of subjects with non-missing value at Week 12. [a] This is a nominal p-value as 75 mg solriamfetol group was below the hierarchical break.				
Analysis description	**Secondary analysis** Please refer to respective sections in the AR				

Table 15: Summary of efficacy for trial 14-003

Title: A Twelve-Week, Double-Blind, Placebo-Controlled, Randomized, Parallel-Group, Multicentre Study of the Safety and Efficacy of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the Treatment of Excessive Sleepiness in Subjects with Obstructive Sleep Apnea (OSA).		
Study identifier	14-003	
Design	Phase III, prospective, randomized, double-blind, 4 fixed dose arms of test drug, placebo-controlled, parallel group, pivotal, multicentre	
	Duration of main phase:	12 weeks of db treatment
	Duration of Run-in phase:	No run-in; screening within 1 month prior to randomization
	Duration of Extension phase:	Option to enter 52-wk open label long term safety study 14-005; if not continuing, subjects returned at the end of wk-14 for a safety follow-up
Hypothesis	Superiority over placebo The primary objective of the study was to evaluate the efficacy of JZP-110 administered QD for up to 12 weeks in doses of 37.5, 75, 150, and 300 mg compared with placebo in the treatment of excessive sleepiness in adult subjects with OSA. To address this objective, pairwise treatment differences between each of the 4 doses and placebo was tested.	
Treatments groups	placebo	p.o. capsules, identical to the test product, 12-wk, n=114

	JZP-110 37.5 mg QD		p.o. tablet over-encapsulated, 12-wk, n=56
	JZP-110 75 mg QD		p.o. tablet over-encapsulated, 12-wk, n=58
	JZP-110 150 mg QD		p.o. tablet over-encapsulated, 12-wk, n=116
	JZP-110 300 mg QD		p.o. tablet over-encapsulated, 12-wk, n=115
Endpoints and definitions	Co-Primary endpoints	MWT	Change in the mean sleep latency time (in minutes) as determined from the first 4 trials of a 40-minute MWT from Baseline to Week 12
		ESS	Change in ESS score from Baseline to Week 12
	Key Secondary endpoint	PGIc	Patient Global Impression of change (PGIc): Percentage of subjects reported as improved (minimally, much, or very much) on the PGIc at Week 12
	Other Secondary endpoints	Time course of efficacy on the MWT	Change in sleep latency time (in minutes) on each of the 5 MWT trials at Week 4 and Week 12
		CGIc	Clinical Global Impression of change: Percentage of subjects reported as improved (minimally, much, or very much) at Week 12
		MWT	Change in the mean sleep latency time (in minutes) as determined from the first 4 trials of a 40-minute MWT from Baseline to Week 4
		ESS	Change in ESS score from Baseline to Week 1, Week 4, and Week 8
		PGIc	Percentage of subjects reported as improved at Week 1, Week 4, and Week 8
		CGIc	Percentage of subjects reported as improved at Week 1, Week 4, and Week 8
Database lock	03 March 2017		

Results and Analysis

Analysis description	**Primary Analysis**					
Analysis population and time point description	Co-primary endpoints were calculated as change from baseline to week 12 in the modified Intention-to-treat population (mITT) consisting of subjects who received at least 1 dose of study medication and had baseline and at least 1 post-baseline evaluation of MWT or ESS (total rand. N=476; mITT N=459). A total of 476 subjects were enrolled in the study and were randomized to receive 37.5, 75, 150, or 300 mg JZP-110 or placebo in a 1:1:2:2:2 ratio.					
Descriptive statistics and effect estimate per comparison	Treatment group	Placebo	JZP-110 37.5 mg	JZP-110 75 mg	JZP-110 150 mg	JZP-110 300 mg
	Number of subject	N=114	N=56	N=58	N=116	N=115

vs placebo Co-primary endpoints	Change in **MWT** from baseline to week 12 LS Mean (SE)	0.21 (0.997)	4.74 (1.418)	9.08 (1.358)	10.96 (0.973)	12.99 (1.038)
	LS Mean Difference	N/A	4.53	8.87	10.74	12.77
	95% CI	N/A	1.16, 7.90	5.59, 12.14	8.05, 13.44	10.00, 15.55
	P-value	N/A	**0.0086**	**<0.0001**	**<0.0001**	**<0.0001**
	Change in **ESS** score from baseline to week 12 LS Mean (SE)	-3.3 (0.45)	-5.1 (0.64)	-5.0 (0.62)	-7.7 (0.44)	-7.9 (0.46)
	LS Mean Difference	N/A	-1.9	-1.7	-4.5	-4.7
	95% CI	N/A	-3.4, -0.3	-3.2, -0.2	-5.7, -3.2	-5.9, -3.4
	p-value	N/A	**0.0161**	**0.0233**	**<0.0001**	**<0.0001**
Key secondary endpoint	**PGIc**: Subjects reported improved at week 12					
	Yes (%)	56 (49.1)	31 (55.4)	42 (72.4)	104 (89.7)	102 (88.7)
	No (%)	58 (50.9)	25 (44.6)	16 (27.6)	12 (10.3)	13 (11.3)
	% Difference from placebo (Yes)	N/A	6.2	23.3	40.5	39.6
	95% CI	N/A	-9.69, 22.16	8.58, 38,01	29.81, 51.25	28.72, 50.42
	p-value	N/A	0.4447	**0.0035**	**<0.0001**	**<0.0001**

Notes	Note: P-value for MWT and ESS are based on MMRM model with change from baseline as response variable and fixed effect of treatment, visit, treatment-by-visit, randomization factor, and covariate of baseline value. P-value of PGIc is based on Chi-square test. Percentage of subjects reported improved on PGIc is based on n, the number of subjects with non-missing value at Week 12.
Analysis description	**Secondary analysis** Please refer to respective sections in the AR

Supportive studies

Apart from the two 12-week phase III studies 14-002 and 14-003, data on randomized withdrawal are additionally obtained from phase III, 6-week randomized withdrawal study 14-004 in OSA patients and long-term extension study 14-005, which recruited combined narcolepsy and OSA patient populations from previous phase II and phase III studies.

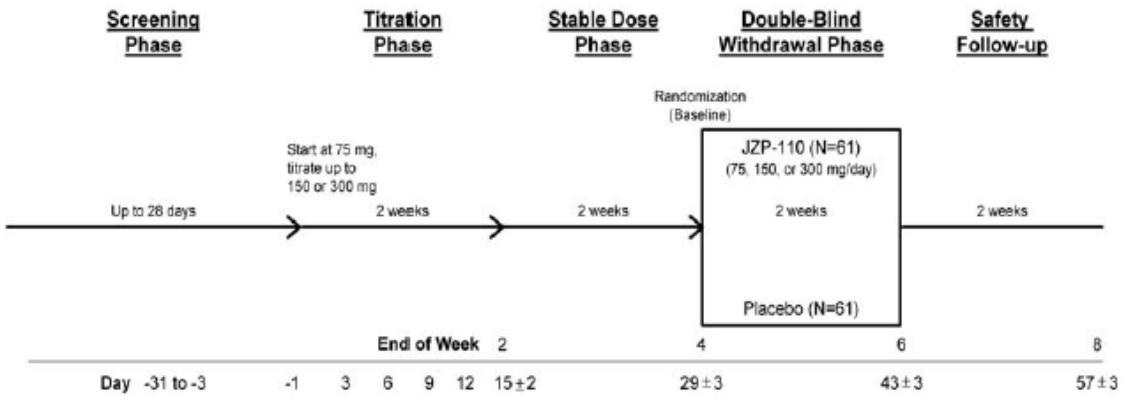
Study 14-004

Study 14-004 was a 6-week, double-blind, placebo-controlled, randomized-withdrawal study of the safety and efficacy of solriamfetol for the treatment of EDS in adult subjects with OSA. A total of 174 subjects were enrolled at 34 study centres (25 in the United States and 9 in Europe).

The study comprised a Screening, Titration, Stable-dose, Double-bind Withdrawal, and a Safety Follow-up Phase. After completion of Screening, subjects entered the 2-week open-label Titration Phase. Dosing started at 75 mg once daily and was titrated up 1 dose level every 3 days to 150 mg/day or a maximum dose of 300 mg/day. Subjects could also titrate down to 75 mg or 150 mg at any time following consultation with investigative site staff. Subjects who were titrated to an efficacious and tolerable dose in the Titration Phase then entered the 2-week open-label Stable-dose Phase and remained on the same dose regimen.

At Week 4, subjects, who reported "much" or "very much" improvement on the PGIc and showed a numerical improvement in MWT and ESS from the beginning of titration, were entered into the Double-blind Withdrawal Phase and were randomized to continue solriamfetol at the dose received in the Stable-dose Phase or to receive placebo for 2 weeks.

Figure 6: Study Schema

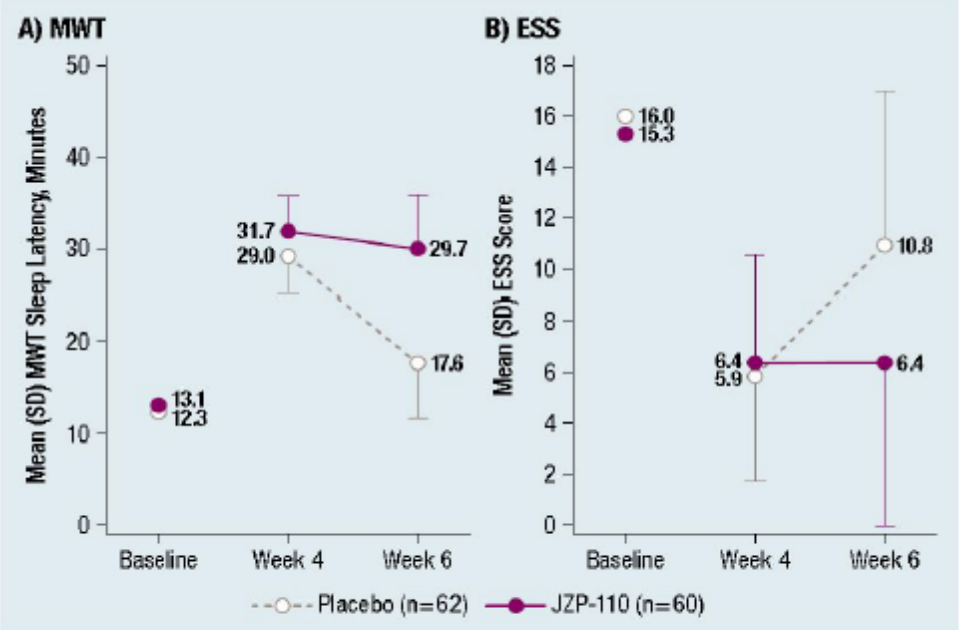


The co-primary efficacy endpoints for the study were change in the mean sleep latency time (MWT, in minutes) and ESS as determined from the end of the Stable-Dose phase (Week 4) to the end of the Double-Blind Withdrawal phase (Week 6).

During the Double-Blind Withdrawal Phase (from wk 4 to wk 6), subjects who continued to receive JZP-110 remained improved on the MWT, whereas subjects who were switched to placebo worsened. The difference was statistically significant in favor of the active treatment group (p<0.0001).

At Week 6 the mean ESS score (SE) increased by 4.5 (0.71) for the Placebo group, compared with a mean decrease of -0.1 (0.73) for those who stayed on JZP-110, resulting in a statistically significant LS mean difference of -4.6 (95% CI: -6.4, -2.8) in favor of the JZP-110 group (p<0.0001).

Figure 7: MWT and ESS values for Subjects Who Entered the Double-Blind Withdrawal Phase (mITT Population)



Values are modified intent-to-treat population (n=122).
ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness Test.

Study 14-005

This was a long-term phase III study of JZP-110 combining narcoleptic and OSA subjects who had completed Study 14-002, 14-003, 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202. The objectives of this study were 2-fold, i.e. to assess the maintenance of efficacy of JZP-110 during the double-blind, placebo-controlled portion of the study and to assess the long-term safety and maintenance of efficacy of JZP-110.

Subjects from the 12-week Studies 14-002 and 14-003 rolled directly into this study on completion of the previous study and were designated Group A. As these subjects already had 12 weeks of treatment, and had no disruption in treatment, their duration on this study was approximately 40 weeks to obtain 52 weeks of treatment. Subjects from the other studies did not roll directly over from prior studies were designated Group B; their duration on this study was approximately 52 weeks.

During the maintenance phase, a 2-week randomized withdrawal period was conducted, from Weeks 27 to 29 for Group A and from Weeks 26 to 28 for Group B. At the beginning of the randomized withdrawal period, subjects were assigned in a 1:1 ratio to continue to receive JZP-110 at the dose they were currently receiving or to receive placebo for 2 weeks. At the end of that period, subjects who had received placebo resumed treatment

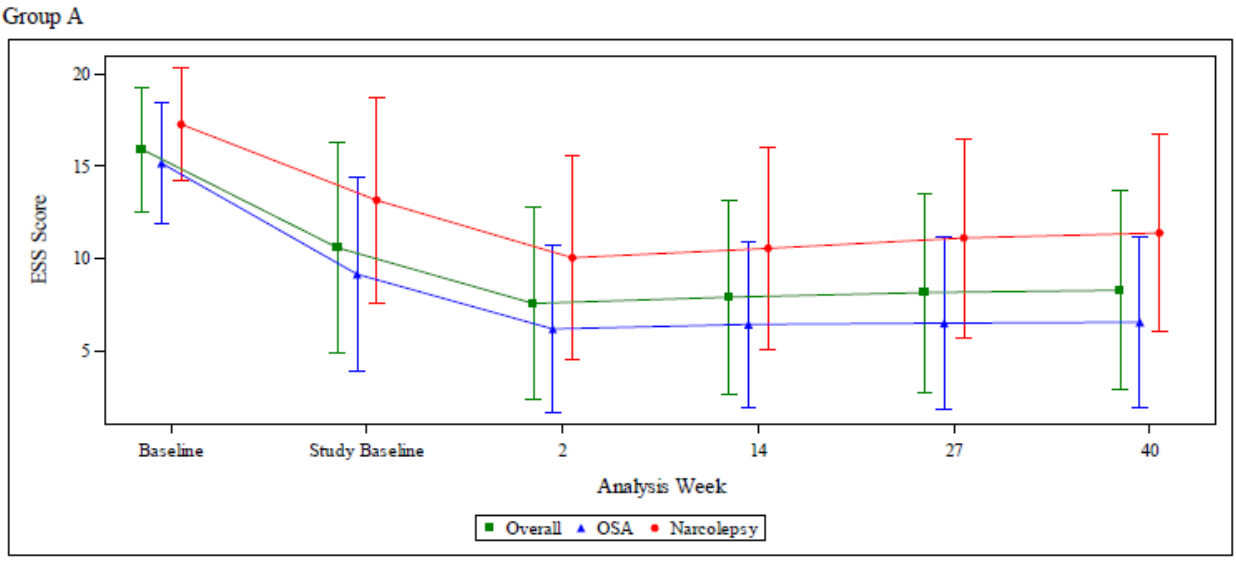
with 75 mg of JZP-110. Subjects who had been receiving the 150 mg/day received 75 mg/day for the first 3 days, followed by 150 mg/day thereafter. Subjects who had been receiving 300 mg/day received 150 mg/day for the first 3 days, followed by 300 mg/day thereafter.

The majority of subjects in the Safety Population were enrolled after completing either Study 14-003 (n = 333) or Study14-002 (n = 186). Hence, majority of subjects treated in this study were in Group A (521 enrolled and 519 treated of 645). Fewer than 100 subjects were enrolled from each of the other parent studies.

Primary efficacy endpoint was the change in ESS score from the beginning to the end of the 2-week randomized withdrawal period.

At the beginning of the randomized withdrawal period (ie, efficacy baseline), mean ESS scores were similar for both the placebo and JZP-110 groups (7.8 vs. 7.3, respectively). At the end of the 2-week randomized withdrawal period, the placebo group had a greater mean ESS score than the JZP-110 group (12.6 vs. 8.5, respectively), which indicated greater sleepiness in the placebo group. The resulting LS mean difference (JZP-110 - placebo) of -3.7 was statistically significant (p <0.0001). Similar results were seen both for subjects with OSA and subjects with narcolepsy.

Figure 8: ESS Score over Time (± SD) in the Open-label period Overall and by Indication, Safety Population



In the overall Safety Population, mean ESS scores were 15.9 for both Group A and Group B at baseline of the parent or current study, respectively. At Week 2, mean ESS scores were 7.6 for Group A and 7.8 for Group B, and this improvement (ie, decrease in mean ESS scores) was maintained for the duration of the study. In the overall study population, mean ESS scores for the combined JZP-110 group were below 10 (ie, the threshold for normal levels of sleepiness as defined by Johns [1991]) at all visits starting at Week 2 and for the remainder of the open-label period.

Mean values and decreases from baseline for subjects with OSA were similar to those observed for the overall study population. Similar to the overall study population, mean ESS scores post baseline were less than 10 for subjects with OSA for the combined JZP-110 group.

Subjects with narcolepsy had higher ESS scores at baseline than subjects with OSA. For subjects with narcolepsy, the magnitude of change at each post-baseline visit (ie, decrease from baseline to each visit) was similar to that observed for the overall patient population and in subjects with OSA. Mean ESS scores generally remained below or slightly above 10 post-baseline for subjects with narcolepsy for the combined JZP-110 group.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Target population

The narcolepsy and OSA target population was adequately chosen based on standard diagnostic criteria (ICSD-3). The baseline requirements in terms of disease severity (ESS $\geq$ 10, representing higher normal daytime sleepiness) were on the low side, however, the ESS score of actually recruited subjects was considerably higher (ESS 16.9 to 17.1 in study 14-002 resp. ESS 14.8 to 15.6 across dose arms in study 14-003). Equally, the inclusion criterion regarding sleep latency (first 4 trials of MWT) at screening was very low, i.e. requiring sleep latency < 25 min (14-002) or < 30 min (14-003, 14-004). MWT values higher than 19.4 min are considered as normal (healthy) wakefulness (Doghramji et al. 1997). Observed MWT at baseline of 12-13 (in OSA, 14-003) resp. 6-8 (narcolepsy, 14-002), however, point to more severe disease states of study participants. Baseline assessment of disease severity (CGI-S) revealed that the majority of subjects was categorized as *5=markedly ill* (14-002) resp. *4=moderately ill* (14-003).

The exclusion criteria are acceptable. As regards the CV risk profile of included OSA patients, it is noted that there were several exclusion criteria, mainly excluding those with acutely unstable conditions or presence of significant cardiovascular disease including but not limited to: myocardial infarction within the past year, unstable angina pectoris, uncontrolled hypertension, systolic blood pressure ≥155 mmHg or diastolic blood pressure ≥95 mmHg and others.

Any other medication used to counteract EDS was prohibited throughout the trials and was washed out. The mode of action of solriamfetol (claimed selective DA / NE reuptake inhibitor) is typical for antidepressants. The exclusion of bipolar disorder resp. schizophrenic patients is therefore justified. The same applies to subjects with a history of suicidal ideation.

Baseline Narcolepsy (14-002)

Analysis of patients' baseline characteristics in study 14-002 does not reveal relevant differences across study arms. Disease severity in terms of ESS (16.9 -17.3 min), MSLT (6.14 – 8.73 min) is in the same order of magnitude as compared to previous MAAs in narcolepsy and demonstrate an adequately chosen patient population. About every second subject presents with cataplectic events.

As concerns baseline demographics, about two thirds of recruited subjects were female (65.3%), while according to literature reviews there are no differences in rates of narcolepsy among men and women (Bhattarai J et al. 2017). The mean age of included subjects was around 36 years (range 18-70) reflecting the predominantly young target population. Although narcolepsy can have an onset at any age, for most individuals, narcolepsy symptoms present in the first two decades of life, typically prior to 25. It often remains undiagnosed until many years after initial symptom onset (Thorpy MJ et al. 2015). Around 25% of subjects presented with a history of depression, a condition which might also be favourably influenced by the treatment with solriamfetol due to its pharmacological mode of action. The percentage of subjects with a medical history of depression was

about equal across treatment arms, hence, it is not expected to bias the study outcome. While subjects with moderate or severe obstructive sleep apnoea were excluded from study participation, subjects reporting mild sleep apnoea syndrome were allowed. The portion of included subjects with mild OSAS was similar across dose arms: 9/59 (15.3%) in the placebo arm, 11/59 (18.6%) for 75 mg, 15/59 (25.4%) for 150 mg and 7/59 (11.9%) in the 300 mg arm. A consistent dose-dependent response was observed for the co-primary ESS endpoint (change from baseline to wk-12: placebo -1.6, 75 mg -3.8, 150 mg -5.4, 300 mg -6.4). There remains a potential that part of the reduction in EDS may reflect improvement of co-morbid mild OSAS. It would have been preferable to completely exclude co-morbid OSAS in the narcolepsy study. Although a partial impact of co-morbid mild OSAS on the ESS reduction cannot be excluded with certainty, inclusion of a portion of subjects with co-morbid OSAS in the narcolepsy study does not principally question validity of obtained results for the co-primary ESS endpoint.

Baseline OSA (14-003)

Disease severity in terms of ESS (14.8 -15.6 min) and MWT-MSLT (12.00 – 13.64 min) is less pronounced as compared to the narcolepsy population of study 14-002. Recruited subjects were stratified on the basis of compliant or noncompliant use of a primary OSA therapy. Compliant use of a primary OSA therapy was defined as PAP use of ≥4 hours per night on ≥70% of nights (≥5 of 7 nights/week), historical report (with investigator concurrence) of use of an oral appliance on ≥70% of nights (≥5 of 7 nights/week), or receipt of an effective surgical intervention for OSA symptoms. Compliance with primary OSA therapy use, which was allowed to be continued throughout the study, was recorded for 70.5% (334/474) of OSA patients.

About two thirds of recruited subjects were male (62.7%). The mean age of included subjects was between 52.7 to 57.1 years (range 20-75) reflecting the OSA target population. According to literature (Malhotra A et al. 2002 The Lancet. Obstructive sleep apnoea), obesity, male sex, and increasing age were identified as risk factors for OSA. Obesity is considered the most important, estimated to be present in about 70% of affected subjects. The mean BMI of recruited subjects ranged from 32.92 to 34.07 kg/m^2 across treatment arms reflecting obesity of the study population. The OSA population is typically presenting with a number of co-morbidities, with hypertension being one of the most significant. This is reflected by the medical history of included subjects: hypertension is present in 44.9-58.6% of subjects across the five study arms. Importantly, the portion of subjects compliant with primary OSA therapy is consistent across treatment arms (68.4-72.9% across treatment arms, 70.5% of overall safety population).

Choice of Co-Primary Efficacy Endpoints

Two co-primary efficacy endpoints were chosen (MWT, ESS), both are standard validated parameters to assess ability to maintain wakefulness resp. the degree of excessive sleepiness and were used in previous MAAs. Both are tested independently for superiority over placebo per dose arm.

The ESS score reflects the patient's self-assessment, i.e. the self-evaluated patient's propensity to fall asleep in eight every-day situations (0 = would never doze, 1 = slight chance of dozing, 2 = moderate chance of dozing, 3 = high chance of dozing, worst possible score is 24). Hence, ESS is a subjective measure.

On the contrary, during the maintenance of wakefulness test (MWT) the onset of sleep is recorded by PSG (EEG), i.e. the MWT is an objective measure. For MWT testing (five sessions per day, each of a maximum duration of 40 min, separated by 2-hr intervals during which the patient has to stay awake), the subject is placed under soporific conditions (i.e. in a semi-recumbent position in a darkened room) and is instructed to stay awake as long as possible. The combination of subjective and objective measures as co-primary efficacy endpoints is considered to adequately reflect the treatment outcome.

Statistical analysis

In both pivotal studies, the primary analysis used a MMRM as analysis method. The factors included in the model are considered appropriate, as also the stratification factors used for randomisation were included. Methods for secondary and exploratory analyses are generally acceptable.

Missing data is an issue in both studies, as the number of study withdrawals was in a relevant range. For overall withdrawals in all study arms combined, there were 14.6% missing in Study14-003 and 19.2% missing in Study 14-002. Most withdrawals occurred in the dose arm with the highest dose in both studies with adverse events as an important reason for drop out in both studies, while numbers for withdrawals due to lack of efficacy were very different in both studies (none in Study14-003 and 10.2% at maximum in the highest dose arm in Study 14-002).

For the primary analysis, missing data were handled by the implicit completion of measurement profiles by the MMRM method and no explicit imputations were performed. The Applicant addressed the missing data issue with sensitivity analyses. Two single imputation methods were used, applying LOCF and a mean imputation approach. Single imputation methods are not endorsed, as usually the variability of the effect estimates is underestimated, and a bias cannot be excluded in depending on dropout patterns. Alternatively, multiple imputation methods were used to handle missing observations. Thereof, the pattern mixture approach is the most relevant of the sensitivity analyses performed. For this, a tipping point analysis was applied for three scenarios with data assumed to be missing not at random if patients withdrew due to lack of efficacy (scenario 1), adverse events (scenario 2) or due to both (scenario 3). Scenario 3 is considered the most appropriate. It is therefore reassuring that even in extreme realisations of the delta method for the tipping point analysis in scenario 3 (subtracting increasing proportions of the treatment effect), conclusions on statistical significance with very low p-values are not changed for all doses in Study 14-003 and except for the lowest dose strength in Study 14-002.

With regard to general design features (choice of target population, study duration, choice of endpoints and statistical analysis, parallel group placebo control) there are no major objections. It is noted, however, that for studies 14-002 and 14-003 subjects were assigned to fixed dose arms. In clinical practice, subjects beginning solriamfetol therapy are proposed to titrate according to clinical response starting with the 75 mg dose. Data on titration are obtained from 6-week randomized withdrawal study 14-004 and long-term extension study 14-005.

Efficacy data and additional analyses

Participants flow

In narcoleptic patients of study 14-002, the overall rate of study completion was high ranging from 88.1% in the placebo arm to 72.8% in the 300 mg highest dose arm. Contrary to expectations, however, "lack of efficacy" given as reason for withdrawal was lowest in the placebo arm (n=1, 1.7%) and highest in the 300 mg highest dose arm (n=6, 10.2%). This finding remains hard to explain. On the other side, there is clear dose-dependent increase in the number of subjects withdrawing for AEs from placebo (1.7%) to the 300 mg dose (8.5%). A potential overlap in the subject's perception between "lack of efficacy" and "AE", when the reason for withdrawal is defined, could be assumed to explain the unexpected finding.

Also in OSA patients of study 14-003, the rate of study completion was high, ranging from 90.6% in the JZP 150 mg dose arm to 79.7% in the 300 mg highest dose arm. In none of the study arms (incl. placebo), "lack of efficacy" was given as reason for withdrawal in any one subject. A possible explanation could be that throughout

the study subjects could continue to use their positive airway pressure (PAP) oxygen therapy, which guarantees the current maintenance of standard of care level. As concerns "withdrawal due to AE", the rate was clearly highest in the highest 300 mg dose arm (13.6%) vs 3.4% for placebo and 4.3% in the second highest 150 mg dose arm.

Less than 10% of subjects recruited for phase III studies 14-002 and 14-003 were European, the vast majority of recruited patients were North American. Therefore, any comparison between the subgroups by region is cautioned. However, both sub-populations were largely similar in terms of baseline disease characteristics (both for narcolepsy and OSA). Subgroups by region were examined as extrinsic factors for efficacy outcome. As far as can be concluded given the disparity in subgroup size, the response to solriamfetol treatment was similar between groups for both conditions.

Efficacy outcome in narcolepsy study 14-002

For the co-primary MWT (change from baseline) efficacy endpoint a clear dose-dependent effect was observed delivering highly significant ($p < 0.0001$) superiority over placebo for the 150 mg and 300 mg dose arm. In both arms patients achieved maintenance of wakefulness more than twice as long as compared to baseline (150 mg: from 7.85 min at baseline to 17.67 min at week 12; 300 mg: from 8.73 min at baseline to 19.91 min at week 12 [means]). Also, for the lowest JZP 75 mg dose arm, maintained wakefulness improved, however, the change from baseline does not significantly separate from placebo (change from baseline [min]: placebo 2.12, JZP 75 mg: 4.74 [-1.04, 6.28; p=0.1595]).

Also, for the co-primary ESS (change from baseline) efficacy endpoint again a dose-related effect was observed delivering significant (75 mg: p=0.02) or highly significant ($p < 0.0001$) superiority over placebo for the 150 mg and 300 mg dose arm. In absolute figures, the decline in subjective, self-assessed propensity to fall asleep in typical everyday situations was superior over placebo particularly for the 150 mg and 300 mg dose arm for which ESS score could be reduced to about 11 corresponding to mild EDS (150mg: from 17.0 ESS score at baseline to 11.5 ESS score at week 12; 300mg from 17.2 ESS score at baseline to 11.1 ESS score at week 12.)The clinical relevance of the achieved difference (in ESS) over placebo was further characterized by the post-hoc calculated responder analysis of subjects achieving an ESS score of $\leq$ 10, which is cut-off value from higher normal DS to mild EDS. The cumulative distribution for ESS demonstrates that only 15.5% of placebo patients achieved an ESS score $\leq$ 10. The proportion of subjects with ESS scores equal to or below 10 increased across JZP arms in a dose-dependent manner. It was doubled in the 75 mg dose arm (30.5%) and more than tripled for the highest 300 mg dose (49.2%). The cumulative distribution curves support concluding on a relevant dose dependent separation from the placebo response across a large range of response thresholds and point to clinically relevant improvement of EDS in narcoleptic patients.

For both primary efficacy endpoints, the main effect is achieved within the first week of treatment. Thereafter the effect is maintained in a dose-related manner over the entire 12-week treatment period.

The study outcome in terms of the key secondary PGIc endpoint went along with the results for the MWT and ESS co-primary endpoints. The percentage of subjects reporting clinical improvement (minimal, much or very much) was highly significantly higher for the 150 mg and 300 mg dose arm, while the lowest 75 mg dose arm does not significantly separate from placebo (p=0.0023 only nominal, since the 75 mg solriamfetol group was in a position in the hierarchy below a non-significant test). The results obtained for the patient-assessed PGIc key secondary endpoint were also reflected by the investigator-assessed CGIc endpoint.

A post-hoc analysis was conducted to assess the correlation between PGIc and ESS in subjects treated with solriamfetol (all doses). A reasonable degree of congruence between the ESS primary endpoint and the PGIc key secondary endpoint could be shown.

For all three sensitivity analyses (SA1: ANCOVA-LOCF, SA2: ANCOVA-imputation of means of corresponding treatment group, SA3: MMRM-MI) the results for the 150 mg and 300 mg JZP dose arms remained highly significant. Also, for the 75 mg dose arm the results obtained using the primary statistical analysis method were largely reproduced, delivering non-significant results for MWT (exception for SA2: p=0.0413) and significant results for the ESS co-primary endpoint. Sensitivity analysis 4, considered the most relevant, delivered highly significant results for both the 150 mg and 300 mg dose arm for both co-primary endpoints even if the maximum 100% k-value is subtracted from the treatment effect. Equally, results for ESS remained significant for the 75 mg lowest dose arm.

MWT testing was performed at baseline, at the week 4 visit and at week 12 or study discontinuation. Prior to MWT testing the subject has to stay overnight at the study centre. MWT testing is time-consuming, it spans over approximately 9 hours post-administration since the five testing sessions (up to 40 min duration per session) are separated by 2-hours intervals. Looking separately at the 5 consecutive testing sessions per day, for the 150 mg and 300 mg dose arm the difference over placebo remains significant for each of the five sessions. There is no clear sign for a declining effect over the course of the testing day. On the other hand, for the 75 mg dose arm, for which placebo superiority in terms of the primary MWT endpoint (mean of the first 4 trials) could not be shown, did neither significantly separate from placebo at any of the five sessions per testing day. Solriamfetol is proposed to be administered once daily upon awakening in the morning. Time course of efficacy on MWT data as obtained from study 14-002 support the proposed posology.

Narcoleptic patients were stratified for presence resp. absence of cataplexy. About half of the subjects of the mITT (117/231, 50.6%) population presented with cataplectic events. In absolute figures, the clinical effect in terms of MWT change from baseline was more pronounced in subjects without cataplexy. However, there was no difference between the two subgroups as regards statistical comparison with placebo for MWT, ESS and the PGIc key secondary endpoint.

Based on subjects' cataplectic diary entries, the number of cataplectic events was recorded in an exploratory way. Interpretation of results is complicated due to differences in the mean number of weekly cataplectic attacks across treatment arms during the baseline period (mean number of cataplectic attacks at baseline: placebo 13.0, JZP 75 mg 18.4, JZP 150 mg 12.5, JZP 300 mg 9.4,). There was a tendency observable of a decline in the mean number of weekly cataplectic events over the course of the 12-wk treatment period in the placebo, JZP 75 mg and JZP 150 mg dose arm, but not in the 300 mg dose group. Overall, there was no consistent pattern across dose arms. It is therefore rather unlikely that there is a clear positive impact of solriamfetol on the cataplectic attack frequency. On the other hand, there is no signal that cataplexy may be negatively influenced by solriamfetol treatment.

Apart from EDS, cataplexy is the second commonest symptom of narcolepsy and the most specific one (Billiard M et al. 2006 EFNS Guidelines on management of narcolepsy). The exploratory data on solriamfetol's (non)-influence on cataplectic event frequency points to adequacy of the Applicant's clinical development plan to focus on a symptom-oriented approach (reduction of EDS) instead of pursuing a more comprehensive treatment claim (e.g. "Treatment of narcolepsy").

Efficacy outcome in OSA study 14-003

For the co-primary MWT (change from baseline) efficacy endpoint a dose-dependent effect was observed delivering highly significant ($p < 0.0001$) superiority over placebo for the 75 mg, 150 mg and 300 mg dose arms. In these 3 arms patients achieved maintenance of wakefulness about twice as long as compared to baseline (75 mg: from 12.44 min at baseline to 21.79 min at week 12; 150 mg: from 12.54 min to 23.64 min; 300 mg: from 12.10 min to 25.28 min at week 12 [means]). Also for the lowest JZP 37.5 mg dose arm, maintained

wakefulness improved significantly (change from baseline [min]: placebo 0.21, JZP 37.5 mg: 4.74 [1.16, 7.90; p=0.0086]).

Hence, results for MWT in the OSA population were overall more positive as compared to the results obtained in narcoleptic patients (study 14-002: 75 mg dose arm did significantly separate from placebo). In absolute figures, the mean differences over placebo in terms of maintained wakefulness (as compared to baseline) were slightly larger in the OSA population as compared to narcoleptic patients (MWT LS Mean Difference over placebo: 14-002 narcolepsy: 75 mg 2.62, 150 mg 7.65, 300 mg 10.14; 14-003 OSA: 75 mg 8.87, 150 mg 10.74, 300 mg 12.77).

Along the same lines, for the co-primary ESS (change from baseline) efficacy endpoint again a dose-related effect was observed delivering significant (37.5 mg: p=0.0161; 75 mg: p=0.0233) or highly significant ($p < 0.0001$) superiority over placebo for the 150 mg and 300 mg dose arm. In absolute figures, the decline in subjective, self-assessed propensity to fall asleep in typical everyday situations demonstrated that subjects allocated to the four JZP dose arms reached mean ESS scores < 10 at week 12 (37.5 mg: 9.7; 75 mg: 10.0; 150 mg; 7.5; 300 mg: 7.1) pointing to a level of higher normal DS (ESS category 6-10). At baseline subjects presented with an ESS score of about 15 across treatment arms reflecting moderate excessive daytime sleepiness (ESS category 13-15).

The post-hoc calculated responder analysis of subjects achieving an ESS score of < 10 further underlined the clinical relevance of the achieved difference over placebo. Cumulative distribution demonstrated that placebo response was more pronounced in OSA patients as compared to narcoleptic patients. While in study 14-002 only 15.5% of subjects allocated to placebo achieved ESS scores $\leq$ 10, the respective portion of subjects receiving placebo was 37.7%. On the other side, the treatment effect in JZP dose groups was also higher for OSA patients: In study 14-003, more than 70% of subjects receiving 150 mg resp. 300 mg JZP achieved ESS scores $\leq$ 10.

The magnitude of effect was dose-dependent, was observed by Week 1, and was maintained over the 12 weeks of treatment on both the MWT and ESS.

The results for the MWT and ESS co-primary endpoints aligned with those of the key secondary PGIc endpoint. The percentage of subjects reporting clinical improvement (minimal, much or very much) was significantly higher for the 75 mg dose, and highly significantly higher for the 150 mg and 300 mg dose arms, while the lowest 37.5 mg dose arm does not significantly separate from placebo (p=0.4447). As compared to study 14-002 in narcoleptic patients, placebo response was more pronounced in OSA patients: 49.1% of OSA patients receiving placebo reported to have (at least) minimally improved (placebo response in narcolepsy patients: 39.7%).

Interestingly, Global Impression as improved in the placebo group was equally high, irrespective whether it was investigator-assessed (CGIc placebo: 49.1%) or self-assessed (PGIc placebo: 49.1%). The rate of placebo subjects investigator-rated as improved was high and consistent over the entire study duration (CGIc improvement in placebo patients: wk1: 46.5%, wk4: 52.6%, wk8: 49.1%, wk12:49.1%).

The results of sensitivity analyses 1, 2, and 3 were consistent with and supported the primary analyses, with increases observed from Baseline to Week 12 in MWT (in minutes) and reductions in mean ESS Score for all JZP-110 dose groups compared with placebo. Highly significant (150 mg and 300 mg dose arms) or significant (37.5 mg and 75 mg dose arms) results were maintained for both co-primary endpoints for sensitivity analyses 1-3. Also, for sensitivity analysis 4, applying progressively more stringent analysis criteria by subtracting an increasingly greater percentage of the treatment effect (K) which accounted for dropouts due to AEs, lack of efficacy (LOE), and AEs or LOE, the treatment differences in the response (change in mean MWT and ESS), were maintained compared with placebo after all adjustments were made for all 4 JZP-110 dose groups.

Looking separately at the 5 consecutive testing sessions per MWT testing day (conducted at baseline, week 4, week 12), overall results are more favourable in the OSA population as compared to narcoleptic patients (study 14-002). In both populations, for the 150 mg and 300 mg dose arm the difference over placebo remains significant resp. highly significant for each of the five sessions. In OSA patients, however, significant results were also obtained for the 75 mg dose arm across all 5 MWT testing sessions, whereas in narcoleptic patients only numerical improvement over placebo could be shown.

In absolute figures (maintained wakefulness [in min] change from baseline), there is no clear tendency for a declining effect over the course of the testing day. However, at the second and third testing session per day, in general, wakefulness is maintained for the longest period of time.

OSA patients were stratified for their compliance with primary OSA therapy. Baseline values for MWT were lower in the sub-group of subjects non-compliant with primary OSA therapy as compared to the total mITT population (MWT at baseline total mITT vs non-compliant sub-group: placebo 12.40 vs 11.19, 37.5 mg 13.64 vs 10.40, 75 mg 13.08 vs 10.68, 150 mg 12.50 vs 10.41, 300 mg 12.00 vs 10.31 min). The difference in the ability to maintain wakefulness at baseline may be indicative of the beneficial effect of compliance with primary OSA therapy.

About 30% of recruited subjects were non-compliant with their primary OSA therapy. While baseline values in terms of MWT were slightly lower in the non-compliant sub-group as compared to the total mITT resp. compliant population, the outcome after 12 weeks of JZP treatment is largely similar across the compliant, non-compliant and total mITT population. The results do therefore not suggest that the effect of JZP was dependent upon compliance with primary OSA therapy (e.g. positive airway pressure). The results for ESS in the two sub-groups go along the same lines.

6-Week randomized withdrawal study 14-004

Study 14-004 was conducted in subjects meeting the ICSD-3 diagnostic criteria for OSA.

While subjects receiving JZP were assigned to fixed dose arms in studies 14-002 and 14-003, solriamfetol was individually titrated in study 14-004, which is considered to provide valuable information for clinical practice. Starting with 75 mg once daily, the patient could escalate the dose by one dose step every 3 days up to a maximum of 300 mg once daily. Dose titration was successfully completed by 90.2% (157/174) of included subjects. More than every second subject completing the titration period (84/157, 53.5%) titrated up to the highest 300 mg dose (150 mg: 50/157, 31.8%; 75 mg: 23/157, 14.6%).

Subjects were instructed to titrate towards the most efficacious / tolerable dose. ESS self-assessment was undertaken at the beginning and the end of the titration period, resp. beginning and end of the randomized withdrawal period. On the other side, AEs were reported daily. It remains somehow questionable how up- resp. down-titration could be efficacy-driven given the schedule of assessment.

The same co-primary resp. key secondary endpoints were evaluated as in phase III studies 14-002 and 14-003. Since subjects included in study 14-004 individually titrated the JZP dose according to efficacy resp. tolerability, results are presented for all JZP dose arms combined. Being a randomized withdrawal study, the period for measuring the efficacy endpoints was between week 4 (at the end of the 2-wk stable dose period) and week 6 (end of randomized withdrawal). It is considered acceptable to examine randomized withdrawal effects only in subjects presenting with a positive treatment effect at week 4 ("much" or "very much improved" on PGIc plus numerical improvements in terms of sleep latency [MWT] and EDS [ESS]).

A considerable portion of subjects (21/157, 13.4%) did not meet entry criteria to enter the randomized withdrawal period at the end of the two-week stable dose treatment period, because they did not present with

a positive treatment outcome by that time ("much or very much improved" on PGIc plus numerical improvements in MWT and ESS). During the pivotal studies 14-002 and 14-003 it could consistently be shown that the main treatment effect in terms of MWT and ESS occurs within the first week of treatment, hence the 2-week stable dose period would be expected sufficient to meet the modest requirements for definition of positive treatment effect.

After exclusion of subjects not qualifying for randomized withdrawal (mITT) a remarkable treatment effect is observed across all efficacy endpoints (Safety population vs mITT: MWT: 12-13 vs 28-32, ESS 15-16 vs 5-6) between baseline disease characteristics at study entry and those at week 4.

Subjects who continued to receive solriamfetol in the Double-blind Withdrawal Phase maintained the treatment benefits noted at Week 4, with little change in mean sleep latency (-0.96 minutes) and minimal change in ESS score (-0.1). In contrast, the placebo group showed a mean reduction of 12.11 (1.316) minutes in mean sleep latency and a 4.5 increase in ESS score at the end of the Double-blind Withdrawal Phase, resulting in statistically significant LS mean differences of 11.16 minutes on the MWT and -4.6 on the ESS ($p < 0.0001$ for both measures).

The efficacy data obtained during the 2-wk randomized withdrawal period reveal the symptomatic nature of solriamfetol's beneficial effect. After abrupt cessation of solriamfetol therapy symptoms in terms of daytime sleepiness and ability to maintain wakefulness worsen. However, at least at week 6 a minimum positive effect is retained: The mean MWT score at baseline of study entry was around 12 in the mITT population, two weeks after abrupt cessation subjects in the placebo group could still maintain wakefulness for 17.55 min (mean). The mean self-rated EDS (ESS) at baseline was around 16 (categorized as moderate to severe excessive daytime sleepiness), two weeks after abrupt cessation subjects in the placebo group still rated their propensity to fall asleep in typical everyday situations as 10.8 (mean ESS, thereby achieving the category between higher normal and mild excessive daytime sleepiness). Hence, no rebound hypersomnia was observed.

Long-term extension study 14-005

In long-term extension study 14-005, the narcolepsy and OSA populations terminating the phase II/III parent studies are combined. Subjects from parent studies 14-002 and 14-003 were directly enrolled (Group A), for subjects recruited from previous phase II studies there was a treatment gap in between the two studies (Group B). Irrespective of the dose received in the parent study, all subjects underwent a 2-wk titration at the start of study 14-005, which originally was planned as a long-term open label trial.

With Protocol Amendment 3, however, the 2-wk randomized withdrawal period was introduced while recruitment had already started. The Applicant explains that the rationale for making this change was that the US Food and Drug Administration (FDA) has expressed strong interest in having long-term controlled efficacy data for the studied indications. The design of the randomized withdrawal period in this study was declared to have been modelled after the ongoing 6-week randomized withdrawal study of JZP-110 in subjects with OSA (14-004) in an attempt to satisfy the requests and anticipated requirements from regulatory authorities.

Both in study 14-004 and 14-005 subjects followed the identical schedule to titrate to their individual dose during the initial two study weeks. In line with study 14-004, there are reservations regarding the question how far titration was actually efficacy-driven in study 14-005. "Investigators were instructed to titrate to the maximum dose that was tolerated to maximize therapeutic efficacy". From its wording, the latter plan would be considered a dose escalation scheme rather than dose titration.

According to the study's schedule of events, during the first two weeks efficacy parameters (ESS, PGIc, CGIc) were only recorded once at the end of the titration period (wk 2). Instead, phone calls were undertaken every

three days. As far as efficacy-driven, the titration process is therefore not quantifiable, but purely relies on subjects' self-estimation.

Furthermore, it is noted that in study 14-004 subjects had to qualify for being randomized for the withdrawal period by demonstrating a positive treatment outcome after two weeks of stable dose treatment (PGIc rating as "much or very much improved" plus numerical improvements in MWT and ESS). No such qualification test was implemented in study 14-005.

Despite the uncertainties regarding the titration process, it is considered that with the introduction of an intermediate 2-wk randomized placebo-controlled withdrawal period the clinical meaningfulness of study 14-005 in terms of efficacy was considerably enhanced. Overall, the design of study 14-005 contains a number of interesting aspects adding relevant information to the overall data package:

1. It is the first and only study including both narcoleptic and OSA patients.
2. Subjects start with a 2-wk titration period irrespective of the dose they received in the preceding study (studies 14-002 and 14-003 were fixed dose arm studies). Further dose adjustments are permitted until week 14 (after 12 weeks of open label treatment).
3. Subjects randomized to placebo during the 2-wk randomized withdrawal period resume medication thereafter starting one dose level below their previous dose.

There was a tendency to titrate towards higher doses during the initial 2-wk titration period of study 14-005. Of the N=643 Combined JZP-110 overall safety population of the open label phase 10.0% (64/643), 32.2% (207/643) and 57.9% (372/643) titrated to the 75 mg, 150 mg resp. 300 mg dose.

While the majority of subjects receiving 300 mg in the parent study (68/115, 59.1%) also titrated to the 300 mg dose at the beginning of study 14-005, subjects receiving lower doses in the parent studies (allocated to the lower fixed dose arms, e.g. in studies 14-002 resp. 14-003) were more likely to titrate to a higher dose level.

Throughout the parent studies (14-002 and 14-003) subjects were assigned to fixed dose arms. Given the tendency to titrate towards higher doses (irrespective of the dose received in the parent study) observed during the initial titration period of study 14-005, one may assume that during the fixed dose trials subjects tended to be rather underdosed than overdosed.

As concerns representation of the two disease subgroups (narcolepsy, OSA), about two thirds of subjects were OSA patients (417/643 [64.9%]), the remaining subjects were narcoleptic patients (226/643 [35.1%]). With regard to their overall health conditions and spectrum of co-morbidities resp. co-medication, long term safety data obtained in OSA patients are considered particularly informative.

Across all four dose levels of the parent studies the highest completion rates were achieved in subjects titrating to 150 mg resp. 300 mg solriamfetol during the open label phase of study 14-005.

The study completion rate was slightly higher in the OSA patients subgroup (73.9%) as compared to narcoleptic patients (66.4%). About 10% of subjects did not complete the study due to AEs. The portions of subjects discontinuing because of adverse events was about equal between the two subgroups (OSA: 9.1%, narcolepsy 10.2%). Interestingly, there was an inverse relationship between the titrated dose level and the rate of discontinuation due to AE in the overall population and for both subgroups. The data are to be interpreted with caution because numbers of subjects per dose group are not equally distributed.

As concerns discontinuation due to lack of efficacy there is some disparity between the two subgroups: while 39/226 (17.3%) of narcoleptic patients discontinued the open label period due to lack of efficacy, the respective portion was considerably lower in OSA patients (15/417, 3.6%).

Different subject numbers per dose level between the two disease subgroups data require cautious data interpretation. However, taking into consideration that study 14-005 started with a 2-wk individual dose titration period and the opportunity to adjust the titrated dose three times over the subsequent 12 weeks of treatment, the high incidence of discontinuation due to lack of efficacy in the two lower dose groups (75 mg: 26.7%; 150 mg: 25.4%) in narcoleptic patients (but not in OSA patients) appears unexpected. It is noted that OSA patients were allowed to continue their primary OSA therapy (e.g. PAP), while narcolepsy patients had to discontinue any previous medication taken for narcolepsy (OTC sleeping aids, stimulants (pseudoephedrine), methylphenidate, amphetamines, modafinil, sodium oxybate etc.). However, the effect of discontinuing previous medication would be expected to be diminished by individual dose titration, in particular in a long-term study where the majority of subjects already have been treated with solriamfetol over 12 weeks.

Compared to the ESS score of last assessment in the parent study (ESS: placebo: 10.54, JZP combined 9.26), daytime sleepiness further improved over the 26 weeks open label treatment before randomization to the withdrawal period in the overall mITT population (ESS at efficacy baseline: placebo 7.8, JZP combined 7.3). When treatment was withdrawn, sleepiness worsens in the placebo group (ESS 12.6 at the end of the 2-wk withdrawal period),but remains almost unchanged in those subjects remaining on JZP treatment (ESS 8.5). The difference between the placebo and JZP combined group was highly significant for the overall mITT population and for both disease subgroups.

Looking at Efficacy Baseline ESS scores after 26 weeks of open label treatment, there was a difference in the treatment outcome between OSA and narcolepsy patients. While EDS markedly improved in OSA patients (efficacy baseline ESS 6.5-5.9), the effect was less favourable in narcolepsy patients (efficacy baseline ESS 11.0-10.9).

Focussing on Group A for ESS over time, it is to be noted that subjects of Group A (originating from studies 14-002 resp. 14-003) directly enrolled in study 14-005 after termination of the parent study without treatment interruption. In Group A "Baseline" data represent baseline ESS scores at the start of the parent study (Overall 15.9, Narcolepsy 17.3, OSA 15.2). Data referred to as "Study Baseline" represent the treatment outcome of the 12-wk treatment during the parent study (Overall 10.6, narcolepsy 13.2, OSA 9.1). "Week 2" data represent the effect of the 2-wk titration period at the beginning of study 14-005 (Overall 7.6, Narcolepsy 10.0, OSA 6.2). Without considering the intermediate 2-wk randomized withdrawal period in a subset of the presented Safety Population, open label treatment is continued until week 40 (Overall 8.3, Narcolepsy 11.4, OSA 6.5). Adding the 12 weeks treatment of the parent study, thereby an overall treatment duration of 52 weeks is obtained in Group A subjects.

Throughout the entire timespan from baseline of the parent study to baseline of study 14-005, and the titration effect until the end of the 40-wk open label phase, ESS scores in narcoleptic subjects are considerably higher as compared to OSA subjects. After the titration period daytime sleepiness remained at a "higher normal" level, as reflected by ESS scores in the range of (or below) 10 in narcoleptic patients.

Despite the slightly increasing ESS scores in narcoleptic patients (Group A: ESS at wk 2: 10.0, at wk 40: 11.4) with increasing treatment duration, it is concluded that maintenance of efficacy was demonstrated throughout the 40 weeks (Group A) resp. 52 weeks (Group B) treatment period in study 14-005 for both narcoleptic and OSA patients.

2.5.4. Conclusions on the clinical efficacy

Efficacy data obtained from pivotal trials conducted in narcoleptic patients (study 14-002) and OSA patients (study 14-003) demonstrated superiority over placebo and therefore support the use of solriamfetol to improve wakefulness and reduce excessive daytime sleepiness in both subpopulations. No curative intent is associated with the product. Indeed, other clinical symptoms of narcolepsy (e.g. the number of cataplectic events) were unaffected by solriamfetol treatment, thereby confirming the symptom-oriented approach. Similarly, the symptomatic treatment of sleepiness with solriamfetol would not affect the pathophysiology of OSA being upper airway obstruction the leading cause of hypoxia and hypercapnia during sleep -important determinants of daytime ES- and increased CV risk. The two pivotal trials are complemented by data obtained from a 6-week randomized withdrawal study (14-004) in OSA patients after individual dose titration over two weeks. No rebound excessive sleepiness was observed in patients allocated to placebo during the 2-week randomized withdrawal period.

Maintenance of effect was demonstrated in long term extension study 14-005 including subjects with both underlying conditions (narcolepsy and OSA). In summary, from the efficacy perspective, the clinical development is considered to adequately support the proposed indication of solriamfetol.

2.6. Clinical safety

Patient exposure

The clinical programme supporting the development of solriamfetol for the treatment of EDS in narcolepsy and OSA consisted of 9 studies in healthy volunteers and special populations, 3 studies in subjects with MDD and 6 studies in subjects with narcolepsy or OSA. Safety data from this development programme are summarized, with particular focus on the safety profile of solriamfetol in the target population (patients with narcolepsy or OSA) at dose ranges studied in the Phase 3 clinical studies (37.5 mg to 300 mg).

To characterize the safety of solriamfetol in subjects with narcolepsy and subjects with OSA, studies of similar design and/or population were pooled for integrated analysis. Pool 1 consists of the 12-week, placebo-controlled, parallel-group studies in subjects with narcolepsy or OSA (ADX-N05 202, 14-002, 14-003). After completing participation in one of the parent narcolepsy or OSA studies (ADX-N05 201, ADX-N05 202, 14-002, 14-003, 14-004, 15-004, or 15-005), subjects meeting entry criteria could enrol in the open-label, long-term extension, Study 14-005. Safety data from these parent studies were combined with Study 14-005 data in Pool 2.

Across the development program through 08 February 2018 (comprising all completed studies), the overall number of unique subjects exposed to solriamfetol is N=1605. A total of N=741 subjects received placebo (some of whom also received solriamfetol).

Across the studies in subjects with narcolepsy and OSA, N=935 subjects were exposed to solriamfetol. Exposure was at least 6 months for N=531 subjects and at least 12 months for N=281 subjects. By design, placebo was not administered for longer than 3 months in any of the studies. Among the N=321 subjects with narcolepsy, exposure was at least 6 months for N=172 subjects and at least 12 months for N=95 subjects. Among the N=614 subjects with OSA, exposure was at least 6 months for N=359 subjects and at least 12 months for N=186 subjects.

Table 16: Exposure and Duration by Modal Daily Dose in Subjects with Narcolepsy and Obstructive Sleep Apnea by Indication (Safety Population)

	Narcolepsy				OSA					ALL
Duration	Combined JZP-110 N = 321	75 mg N=32	150 mg N=90	300 mg N=199	Combined JZP-110 N=614	37.5 mg N=33	75 mg N=82	150 mg N=198	300 mg N=301	Combined JZP-110 N=935
Exposure Duration (days)[a]										
Mean (SD)	212.0 (147.71)	126.7 (128.13)	179.5 (151.47)	240.4 (141.11)	221.7 (146.62)	80.4 (49.52)	164.8 (153.32)	233.3 (138.03)	245.1 (145.23)	218.4 (146.99)
Median	262.0	98.0	120.5	286.0	274.0	84.0	99.0	281.5	287.0	270.0
Range	4, 500	7, 451	4, 387	8, 500	1, 437	9, 229	1, 414	2, 437	4, 422	1, 500
Person-Time (days)[b]	68049	4053	16159	47837	136141	2654	13517	46200	73770	204190
≥3 Months, n (%)	213 (66.36)	18 (56.25)	52 (57.78)	143 (71.86)	409 (66.61)	8 (24.24)	42 (51.22)	145 (73.23)	214 (71.10)	622 (66.52)
≥6 Months, n (%)	172 (53.58)	6 (18.75)	41 (45.56)	125 (62.81)	359 (58.47)	2 (6.06)	35 (42.68)	123 (62.12)	199 (66.11)	531 (56.79)
≥12 Months, n (%)	95 (29.60)	3 (9.38)	23 (25.56)	69 (34.67)	186 (30.29)	0	14 (17.07)	54 (27.27)	118 (39.20)	281 (30.05)

Modal dose was defined as the dose administered to a patient most frequently (i.e., with the highest number of days) throughout the JZP-110 program. If there was a tie in number of days for different doses, the lower dose was used as the modal dose. OSA=obstructive sleep apnea; SD=standard deviation

[a] Exposure duration (days) = sum of (last dose date – first dose date + 1 of each dosing period). Exposure duration was calculated separately for placebo and JZP-110 using the same algorithm if a subject has received both treatments either within a study or across studies. Periods during which doses were not received were excluded from the calculation (e.g., in the gap before extension study started or wash-out period in cross-over study).

[b] Person-time = sum of total days of treatment exposure (or study duration) of all subjects in the treatment group.

Adverse events

Adverse Events by System Organ Class in Pools 1 and 2

In the studies in narcolepsy and OSA, among subjects who received solriamfetol, the SOCs with the highest incidence of AEs were Gastrointestinal Disorders, Nervous System Disorders, Psychiatric Disorders, and Infections and Infestations; except for Infections and Infestations, the incidence in these SOCs was higher with solriamfetol than with placebo in the 12-week studies.

Table 17: Adverse Events in 12-Week Placebo-controlled Parallel-Group Studies in Narcolepsy and Obstructive Sleep Apnea Subjects (Pool 1 and by Individual Population), and All Narcolepsy and OSA Studies (Pool 2) by System Organ Class Only (⩾ 5% in any Group)(Safety Population)

	Narcolepsy & OSA (Pool 1)		Narcolepsy (12-week PBO-controlled)		OSA (12-Week PBO-controlled)		All Narcolepsy & OSA (Pool 2)
System Organ Class, n (%)	Placebo N=226	Combined JZP-110 N=573	Placebo N=108	Combined JZP-110 N=220	Placebo N=118	Combined JZP-110 N=353	All N=935
Subjects with at Least One TEAE[a]	113 (50.00)	396 (69.11)	56 (51.85)	156 (70.91)	57 (48.31)	240 (67.99)	727 (77.75)
Gastrointestinal Disorders	30 (13.27)	144 (25.13)	15 (13.89)	61 (27.73)	15 (12.71)	83 (23.51)	303 (32.41)
Nervous System Disorders	34 (15.04)	119 (20.77)	19 (17.59)	60 (27.27)	15 (12.71)	59 (16.71)	279 (29.84)
Psychiatric Disorders	18 (7.96)	109 (19.02)	8 (7.41)	49 (22.27)	10 (8.47)	60 (17.00)	272 (29.09)
Infections and Infestations	43 (19.03)	106 (18.50)	25 (23.15)	45 (20.45)	18 (15.25)	61 (17.28)	269 (28.77)
General Disorders and Administration Site Conditions	10 (4.42)	68 (11.87)	7 (6.48)	25 (11.36)	3 (2.54)	43 (12.18)	145 (15.51)
Metabolism and Nutrition Disorders	7 (3.10)	61 (10.65)	5 (4.63)	28 (12.73)	2 (1.69)	33 (9.35)	113 (12.09)
Musculoskeletal and Connective Tissue Disorders	15 (6.64)	58 (10.12)	6 (5.56)	19 (8.64)	9 (7.63)	39 (11.05)	165 (17.65)
Investigations	12 (5.31)	46 (8.03)	7 (6.48)	22 (10.00)	5 (4.24)	24 (6.80)	92 (9.84)
Skin and Subcutaneous Tissue Disorders	8 (3.54)	40 (6.98)	4 (3.70)	22 (10.00)	4 (3.39)	18 (5.10)	77 (8.24)
Respiratory, Thoracic and Mediastinal Disorders	11 (4.87)	34 (5.93)	5 (4.63)	15 (6.82)	6 (5.08)	19 (5.38)	99 (10.59)
Injury, Poisoning and Procedural Complications	11 (4.87)	33 (5.76)	7 (6.48)	12 (5.45)	4 (3.39)	21 (5.95)	94 (10.05)
Cardiac Disorders	3 (1.33)	23 (4.01)	3 (2.78)	9 (4.09)	0	14 (3.97)	62 (6.63)
Reproductive System and Breast Disorders	9 (3.98)	14 (2.44)	6 (5.56)	7 (3.18)	3 (2.54)	7 (1.98)	30 (3.21)

Note: Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.0.
Note: Percentages are based on N, number of subjects within each treatment group in safety population treated in studies ADX-N05 202, 14-002 and 14-003 for Pool 1 and for Studies ADX-N05 202, 14-002 and 14-003, ADX-N05 201, 14-004, and 14-005 for Pool 2. AE=adverse event; OSA = obstructive sleep apnea; PBO = placebo; TEAE = treatment-emergent adverse event.
[a] TEAE = defined as an AE with onset date on or after the first dose date. Multiple entries for an individual under each preferred term (PT) are only counted once in each treatment group. TEAEs with onset in the safety follow-up period (i.e., after last dose) are included.

Common Adverse Events

In the 12-week placebo-controlled studies in subjects with narcolepsy and OSA, in the overall population the most frequent (≥5%) AEs that also had a higher incidence with solriamfetol than with placebo were headache, nausea, decreased appetite, anxiety, nasopharyngitis, diarrhoea, and dry mouth.

Table 18: Adverse Events With Higher Incidence in Combined JZP-110 Treatment Group than Placebo (and ⩾2% in 75, 150, or 300 mg JZP-110 dose group) in 12-Week Placebo-Controlled Parallel-Group Studies in Narcolepsy and OSA Overall and by Indication (Safety Population)

	Narcolepsy & OSA		Narcolepsy		OSA	
Number (%) of Subjects	Placebo N=226	Combined JZP-110 N=573	Placebo N=108	Combined JZP-110 N=220	Placebo N=118	Combined JZP-110 N=353
Headache	18 (7.96)	80 (13.96)	8 (7.41)	44 (20.00)	10 (8.47)	36 (10.20)
Nausea	11 (4.87)	53 (9.25)	4 (3.70)	25 (11.36)	7 (5.93)	28 (7.93)
Decreased appetite	2 (0.88)	52 (9.08)	1 (0.93)	25 (11.36)	1 (0.85)	27 (7.65)
Anxiety	1 (0.44)	39 (6.81)	1 (0.93)	14 (6.36)	0	25 (7.08)
Nasopharyngitis	12 (5.31)	35 (6.11)	4 (3.70)	18 (8.18)	0	0
Diarrhoea	5 (2.21)	30 (5.24)	4 (3.70)	13 (5.91)	1 (0.85)	17 (4.82)
Dry mouth	4 (1.77)	29 (5.06)	2 (1.85)	13 (5.91)	2 (1.69)	16 (4.53)
Insomnia	3 (1.33)	26 (4.54)	1 (0.93)	11 (5.00)	2 (1.69)	15 (4.25)
Dizziness	4 (1.77)	19 (3.32)	3 (2.78)	9 (4.09)	1 (0.85)	10 (2.83)
Feeling jittery	0	17 (2.97)	0	3 (1.36)	0	14 (3.97)
Palpitations	1 (0.44)	14 (2.44)	1 (0.93)	6 (2.73)	0	8 (2.27)
Sinusitis	4 (1.77)	14 (2.44)	1 (0.93)	6 (2.73)	3 (2.54)	8 (2.27)
Irritability	1 (0.44)	13 (2.27)	1 (0.93)	5 (2.27)	0	8 (2.27)
Constipation	2 (0.88)	12 (2.09)	1 (0.93)	6 (2.73)	1 (0.85)	6 (1.70)
Arthralgia	5 (2.21)	11 (1.92)	1 (0.93)	4 (1.82)	4 (3.39)	7 (1.98)
Back pain	3 (1.33)	11 (1.92)	1 (0.93)	3 (1.36)	2 (1.69)	8 (2.27)
Urinary tract infection	1 (0.44)	11 (1.92)	1 (0.93)	2 (0.91)	0	9 (2.55)
Chest discomfort	0	10 (1.75)	0	1 (0.45	0	9 (2.55)
Cough	0	10 (1.75)	0	3 (1.36)	0	7 (1.98)
Pyrexia	0	10 (1.75)	0	5 (2.27)	0	5 (1.42)
Fatigue	3 (1.33)	9 (1.57)	1 (0.93)	5 (2.27)	2 (1.69)	4 (1.13)
Hyperhidrosis	0	9 (1.57)	0	3 (1.36)	0	6 (1.70)
Heart rate increased	0	8 (1.40)	0	5 (2.27)	0	3 (0.85)
Muscle spasms	1 (0.44)	8 (1.40)	0	2 (0.91)	1 (0.85)	6 (1.70)
Myalgia	0	5 (0.87)	0	2 (0.91)	0	3 (0.85)

Note: Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.0.
Note: Percentages (i.e., incidences) are based on N, number of subjects within each treatment group in safety population treated in studies ADX-N05 202, 14-002 and 14-003.
OSA= obstructive sleep apnea

Adverse Events of Interest

Adverse events of interest (AEOI) for narcolepsy and OSA were selected based on the pharmacology of solriamfetol and experience from clinical studies, comorbidities in the target patient population, safety issues associated with current available treatments, and regulatory considerations for New Chemical Entities or regulatory requests.

Table 19: Adverse Events of Interest with Narrow Search Term Results (SMQ and AHQ) in 12-Week Placebo-Controlled Parallel-Group Studies in Narcolepsy and Obstructive Sleep Apnea (Safety Population)

Category of Adverse Event of Interest	Placebo N=226	Combined JZP-110 N=573	37.5 mg N=58	75 mg N=120	150 mg N=218	300 mg N=217
Hypertension/Blood Pressure Increased	1 (0.44)	13 (2.27)	0	0	7 (3.21)	6 (2.76)
Ischemic Heart Disease and Chest Pain	0	0	0	0	0	0
Cardiac Failure	0	0	0	0	0	0
Cardiomyopathy	0	0	0	0	0	0
Cardiac arrhythmias	2 (0.88)	10 (1.75)	4 (6.90)	1 (0.83)	2 (0.92)	3 (1.38)
QT Prolongation	0	1 (0.17)	1 (1.72)	0	0	0
Stroke/CNS Vascular Disease	0	0	0	0	0	0
Insomnia	7 (3.10)	33 (5.76)	1 (1.72)	2 (1.67)	9 (4.13)	22 (10.14)
Anxiety Disorders	4 (1.77)	74 (12.91)	7 (12.07)	8 (6.67)	22 (10.09)	39 (17.97)
Depression/Suicidality	6 (2.65)	8 (1.40)	0	0	5 (2.29)	3 (1.38)
Hostility/Aggression	0	0	0	0	0	0
Psychosis/Psychotic Disorders	0	1 (0.17)	0	0	0	1 (0.46)
Neuromotor Events	0	1 (0.17)	0	0	0	1 (0.46)
Hypersensitivity	9 (3.98)	15 (2.62)	1 (1.72)	2 (1.67)	8 (3.67)	4 (1.84)
Anaphylactic Reaction	0	0	0	0	0	0
Angioedema	0	3 (0.52)	0	0	3 (1.38)	0
Severe Cutaneous Adverse Reactions	0	1 (0.17)	1 (1.72)	0	0	0
Rhabdomyolysis/Elevated Creatinine Kinase	0	0	0	0	0	0
Drug-related Hepatic Disorders	3 (1.33)	4 (0.70)	0	2 (1.67)	1 (0.46)	1 (0.46)

Note: Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.0.
Note: Percentages are based on N, number of subjects within each treatment group in safety population treated in studies ADX-N05 202, 14-002 and 14-003.
Subjects from Study ADX-N05 202 who received multiple dose levels of JZP-110 are summarized in both 150 mg and 300 mg groups.
AE= adverse event; CNS: central nervous system; PT=preferred term; TEAE= treatment emergent adverse event
TEAE Defined as an AE with onset date on or after the first dose date. Multiple entries for an individual under each SMQ (or sub-SMQ or AHQ) /preferred term (PT) are only counted once in each treatment group.
AHQ=ad hoc query, SMQ=Standardised MedDRA Query

Cardiovascular Adverse Events of Interest

Based on the pharmacology of solriamfetol, together with the experience from clinical studies and the comorbidities in the target patient population (especially OSA) cardiovascular events (CV) were identified as Adverse Events of Special Interest.

In **Pool 1**, Serious CV events occurred in one subject (0.17%; non cardiac chest pain in a narcolepsy subject), compared to no serious events in placebo; CV events leading to discontinuation occurred in 7/573 (1.2%) among solriamfetol treated subjects (all in subjects with OSA except for 1 event of palpitations in a subject with narcolepsy), compared with no such event in the placebo group. The 7 CV events leading to discontinuation were the following: chest discomfort (3 events), non-cardiac chest pain (2 events), palpitations (2 events).

As regards to the adverse events positively adjudicated as cardiovascular in **Pool 1**, 3/573 (0.5%) subjects treated with solriamfetol presented cardiovascular events [1 coronary heart disease (non treatment emergent), 1 blood pressure increased (0.2%), 1 hypertension (0.2%)], compared with no such events in the placebo group. All of the positively adjudicated events occurred in subjects with OSA, at the higher doses 150 and 300 mg.

In the 12-week placebo-controlled study (14-003), AEs of hypertension/BP increased occurred at a greater frequency in those treated with solriamfetol (10/353, 2.8%) compared to placebo (no subjects). All cases were mild or moderate in severity and occurred at the 150 or 300 mg doses.

Table 20: Hypertension/Blood Pressure Increased in the 12-Week Placebo-Controlled Study in OSA (Study 14-003 - Safety Population)

SMQ Preferred Term (n%)	MedDRA Search Scope	Study 14-003					
		Placebo N=118	Combined Solriamfetol N=353	Solriamfetol 37.5 mg N=58	Solriamfetol 75 mg N=61	Solriamfetol 150 mg N=116	Solriamfetol 300 mg N=118
Hypertension/BP increased (SMQ)		0	10 (2.8)	0	0	5 (4.3)	5 (4.2)
Blood pressure increased	Narrow	0	4 (1.1)	0	0	2 (1.7)	2 (1.7)
Hypertension	Narrow	0	6 (1.7)	0	0	3 (2.6)	3 (2.5)

In **Pool 2** (all narcolepsy and OSA studies) serious CV occurred in 5/935 (0.5%) of subjects, all in OSA subjects (Acute myocardial infarction, Atrial fibrillation [2 subjects], Angina pectoris, and Deep vein thrombosis). In addition, one SAE of cerebrovascular accident (haemorrhage) occurred in subjects with OSA; a further non serious event of aphasia occurred in another subject with OSA.

As regards to the adverse events positively adjudicated as cardiovascular in **Pool 2**, 20/935 subjects (2.1%) had at least one event: blood pressure increased (8 subjects), hypertension (6 subjects), acute myocardial infarction (1 subject), atrial fibrillation (in 3 subjects; 1 prior to solriamfetol exposure), cerebrovascular accident, pulmonary embolism, ventricular tachycardia (1 subject each). All positively adjudicated CV events occurred in subjects with OSA.

In the long-term study (14-005), in the OSA population, AEs of hypertension/BP increased were reported in 22 subjects (5.3%) treated with solriamfetol; a greater percentage of subjects had an event at the 300 mg dose (Table below). Most events were mild or moderate in severity; none were serious. The majority of these subjects (13/22 [59.1%]) had a medical history of BP increased or hypertension and required anti-HTN treatment or modification of their current anti-HTN therapy. The majority of the events resolved with continued dosing of solriamfetol; three subjects (0.72%) discontinued the study due to the AEs of BP increased (2 subjects) and hypertension (1 subject) (see Table 21)

Table 21: Hypertension/Blood Pressure Increased in the Long-Term Study in the OSA Subpopulation (Study 14-005 - Safety Population)

SMQ Preferred Term (n%)	MedDRA Search Scope	Study 14-005 (OSA)			
		Combined Solriamfetol N=417	Solriamfetol 75 mg N=417	Solriamfetol 150 mg N=402	Solriamfetol 300 mg N=326
Hypertension/BP increased (SMQ)		22 (5.3)	4 (1.0)	6 (1.5)	12 (3.7)
Blood pressure increased	Narrow	11 (2.6)	2 (0.5)	2 (0.5)	7 (2.1)
Hypertension	Narrow	11 (2.6)	2 (0.5)	4 (1.0)	5 (1.5)

In **Pool 3** (Major Depressive Disorder Pooled Studies) adverse events positively adjudicated as cardiovascular occurred in 3/327 subjects (0.9%), compared with no event in placebo (N=141). One event of myocardial infarction occurred in the ≤300 mg group and 2 events of hypertension occurred (one each in the ≤300 mg and >300 mg groups.

Adverse Drug Reactions

Common ADRs are those occurring at a rate of ≥1% in the combined solriamfetol treatment group and higher than the placebo rate; less common adverse reactions are those occurring at a rate < 1% but higher than the placebo rate.

Except for headache, which was more frequent in subjects with narcolepsy than with OSA, the profile of adverse drug reactions was comparable between the populations with narcolepsy and with OSA. Therefore, the proposed label presents adverse drug reactions for the combined population.

The most common adverse reactions (≥ 5%) associated more often with the use of solriamfetol than placebo were headache, nausea, decreased appetite, anxiety, diarrhoea, dry mouth, and insomnia. A majority of these events were mild to moderate in severity and occurred within the first 2 weeks of initiating study drug.

Table 22: Common Adverse Drug Reactions in the 12-Week Placebo-controlled Parallel-Group Studies in Narcolepsy and Obstructive Sleep Apnea (Safety population)

System Organ Class Adverse Reaction, n (%)	Narcolepsy & OSA		Narcolepsy		OSA	
	Placebo (N=226)	Combined JZP-110 (N=573)	Placebo (N=108)	Combined JZP-110 (N=220)	Placebo (N=118)	Combined JZP-110 (N=353)
Cardiac Disorders						
Palpitations	1 (<1.0)	14 (2)	1 (<1.0)	6 (3)	0	8 (2)
Gastrointestinal Disorders						
Nausea	11 (5)	53 (9)	4 (4)	25 (11)	7 (6)	28 (8)
Diarrhoea	5 (2)	30 (5)	4 (4)	13 (6)	1 (<1.0)	17 (5)
Dry mouth	4 (2)	29 (5)	2 (2)	13 (6)	2 (2)	16 (5)
Abdominal pain[a]	5 (2)	18 (3)	3 (3)	6 (3)	2 (2)	12 (3)
Constipation	2 (<1.0)	12 (2)	1 (<1.0)	6 (3)	1 (<1.0)	6 (2)
Vomiting	2 (<1.0)	6 (1)	1 (<1.0)	2 (<1.0)	1 (<1.0)	4 (1)
General Disorders and Administration Site Conditions						
Feeling jittery	0	17 (3)	0	3 (1)	0	14 (4)
Chest discomfort	0	10 (2)	0	1 (<1.0)	0	9 (3)
Investigations						
Heart rate increased	0	8 (1)	0	5 (2)	0	3 (<1.0)
Blood pressure increased	1 (<1.0)	7 (1)	1 (<1.0)	3 (1)	0	4 (1)
Weight decreased	0	7 (1)	0	5 (2)	0	2 (<1.0)
Metabolism and Nutrition Disorders						
Decreased appetite	2 (<1.0)	52 (9)	1 (<1.0)	25 (11)	1 (<1.0)	27 (8)
Nervous System Disorders						
Headache[b]	18 (8)	84 (15)	8 (7)	46 (21)	10 (8)	38 (11)
Dizziness	4 (2)	19 (3)	3 (3)	9 (4)	1 (<1.0)	10 (3)
Psychiatric Disorders						
Anxiety	1 (<1.0)	39 (7)	1 (<1.0)	14 (6)	0	25 (7)
Insomnia[c]	7 (3)	33 (6)	4 (4)	17 (8)	3 (3)	16 (5)
Irritability	1 (<1.0)	13 (2)	1 (<1.0)	5 (2)	0	8 (2)
Bruxism	0	8 (1)	0	4 (2)	0	4 (1)
Agitation	1 (<1.0)	7 (1)	0	4 (2)	1 (<1.0)	3 (<1.0)
Respiratory, Thoracic and Mediastinal Disorders						
Cough	0	10 (2)	0	3 (1)	0	7 (2)
Skin and Subcutaneous Tissue Disorders						
Hyperhidrosis	0	9 (2)	0	3 (1)	0	6 (2)
Vascular Disorders						
Hypertension	0	6 (1)	0	0	0	6 (2)

Note: Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.0.
Note: Percentages are subject incidences based on N, number of subjects within each treatment group in safety population treated in 12-week randomized studies ADX-N05 202, 14-002 and 14-003.
Note: Common adverse reactions are those occurring at a rate of ≥1% in the combined JZP-110 treatment group and higher than the placebo rate.
Note: Events occurring at a rate of >1% were rounded to the nearest whole percent. Events occurring <1% are noted as such.

AE= adverse event; OSA= obstructive sleep apnea; pT= preferred term

[a] Abdominal pain is a combined term of 'abdominal pain,' 'abdominal pain upper,' and 'abdominal discomfort.

[b] Adverse reaction 'Headache' is a combined term of 'headache,' 'tension headache,' and 'head discomfort.

[c] Insomnia' is a combined term of 'insomnia,' 'initial insomnia,' 'middle insomnia,' and 'terminal insomnia.

Serious adverse event/deaths/other significant events

Deaths

No subjects died during the 12-week placebo-controlled studies in narcolepsy and OSA, the studies in MDD, the studies in healthy volunteers or in studies in special populations.

One subject with OSA died during the open-label extension Study 14-005. The subject was a 70-year-old immunosuppressed white male with OSA, with a medical history of diabetes mellitus, rheumatoid arthritis, pulmonary fibrosis, coronary artery disease and bipolar disorder.

Serious AE in all studies in narcolepsy and OSA (Pool 2)

Across all studies in subjects with narcolepsy or OSA receiving solriamfetol, 3.6% of subjects (34/935) had at least 1 SAE during the study; onset of SAEs was during solriamfetol exposure in 3% of subjects (28/935) and after the last dose in 1.1% of subjects (10/903). The only SAEs that occurred in more than 1 subject during treatment or after the last dose were atrial fibrillation (occurred in 1 subject after last dose), non-cardiac chest pain, cholecystitis acute, alcohol poisoning, and dizziness, each of which occurred in 2 subjects (2/935; 0.21%).

Table 23: Treatment-Emergent Serious Adverse Events During or After JZP-110 Exposure in All Studies in Narcolepsy and Obstructive Sleep Apnea (Pool 2) by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Narcolepsy and OSA N=935 n (%)	Narcolepsy N=321 n (%)	OSA N=614 n (%)
Subjects with at least 1 SAE	**34 (3.64)**	**9 (2.80)**	**25 (4.07)**
Cardiac Disorders	4 (0.43)	0	4 (0.65)
Atrial fibrillation	2 (0.21)	0	2 (0.33)
Acute myocardial infarction	1 (0.11)	0	1 (0.16)
Angina pectoris	1 (0.11)	0	1 (0.16)
Ear and labyrinth disorders	1 (0.11)	0	1 (0.16)
Vertigo	1 (0.11)	0	1 (0.16)
Eye Disorders	1 (0.11)	0	1 (0.16)
Retinal vein occlusion	1 (0.11)	0	1 (0.16)
Gastrointestinal disorders	3 (0.32)	0	3 (0.49)
Abdominal pain	1 (0.11)	0	1 (0.16)
Gastrointestinal inflammation	1 (0.11)	0	1 (0.16)
Nausea	1 (0.11)	0	1 (0.16)
Vomiting	1 (0.11)	0	1 (0.16)
Duodenal ulcer haemorrhage	1 (0.11)	0	1 (0.16)
General disorders and administration site conditions	4 (0.43)	1 (0.31)	3 (0.49)
Non-cardiac chest pain	2 (0.21)	1 (0.31)	1 (0.16)
Chest discomfort	1 (0.11)	0	1 (0.16)
Chest pain	1 (0.11)	0	1 (0.16)
Hepatobiliary disorders	3 (0.32)	1 (0.31)	2 (0.33)
Cholecystitis acute	2 (0.21)	1 (0.31)	1 (0.16)
Bile duct obstruction	1 (0.11)	0	1 (0.16)
Immune system disorders	1 (0.11)	1 (0.31)	0
Anaphylactic reaction	1 (0.11)	1 (0.31)	0
Infections and infestations	4 (0.43)	0	4 (0.65)
Bronchitis	1 (0.11)	0	1 (0.16)
Cellulitis	1 (0.11)	0	1 (0.16)
Sepsis	1 (0.11)	0	1 (0.16)
Staphylococcal infection	1 (0.11)	0	1 (0.16)
Streptococcal endocarditis	1 (0.11)	0	1 (0.16)
Clostridium difficile infection	1 (0.11)	0	1 (0.16)
Injury, poisoning and procedural complications	4 (0.43)	1 (0.31)	3 (0.49)
Alcohol poisoning	2 (0.21)	1 (0.31)	1 (0.16)
Anaemia postoperative	1 (0.11)	0	1 (0.16)

System Organ Class Preferred Term	Narcolepsy and OSA N=935 n (%)	Narcolepsy N=321 n (%)	OSA N=614 n (%)
Ear canal injury	1 (0.11)	0	1 (0.16)
Fall	1 (0.11)	0	1 (0.16)
Head injury	1 (0.11)	0	1 (0.16)
Intentional overdose	1 (0.11)	1 (0.31)	0
Procedural hypotension	1 (0.11)	0	1 (0.16)
Skull fracture	1 (0.11)	0	1 (0.16)
Skull fractured base	1 (0.11)	0	1 (0.16)
Metabolism and nutrition disorders	2 (0.21)	0	2 (0.33)
Dehydration	1 (0.11)	0	1 (0.16)
Hyperglycaemia	1 (0.11)	0	1 (0.16)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.21)	0	2 (0.33)
Malignant melanoma	1 (0.11)	0	1 (0.16)
Prostate cancer stage I	1 (0.11)	0	1 (0.16)
Nervous system disorders	6 (0.64)	2 (0.62)	4 (0.65)
Dizziness	2 (0.21)	0	2 (0.33)
Cerebrovascular accident	1 (0.11)	0	1 (0.16)
Cervical radiculopathy	1 (0.11)	0	1 (0.16)
Migraine	1 (0.11)	1 (0.31)	0
Cluster headache	1 (0.11)	1 (0.31)	0
Pregnancy, puerperium and perinatal conditions	2 (0.21)	1 (0.31)	1 (0.16)
Abortion spontaneous	1 (0.11)	1 (0.31)	0
Stillbirth	1 (0.11)	0	1 (0.16)
Psychiatric disorders	5 (0.53)	4 (1.25)	1 (0.16)
Agitation	1 (0.11)	1 (0.31)	0
Hallucination, auditory	1 (0.11)	1 (0.31)	0
Anxiety	1 (0.11)	1 (0.31)	0
Bipolar I disorder	1 (0.11)	0	1 (0.16)
Suicide attempt	1 (0.11)	1 (0.31)	0
Conversion disorder	1 (0.11)	1 (0.31)	0
Depression	1 (0.11)	1 (0.31)	0
Renal and urinary disorders	1 (0.11)	0	1 (0.16)
Haematuria	1 (0.11)	0	1 (0.16)
Reproductive system and breast disorders	1 (0.11)	0	1 (0.16)
Prostatomegaly	1 (0.11)	0	1 (0.16)
Respiratory, thoracic and mediastinal disorders	1 (0.11)	0	1 (0.16)
Pulmonary embolism	1 (0.11)	0	1 (0.16)
Vascular disorders	1 (0.11)	0	1 (0.16)
Deep vein thrombosis	1 (0.11)	0	1 (0.16)

Note: Includes TEAEs with onset after last dose of study drug.

Note: Multiple entries for an individual under each SOC/PT are only counted once in each treatment group.

AE= adverse event; OSA= obstructive sleep apnea; PT=preferred term; SAE= serious adverse event; SOC= system organ class; TEAE= treatment emergent adverse event

Laboratory findings

Clinical Laboratory Evaluations

Across the solriamfetol clinical development programme, and across all populations studied, no evidence of clinically meaningful changes associated with solriamfetol was identified in review of clinical laboratory data.

Regular Vital Sign Measurements

12-Week Placebo-Controlled Studies

Vital signs (including BP and HR) were comprehensively characterized across the solriamfetol clinical development programme, and were assessed in 3 ways in the Phase 3 narcolepsy and OSA studies:

- Regular vital sign measurements at each clinic visit with no relationship to dosing time (i.e., the time of dosing relative to the assessment of the vital signs is not specified)
- Multiple sequential vital sign measurements on MWT days at fixed times relative to dosing to characterize the time course across the day while subject is in the clinical setting (i.e., time of dosing is specified)
- 24-hour ambulatory blood pressure monitoring (ABPM) while subjects were in the outpatient environment with no relationship to dosing time

Due to the three ways of measurement, a multitude of data was provided. In general, the effects of solriamfetol on HR and BP point to dose relationship with the largest magnitude and duration of effect observed for the solriamfetol 300 mg dose. However, dose dependency was not fully consistent, in particular with regard to the 150 mg dose arm.

Studies 14-002 and 14-003 assessed BP and HR over 24 hours via 24-hr ambulatory monitoring, which is considered particularly informative. For ABPM, BP and pulse were collected every 30 minutes for a 24-hour period at Screening (baseline) and the Week 8 visit. Subjects were instructed to take study drug in the morning after waking up, but the precise time of dosing was not recorded.

For both the narcolepsy and OSA populations, the largest mean increases in blood pressure and heart rate from baseline to Week 8 were observed at the 300 mg solriamfetol dose. However, in the OSA population, mean increases in SBP were similar for the 75 and 300 mg solriamfetol doses. In general, the magnitude of increase in BP for the 300 mg solriamfetol dose relative to placebo was similar between the narcolepsy and OSA populations. The magnitude of increase in HR was higher for subjects with narcolepsy compared with subjects with OSA. The duration of effect for the 300 mg solriamfetol dose on BP and HR was similar between the narcolepsy and OSA populations and was observed early in the morning (~6-8 AM) and tapered in the evening (~4-8 PM).

Categorical Changes on Maintenance of Wakefulness Test Days

The categorical change criteria for BP were increases or decreases from baseline by $\geq$ 5 mmHg, 10 mmHg, 20 mmHg, and 30 mmHg. For HR, categorical change criteria were $\geq$ 5 bpm, 10 bpm, 15 bpm, and 30 bpm. The percentage of subjects who had changes below or above the normal range values in BP (< 90 mmHg or $\geq$ 140

mmHg for SBP, and < 60 mmHg or ≥ 90 mmHg for DBP), as well as the percentage of subjects who had changes below or above the normal range values for HR (< 60 bpm or >100 bpm) are also summarized for Week 12.

For categorical changes in SBP:

- Differences in the percentage of subjects with categorical increases in systolic blood pressure were most apparent for 300 mg solriamfetol for each indication compared to placebo. For other solriamfetol dose groups, the percentage of subjects with categorical increases in SBP was not dose-related and there were no clear differences compared to placebo.
- A higher percentage of narcolepsy subjects receiving 300 mg solriamfetol had increases ≥ 5 mmHg (40.5%), compared to placebo (33.3%); the percentage of subjects with categorical increases ≥ 10 mmHg was similar between treatment groups and no subjects had increases ≥ 20 mmHg.
- A higher percentage of OSA subjects receiving 300 mg solriamfetol had increases ≥ 10 mmHg and ≥ 20 mmHg (25.5% and 6.4%, respectively) compared to placebo (8.0% and no subjects, respectively). One subject with OSA who received 300 mg solriamfetol had an increase ≥ 30 mmHg.

For categorical changes in HR:

- A higher percentage of subjects receiving solriamfetol had categorical increases ≥ 5 and ≥ 10 bpm for each indication and this was generally dose-related. No subject had increases ≥ 30 bpm.
- A higher percentage of narcolepsy subjects receiving solriamfetol were found to have categorical increases ≥ 5 bpm (28.6%, 32.0%, and 43.0% for 75 mg, 150 mg, and 300 mg solriamfetol, respectively) and ≥ 10 bpm (10.2%, 8.0%, and 15.2% for 75 mg, 150 mg, and 300 mg solriamfetol, respectively), compared to placebo (18.9% and 6.7%, respectively). A higher percentage of subjects receiving 300 mg solriamfetol had increases ≥ 15 bpm (7.6%) compared to placebo (3.3%).
- A higher percentage of OSA subjects receiving solriamfetol were found to have categorical increases ≥ 5 bpm (24.5%, 20.8%, 33.3%, and 41.5% for 37.5 mg, 75 mg, 150 mg, and 300 mg solriamfetol, respectively) and ≥ 10 bpm (8.2%, 3.8%, 10.5%, and 6.4% for 37.5 mg, 75 mg, 150 mg, and 300 mg solriamfetol, respectively), compared to placebo (18.0% and 2.0%, respectively). Few subjects had increases ≥ 15 bpm in heart rate, with no differences between treatment groups.
- Three narcolepsy subjects had changes above the normal range values in HR (> 100 bpm; 1 subject who received 150 mg solriamfetol, and 2 subjects who received 300 mg solriamfetol). No subjects with OSA had changes above the normal range values in heart rate.

In the overall OSA safety population of study 14-005 (N=417 combined solriamfetol), a total of 263 subjects (63.1%) treated with solriamfetol had changes in SBP that were >5 mmHg; 216 subjects (51.8%) treated with solriamfetol had changes in DBP that were >5 mmHg; 232 subjects (55.6%) treated with solriamfetol had changes in HR that were >5 bpm; the effects were dose-related.

Safety in special populations

Age

In narcolepsy and OSA subjects within the 12-week placebo-controlled studies and for all studies in narcolepsy and OSA by solriamfetol exposure duration (Pool 2), subgroup analyses of TEAEs by age (< 65 years vs ≥ 65 years) did not show meaningful differences.

Weight and BMI

Based on the AE overview of subgroups by baseline BMI (< 30 kg/m^2 vs ≥ 30 kg/m^2) in the 12-week placebo-controlled studies in narcolepsy and OSA, subjects with higher BMI did not have a higher incidence of TEAEs, SAEs, or TEAEs leading to study treatment discontinuation compared with those having lower BMI. No trends were observed for the subgroup analyses by baseline BMI in narcolepsy and OSA subjects.

Discontinuation due to adverse events

Discontinuation due to adverse events was twice as frequent in Combined JZP-110 OSA and Narcolepsy groups as compared with Placebo groups. The main reason leading discontinuation were psychological in OSA (anxiety and feeling jittery) and cataplexy in Narcolepsy.

Table 24: Adverse Events Leading to Study Drug/Study Withdrawal in 12-Week Placebo-Controlled Parallel-Group Studies in Narcolepsy and Obstructive Sleep Apnea (Pool 1) by Preferred Term (⩾ 2 Subjects in Combined JZP-110) (Safety Population)

Preferred Term	Narcolepsy and OSA		Narcolepsy		OSA	
	Placebo N = 226	Combined JZP-110 N = 573	Placebo N = 108	Combined JZP-110 N = 220	Placebo N = 118	Combined JZP-110 N = 353
Any TEAEs Leading to Study Drug / Study Withdrawal	7 (3.10)	37 (6.46)	3 (2.78)	12 (5.45)	4 (3.39)	25 (7.08)
Anxiety	0	5 (0.87)	0	1 (0.45)	0	4 (1.13)
Dizziness	0	4 (0.70)	0	1 (0.45)	0	3 (0.85)
Nausea	0	4 (0.70)	0	1 (0.45)	0	3 (0.85)
Feeling jittery	0	4 (0.70)	0	0	0	4 (1.13)
Chest discomfort	0	3 (0.52)	0	0	0	3 (0.85)
Agitation	0	2 (0.35)	0	0	0	2 (0.57)
Restlessness	0	2 (0.35)	0	0	0	2 (0.57)
Tic	0	2 (0.35)	0	0	0	2 (0.57)
Insomnia	0	2 (0.35)	0	1 (0.45)	0	1 (0.28)
Non-cardiac chest pain	0	2 (0.35)	0	1 (0.45)	0	1 (0.28)
Cataplexy	1 (0.44)	2 (0.35)	1 (0.93)	2 (0.91)	0	0
Palpitations	0	2 (0.35)	0	1 (0.45)	0	1 (0.28)

Ae= adverse event; OSA= obstructive sleep apnea; PT = preferred term; SOC = system organ class; TEAE = treatment emergent adverse event
Note: Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.0.
Note: Percentages are based on N, number of subjects within each treatment group in safety population treated in studies ADX-N05 202, 14-002 and 14-003. Subjects from study ADX-N05 202 who received multiple dose levels of JZP-110 are summarized in both 150 mg and 300 mg groups.
Note: TEAE = defined as an AE with onset date on or after the first dose date. Multiple entries for an individual under each PT are counted once in that SOC/PT category in each treatment group.

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Exposure

Considering the target population as a whole (incl. narcolepsy and OSA), the scope of overall exposure (N=1605, incl. MDD patients and healthy subjects), exposure over 6 resp. 12 months is considered adequate and largely concordant with the provisions with the Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety, CPMP/ICH/375/95. Across the studies in subjects with narcolepsy and OSA, 935 subjects were exposed to solriamfetol. Exposure was at least 6 months for 531 subjects and at least 12 months for 281 subjects (95 narcoleptic and 186 OSA patients received solriamfetol for > 12 months).

Target population

Baseline characteristics in terms of age, sex, BMI and co-morbidities are considered to typically represent the target OSA resp. narcoleptic subpopulations. Studies in subjects with narcolepsy enrolled a younger population (36-37 years) compared with studies in subjects with OSA (53-54 years). The majority of subjects enrolled in narcolepsy studies were female (60-67%) while the majority of subjects enrolled in OSA studies were male (61-64%). Baseline body mass index (BMI, kg/m^2) was higher for subjects with OSA (appr. 33 kg/m^2) compared with subjects with narcolepsy (appr. 28 kg/m^2). As concerns heart rate (narcolepsy: 70.8 – 73.3, OSA 75.9 – 76.6) and systolic blood pressure (narcolepsy: 117.2 – 119.8, OSA: 127.6 – 127.4) mean values are slightly higher in the OSA subpopulation. Mean values for vital signs HR and BP are in the normal range across both disease subgroups.

OSA is a risk factor for hypertension, coronary artery disease, and stroke. Patients with OSA are also at increased risk of atrial fibrillation, Type II diabetes and cancer (Garvey et al. 2015). Apart from the higher BMI value, OSA patients often present with medical history suggestive of metabolic syndrome. This is reflected by a considerably higher portion of OSA subjects receiving antihypertensive medication ([narcolepsy / OSA] ACE inhibitors: 3.7-6.8% / 14.4-18.1%, AT II antagonists 0.9 – 2.3% / 12.7 – 12.8%, beta blockers 3.7 – 4.6% / 12.7 – 9.9%), lipid modifying agents (narcolepsy 4.6 – 7.7%, OSA 35.6 – 37.4%), and antidiabetics incl. insulin (narcolepsy 3.7 – 4.1%, OSA 23.7 – 23.0%).

Evidence was provided that demonstrates that the recruited OSA population is representative for OSA patients in clinical practice in terms of mean age, gender distribution, BMI, comorbid hypertension, and hyperlipidaemia and diabetes. As concerns the CV risk profile of recruited subjects, a number of CV risk patient groups were excluded according to the exclusion criteria (see relevant sections in AR).

Overall, it is concluded that the specified exclusion criteria regarding CV risk patients (mainly excluding those with acutely unstable or uncontrolled conditions) are acceptable and do not principally question representativeness of the study population. Respective warning statements are implemented in SmPC section 4.4.

Also with regard to the portion of included OSA patients > 65 years (116/615, 19%), the targeted population is considered representative. In a recent literature overview on sleep apnoea in older people the prevalence of OSA in people over 65 years was estimated to range between 13-32% (Glassner et al. 2011). With regard to the overall target population (OSA + narcolepsy) the portion of patients > 65 years is about 13%, hence, elderly are higher represented in the OSA as compared to the narcolepsy population, which is consistent with the mean age of affected subjects for each condition.

While subjects with bipolar disorders or schizophrenia were excluded from phase III studies, about a quarter of subjects included in long-term study 14-005 presented with comorbid depression (narcolepsy 26.5%, OSA 22.5%). Through reported enhancement of neurotransmitter (DA, NE) signalling the whole range of potential CNS-related undesirable effects plus effects on vital signs (BP, HR) are considered typical class-related ADRs. In other drug substances with similar mode of action symptoms like anxiety, nervousness, insomnia, increase in systolic blood pressure and heart rate were observed. In long-term study 14-005 a considerable portion of both narcoleptic (12.8%) and OSA patients (12.5%) presented with a history of anxiety. As a general safety measure, the influence on suicidal ideation was routinely monitored by means of the Columbia-Suicide Severity Rating Scale (C-SSRS) throughout the clinical trial programme of solriamfetol.

Frequent AEs by SOC

Solriamfetol's molecular mode of action is reported to be based on selective dopamine and norepinephrine reuptake inhibition (DNRI). In line with assumed enhancement of NE and DA signalling, the highest incidence of AEs by SOC were Gastrointestinal Disorders, Nervous System Disorders, Psychiatric Disorders. The summary of AEs per SOC, disease subpopulation and treatment duration (12-wk Pool 1 vs 1-yr Pool 2) shows a general tendency for higher AE incidence in the narcoleptic population as compared to OSA patients (with the most striking difference for Nervous System Disorders: Pool 1: narcolepsy 27.27%, OSA 16.71). Notably, over the 12-wk treatment period (Pool 1) the incidence in Cardiac Disorders was three times higher for JZP combined (4.01%) as compared to placebo (1.33%).

Common AE

Cardiac disorders (SOC 3-times elevated over placebo) mainly refer to palpitations and increase of heart rate. The higher incidence of Psychiatric Disorders reflects the symptom complex of anxiety, feeling jittery and irritability. Nervous System Disorders mainly correspond to headache, dry mouth and dizziness. Further groups of AEs occurring more often in JZP treatment (as compared to placebo) concern the gastrointestinal system (nausea 9.25%, decreased appetite 9.08%, diarrhoea 5.24%, constipation 2.09%), respiratory tract infections (nasopharyngitis, sinusitis, cough) and bone / muscle related AEs (arthralgia, muscle spasms, myalgia).

Broken down to the four dose levels of JZP examined throughout the 12-wk trials, there is either a clear dose-response relationship for AEs (headache, decreased appetite, anxiety, diarrhoea, dry mouth), a tendency towards higher incidence with increasing dose (nausea, insomnia, dizziness, feeling jittery, heart rate increased) or no dose response relation discernible (nasopharyngitis, palpitations, sinusitis, constipation, arthralgia, muscle spasms).

TEAEs

During treatment with solriamfetol, 76.9% of subjects (719/935) had at least one TEAE. The profile of AEs during solriamfetol exposure across all narcolepsy and OSA studies including from the long-term Study 14-005 was generally comparable with that for the 12-week placebo-controlled studies in narcolepsy and OSA studies. TEAEs that were most commonly (≥5%) reported during solriamfetol exposure were headache (16.8%), nausea (12.9%), insomnia (9.0%), decreased appetite (9.2%), anxiety (9.4%), nasopharyngitis (8.9%), dry mouth (8.6%), dizziness (6.0%), diarrhoea (5.4%), and feeling jittery (5.0%). There was no obvious pattern with respect to AEs following long term exposure.

TEAEs were observed during treatment initition periods by the majority of the subjects. The most commonly reported TEAEs in the 12-week placebo controlled studies were reported in the first 2 weeks of treatment. With regard to duration of adverse events, a number of AEs resolve within a few days after treatment initiation (diarrhoea, dizziness, feeling jittery, headache) for the majority of affected subjects. Other AEs appear to persist for longer (median duration in days: Decreased appetite 18.0, dry mouth 35.5, irritability 62.0, pruritis 28.0)

Adverse drug reactions (ADRs)

Common ADRs were defined as those occurring at a rate of ≥1% in the combined solriamfetol treatment group and higher than the placebo rate. The most common adverse reactions (≥ 5%) associated more often with the use of solriamfetol than placebo were headache, nausea, decreased appetite, anxiety, diarrhea, dry mouth, and insomnia. In fact, headache is the only ADR with an apparent unbalance in incidence between the two disease populations (for combined JZP: narcolepsy 46/220, 21%; OSA: 38/353, 11%). The listed common ADRs are adequately reflected in section 4.8 of the proposed SmPC.

Adverse events of interest (AEOI)

Cardiovascular Events

Hypertension / Blood Pressure Increased / Heart rate increased

In the 12-week placebo-controlled studies in narcolepsy and OSA, events of hypertension/increased BP occurred at a greater frequency in those treated with solriamfetol (13/573, 2.27%) compared to placebo (1/226, 0.44%). The frequency of the TEAE increased blood pressure was similar between indications (narcolepsy, OSA). All cases were mild or moderate in severity and occurred at the 150 or 300 mg solriamfetol dose level. One subject discontinued the study due to the TEAE of increased blood pressure.

Frequencies of TEAEs of hypertension/ blood pressure increased (SMQ) displayed by exposure duration time interval in Pool 2 showed that events of hypertension continue to occur also with longer exposure durations.

Vital sign measurement was undertaken within three different testing settings (at each clinical study visit [with no relationship to dosing time], through multiple sequential measurements on MWT testing days [at fixed times relative to dosing], and through 24-hour ambulatory BP monitoring (ABPM) while subjects were in the outpatient environment with no relationship to dosing time). Thereby, a comprehensive data package was provided. ABMP measurement is considered particularly informative since it allows continuous BP / HR monitoring over 24 hours, thereby allowing to identify peak levels and maintenance of effects. The duration of effect for the 300 mg solriamfetol dose on BP and HR was similar between the narcolepsy and OSA populations, and was observed early in the morning (~6-8 AM) and tapered in the evening (~4-8 PM). Overall, there were consistent increases in BP and HR in subjects receiving 300 mg solriamfetol, however, the natural diurnal course of vital signs was unchanged.

For both the narcolepsy and OSA populations, the largest mean increases in blood pressure and heart rate from baseline to Week 8 were observed at the 300 mg solriamfetol dose (ABPM). However, in the OSA population, mean increases in SBP were similar for the 75 and 300 mg solriamfetol doses. In general, the magnitude of increase in BP for the 300 mg solriamfetol dose relative to placebo was similar between the narcolepsy and OSA populations. In absolute figures, mean increases of SBP were 2.1 -2.7 mm Hg for the 75 mg resp. 300 mg dose in narcoleptic patients and 1.5 -3.7 mm Hg in OSA patients. Mean increases in HR were slightly higher in narcolepsy (1.6-5.9 bpm) as compared to OSA (1.2 – 2.4 bpm) 8 weeks after treatment initiation in 12-wk studies 14-002 and 14-003.

Apart from mean values for BP / HR increase, particular attention is to be paid to categorical changes from baseline. When BP was assessed at each clinical study visit, even for the 300 mg solriamfetol dose there was no elevation in categorical changes from baseline for $\geq$5, $\geq$10, $\geq$20 mm Hg SBP in the overall safety population. However higher frequencies compared to placebo were observed for the 300 mg solriamfetol dose in categorical changes from baseline for $\geq$5, $\geq$10, $\geq$20 mm Hg SBP assessed through multiple sequential measurements on MWT testing days ($\geq$ 5 bpm: 30% vs 37%, $\geq$10 bpm: 11% vs 20%, $\geq$ 15 bpm: 0% vs 3%). Similarly, higher frequencies compared to placebo were observed for the 300 mg solriamfetol dose in categorical changes from baseline for ≥10 mm Hg SBP assessed through ABPM.

For HR, categorical changes observed for the 300 mg dose were considerably higher as compared to placebo, regardless of the method used to assess HR (regularly vital signs assessment at each clinical study visit: ($\geq$ 5 bpm: 69.6% vs 56.9%, $\geq$10 bpm: 49.1% vs 38.1%, $\geq$ 15 bpm: 28.5% vs 23.8%) in the overall safety population.

A more heterogeneous picture is obtained, if broken down to disease sub-populations. In terms of SBP, in narcolepsy categorical changes from baseline are lower for the 300 mg dose arm (≥ 5 mm Hg: 59.8%, ≥ 10 mm Hg: 41.2%, ≥ 20 mm Hg: 16.5%) as compared to placebo (≥ 5 mm Hg: 67.9%, ≥ 10 mm Hg: 51.9%, ≥ 20 mm Hg: 21.7%). In OSA patients, however, the respective categorical changes were higher in the 300 mg dose arm (≥ 5 mm Hg: 57.3%, ≥ 10 mm Hg: 40.2%, ≥ 20 mm Hg: 14.5%) as compared to placebo (≥ 5 mm Hg: 54.7%, ≥ 10 mm Hg: 30.8%, ≥ 20 mm Hg: 11.9%.

Epidemiological evidence shows that even a 2-3 mmHg increase in existing high blood pressure increases rates of stroke, heart attack and death. Therefore, particular concern was raised with regard to the CV risk profile of solriamfetol in the OSA population.

The results for the mean changes in vital signs from baseline relative to placebo in BP and HR in the 12-wk OSA population do not show a clear dose dependency across the four dose arms for SBP and DBP. Only for HR, a consistent increase in HR is observed across dose arms. What both changes in BP and HR have in common, however, is the fact that the change versus baseline was most prominent in the highest dose group.

Taking the change in vital signs during long term study 14-005 into consideration, dose dependency of categorical changes in SBP, DBP, resp. HR is more evident. Across the categorical changes, almost consistent dose dependency for SBP, DBP, and HR increases was observed. Importantly, portions of patients with categorical increases in vital signs was consistently highest for the 300 mg dose arm.

It is noted that the overall incidence of Hypertension / BP increase AEs in the 12-wk OSA population was not particularly high (10/353, 2.8%), given the overall physical condition of recruited subjects. On the other side, no case of hypertension / BP increase was observed in the placebo arm (N=118).

Along the same lines with the mean change from baseline in vital signs, dose dependency for Hypertension / BP increase in 12-wk OSA population is not clear across all dose arms. There was no difference in AEs of Hypertension / BP increase between the 37.5 mg and 75 mg on the one side, and the 150 mg and 300 mg arm on the other side. Again, however, AE incidence was highest for the higher doses.

Long-term study 14-005 did not include a placebo group for the full duration of study. Information given for the "placebo arm" can only relate to the intermediate 2-wk randomized withdrawal period. Therefore, no meaningful control group can help to contextualize the incidence of adverse events. AEs of hypertension/BP increased were reported in 22/417 subjects (5.3%) treated with solriamfetol. The majority of these subjects (13/22 [59.1%]) had a medical history of BP increased or hypertension and required anti-HTN treatment or modification of their current anti-HTN therapy.

Focussing on TEAESIs of HR Increased, BP Increased, and Palpitations, a clear dose-dependent increase in incidence rates is observed in the overall population (OSA + narcolepsy) in all three cases. TEAESIs of HR Increased were related in most cases, however, resolved after a mean duration of 3-20 days. No case was rated as severe. Observed cases of BP Increased lasted for longer with a mean duration between 20 and 96 days across dose arms. The duration of observed cases of Palpitations was shortest with a mean duration between 2.5 and 10.5 days. Again, no case of palpitations was rated as severe.

In summary, it is concluded that for a long-term study an incidence rate of 5.3% (22/417) OSA subjects with hypertension / BP increase is not considered unexpectedly high. On the other side, a clear dose dependency was observed in study 14-005 for TEAESIs of HR Increased, BP Increased, and Palpitations across the solriamfetol dose arms, which is plausible given the dose dependent categorical change in vital signs (BP, HR) observed after solriamfetol administration, and the pharmacological mode of action (increasing NE and DA neurotransmission)

of this wake-promoting agent. It is reassuring, however, that the vast majority of BP Increased / hypertension AEs was rated as mild and resolved with continued solriamfetol treatment in study 14-005.

Ischemic Heart Disease and Chest Pain

Across all narcolepsy and OSA studies (Pool 2), 2 subjects (0.22%) had cardiovascular events related to potential ischemic heart disease during exposure to solriamfetol. Both subjects were multi-morbid OSA patients. The events were acute myocardial infarction and angina pectoris and were serious for both subjects. No subjects discontinued due to ischemic heart disease, however the subject with the SAE of acute myocardial infarction later died due to a subsequent adverse event. The other subject (for which a number of independent risk factors were confirmed) resumed JZP treatment 3 days after the angina pectoris event.

The incidence of unspecific chest discomfort was higher (10/517, 1.75%) in the 12-wk study safety population. Nine out of ten of these cases were OSA patients. Chest discomfort / Chest pain are labelled in section 4.8.

In Pool 1, Serious CV events occurred in one subject (0.17%; non cardiac chest pain in a narcolepsy subject), compared to no serious events in placebo; CV events leading to discontinuation occurred in 7/573 (1.2%) among solriamfetol treated subjects (all in subjects with OSA except for 1 event of palpitations in a subject with narcolepsy), compared with no such event in the placebo group.

In Pool 2 (all narcolepsy and OSA studies) serious cardiovascular events occurred in 5/935 (0.5%) of subjects, all in OSA subjects (Acute myocardial infarction, Atrial fibrillation [2 subjects], Angina pectoris, and Deep vein thrombosis). In addition, one SAE of cerebrovascular accident (haemorrhage) occurred in a subject with OSA; a further non serious event of aphasia occurred in another subject with OSA.

As regards to the adverse events positively adjudicated as cardiovascular in Pool 2, 20/935 subjects (2.1%) had at least one event: blood pressure increased (8 subjects), hypertension (6 subjects), acute myocardial infarction (1 subject), atrial fibrillation (in 3 subjects; 1 prior to solriamfetol exposure), cerebrovascular accident, pulmonary embolism, ventricular tachycardia (1 subject each). All positively adjudicated CV events occurred in subjects with OSA.

Psychiatric symptoms

Insomnia / Anxiety

Like for TEAE insomnia, anxiety (narrow term) and associated symptoms (feeling jittery, irritability, agitation) were predominantly observed during treatment initiation and declined with increasing treatment duration. The fact that anxiety was also observed in healthy subjects strongly points to a causal relation with solriamfetol's pharmacological mode of action. Adequate warning notes regarding anxiety / insomnia were included in SmPC section 4.4.

Depression / Suicidality

Depression is a common co-morbidity both in narcoleptic and OSA patients. In long term study 14-005 94/417 (22.5%) of OSA patients resp. 60/226 (26.5%) narcoleptic patients reported a medical history of depression. In line with these baseline conditions the rate of subjects reporting depression / suicidality was higher in the placebo group (2.65%) as compared to JZP combined (1.4%) in the pooled 12-week studies. Equally, the portion of subjects of Pool 2 (incl. long term data) presenting with AE depression / suicidality (28/935, 2.99%) does not point to an increased risk due to JZP therapy. The C-SSRS data did not show suicidal ideation or behaviour leading up to, or after the attempt.

Psychosis/Psychotic Disorders

Psychotic episodes and mania have been associated with the use of amphetamines and were therefore examined in the solriamfetol programme. During the narcolepsy resp. OSA trials there was no signal for AEs indicative of psychotic disorders. However, patients with a history of bipolar disorder / psychosis were excluded. In healthy PK studies and during study 14-005 there were single well described cases of confabulation resp. paranoid symptoms.

There was one case of serious TEAE of bipolar I disorder and moderate mania (manic behaviour). The investigator's judgement "not related to study drug" is endorsed.

Abuse / Misuse / Overdose

There have been no reports describing individuals who have taken an overdose of solriamfetol in the clinical studies.

In Human Abuse Liability (HAL) study 14-001 JZP doses of 300 mg, 600 mg and 1200 mg were tested. In terms of the primary endpoint "Drug Liking at the Moment" all three JZP doses achieved highly significant higher sores than placebo. If compared with the positive control phentermine (a central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine, not approved in Europe) the score was equal for both substances, if administered at the highest dose each (phentermine 90 mg, JZP 1200 mg). An abuse potential similar or lower as compared to phentermine is concluded. In the US, phentermine is scheduled as C-IV, i.e. it has a low potential for abuse (relative to class III drugs), but is currently accepted for medical use. Other substances labelled as C-IV in the US, e.g. are benzodiazepines, stimulants (modafinil, sibutramine,), tramadol or anorectics (fenfluramine). To contextualize, methyphenidate and morphine are labelled C-II. A paragraph was introduced in SmPC section 4.4 to adequately inform about the potential risk of abuse associated with the use of solriamfetol.

Decreased appetite was reported in 51/251 (20.3%) of healthy volunteers and 86/935 (9.2%) of the narcolepsy / OSA safety population. Phentermine, which was used in the HAL study as positive control and for which a similar abuse liability was shown, is approved in the US as anorectic (Adipex®). Monitoring of body weight in studies 14-002 resp. 14-003, however, did not point to significant weight loss among included subjects receiving solriamfetol as compared to baseline.

Abrupt cessation of solriamfetol therapy, even after a previous duration of 26-wk treatment, did not lead to any signs of drug withdrawal.

No rebound hypersomnia was observed in those subjects assigned to placebo during the randomized withdrawal periods. As could be expected, sleepiness increased as evidenced by higher ESS scores, but ESS score levels remained below baseline values both in study 14-004 and 14-005.

Angle Closure Glaucoma

Due to the pharmacological properties of solriamfetol (increasing NE signalling), there may be potential to induce mydriasis and precipitate angle closure glaucoma in predisposed individuals. In all studies in narcolepsy and OSA, no TEAEs of acute angle-closure glaucoma were observed in any subjects who received solriamfetol.

Subjects with a history of glaucoma were not explicitly excluded from clinical trials. Ten (10) included subjects (2 narcolepsy and 8 OSA) had a history of glaucoma. Two related events occurred in Study 14-005: One OSA subject reported an AE of worsening glaucoma (received no treatment and the event resolved with continuation of study drug). Another OSA subject without prior relevant medical history reported 1 event of ocular hypertension (treated with latanoprost while continuing participation in the study).

Two TEAEs of mydriasis, which can potentially precipitate or exacerbate acute angle glaucoma, occurred during solriamfetol treatment (1 in an MDD and 1 in a healthy volunteer study), both of which resolved with continuation of study drug.

The warning proposed for section 4.4 of the SmPC was revised to state that under solriamfetol therapy mydriasis may occur. Therefore, caution is advised in patients with increased ocular pressure or risk of angle closure glaucoma.

Serious Adverse Events / Deaths

Overall, 38 patients experienced treatment-emergent SAEs among the 1605 patients using solriamfetol. There was no pattern in SAE, neither with regard to their nature, nor to the dose received. The overall number of SAE was low. The cardiovascular SAEs were primarily reported in subjects with OSA, which is consistent with the high prevalence of cardiovascular comorbidities in that population. One 70-yr old OSA patient died (also reported SAEs bipolar disorder and myocardial infarction) due to sepsis.

Regarding safety population, comparisons of TEAs per age and BMI groups did not reveal any significant increases in TEAE incidence in the elderly and obese populations.

It is agreed that with regard to safety no dose adjustments are required according to body weight.

2.6.2. Conclusions on the clinical safety

The overall AE profile obtained for solriamfetol mainly concerned psychiatric disorders (symptom complex of anxiety, feeling jittery and irritability), nervous system disorders (headache, dry mouth, dizziness), gastrointestinal disorders (nausea, decreased appetite, diarrhoea) and influence on vital signs (BP and HR increase). In most cases a clear dose-response or tendency towards higher incidence with increasing doses was observed.

For the vast majority of ADRs the incidence was similar across the two disease populations, thereby confirming the approach to combine both subgroups into a common safety database.

Overall exposure is considered adequate and solriamfetol's safety profile is concluded to align with the one of other wake promoting treatment alternatives (e.g. modafinil).

However, there are uncertainties which are considered to be three-fold. Firstly, patients with bipolar disorders or schizophrenia were excluded from the trials. On the other hand, there were single cases of subjects developing corresponding serious AE (bipolar disorder with manic episode, confabulation). Therefore, warnings were implemented in SmPC and the incidence of these disorders' symptoms should be monitored as an AE of interest post-marketing.

Secondly, no PD interaction studies were conducted. All medications potentially interfering with sleep (sleeping aids, wake promotors) were prohibited. Therefore, data on interactions with other CNS active substances are sparse.

Ultimately, the safe use of solriamfetol in the OSA patient population which often present with a history of CV events and a number of additional risk factors (obesity, hypertension, diabetes, hyperlipidaemia) was thoroughly evaluated. There remain concerns regarding the dose-dependent increase in vital signs (SBP, DBP, HR) and associated TEAESIs (dose dependency was most prominent in the long term study 14-005).

Given the fact, that both (categorical) vital sign changes and the incidence of TEAEs was highest for the highest 300 mg dose, it is considered that the additional benefit of the 300 mg dose as compared to the second highest

150 mg dose does not outweigh the associated risks in the OSA population. The maximum daily dose in the OSA population is therefore limited to 150 mg once daily. Since measurable efficacy was already observed using the lowest 37.5 mg dose, the proposed dose range for the use of solriamfetol in OSA is defined as 37.5 mg to 150 mg per day.

Non-adherence resp. incomplete compliance with primary OSA therapy is widespread and largely described in the literature. Both compliant and non-compliant subjects were included in study 14-003. Throughout the 12-week treatment period the use of solriamfetol did not have an impact on the use of primary OSA therapy. Based on stratified evaluation of efficacy measures it was shown that there was no significant difference between both subgroups in terms of improved wakefulness and sleepiness over the course of the 12-week treatment period. Overall, with regard to the baseline severity of OSA symptoms, general demographic criteria (age, gender, BMI), adherence resp. non-adherence to primary OSA therapy, and comorbid conditions the 14-003 study population is considered representative for the general OSA population. Stratified evaluation of efficacy measures did not point to significant differences across subgroups.

Besides the dose reductions to 37.5 mg – 150, other risk minimization measures have been included into the SmPC by the Applicant in order to guarantee a safe and appropriate use of solriamfetol. Indeed, the Applicant has accepted revisions to the warnings and precautions section of the SmPC with regard to patient selection, monitoring, and management of the dose-related effects on BP and HR.

Furthermore, patients enrolled in the OSA studies were additionally selected because the eligibility criteria excluded patients who had significant CV disease, including but not limited to: "myocardial infarction within the past year, unstable angina pectoris, symptomatic congestive heart failure (American College of Cardiology/American Heart Association stage C or D), revascularization procedures within the past year, ventricular cardiac arrhythmias requiring an automatic implantable cardioverter defibrillator (AICD) or medication therapy, uncontrolled hypertension, systolic blood pressure $\geq$ 155 mmHg or diastolic blood pressure $\geq$ 95 mmHg (at screening, or consistently across baseline measures according to protocol specifications), or any history of CV disease or any significant CV condition that in the Investigator's opinion could jeopardize subject safety in the study".

In line with the exclusion criteria applied in study 14-003 conditions like "myocardial infarction within the past year, unstable angina pectoris, uncontrolled hypertension, serious cardiac arrhythmias and other serious heart problems" were formally listed as contraindications in SmPC section 4.3.

In the context of reducing the MDD in OSA, the question was also raised for a focused evaluation of the B/R balance for the 300 mg dose in narcoleptic patients. Solriamfetol is described as a substance enhancing dopaminergic resp. noradrenergic neurotransmission. In line with its pharmacological profile, there were dose dependent increases in vital signs (SBP, DBP, HR) in the narcolepsy population with the highest increases observed for the 300 mg dose. Increases in the means for all 3 vital signs parameters also translated into dose-dependent increases in categorical vital sign changes. Interpretation of categorical changes, however, should take into account that categorical vital sign increases were also frequently observed in placebo patients (e.g. SBP > 5 mm Hg 33-34% in both the placebo and 150 mg dose group; 40.5% for 300 mg). In particular for the 300 mg dose group, increases in vital signs (SBP, HR) did not taper shortly after solriamfetol administration in the morning but were maintained during daytime (SBP) or even almost the entire 24-hour dosing interval (HR). Most importantly, however, it is noted that these increases in vital signs (explainable by solriamfetol's inherent mode of action) did not translate into increased incidence of cardiovascular AEs in the narcoleptic population. In pivotal study 14-002 Hypertension / Increased BP was reported by very few subjects without a

clear dose relationship (1 placebo, 2/102 subjects receiving 150 mg, 1/99 subject in the 300 mg group). Overall, as a further safety measure, the maximum daily dose of solriamfetol for the use in narcolepsy was limited to 150 mg in accordance with the dose recommendations given in OSA patients.

Apart from data obtained from abuse liability study 14-001 in recreational drug users, it is noted that there were no signs for drug abuse observed in the target population.

2.7. Risk Management Plan

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 Use in Lactating Women

Pharmacovigilance plan

Table Part III.3 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 prospective, non-interventional, post-authorisation safety study to evaluate the long term safety of solriamfetol in adult patients with obstructive sleep apnoea (OSA) treated with solriamfetol	Primary objective Among patients with OSA managed according to routine clinical practice in Europe and the US: • To estimate and compare the incidence rate of incident major	• Serious CV events (MACE) • Neuropsychiatric events • Abuse, misuse and diversion • Pharmacodynamic (PD) interactions	Protocol submission Progress reports Final report	3 months after granting of the marketing authorization PSURs

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
according to an agreed protocol. Planned	adverse cardiovascular events (MACE) within current person-time exposed to Sunosi™ (solriamfetol) versus current person-time unexposed to Sunosi Secondary objectives • To estimate and compare the incidence rate of individual MACE components (acute myocardial infarction, stroke, and cardiovascular (CV) mortality) within current person-time exposed to Sunosi versus current person-time unexposed to Sunosi and by subgroups defined by: – Patient demographics (i.e. age, gender) – Populations at high CV risk (e.g. hypertension, high body mass index (BMI),			1Q 2024*

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	diabetes, hyperlipidaemia, history of CV event) • Neuropsychiatric events • Sensitivity analysis of the primary objective, whereby patients who receive supratherapeutic doses are identified and removed from the study population to assess for possible aberrant drug-related behaviours • Data on concomitant medications will be collected and events of interest analysed for possible PD interactions			
Post-marketing pregnancy registry (prospective, observational) Planned	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 • Pregnancy outcomes	Annual update	Updates will be provided in the Periodic Safety Update Reports
			Final report	2030
Post-marketing pregnancy registry (retrospective database study) Planned	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	• Reproductive toxicity • Pregnancy outcomes	Final report	TBD

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	following: • Pregnancy outcomes (e.g., live birth, spontaneous abortion, foetal death/stillbirth and induced abortion) • Low birth weight • Minor congenital malformations			
Post-marketing lactation study in healthy volunteers Planned	Primary Objectives: 1) Evaluate solriamfetol pharmacokinetics (PK) in breast milk; 2) Estimate the daily solriamfetol dose received by the infant from the breast milk of the nursing mother. Secondary objective: Assess the safety and tolerability of single oral doses of solriamfetol in healthy postpartum women	• Use in lactating women	Final report	TBD

**The study duration might be extended, depending on the evaluation of the risk difference between exposed and unexposed groups in the development of MACE events and sample size.*

Risk minimisation measures

Table 3: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious CV Events	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4 and 4.8 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 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
Potential for abuse, misuse and diversion	Routine risk minimisation measures: SmPC section 4.4 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.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		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 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Two Post-marketing pregnancy registries
Potential for PD interactions	Routine risk minimisation measures: SmPC sections 4.2, 4.3 and 4.5 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
Use in lactating women	Routine risk minimisation measures: SmPC sections 4.6 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Post-marketing lactation study.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 20 March 2019.The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of solriamfetol with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers solriamfetol to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Sunosi (solriamfetol) is included in the additional monitoring list as it contains new active substance.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Narcolepsy is a chronic sleep disorder which affects the ability to regulate sleep-wake cycles EDS, typically associated with cataplexy (Narcolepsy I) and other REM sleep conditions. The presence of EDS is a defining characteristic of narcolepsy and a major diagnostic criterion. The degree of EDS is severe in most patients. OSA is a serious disorder characterized by sleep fragmentation caused by repeated arousals secondary to partial or complete obstruction of the upper airway during sleep. Persistent EDS is a major presenting complaint in many patients and most patients with OSA awaken in the morning feeling tired and unrefreshed regardless of the duration of their time in bed. As with narcolepsy, the persistent sleepiness in patients with OSA occurs at inappropriate times, for instance while actively conversing, eating, working, and driving (American Academy of Sleep Medicine [AASM] 2014). In the presented studies, both narcolepsy and OSA diagnosis were established according to the International Classification of Sleep Disorders 3rd ed. (ICSD-3). For narcolepsy, about every second narcoleptic patient included in the pivotal trial 14-002 presented with cataplectic events.

The clinical development of solriamfetol follows a symptom-oriented approach, intended to improve wakefulness and reduce EDS. Sunosi film-coated tablets are proposed to improve wakefulness and reduce EDS in adult patients with narcolepsy (with or without cataplexy) (75-150 mg) or obstructive sleep apnoea (OSA) (37.5 – 150 mg).

3.1.2. Available therapies and unmet medical need

Three drugs are authorized in the EU for the "treatment of narcolepsy" in adult patients: sodium oxybate (Xyrem®) for narcolepsy type I, pitolisant (Wakix®) for narcolepsy types I and II and modafinil (Provigil®) considered the first line pharmacological treatment of EDS adult patients with narcolepsy types I or II.

Currently there are no available pharmacological therapies for treating EDS in patients with OSA in the EU. In OSA, positive airway pressure (PAP) applied through a nasal, oral, or oronasal interface during sleep is considered to be the reference standard treatment by the European Respiratory Society (Fietze et al, 2011; Randerath et al, 2011) with the aim to stabilize the upper airway. During clinical trials solriamfetol was used in OSA patients with previous or current use of cPAP. As a wake-promoting agent solriamfetol is not suitable to treat underlying airway obstruction in OSA. Sunosi is not designed as a substitute, but an addition of primary cPAP therapy.

Pathological EDS often continues despite primary treatment of the airway obstruction with positive airway pressure or other therapies (Gay et al. 2006; Fietze et al. 2011; and 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, or surgical intervention (Epstein et al, 2009; Randerath et al, 2011).

Overall, it is concluded that solriamfetol could potentially add to the array of available treatment options in narcoleptic patients (oxybate, pitolisant, modafinil) and could constitute the first medication approved to reduce

EDS in OSA patients. While oxybate (GABA-ergic mechanism) and pitolisant (selective histamine H3 antagonist / inverse agonist) represent distinct pharmacological profiles, there may be more similarities between the molecular mode of action between modafinil and solriamfetol.

3.1.3. Main clinical studies

A comprehensive phase III study programme was undertaken. The primary evidence of solriamfetol's efficacy was derived from two pivotal randomized, double-blind placebo-controlled 12-week trials: study 14-002 in narcolepsy (N=239, randomized 1:1:1:1 to receive fixed-dose JZP 75 mg, 150 mg, 300 mg or placebo) and study 14-003 in OSA (N=476, randomized 1:1:2:2:2 to receive fixed-dose JZP 37.5 mg, 75 mg, 150 mg, 300 mg, or placebo).

Apart from the use of different stratification factor (*presence or absence of cataplexy for 14-002 and subjects' compliant or noncompliant use of their primary OSA therapy for 14-003) and an* additional low-dose arm in study 14-003, both studies were identical in design. The two pivotal trials were complemented by the 6-week, double-blind, placebo-controlled randomized withdrawal study 14-004 in OSA (N=174; 2-wk individual dose titration, 2-wk stable dose treatment, 2-wk randomized withdrawal).

While narcoleptic and OSA patients were separately examined during the preceding phase 2/3 studies, the combined disease populations could enter into a 40- or 52-week open-label extension study (14-005) of JZP 75, 150, 300 mg (including an initial 2-wk titration period and a 2-wk, double-blind, randomized withdrawal period after about 26 weeks of open label treatment).

The population chosen in the pivotal trials is representative of narcoleptic or OSA patients according to the International Classification of Sleep Disorders (ICSD-3). Included patients presented with moderate to severe EDS, as evidenced by their ESS scores at baseline.

Narcolepsy patients were stratified for presence of cataplectic events (around 50% at baseline), OSA patients were stratified for compliance (approx. 70%) vs non-compliance with primary OSA therapy (i.e. PAP). Throughout the trials primary OSA therapy was allowed to be continued, however, any medication interfering with sleep (stimulants, amphetamines, hypnotics, sodium oxybate, modafinil etc.) had to be washed out before study entry. Subjects were excluded if presenting with significant cardiovascular disease, bipolar related and other psychiatric (apart from depression) disorders (incl. suicidal ideation).

The efficacy of solriamfetol in reducing EDS and improving wakefulness throughout the day was demonstrated using both objective (MWT, polysomnographic incl. EEG recording, in minutes, lower values indicating decreased ability to stay awake in soporific ambiance) and subjective measures including both the ESS (self-administered questionnaire to reflect the patient's propensity to fall asleep in 8 typical everyday situations, scale 0-24, higher values pointing to higher sleepiness), and the PGIc scale (key secondary endpoint). MWT and ESS were defined as co-primary endpoints. The efficacy measures are validated in both patient populations and were adequately chosen.

The pivotal trials 14-002 and 14-003 were complemented by 6-week randomized withdrawal study 14-004. Contrary to studies 14-002 and 14-003, which followed a fixed dose arm design, subjects in study 14-004 titrated solriamfetol individually over the first two weeks of treatment. Long-term maintenance of efficacy was examined in 1-yr extension study 14-005, which primarily was designed as open-label. Following FDA advice, a 2-wk intermittent double-blind randomized withdrawal period after 26-week open label treatment was included with Protocol Amendment 3, thereby increasing clinical meaningfulness of study 14-005 in terms of efficacy.

3.2. Favourable effects

In narcolepsy study **14-002**, for the co-primary MWT and ESS efficacy endpoints (change from baseline) a clear dose-dependent effect was observed delivering highly significant ($p < 0.0001$) superiority over placebo for the 150 mg and 300 mg dose arm. As concerns MWT, in both arms patients achieved maintenance of wakefulness more than twice as long as compared to baseline (150 mg: from 7.85 min at baseline to 17.67 min at week 12; 300 mg: from 8.73 min at baseline 19.91 min at week 12 [means]). Also for the lowest JZP 75 mg dose arm, maintained wakefulness improved, however, the change from baseline does not significantly separate from placebo (change from baseline [min]: placebo 2.12, JZP 75 mg: 4.74 [-1.04, 6.28; p=0.1595]).

For the co-primary ESS endpoint, in absolute figures, the decline in subjective, self-assessed propensity to fall asleep in typical everyday situations was more modest, however, still highly significant over placebo for the two higher doses EDS (150mg: from 17.0 ESS score at baseline to 11.5 ESS score at week 12; 300mg from 17.2 ESS score at baseline to 11.1 ESS score at week 12.)

The clinical relevance of the achieved difference over placebo was underlined by post-hoc cumulative distribution analyses for ESS demonstrating that only 15.5% of placebo patients achieved an ESS score $\leq$ 10, however, the rate was doubled in the 75 mg dose arm (30.5%) and more than tripled for the highest 300 mg dose (49.2%).

In OSA study **14-003**, baseline disease severity in terms of ESS (14.8 -15.6 min) and MWT-MSLT (12.00 – 13.64 min) was less pronounced as compared to the narcolepsy population of study 14-002.

For the two co-primary MWT and ESS efficacy endpoints (change from baseline) a dose-dependent effect was observed delivering significant superiority over placebo for the 75 mg, 150 mg and 300 mg dose arms. In these 3 arms patients achieved maintenance of wakefulness about twice as long as compared to baseline (75 mg: from 12.44 min at baseline to 21.79 min at week 12; 150 mg: from 12.54 min to 23.64 min; 300 mg: from 12.10 min to 25.28 min at week 12 [means]). Also, for the lowest JZP 37.5 mg dose arm (proposed as starting dose in subjects with severe renal impairment), maintained wakefulness improved significantly (change from baseline [min]: placebo 0.21, JZP 37.5 mg: 4.74 [1.16, 7.90; p=0.0086]).

Hence, results for MWT in the OSA population were overall more positive as compared to the results obtained in narcoleptic patients (study 14-002: 75 mg dose arm did significantly separate from placebo).

Post-hoc cumulative distribution analysis demonstrated that placebo response (in terms of ESS) was more pronounced in OSA patients as compared to narcoleptic patients. While in study 14-002 only 15.5% of subjects allocated to placebo achieved ESS scores $\leq$ 10, the respective portion of OSA subjects receiving placebo was 37.7%. On the other side, the treatment effect in JZP dose groups was also higher for OSA patients: In study 14-003, more than 70% of subjects receiving 150 mg resp. 300 mg JZP achieved ESS scores $\leq$ 10.

Robustness of the results for the co-primary endpoint of both pivotal studies was shown by calculating a set of four sensitivity analyses, largely confirming the results obtained with the primary MMRM method.

As regards a potential influence of JZP on the number of cataplectic events in narcolepsy patients, there was no consistent pattern across dose arms. It is therefore rather unlikely that there is a clear positive impact of solriamfetol on the cataplectic attack frequency. On the other hand, there is no signal that cataplexy may be negatively influenced by solriamfetol treatment.

MWT testing is time-consuming, it spans over approximately 9 hours post-administration since the five testing sessions (up to 40 min duration per session) are separated by 2-hours intervals. Looking separately at the 5 consecutive testing sessions per day, for the 150 mg and 300 mg dose arm the difference over placebo remains significant for each of the five sessions. There is no clear sign for a declining effect over the course of the testing day.

In both pivotal trials, for both primary efficacy endpoints the main effect is achieved within the first week of treatment. Thereafter the effect is maintained in a dose-related manner over the entire 12-week treatment period. Furthermore, in both populations the study outcome in terms of the key secondary PGIc endpoint fully goes along with the results for the MWT and ESS co-primary endpoints.

Results obtained from the two pivotal studies are complemented by 6-week randomized withdrawal study **14-004**. Solriamfetol was individually titrated to an efficacious and tolerable dose in study 14-004, which is considered to provide valuable information for clinical practice. Starting with 75 mg once daily, the patient could escalate the dose by one dose step every 3 days up to a maximum of 300 mg once daily. Dose titration was successfully completed by 90.2% (157/174) of included subjects. More than every second subject completing the titration period (84/157, 53.5%) titrated up to the highest 300 mg dose (150 mg: 50/157, 31.8%; 75 mg: 23/157, 14.6%). After further 2 weeks of stable dose treatment subjects presenting with a positive treatment effect at week 4 ("much" or "very much improved" on PGIc plus numerical improvements in terms of MWT and ESS) were eligible for entering the randomized withdrawal period.

Subjects who continued to receive solriamfetol in the Double-blind Withdrawal Phase maintained the treatment benefits noted at Week 4, with little change in mean sleep latency (-0.96 minutes) and minimal change in ESS score (-0.1; for all JZP dose arms combined). In contrast, the placebo group showed a mean reduction of 12.11 (1.316) minutes in mean sleep latency and a 4.5 increase in ESS score at the end of the Double-blind Withdrawal Phase, resulting in statistically significant LS mean differences of 11.16 minutes on the MWT and -4.6 on the ESS ($p < 0.0001$ for both measures).

After abrupt treatment cessation, the ability to maintain wakefulness and daytime sleepiness worsen, however, no rebound hypersomnia was noticed. Values for MWT and ESS at the end of the randomized withdrawal period are still favourable, if compared with baseline at study entry.

There were no signs of withdrawal symptoms.

Maintenance of effect was demonstrated in long term extension study **14-005** in both the narcoleptic (226/643, 35.1%) and OSA (417/643, 64.9%) subpopulations.

3.3. Uncertainties and limitations about favourable effects

The clinical development programme of solriamfetol did not include an active comparator arm. While no medication is approved to reduce EDS in OSA patients, the inclusion of an active comparator would have been useful for a better contextualization of efficacy and safety results in narcoleptic patients. However, the CHMP agrees that comprehensive clinical data under placebo control are at hand that suffice to strike the benefit risk balance.

No dose-response data were provided informing about sub- or supra-therapeutic doses in the target population. However, doses tested during phase II study ADX-N05 202 were taken over into phase III (150 mg, 300 mg)

and delivered efficacy results superior over placebo. As regards safety, data on supra-therapeutic doses (obtained from PK and MDD studies) were provided.

In terms of the co-primary endpoint MWT, numerical improvements over placebo were shown, however, not significant, for the 75 mg lowest dose arm in narcolepsy study 14-002. In OSA study 14-003, however, MWT results for the 75 mg dose arm were highly significant. Significance was also achieved for the lowest 37.5 mg dose arm (MWT, p=0.0086; 37.5 mg is proposed as starting dose in subjects with OSA). Furthermore, in study 14-002 the 75 mg dose arm delivered significant results for the other co-primary endpoint (ESS, p=0.0211). Given the fact that solriamfetol is proposed to be individually titrated according to efficacy and tolerability, the non-significant MWT result for the 75 mg dose arm in study 14-002 is of low concern.

In absolute figures, ESS results were more favourable in OSA as compared to narcolepsy patients. Throughout the entire timespan from baseline of the parent study to baseline of study 14-005, and the titration effect until the end of the 40-wk open label phase, ESS scores in narcoleptic subjects were higher as compared to OSA subjects. This, however, was not considered to question the efficacy of solriamfetol in narcolepsy patients, since for improvement of EDS significant (75 mg) or highly significant (150 mg, 300 mg) placebo superiority was shown in the pivotal narcolepsy trial (14-002).

Subjects with moderate or severe OSA on the baseline PSG were excluded from participation in narcolepsy study 14-002, in order to uniquely demonstrate efficacy in narcoleptic patients (and not in mixed clinical conditions). However, in up to 25.4% of included subjects (150 mg arm) sleep apnoea syndrome was reported (percentages were lower in other doses: 18.6% for 75 mg and 11.9% in the 300 mg arms).

Solriamfetol shares mood increasing properties; however, factors in the assessment of ES, such as depression for both the conditions and fatigue in OSA were not taken into account in the evaluation of treatment effect. In particular, results on the PGIc endpoint may be related not only to the effect on ES but also confounded by an effect on mood.

The recommended starting dose is 75 mg once daily in narcolepsy and 37.5 mg in OSA patients. Depending on clinical response, the dosage can be titrated to a higher level by doubling the dose at intervals of at least 3 days. Studies 14-002 and 14-003 followed a fixed dose arm design. Solriamfetol was titrated in studies 14-004 and 14-005. In study 14-004, however, ESS was only recorded at the beginning and the end of the 2-week initial titration process. It is therefore unclear how up- or down-titration could be efficacy-driven given the schedule of assessment. From the wording of the titration process in the study 14-005 Protocol, "investigators were instructed to titrate to the maximum dose that was tolerated to maximize therapeutic efficacy", this would correspond to a dose escalation scheme rather than dose titration.

Given the fact, that both (categorical) vital sign changes and the incidence of TEAEs (see unfavourable effects below) was highest for the highest 300 mg dose, the question arises for the additional benefit of the 300 mg dose as compared to the second highest 150 mg dose.

In the OSA pivotal trial (14-003) the response was dose dependent, however, in particular in terms of the ESS co-primary endpoint the difference between the 150 mg and the 300 mg dose arm was modest: mean ESS scores after 12 weeks of treatment were decreased to 7.5 resp. 7.1 with the 150 mg resp. 300 mg dose.

For the responder analysis, the portion of subjects achieving an ESS score < 10, the difference between the two dose arms was small (70.0% resp. 73.0% for the 150 mg resp. 300 mg dose).

For the second MWT co-primary endpoint the difference between the two highest doses is clearer, however, it is noted, that in both dose arms (and also in the 75 mg dose arm) the MWT score is > 19.4, which is considered the minimum wakefulness score in healthy subjects according to the literature.

It is concluded, that although efficacy results in OSA patients were largely dose dependent, the additional benefit (in terms of ESS, MWT, responder analysis) obtained from the highest 300 mg dose as compared to the second highest 150 mg dose in only modest.

3.4. Unfavourable effects

Overall exposure is considered adequate. N=1605 unique subjects were exposed (thereof healthy volunteers, MDD patients from a previous clinical trial programme and N=935 subjects of the OSA / narcolepsy target population). Exposure was at least 6 months for 531 subjects and at least 12 months for 281 subjects. Broken down to minimum requirements on patient exposure over one year per subpopulation, 95 narcoleptic and 186 OSA patients received solriamfetol for $\geq$ 12 months.

Baseline characteristics in terms of age, sex, BMI and co-morbidities are considered to typically represent the target OSA and narcoleptic subpopulations. Obesity is common among OSA patients, as reflected by the baseline BMI in recruited OSA patients (33-34 kg/m^2). Apart from the high BMI value, OSA patients often present with medical history suggestive of metabolic syndrome. A considerably higher portion of recruited OSA subjects (as compared to narcolepsy) received concomitant antihypertensive medication, lipid modifying agents, antidiabetics and insulin.

While subjects with bipolar disorders or schizophrenia were excluded from phase III studies, about a quarter of subjects included in pivotal studies 14-002 (25.8%), 14-003 (23.1%) and long-term study 14-005 presented with comorbid depression (narcolepsy 26.5%, OSA 22.5%).

In the studies in narcolepsy and OSA, the SOCs with the highest incidence of AEs were Gastrointestinal Disorders, Nervous System Disorders, Psychiatric Disorders, and Infections and Infestations; except for Infections and Infestations, the incidence in these SOCs was higher with solriamfetol than with placebo in the 12-week studies.

The summary of AEs per SOC, disease subpopulation and treatment duration showed a general tendency for higher AE incidence in the narcoleptic population as compared to OSA patients (with the most striking difference for Nervous System Disorders: Pool 1: narcolepsy 27.27%, OSA 16.71).

Cardiac disorders (SOC 3-times elevated over placebo) mainly refer to palpitations and increase of heart rate. The higher incidence of SOC Psychiatric Disorders reflects the symptom complex of anxiety, feeling jittery and irritability. Nervous System Disorders mainly correspond to headache, dry mouth and dizziness. Further groups of AEs occurring more often in JZP treatment (as compared to placebo) concern the gastrointestinal system (nausea 9.25%, decreased appetite 9.08%, diarrhoea 5.24%, constipation 2.09%), respiratory tract infections (nasopharyngitis, sinusitis, cough) and bone / muscle related AEs (arthralgia, muscle spasms, myalgia).

Broken down to the four dose levels of JZP examined throughout the 12-wk trials, there was either a clear dose-response relationship for AEs (headache, decreased appetite, anxiety, diarrhoea, dry mouth), a tendency towards higher incidence with increasing dose (nausea, insomnia, dizziness, feeling jittery, heart rate increased) or no dose response relation discernible (nasopharyngitis, palpitations, sinusitis, constipation, arthralgia, muscle spasms).

Adverse events of interest (e.g. depression / suicidality, anxiety / irritability, cardiovascular effects, angle closure glaucoma), the abuse potential and intrinsic / extrinsic factors potentially requiring particular dose recommendations were adequately addressed.

Overall, solriamfetol's safety profile is concluded to align with the one of other wake promoting treatment alternatives (e.g. modafinil).

Vital sign measurement (BP, HR) was undertaken within three different testing settings (at each clinical study visit [with no relationship to dosing time], through multiple sequential measurements on MWT testing days [at fixed times relative to dosing], and through 24-hour ambulatory BP monitoring (ABPM) while subjects were in the outpatient environment with no relationship to dosing time). Thereby, a comprehensive data package was provided.

Across the vital sign change categories, almost consistent dose dependency for SBP, DBP, and HR increases was observed. Importantly, portions of patients with categorical increases in vital signs was consistently highest for the 300 mg dose arm.

Summaries of TEAESI by dose level and disease population of study 14-005 were provided. Focussing on TEAESIs of HR Increased, BP Increased, and Palpitations, a clear dose-dependent increase in incidence rates is observed in the overall population (OSA + narcolepsy) in all three cases.

In long-term study 14-005 an incidence rate of 5.3% (22/417) OSA subjects with hypertension / BP increase was observed, which is not considered unexpectedly high. On the other side, a clear dose dependency was observed in study 14-005 for TEAESIs of HR Increased, BP Increased, and Palpitations across the solriamfetol dose arms, which is plausible given the dose dependent categorical change in vital signs (BP, HR) observed after solriamfetol administration, and the pharmacological mode of action (increasing NE and DA neurotransmission) of this wake-promoting agent.

3.5. Uncertainties and limitations about unfavourable effects

A very comprehensive data package was provided regarding monitoring of vital sign changes and the potential association with TEAESIs. Uncertainty about unfavourable CV effects (in particular in OSA patients) is not caused by a lack of data within the constraints of a maximum of a 1-year long term observation period.

To some degree, instead, interpretation of the clinical implications of the observed increases in BP and HR is compromised by concerns about the representativeness of the recruited OSA population, since subjects with present significant CV disease were excluded from the phase III studies. This, however, is acceptable within the given clinical trial scenario. Respective warning statements alert the prescribing physician on the use of solriamfetol in patients with unstable CV disease, serious heart arrhythmias and other serious heart problems.

Patients with bipolar disorders or schizophrenia were excluded from the trials. On the other hand, there were single cases of subjects developing corresponding serious AE (bipolar disorder with manic episode, confabulation). Therefore, respective patients with a history of bipolar disorder were not proposed to be contraindicated and respective warnings were implemented instead.

No PD interaction studies were conducted. While in particular OSA patients presented with an extensive list of concomitant medication (antihypertensives, antidiabetics, lipid modifying agents etc.), all medications potentially interfering with sleep (sleeping aids, wake promotors) were prohibited. Therefore, data on PD interactions with other CNS active substances are sparse.

Dopamine and noradrenaline have been implicated in the physiological/pathophysiological regulation of the activity of the HPA axis. Inhibitors of dopamine and noradrenaline reuptake in the CNS (like cocaine and amphetamines) have been shown to activate the HPA axis and this effect has been considered to be involved in

the increased morbidity and mortality rate associated with the (chronic) application of these drugs. The question whether solriamfetol activates the HPA axis is therefore not trivial. While the available nonclinical data were not considered sufficient to allow for definite conclusions concerning an activation of the HPA axis by solriamfetol, they raise considerable concern. Clinical data concerning effects of solriamfetol on main components of the HPA axis (i.e. CRH, vasopressin, ACTH, cortisol) are not available.

3.6. Effects Table

Table 1. Effects Table for Sunosi

Effect	Short description	Unit	Treatment (SE)	Control (SE)	Uncertainties / Strength of evidence	References
Favourable Effects (150mg)						
ESS change from baseline (narcolepsy)	excessive daytime sleepiness		-5.4 (0.66)	-1.6 (0.65)	p < 0.0001	14-002
MWT change from baseline (narcolepsy)	Mean sleep latency	min	9.77 (1.33)	2.12 (1.29)	p < 0.0001	14-002
ESS change from baseline (OSA)	excessive daytime sleepiness		-7.7 (0.44)	-3.3 (0.45)	p < 0.0001	14-003
MWT change from baseline (OSA)	Mean sleep latency	min	10.96 (0.97)	0.21 (1.0)	p < 0.0001	14-003
Unfavourable Effects						
Headache		%	13.96	7.96		
Nausea		%	9.25	4.87		
Decreased appetite		%	9.08	0.88		
Anxiety		%	6.81	0.44		

Abbreviations: MWT: Maintenance of Wakefulness Test; ESS: Epworth Sleepiness Scale; OSA: Obstructive Sleep Apnoea

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A symptom-oriented approach is followed in solriamfetol's clinical development programme, intended to improve wakefulness and reduce EDS in adult patients with narcolepsy or obstructive sleep apnoea. Efficacy was measured using meaningful clinical co-primary endpoints (objective MWT [incl. EEG recording] and subjective self-assessed ESS). The observed clinical benefit is considered relevant across both sub-populations and was shown to be robust. Other clinical symptoms of narcolepsy (e.g. the number of cataplectic events) were

unaffected by solriamfetol treatment, thereby confirming the symptom-oriented approach. Similarly, the symptomatic treatment of EDS with solriamfetol would not affect the pathophysiology of OSA being upper airway obstruction the leading cause of hypoxia and hypercapnia during sleep -important determinants of daytime ES- and increased CV risk.

The target populations were adequately chosen. Improvement in EDS was observed early after treatment initiation within 1-2 weeks and was shown to be maintained over (at least) one year. Initially solriamfetol was proposed to be used with a maximum daily dose of 300 mg in both conditions. Based on considerations about the balance between the added benefit of the 300 mg dose (as compared to the second highest 150 mg dose) on the one side and the associated safety risks on the other side, the Applicant agreed to limit the dose ranges to 37.5 – 150 mg in OSA and 75 - 150 mg in narcolepsy.

Solriamfetol molecular mode of action is described as being based on selective dopamine and norepinephrine reuptake inhibition (DNRI), thereby leading to enhanced dopaminergic resp. noradrenergic signalling. As could therefore be expected, the overall AE profile obtained for solriamfetol mainly concerned psychiatric disorders (symptom complex of anxiety, feeling jittery and irritability), nervous system disorders (headache, dry mouth, dizziness), gastrointestinal disorders (nausea, decreased appetite, diarrhoea) and influence on vital signs (slight HR increase). In most cases a clear dose-response or tendency towards higher incidence with increasing doses was observed.

Cardiac disorders (SOC 3-times elevated over placebo) mainly refer to palpitations and increase of heart rate. Abuse potential for solriamfetol was shown in recreational drug users. In the target population, however, there were no signs for abuse. After abrupt treatment cessation in two randomized trials, no signs for drug withdrawal were observed.

Adverse events of interest (e.g. depression / suicidality, anxiety / irritability, cardiovascular effects, angle closure glaucoma), the abuse potential and intrinsic / extrinsic factors potentially requiring particular dose recommendations were adequately addressed.

With regard to the OSA subpopulation, treatment with PAP or other therapies (e.g. oral appliances, surgical procedures) is considered primary therapy to treat the underlying airway obstruction and to reduce EDS. However, there is a proportion of patients that continue to suffer from pathological EDS for multiple causes, probably related to residual hypoxia- and/or sleep fragmentation, despite an optimized primary therapy of the airway obstruction or because of the need to interrupt the primary OSA therapy for reasons related to intolerance or non-compliance. The OSA population examined in the clinical trial programme contained both patients adherent or non-adherent to primary OSA therapy and was stratified accordingly.

It is therefore concluded that baseline severity of OSA symptoms, general demographic criteria (age, gender, BMI), adherence or non-adherence to primary OSA therapy, and comorbid conditions in the 14-003 study population are considered representative for the general OSA population. Statistically significant and clinically relevant improvement of wakefulness and reduction of EDS was shown in the studied OSA population. Stratified evaluation of efficacy measures did not point to significant differences across subgroups. A subpopulation with an expected more pronounced benefit could not be identified.

The narcolepsy population was substantially younger (narcolepsy ~36 years vs OSA ~54 years), of lower body mass index (narcolepsy ~28-29, OSA ~33), and had a lower rate of comorbidities related to hypertension, hyperlipidaemia, and diabetes mellitus as compared to the OSA population. This is also reflected by the lower percentage of narcoleptic subjects receiving concomitant medications for these conditions as compared to the OSA population. Also, the recruited narcolepsy patients are considered representative in terms of disease severity. Given the differences in medical history (e.g. hypertension: narcolepsy 16.9-20.3%, OSA 48.7-50.4%)

and other general demographic factors (BMI etc.) it is acknowledged that narcoleptic patients are less prone to CV risks as compared to OSA patients.

Statistically significant and clinically relevant improvement in terms of maintained wakefulness and reduction of EDS was shown in the narcolepsy population.

3.7.2. Balance of benefits and risks

Overall, it is concluded that the benefits outweigh the risks in both the OSA (37.5 mg to 150 mg) and narcolepsy (75 mg to 150 mg per day dose range) subpopulations. Apart from the revised dose range, this conclusion is to be seen in the context of revisions implemented in sections 4.1, 4.3 and 4.4 of the SmPC. In line with the exclusion criteria applied in study 14-003 and given the observed CV risk profile of solriamfetol conditions like "myocardial infarction within the past year, unstable angina pectoris, uncontrolled hypertension, serious cardiac arrhythmias and other serious heart problems" were formally listed as contraindications (4.3).

In the clinical trials OSA patients were included either adherent or non-adherent to standard OSA therapy intended to prevent airway obstruction, e.g. CPAP. The use of solriamfetol as a symptomatic treatment approach is indicated only in those patients with OSA that are not satisfactorily treated by primary OSA therapy, such as continuous positive airway pressure (CPAP). The indication wording in SmPC section 4.1 was revised accordingly.

Furthermore, in SmPC section 4.2 it is stated that Sunosi is not a therapy for the underlying airway obstructions and that primary OSA therapy should be maintained in these patients.

At the top of SmPC section 4.2 information was included to alert the prescribing physician to assess blood pressure and heart rate before initiating treatment with solriamfetol. Likewise, the patient is to be monitored during treatment and the need for continued treatment is to be assessed periodically.

The revised and strengthened warning notes on the risks of BP elevations and associated requirements to thoroughly examine the patient before treatment initiation and throughout treatment apply to both narcoleptic and OSA patients.

In essence, it is concluded that the B/R balance of Sunosi for improvement of wakefulness and reduction of excessive daytime sleepiness is positive in both disease populations given the risk minimization measures as specified above.

3.7.3. Additional considerations on the benefit-risk balance

NA

3.8. Conclusions

The overall B/R of Sunosi is positive.

Divergent position is appended to this report.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Sunosi is not similar to Wakix within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision (30 out of 32 votes) that the benefit-risk balance of Sunosi is favourable in the following indication:

Sunosi is indicated to improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy (with or without cataplexy).

Sunosi is indicated to 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).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being

received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that solriamfetol is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

5. Appendices

1. Divergent positions to the majority recommendation

APPENDIX

DIVERGENT POSITION DATED 14 November 2019

DIVERGENT POSITION DATED 14 November 2019

Sunosi EMEA/H/C/004893/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Sunosi (solriamfetol) for the indication improving wakefulness and reducing excessive daytime sleepiness 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).

The reasons for the divergent opinion are the following:

- The documented symptomatic benefits of solriamfetol in the dose range of 75 mg to 150 mg for the management of OSA does not outweigh its potential risks, following concerns over its safety; apparent cardiovascular side effects in terms of increased blood pressure and heart rate;
- the currently available data on the incidence of cardiovascular adverse events is based on a relatively healthy patient population, and cannot be extrapolated to the patient population at large that would receive solriamfetol, even with the proposed contraindications in place;
- nevertheless that solriamfetol is currently contraindicated in patients with a myocardial infarction within the past year, unstable angina pectoris, uncontrolled hypertension, serious cardiac arrhythmias and other serious heart problems, an increased risk can also apply to patients with OSA to be treated with solriamphetol following the approved indication. Obstructive sleep apnea in itself is an important risk factor for cardiovascular disease, and patients with OSA are likely to be at risk of cardiovascular disease.
- the applicant did propose measures to reduce this risk, but the measures are considered difficult to implement in practice. The proposed contraindications and warnings are considered insufficient to adequately control the risk of cardiovascular events;
- finally, it is highly questionable if more information on the risk of CV events can be achieved from the proposed PASS to evaluate long-term safety of solriamfetol in adult patients with OSA taking into consideration the observational nature of the study, conducted in routine clinical practice, and the low incidence rate of major adverse cardiovascular events.

For the aforementioned reasons, the marketing authorisation application is considered to be not approvable.

Johann Lodewijk Hillege (NL)
Natalja Karpova (LV)