10 November 2022
EMA/CHMP/894270/2022

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Sunosi

solriamfetol

Procedure no: EMEA/H/C/004893/P46/005

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment				
PAM number				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	12.09.2022	12.09.2022	☐
☐	Rapporteur's preliminary Assessment Report	17.10.2022	17.10.2022	☐
☐	CHMP Members comments	28.10.2022	28.10.2022	☐
☐	Updated Rapporteur's Assessment Report	03.11.2022	N/A	☐
☒	CHMP adoption of conclusions:	10.11.2022	10.11.2022	☐

Administrative information

CHMP Rapporteur contact person	**Name: Yasemin Atar** Email: paediatric@bfarm.de
CHMP Rapporteur's assessors	**Name: Michael Bühlen** Email: paediatric@bfarm.de
Product Lead/Risk management specialist/ Quality Specialist	**Name: Marta Kollb-Sielecka** Email: Marta.Kollb-Sielecka@ema.europa.eu

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1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

The MAH submitted a post-authorisation measure (PAM) for Study JZP865-101 to satisfy the requirements of Article 46 of Regulation (EC) No 1901/2006.

Study JZP865-101 is part of the agreed EU Paediatric Investigation Plan development program for Sunosi (EMEA-002184-PIP01-17).

Sunosi was approved via a centralised procedure on 16/01/2020. It is indicated

- to improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy (with or without cataplexy)

  and

- 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).

2. Summary of data submitted

An Open-label, Single Ascending Dose Study to Evaluate the Pharmacokinetics and Safety of Solriamfetol in Pediatric Subjects With Narcolepsy (Study No. JZP865-101, EudraCT No. 2019-003008-11)

Study JZP865-101 was a phase 2a, multi-centre, open-label, 3-period, fixed-sequence, single ascending dose (SAD) study to evaluate the efficacy, PK, and safety of solriamfetol in pediatric participants (6 to < 18 years old) with narcolepsy. It was sponsored by Jazz Pharmaceuticals, Palo Alto, CA.

Time schedule

Date of protocol	28.10.2019 (original), 10.01.2021 (2nd Amendment)
Study initiation	25.11.2020
Study completion	04.02.2022
Date of final report	15.07.2022

Study JZP865-101 was designed to characterize the PK in pediatric participants and evaluate the safety profile, to inform dose selection for future pediatric studies, and to provide preliminary efficacy data on solriamfetol in the pediatric population.

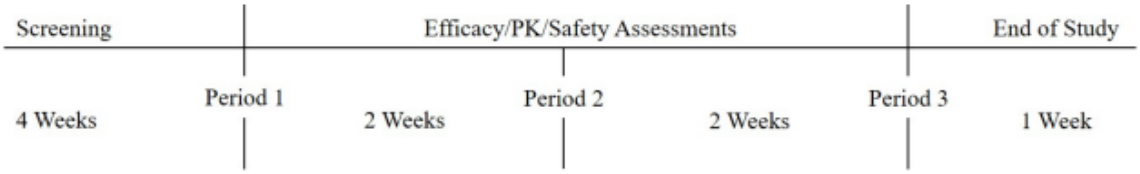
Dose selection for this study was based on population PK simulations from adult PK data and the calculated safety margins from the juvenile toxicology study.

A total of 4 centres from France, Belgium, and Italy enrolled and dosed participants in this study.

The study comprised the following periods:

Screening Period for up to 28 days, 3 Treatment Periods during which participants were administered ascending doses of study intervention, and an End of Study Period (7 ± 2 days after Period 3 dose) to collect final safety evaluations. Each Period begins at Day -1 for Check-in. Single doses are administered on Day 1, followed by safety and efficacy testing for up to 10 hours on the same Day. Periods are separated by wash-out periods of 14 ± 2 days.

Figure 1 Design of Study JZP865-101



Note: Periods 1, 2, and 3 will be separated by washout of 14 ± 2 days. Dose will be escalated only if the previous dose was tolerated.

Pediatric participants with a diagnosis of narcolepsy according to ICSD-3 criteria, or with the permission of the medical monitor, completed a Multiple Sleep Latency Test (MSLT) during screening to confirm the diagnosis of narcolepsy by ICSD-3 criteria (ie, the participant met all other ICSD-3 criteria for narcolepsy).

Twelve pediatric participants who satisfied all eligibility criteria, 6 participants in each age group received study intervention. During screening, an attempt was made to enrol an equal number of male and female participants in each group as well as to enrol at least 2 participants below the age of 9.

- **Group 1**: adolescents 12 to < 18 years old
- **Group 2**: children 6 to < 12 years old)

Table 1 Treatment and Dosing Schedule (Solriamfetol)

Age Group	Period 1	Period 2	Period 3
Group 1, 12 to < 18 years (N = 6)	75 mg	150 mg	300 mg
Group 2, 6 to < 12 years (N = 6)	37.5 mg	75 mg	150 mg

Each participant received 3 ascending doses of solriamfetol, a single dose in each Treatment Period, with a Washout Period of 14 ± 2 days separating the consecutive dosing Treatment Periods within each age group. To minimize intra- and inter-participant variability, the single dose was administered with 240 mL of water in the morning approximately 2 hours after completing a light breakfast.

The bioanalytical analyses were performed by a central bioanalytical laboratory. Determination of solriamfetol in plasma was performed using validated methods consisting of extraction and then analysis using liquid chromatography/mass spectrometry. The bioanalytical method measured solriamfetol in human matrix over 8.42-4210 ng/mL (10.0-5,000 ng/mL for HCl salt) (refer to Bioanalytical Method Validation). Details of the sample analysis are presented in the Bioanalytical Study Report.

Table 2 Objectives and endpoints, Study JZP865-101

Objectives	Endpoints
Primary	
• To evaluate the efficacy in improving wakefulness in pediatric participants with narcolepsy.	• Change in PSS score from Day 1 predose to time of individual T_{max} postdose for each period. • CGIc score on Day 1 relative to Day -1 for each period.
• To characterize the PK of single doses of solriamfetol in pediatric participants with narcolepsy.	• PK parameters including, but not limited to, C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, $t_{½}$, CL/F, and Vd/F at each solriamfetol dose in each age group.
Secondary	
• To assess the safety and tolerability of single doses of solriamfetol in pediatric participants with narcolepsy.	• Change in PSS score from Day 1 predose to 1, 2, 3, 4, 6, 8, and 10 hours postdose for each period. • Percentage of participants with a CGIc of "much improved" or "minimally improved" on Day 1 relative to Day -1 for each period. • The occurrence of and/or change in: AEs, vital signs, physical examinations, 12-lead ECG, clinical laboratory tests, C-SSRS, and serum/urine pregnancy tests (if applicable).

Abbreviations: AE = adverse event; AUC_{0-inf} = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; CGIc = Clinical Global Impression of change; CL/F = apparent oral clearance; C_{max} = maximum (peak) plasma drug concentration; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; PK = pharmacokinetic(s); PSS = Pictorial Sleepiness Scale; $t_{½}$ = half-life; T_{max} = time to reach maximum (peak) plasma concentration; Vd/F = volume of distribution.

Efficacy, Pharmacokinetic, and Safety Assessments (Periods 1, 2, and 3)

Each subject in each age group will receive 3 single oral doses of solriamfetol (if tolerated) during 3 separate periods, in an ascending manner. Dosing in Group 2 (children 6 to < 12 years old) will not start until the dosing in Group 1 (adolescents 12 to < 18 years old) is complete.

Within Group 1 and Group 2, each subject will be allowed to dose escalate from Period 1 to Period 2 and from Period 2 to Period 3 independently of other subjects in the same group. Within each age group, however, not more than 2 subjects can receive the same dose at the same time. A safety evaluation for each subject will be performed by the Safety Review Committee, composed of the principal investigator (or designee) and Jazz medical/clinical staff, before the next higher dose can be received for each subject. The safety evaluation will also include all available safety data from all subjects at any dose level.

In performing these safety evaluations as each subject dose escalates from a lower to a higher dose, the Safety Review Committee will review each subject's safety data in alignment with the known safety profile of solriamfetol. The safety data will include, but not be limited to, vital signs, ECGs, C-SSRS, and AEs. Once each safety review has concluded that adequate safety and tolerability have been demonstrated, each subject will be permitted to proceed to the next higher dose.

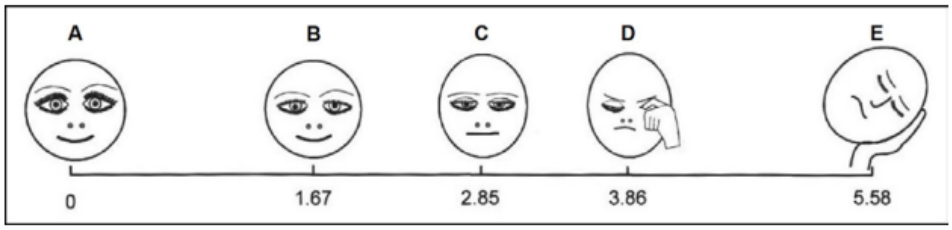
Once the last subject in Group 1 has completed the last study period, PK will be assessed for all subjects in this group. The safety, tolerability, and PK data from all subjects/doses in Group 1 will be reviewed by the Safety Review Committee before dosing can begin in Group 2.

For both Group 1 and Group 2, if 1 subject experiences a study drug-related serious adverse event (SAE), dosing at that level will be withheld until a full safety evaluation is performed and dose continuation at that level is deemed to be safe by the Safety Review Committee.

Efficacy will be assessed by the Pictoral Sleepiness Scale (PSS) and Clinical Global Impression of Change (CGIc) for all subjects (Group 1 and Group 2) in Periods 1, 2, and 3.

The PSS is a pictorial scale used to measure instantaneous perceived sleepiness. The assessment consists of 5 cartoon faces depicting increasing degrees of sleepiness. The faces are designed to be devoid of gender and ethnic features (Maldonado 2004). Use of pictorial representations of sleepiness was selected to facilitate self-report by young children, who may have difficulty completing a verbal or geometric (visual analogue) scale. Subjects will choose the face that best describes how sleepy or alert they feel at that time. Each response will be converted to a numerical ranked score for analysis. For each dosing period, the Day 1 pre-dose assessment will be considered baseline for comparison with the post-dose assessments.

Below, the faces are shown in order from most alert to most sleepy (A through E, with A corresponding to most alert and E corresponding to most sleepy). For statistical analysis, each choice is converted to its corresponding numerical value.



Source: Maldonado 2004

The CGIc is a 5-point Likert-type rating scale widely used to assess efficacy in clinical studies. For each period, investigators will rate their impression of any change in the subject's overall sleepiness on dosing day compared to overall baseline (Day -1) sleepiness on a 5-point scale ranging from 1 = much improved to 5 = much worse (CGIc: 1 = Much Improved, 2 = Minimally Improved, 3 = No Change, 4 = Minimally Worse, 5 = Much worse). The CGIc will be performed on dosing day at approximately 10 hours post-dose, and the investigator should consider the subject's sleepiness across the entire dosing day comparing to the day before.

Disposition of Participants

Fourteen potential participants were screened for this study; 2 failed to meet all entry criteria. A total of 12 participants were enrolled and dosed from 4 centers in the EU (France, Belgium, and Italy), and all 12 participants completed the study.

Protocol Amendment

Efficacy assessments were added as part of Global Amendment 2 of the study protocol (implemented only at sites in Belgium and Italy) when participants from Group 1 had either completed follow-up or were still being followed in the study. Hence, only 1 participant from Group 1 has efficacy data available from a single period (Period 3; 300 mg). Because of this, efficacy data are only presented in-text for Group 2 (6 to < 12 years old).

Table 3 Analysis Populations (All Enrolled Subjects Population)

	Statistic	Group 1: 12 to < 18 years old (N = 7)[a]	Group 2: 6 to < 12 years old (N = 7)[a]	Total (N = 14)
Analysis Populations				
Safety Population	n (%)	6 (85.7)	6 (85.7)	12 (85.7)
Efficacy Population[b] – PSS	n (%)	1 (14.3)	5 (71.4)	6 (42.9)
Efficacy Population[b] – CGIc	n (%)	1 (14.3)	5 (71.4)	6 (42.9)
Pharmacokinetic Population	n (%)	6 (85.7)	6 (85.7)	12 (85.7)

Abbreviations: CGIc = Clinical Global Impression of change; N = number of participants enrolled in the given treatment group; n = number of participants in the given population and treatment group; PSS = Pictorial Sleepiness Scale.
[a] One participant was a screen failure and is not included in any of the analysis populations.
[b] The efficacy assessments were added as part of Global Amendment 2 of the study protocol and implemented only at sites in Belgium and Italy. Therefore, the efficacy populations are much smaller than the Safety and Pharmacokinetic Populations.
Note: Percentages are based on the total number of participants reported in each column (N).
Source: Table 14.1.1.2.

Demographic and Other Baseline Characteristics

A demographic summary of participants enrolled and dosed at sites across Europe is presented below. Of the 6 participants in Group 2 (6 to < 12 years of old), 3 were < 9 years old. Median time since initial narcolepsy diagnosis was less in the younger participants than in the older participants (median of 36.283 months in Group 2 versus 68.125 months in Group 1).

Table 4 Demographic and Other Baseline Characteristics (Safety Analysis Set) (Extract)

	Statistic	Group 1 12 to < 18 years old (N = 6)	Group 2 6 to < 12 years old (N = 6)	Total (N = 12)
Age	n	6	6	12
	Mean	15.612	9.862	12.737
	SD	1.2988	1.5508	3.2980
	Median	15.460	10.545	12.625
	Min, max	14.08, 17.67	7.33, 11.17	7.33, 17.67
Sex				
Male	n (%)	3 (50.0)	2 (33.3)	5 (41.7)
Female	n (%)	3 (50.0)	4 (66.7)	7 (58.3)
Baseline weight (kg)	n	6	6	12
	Mean	84.25	40.73	62.49
	SD	27.451	14.166	30.825
	Median	79.50	42.50	60.50
	Min, max	60.0, 137.0	23.4, 61.0	23.4, 137.0
Time since initial narcolepsy diagnosis (months)[a]	n	6	1	7
	Mean	65.861	36.283	61.635
	SD	40.4630	-	38.5922
	Median	68.125	36.283	53.947
	Min, max	5.23, 117.53	36.28, 36.28	5.23, 117.53

Abbreviations: BMI = body mass index; max = maximum; Min = minimum; N = number of participants enrolled in the giving treatment group; n = number of participants in the given demographic category and treatment group; SD = standard deviation.
[a] Based on date of informed assent/consent.
Note: Percentages are based on the total number of participants reported in each column (N).
Source: Table 14.1.4.1.

Efficacy results

Co-Primary Efficacy Endpoints

Change in PSS Score from Day 1 Pre-dose to Time of Individual Tmax Post-dose

Across all dose levels in Group 2 (6 to < 12 years old), the mean (SD) change in PSS score from Day 1 pre-dose to time of individual Tmax post-dose was -0.719 (1.2778), demonstrating numerical improvement in perceived sleepiness following a single dose of solriamfetol. Mean (SD) change in PSS score was 0.000 (1.1809) at 37.5 mg, -1.450 (1.6088) at 75 mg, and -0.708 (0.6463) at 150 mg.

Table 5 Summary of Change from Baseline in PSS at Individual Solriamfetol Tmax (Efficacy Population – PSS)

Timepoint	Statistic	Group 2: 6 to < 12 years old Solriamfetol Treatment			
		37.5 mg (N = 5)	75 mg (N = 5)	150 mg (N = 5)	Total (N = 5)
Pictorial Sleepiness Scale					
Baseline	n	5	5	5	15
	Mean	1.002	2.118	1.710	1.610
	SD	0.9147	2.0660	1.5610	1.5436
	Median	1.670	1.670	2.850	1.670
	Min, Max	0.00, 1.67	0.00, 5.58	0.00, 2.85	0.00, 5.58
T_{max}[a]	n	5	5	5	15
	Mean	1.002	0.668	1.002	0.891
	SD	0.9147	0.9147	0.9147	0.8624
	Median	1.670	0.000	1.670	1.670
	Min, Max	0.00, 1.67	0.00, 1.67	0.00, 1.67	0.00, 1.67
CFB to T_{max}	n	5	5	5	15
	Mean	0.000	-1.450	-0.708	-0.719
	SD	1.1809	1.6088	0.6463	1.2778
	Median	0.000	-1.670	-1.180	0.000
	Min, Max	-1.67, 1.67	-3.91, 0.00	-1.18, 0.00	-3.91, 1.67

Abbreviations: CFB = change from baseline; Max = maximum; Min = minimum; N = number of participants in the given population and treatment group; n = number of evaluations at the given timepoint, population and treatment group. PSS = Pictorial Sleepiness Scale; SD = standard deviation; T_{max} = time to reach maximum (peak) plasma concentration.

[a] Data shown are the summary statistics for PSS score at each patient's individual T_{max}.

Notes: Data for Group 1 are not shown, as efficacy assessments were not implemented until Period 3 for the last participant in Group 1. Period 1 treatment = 37.5 mg for Group 2; Period 2 treatment = 75 mg for Group 2; Period 3 treatment = 150 mg for Group 2. PSS is presented on a scale of 0 to 5.58, with 0 corresponding to the most alert, and 5.58 corresponding to the most sleepy.

Source: Table 14.2.1.1.

CGIc Score on Day 1 Relative to Day -1

Across all dose levels in Group 2 (participants 6 to < 12 years old), the mean (SD) CGIc score at 10 hours post-dose was 1.5 (0.64), indicating that a majority of participants in Group 2 were "much improved" (CGIc = 1) or "minimally improved" (CGIc = 2) after a single dose of solriamfetol.

Table 6 Summary of CGIc at 10 Hours Post-dose (Efficacy Population – CGIc)

Timepoint	Statistic	Group 2: 6 to < 12 years old Solriamfetol Treatment			
		37.5 mg (N = 5)	75 mg (N = 5)	150 mg (N = 5)	Total (N = 5)
10 hours postdose	n	5	5	5	15
	Mean	2.2	1.2	1.0	1.5
	SD	0.45	0.45	0.00	0.64
	Median	2.0	1.0	1.0	1.0
	Min, max	2, 3	1, 2	1, 1	1, 3

Abbreviations: CGIc = Clinical Global Impression of Change; max = maximum; Min = minimum; N = number of participants in the given population and treatment group; n = number of evaluations at the given timepoint, population and treatment group; SD = standard deviation.
Notes: Data for Group 1 are not shown, as efficacy assessments were not implemented until Period 3 for the last participant in Group 1. Period 1 treatment = 37.5 mg for Group 2; Period 2 treatment = 75 mg for Group 2; Period 3 treatment = 150 mg for Group 2. CGIc: 1 = Much Improved, 2 = Minimally Improved, 3 = No Change, 4 = Minimally Worse, 5 = Much worse.
Source: Table 14.2.2.1.

Safety

Treatment-emergent AEs are summarized by group (Group 1 [12 to < 18 years old] versus Group 2 [6 to < 12 years old]) and solriamfetol dose in the Table below. Overall, solriamfetol was well tolerated, with no serious TEAEs, no severe TEAEs, and no TEAEs leading to study drug discontinuation. All subjects tolerated the full course of doses, and no subjects were unable to complete the study due to tolerability issues. No clinically meaningful changes were observed in clinical laboratory values, vital signs, or ECG parameters.

Table 7 Adverse Events Overall Summary (Safety Population)

Number of Participants, n (%)	Group 1: 12 to < 18 years old Solriamfetol Treatment				Group 2: 6 to < 12 years old Solriamfetol Treatment				Total (N = 12)
	75 mg (N = 6)	150 mg (N = 6)	300 mg (N = 6)	Total (N = 6)	37.5 mg (N = 6)	75 mg (N = 6)	150 mg (N = 6)	Total (N = 6)	
Any TEAE	3 (50.0)	0	2 (33.3)	4 (66.7)	0	1 (16.7)	0	1 (16.7)	5 (41.7)
Any related TEAE	1 (16.7)	0	1 (16.7)	2 (33.3)	0	0	0	0	2 (16.7)
Any serious TEAE	0	0	0	0	0	0	0	0	0
Any related serious TEAE	0	0	0	0	0	0	0	0	0
Any TEAE leading to discontinuation of study drug	0	0	0	0	0	0	0	0	0
Any TEAE with maximum severity of severe, life-threatening, or fatal	0	0	0	0	0	0	0	0	0
Any TEAE leading to death	0	0	0	0	0	0	0	0	0

Abbreviation: eCRF = electronic case report form; N = number of participants in the given population and treatment group; n = number of participants in the given TEAE category, population, and treatment group; TEAE = treatment-emergent adverse event.
Notes: Percentages are based on the total number of participants reported in each column (N). A related adverse event is an adverse event reported as "Related or Suspected to be Related to Study Drug" on the Adverse Event eCRF. A serious TEAE is an adverse event reported as "Serious" on the Adverse Event eCRF. An adverse event leading to discontinuation of study drug is an adverse event reported as "Drug Withdrawn" on the Adverse Event eCRF. An adverse event leading to death is an adverse event reported as "Fatal" on the Adverse Event eCRF. Participants reporting an adverse event more than once within a category have been counted only once for that category.
Source: Table 14.3.1.1.

A total of 5 (41.7%) participants experienced at least 1 TEAE during the study, 4 of 6 (66.7%) participants 12 to < 18 years old and 1 of 6 (16.7%) participants 6 to < 12 years old. A total of 6 TEAEs were reported by these 5 participants, including 1 participant with headache and blood creatine phosphokinase increased (1 event each), 2 participants with disturbance in attention, 1 participant with diarrhoea, and 1 participant with asymptomatic COVID-19.

Table 8 Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)

Number of Participants, n (%) System Organ Class Preferred Term	Group 1: 12 to < 18 years old Solriamfetol Treatment				Group 2: 6 to < 12 years old Solriamfetol Treatment				Total (N = 12)
	75 mg (N = 6)	150 mg (N = 6)	300 mg (N = 6)	Total (N = 6)	37.5 mg (N = 6)	75 mg (N = 6)	150 mg (N = 6)	Total (N = 6)	
With at Least 1 TEAE	3 (50.0)	0	2 (33.3)	4 (66.7)	0	1 (16.7)	0	1 (16.7)	5 (41.7)
Gastrointestinal disorders	0	0	1 (16.7)	1 (16.7)	0	0	0	0	1 (8.3)
Diarrhoea	0	0	1 (16.7)	1 (16.7)	0	0	0	0	1 (8.3)
Infections and infestations	0	0	0	0	0	1 (16.7)	0	1 (16.7)	1 (8.3)
Asymptomatic COVID-19	0	0	0	0	0	1 (16.7)	0	1 (16.7)	1 (8.3)
Investigations	0	0	1 (16.7)	1 (16.7)	0	0	0	0	1 (8.3)
Blood creatine phosphokinase increased	0	0	1 (16.7)	1 (16.7)	0	0	0	0	1 (8.3)
Nervous system disorders	3 (50.0)	0	0	3 (50.0)	0	0	0	0	3 (25.0)
Disturbance in attention	2 (33.3)	0	0	2 (33.3)	0	0	0	0	2 (16.7)
Headache	1 (16.7)	0	0	1 (16.7)	0	0	0	0	1 (8.3)

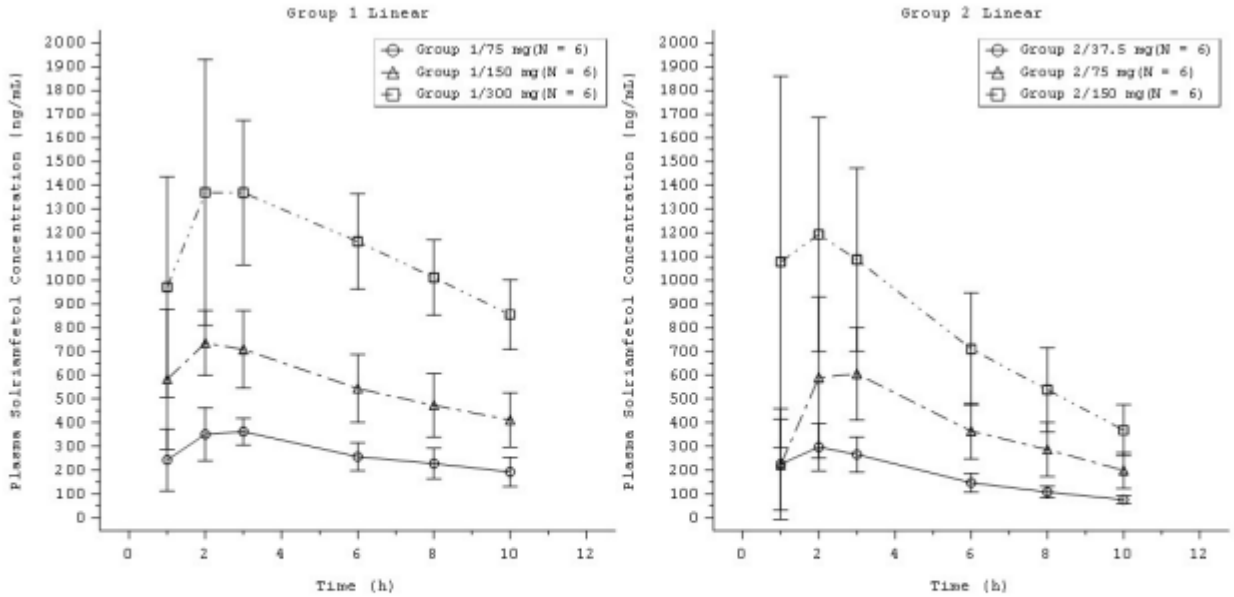
Abbreviation: COVID = Coronavirus disease; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in the given population and treatment group; n = number of participants in the given TEAE category, population, and treatment group; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Notes: Percentages are based on the total number of participants reported in each column (N). Adverse events have been coded using MedDRA Dictionary, version 24.0. Participants reporting an adverse event more than once within a SOC/PT have been counted only once for that SOC/PT. Events are sorted by descending order of the number of participants in the Total column within SOC and PT.
Source: Table 14.3.1.2.

No clinically meaningful changes were observed in clinical laboratory values, vital signs, or ECG parameters.

Pharmacokinetics

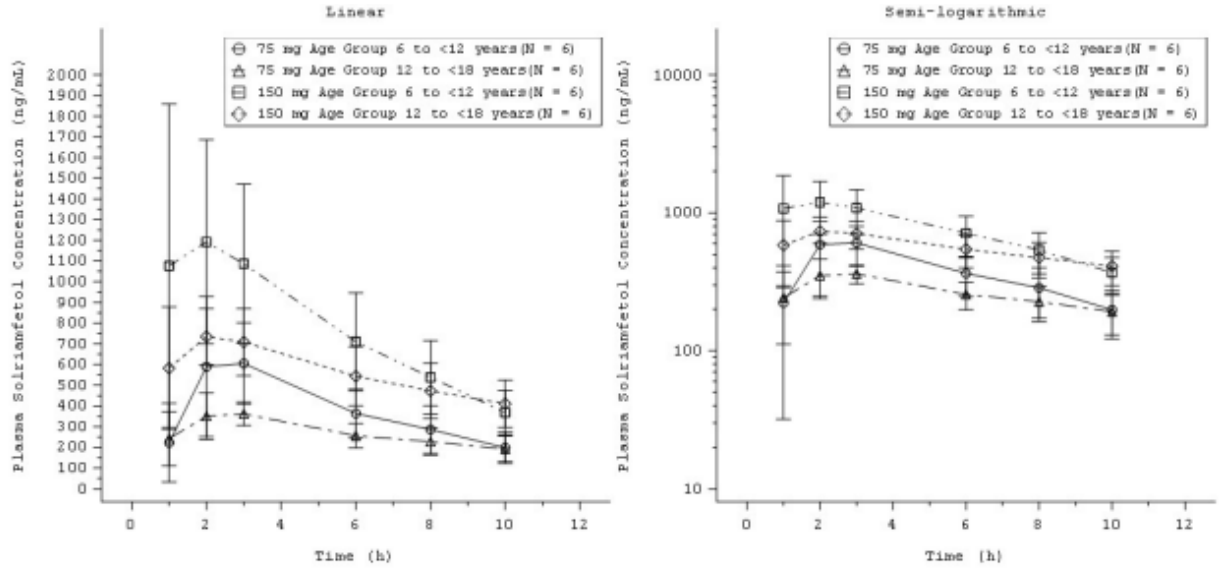
Plasma solriamfetol concentration-time profiles are provided by group and solriamfetol dose on a linear scale.

Figure 2 Mean (±SD) Plasma Solriamfetol Concentration-time Profiles for All Dose Levels on Linear Scale – Groups 1 and 2 (Pharmacokinetic Population)



Abbreviations: h = hour; N = number of participants in the given population and treatment group; SD = standard deviation.
Note: Period 1 treatment = 75 mg for Group 1, 37.5 mg for Group 2; Period 2 treatment = 150 mg for Group 1, 75 mg for Group 2; Period 3 treatment = 300 mg for Group 1, 150 mg for Group 2.
Source: Figure 14.2.7.1.

Figure 3 Mean (±SD) Plasma Solriamfetol Concentration-time Profiles for Dose Levels Common Across Groups 1 and 2 on Linear and Semi-logarithmic Scale (Pharmacokinetic Population)



Abbreviations: h = hour; N = number of participants in the given population and treatment group; SD = standard deviation.
Note: Period 1 treatment = 75 mg for Group 1, 37.5 mg for Group 2; Period 2 treatment = 150 mg for Group 1, 75 mg for Group 2; Period 3 treatment = 300 mg for Group 1, 150 mg for Group 2.

Median plasma solriamfetol concentrations increased proportionally with increasing doses in both Group 1 (12 to < 18 years old) and Group 2 (6 to < 12 years old). Median Tmax was similar across groups, with values ranging from 1.02 to 2.56 hours across all dose levels. Group 1 t½ was similar

across dose levels, with mean t½ ranging from 9.06 to 9.82 hours. Group 2 t½ was also similar across dose levels, with mean t½ ranging from 4.06 to 4.70 hours.

At the same dose (75 mg and 150 mg), exposure (AUC and Cmax) for Group 2 was higher than Group 1.

Table 9 Descriptive Statistics of Solriamfetol Plasma Pharmacokinetic Parameters for Each Age Group and Treatment (Pharmacokinetic Population)

Parameter	Statistic	Group 1: 12 to < 18 years old Solriamfetol Treatment			Group 2: 6 to < 12 years old Solriamfetol Treatment			Overall Solriamfetol Treatment	
		75 mg (N = 6)	150 mg (N = 6)	300 mg (N = 6)	37.5 mg (N = 6)	75 mg (N = 6)	150 mg (N = 6)	75 mg (N = 12)	150 mg (N = 12)
AUC_{0-t} (ng*h/mL)	n	6	6	6	6	6	6	12	12
	Mean	2588	5410	10800	1701	3687	7623	3138	6517
	CV%	22.7	18.2	18.1	31.4	36.2	37.1	36.3	35.7
C_{max} (ng/mL)	n	6	6	6	6	6	6	12	12
	Mean	385.0	811.5	1525	355.7	673.8	1350	529.4	1081
	CV%	20.0	18.4	24.6	40.5	42.4	45.2	47.2	47.0
T_{max} (h)	n	6	6	6	6	6	6	12	12
	Median	2.54	1.02	2.56	1.52	2.53	1.52	2.53	1.03
	Min, max	2.00, 3.08	0.97, 3.03	1.00, 6.02	0.98, 3.00	2.00, 3.00	1.00, 2.97	2.00, 3.08	0.97, 3.03
Lambda z (1/h)	n	5	6	5	6	6	6	11	12
	Mean	0.08842	0.08203	0.08296	0.1739	0.1532	0.1579	0.1238	0.1199
	CV%	36.0	41.9	34.2	13.9	16.4	30.9	34.9	47.1
$t_{½}$ (h)	n	5	6	5	6	6	6	11	12
	Mean	9.060	9.583	9.820	4.060	4.612	4.704	6.634	7.143
	CV%	48.7	35.0	55.9	15.6	14.2	26.8	55.2	49.2

Abbreviations: AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the time t of the last quantifiable concentration; C_{max} = maximum (peak) plasma drug concentration; CV% = percent coefficient of variation; max = maximum; min = minimum; N = number of participants in the given population and treatment group; n = number of participants with PK parameter results in the given population and treatment group; PK = pharmacokinetic; $t_{½}$ = half-life; T_{max} = time to reach maximum (peak) plasma concentration.
Notes: Period 1 treatment = 75 mg for Group 1, 37.5 mg for Group 2; Period 2 treatment = 150 mg for Group 1, 75 mg for Group 2; Period 3 treatment = 300 mg for Group 1, 150 mg for Group 2. 75 mg (Pooled): Group 1 and 2 75 mg Treatments; 150 mg (Pooled): Group 1 and 2 150 mg Treatments. Refer to Listing 16.2.7.5 for data excluded from the PK analysis and/or reporting.
Source: Table 14.2.5.1.

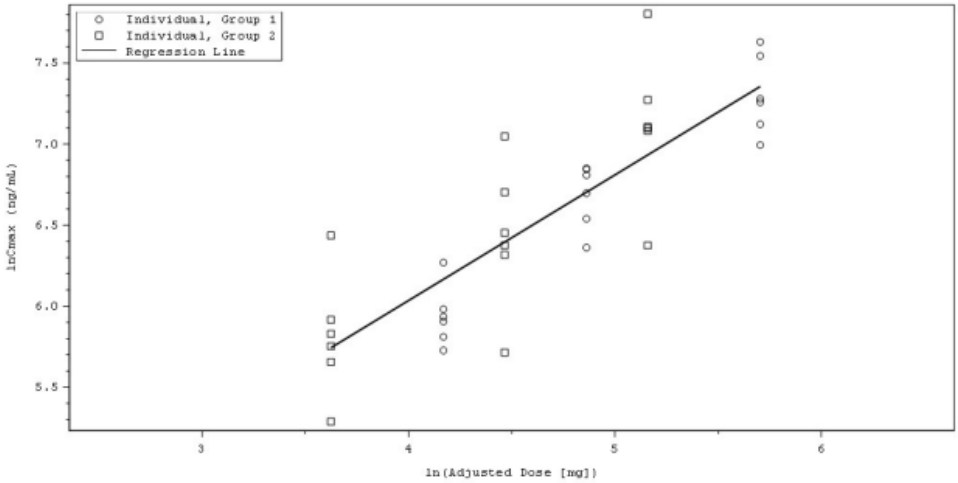
Solriamfetol dose proportionality is summarized by age group and overall for Cmax and AUC0-t in the Table below and are plotted by dose level for Cmax and AUC0-t in the Figures. There appeared to be dose-proportional increases in exposure to solriamfetol following single dose administration of doses ranging from 75 mg to 300 mg in Group 1 (12 to < 18 years old) and doses 37.5 mg to 150 mg in Group 2 (6 to < 12 years old).

Table 10 Summary of Assessment for Solriamfetol Dose Proportionality (Pharmacokinetic Population)

Dose Range (mg)	Parameter	Number of Data Points Used	Slope		Intercept	
			Estimate	95% CI	Estimate	95% CI
Group 1 (12 to < 18 years old)						
75 - 300	C_{max}	18	0.99	(0.87, 1.10)	1.70	(1.13, 2.28)
	AUC_{0-t}	18	1.04	(0.95, 1.12)	3.38	(2.94, 3.81)
Group 2 (6 to < 12 years old)						
37.5 - 150	C_{max}	18	0.94	(0.86, 1.03)	2.38	(1.87, 2.89)
	AUC_{0-t}	18	1.07	(1.00, 1.14)	3.53	(3.12, 3.94)
Overall (6 to < 18 years old)						
37.5 - 300	C_{max}	36	0.96	(0.89, 1.02)	2.08	(1.70, 2.45)
	AUC_{0-t}	36	1.05	(1.00, 1.10)	3.47	(3.18, 3.76)

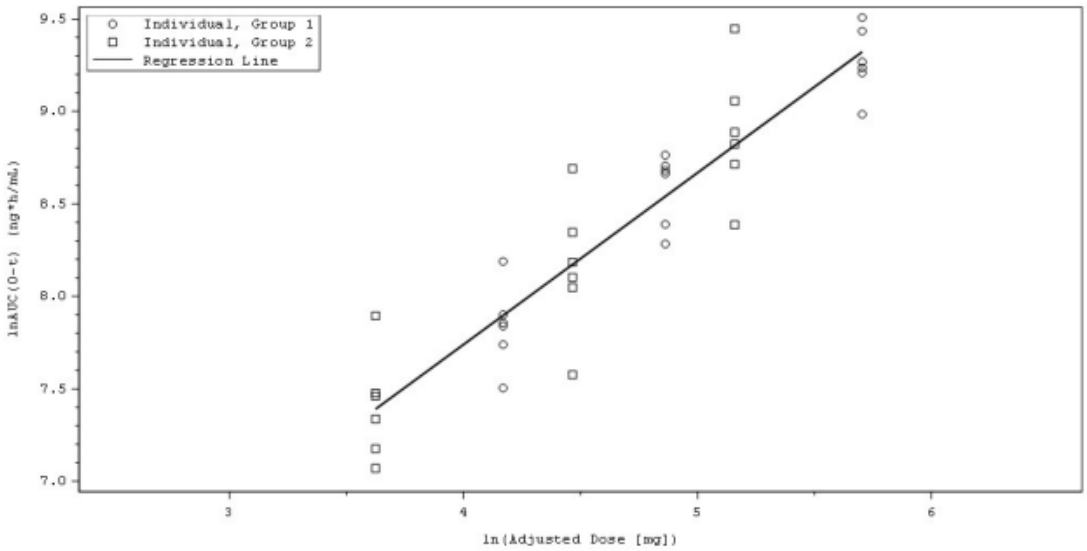
Abbreviations: AUC_{0-inf} = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the time t of the last quantifiable concentration; CI = confidence interval; C_{max} = maximum (peak) plasma drug concentration; PK = pharmacokinetic.
Notes: The linear mixed model used was log (PK parameter) = intercept + slope x log (dose) with a random effect for participant. There was not enough reliable AUC_{0-inf} results between dose range 37.5-300 mg, hence dose proportionality was not assessed for AUC_{0-inf}.
Source: Table 14.2.6.1, Table 14.2.6.2, and Table 14.2.6.3.

Figure 4 Dose Proportionality Plot of Solriamfetol Cmax Versus Dose Level (Includes Regression Line) – Groups 1 and 2 (Pharmacokinetic Population)



Abbreviations: C_{max} = maximum (peak) plasma drug concentration.
Note: Period 1 treatment = 75 mg for Group 1, 37.5 mg for Group 2; Period 2 treatment = 150 mg for Group 1, 75 mg for Group 2; Period 3 treatment = 300 mg for Group 1, 150 mg for Group 2.
Source: Figure 14.2.8.1.

Figure 5 Dose Proportionality Plot of Solriamfetol AUC0-t Versus Dose Level (Includes Regression Line) – Groups 1 and 2 (Pharmacokinetic Population)



Abbreviations: AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration.

Note: Period 1 treatment = 75 mg for Group 1, 37.5 mg for Group 2; Period 2 treatment = 150 mg for Group 1, 75 mg for Group 2; Period 3 treatment = 300 mg for Group 1, 150 mg for Group 2.

Source: Figure 14.2.8.2.

3. Scientific discussion

Study JZP865-101 was submitted as a post-authorisation measure (PAM) to satisfy the requirements of Article 46 of Regulation (EC) No 1901/2006 as part of the agreed EU Paediatric Investigation Plan development program for Sunosi (EMEA-002184-PIP01-17).

The study was designed to characterize the PK in pediatric participants and evaluate the safety profile, to inform dose selection for future pediatric studies, and to provide preliminary efficacy data on solriamfetol in the pediatric population.

Entry criteria were adequately defined. Participating pediatric patients are representative for targeted population. Eligible subjects completed a Multiple Sleep Latency Test (MSLT) during screening to confirm the diagnosis of narcolepsy by ICSD-3 criteria (ie, the participant met all other ICSD-3 criteria for narcolepsy). Median time since initial narcolepsy diagnosis was less in the younger participants than in the older participants (median of 36.283 months in Group 2 versus 68.125 months in Group 1).

Twelve pediatric participants who satisfied all eligibility criteria, 6 participants in each age group (Group 1: adolescents 12 to < 18 years old; Group 2: children 6 to < 12 years old) received study intervention. During screening, an attempt was made to enrol an equal number of male (n=5) and female (n=7) participants in each group as well as to enrol at least 2 participants below the age of 9.

All 12 participants received a single dose of 3 ascending dose levels of solriamfetol (Group 1: 75 mg, 150 mg, 300 mg solriamfetol; Group 2: 37.5 mg, 75 mg, 150 mg solriamfetol) during the course of the study.

It was planned to measure efficacy by means of 2 co-primary endpoints, i.e. the Pictoral Sleepiness Scale (PSS) and Clinical Global Impression of Change (CGIc) for all subjects (Group 1 and Group 2) in Periods 1, 2, and 3. However, efficacy assessments were only added as part of Global Amendment 2 of

the study protocol when participants from Group 1 had either completed follow-up or were still being followed in the study. Hence, efficacy data are presented only for Group 2 (6 to < 12 years old).

In terms of the Pictorial Sleepiness Scale (PSS), numerical improvements (as change from baseline) could be shown for the 75 mg and 150 mg dose. However, there are strong limitations as concerns meaningfulness of data. These relate to the small dataset in general (n=12), availability of efficacy results for only half the population (Group 2, N=5), and the low level of sleepiness expressed by the subjects at baseline. Included subjects were rather on the alert side of the scale at baseline with PSS values between 1 and 2.1.

The co-primary endpoint (CGIc) demonstrated that subjects were much improved (CGIc 1.0 for 150 mg) or minimally improved (CGIc 2.2 for 37.5 mg). A CGIc score of 3 would correspond to "no change".

Overall, it is concluded that due to limitations (small dataset) efficacy results are considered exploratory.

In terms of safety, solriamfetol was well tolerated, with no serious TEAEs, no severe TEAEs, and no TEAEs leading to study drug discontinuation. All subjects tolerated the full course of doses, and no subjects were unable to complete the study due to tolerability issues. No clinically meaningful changes were observed in clinical laboratory values, vital signs, or ECG parameters. The impact of solriamfetol on vital signs such as blood pressure and heart rate was an issue of discussion at the time of approval of solriamfetol, in particular as concerns the use for treatment of daytime sleepiness in patients with obstructive sleep apnoea (OSA), since these often present with relevant cardiovascular comorbidity. In the small pediatric dataset of study JZP865-101, no clinically meaningful change in BP or HR was observed.

The pharmacokinetics of solriamfetol in the pediatric population was also analysed. Median plasma solriamfetol concentrations increased proportionally with increasing doses in both Group 1 (12 to < 18 years old) and Group 2 (6 to < 12 years old).

Median Tmax was similar across groups, with values ranging from 1.02 to 2.56 hours across all dose levels. The elimination half life was about twice as long in subjects from 12 to < 18 years (Group 1: t½ ranging from 9.06 to 9.82 hours) as compared to younger subjects from 6 to < 12 years (Group 2: mean t½ranging from 4.06 to 4.70 hours).

Despite the fact that solriamfetol was eliminated faster in younger subjects of Group 2, at the same dose (75 mg and 150 mg), exposure (AUC and Cmax) for Group 2 was higher than Group 1. There appeared to be dose-proportional increases in exposure to solriamfetol following single dose administration of doses ranging from 75 mg to 300 mg in Group 1 (12 to < 18 years old) and doses 37.5 mg to 150 mg in Group 2 (6 to< 12 years old).

4. Overall conclusion

Overall, the MAH's conclusion on the outcome of pediatric study JZP865-101 is endorsed. The study, due to its design and limited number of pediatric patients, does not allow drawing conclusions on efficacy or safety that would impact on the drug's B/R ratio or lead to labelling updates. Conversely, the study does support the continued development of solriamfetol for pediatric patients with narcolepsy.

☒ PAM fulfilled

No regulatory action required.