

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**211230Orig1s000**

**211230Orig2s000**

**CLINICAL REVIEW(S)**

## REVIEW OF CLINICAL DATA

<b>NDA</b>	#211230
<b>Brand name (generic name)</b>	Sunosi (solriamfetol)
<b>Sponsor</b>	Jazz Pharmaceuticals
<b>Materials reviewed</b>	DCRP Consult review, NDA submission
<b>Reviewer</b>	Marc Stone, MD Deputy Director for Safety
<b>Date Completed</b>	19 March 2019

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### **Background**

Solriamfetol is a drug with stimulant-like effects being considered for the indication of excessive daytime sleepiness in patients with 1) narcolepsy or 2) obstructive sleep apnea. The product appears to be efficacious for these indications. A major review concern has been the effects of solriamfetol on heart rate and blood pressure. The drug is intended for long-term use and the effects of heart rate and blood pressure may increase cardiovascular risk, particularly for patients with other risk factors. The two principal studies for the respective indications, 14-002 and 14-003, incorporated ambulatory blood pressure monitoring (ABPM). The Applicant conducted analyses of standard vital sign measurements as well as ABPM in its Integrated Summary of Safety (ISS). The Division of Cardiorenal Products (DCRP) was consulted to describe and interpret the Sponsor's analyses and provide recommendations about risk implications for labeling.

The thorough QT study for solriamfetol (Study 15-002) was reviewed by the Interdisciplinary Review Team for QT Studies (IRT/QT). The review noted that the solriamfetol dosages used in the study (300 mg and 900 mg) were associated with large increases in heart rate (estimated by them as a mean increase relative to baseline and placebo as 12.8 bpm for 300 mg and 19.5 bpm for 900 mg). With such large changes in heart rate, the Fridericia correction used in the study has questionable accuracy, resulting in considerable uncertainty as to the magnitude of the effect, especially at larger concentrations.

### **Analytical challenges with the submission**

Because of the variability in who, when, where and how measurements of blood pressure are made, it is difficult to characterize drug effects on blood pressure with reliability and precision. The clinic-based data, as presented by the Sponsor, do not take these complexities into account.

In the Sponsor's Table 181 from the ISS, the simple means of all measurements obtained in all subjects at a given visit are averaged. Two narcolepsy studies are combined even though only one included a 75 mg dosage and different subjects are averaged at different time points – note the decrease in the number of narcolepsy subjects between 4 and 8 weeks for the 150 mg dose and the increase for 300mg. No attempt is made to account for within-individual variability. A similar approach was taken on days when multiple measurements (pre-dose and 1, 2, 4, 6, 8, and 10 hours post-dose) were made (Sponsor's Table 183).

There is little reason to assess blood pressure effects separately at different weeks; the effects are not thought to be cumulative. Solriamfetol is intended to be relatively short acting: with once daily dosing and a half-life of about seven hours, its effect is intended to wear off by bedtime to avoid interference with intended sleep.

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**Table 181: Regular Vital Signs at Each Clinic Visit: Summary of Mean Change (SD) from Baseline in Blood Pressure and Heart Rate (By Indication-Safety Population)**

Parameter Mean (SD) Across Time Points	Placebo N = 108	JZP-110 (Narcolepsy)			Placebo N = 118	JZP-110 (OSA)				
		75 mg N = 59	150 mg N = 102	300 mg N = 99		37.5 mg N = 58	75 mg N = 61	150 mg N = 116	300 mg N = 118	
<b>SBP (mmHg)</b>										
Week 1, n	104	58	97	58	113	56	56	114	115	
	1.178 (10.662)	-1.707 (10.109)	1.878 (10.957)	-1.865 (8.798)	-3.487 (10.880)	-0.762 (13.067)	-3.455 (11.513)	-1.836 (11.244)	-0.988 (11.947)	
Week 4, n	98	52	91	55	109	52	54	110	102	
	0.883 (10.943)	-2.385 (10.125)	-0.359 (11.918)	-1.473 (10.129)	-1.428 (10.831)	-1.359 (11.414)	-1.312 (13.081)	-1.286 (10.475)	-0.462 (12.181)	
Week 8, n	91	49	51	83	104	49	53	108	97	
	0.925 (11.704)	-1.330 (10.871)	-0.029 (11.350)	2.667 (11.086)	-3.742 (12.391)	0.847 (11.599)	-1.613 (14.087)	-0.739 (11.415)	0.369 (12.469)	
Week 12, n	89	49	50	79	100	49	53	106	94	
	2.296 (9.498)	-1.878 (10.023)	0.953 (10.922)	0.899 (11.323)	-1.920 (11.938)	1.163 (10.194)	-0.896 (12.249)	0.099 (11.566)	-0.285 (15.135)	
<b>DBP (mmHg)</b>										
Week 1, n	104	97	97	58	113	56	56	114	115	
	1.673 (7.388)	-1.592 (7.308)	1.905 (9.316)	0.851 (8.191)	-1.363 (7.792)	0.673 (7.954)	-0.961 (8.413)	-0.284 (7.208)	0.326 (7.600)	
Week 4, n	98	52	91	55	109	52	54	110	102	
	1.583 (8.447)	-2.631 (6.714)	-0.130 (8.377)	-0.585 (8.422)	-0.190 (7.641)	0.369 (7.340)	-0.543 (8.180)	-0.238 (7.623)	-0.209 (6.885)	
Week 8, n	91	49	51	83	104	49	53	108	97	
	2.020 (8.552)	-0.786 (6.935)	2.275 (9.323)	2.520 (8.676)	-0.223 (9.184)	0.755 (8.492)	-0.016 (9.266)	-0.052 (8.317)	0.302 (8.053)	
Week 12, n	89	49	50	79	100	49	53	106	94	
	2.522 (7.918)	-1.721 (6.836)	1.770 (7.648)	0.977 (8.245)	0.678 (8.419)	1.190 (6.054)	-0.450 (8.280)	0.182 (8.576)	-0.254 (8.073)	
<b>Heart Rate (bpm)</b>										
Week 1, n	104	58	97	58	113	56	56	114	115	
	1.99 (9.548)	-0.66 (8.095)	4.11 (10.691)	3.48 (11.128)	-3.08 (10.066)	-1.28 (10.685)	-0.68 (9.862)	-0.64 (10.146)	-0.37 (9.251)	
Week 4, n	98	52	91	55	109	52	54	110	102	
	1.90 (8.513)	-0.37 (7.830)	4.06 (10.782)	1.95 (12.375)	-0.98 (10.101)	2.82 (11.303)	0.65 (10.635)	1.78 (10.314)	0.49 (9.261)	
Week 8, n	91	49	51	83	104	49	53	108	97	
	1.05 (10.378)	-2.70 (10.915)	2.30 (12.740)	4.40 (13.135)	-3.06 (10.084)	-4.71 (11.408)	-4.61 (10.678)	-1.06 (11.231)	-0.30 (9.980)	
Week 12, n	89	49	50	79	100	49	53	106	94	
	2.12 (9.842)	-1.83 (9.620)	4.04 (9.787)	4.20 (11.657)	-1.43 (9.895)	0.81 (11.171)	1.16 (10.559)	1.36 (10.942)	3.05 (9.623)	

**Table 183: Vital Signs on MWT Day: Summary of Mean Change (SD) from Baseline in Blood Pressure and Heart Rate (By Indication-Safety Population)**

Parameter Mean (SD) Across Time Points	Placebo N = 108	JZP-110 (Narcolepsy)			Placebo N = 118	JZP-110 (OSA)			
		75 mg N = 59	150 mg N = 102	300 mg N = 99		37.5 mg N = 58	75 mg N = 61	150 mg N = 116	300 mg N = 118
<b>SBP (mmHg)</b>									
Week 1, n	23	25	22	24	35	17	17	38	35
	-0.725 (5.715)	-0.527 (6.936)	0.854 (6.546)	-0.430 (7.346)	-0.262 (6.005)	2.532 (7.623)	1.838 (5.140)	0.123 (4.666)	2.086 (7.020)
Week 4, n	96	51	89	53	105	51	53	107	99
	0.912 (7.713)	-0.428 (6.738)	0.705 (7.587)	2.570 (7.733)	0.253 (6.796)	1.243 (8.959)	1.653 (6.696)	1.020 (7.782)	1.782 (8.462)
Week 12, n	88	48	47	79	97	49	52	102	91
	1.892 (8.183)	0.719 (7.254)	1.750 (7.786)	2.493 (7.817)	0.091 (7.892)	2.032 (8.300)	0.661 (9.010)	0.914 (7.597)	2.940 (10.515)
<b>DBP (mmHg)</b>									
Week 1, n	23	25	22	24	35	17	17	38	35
	-0.055 (4.707)	0.060 (4.607)	2.095 (5.424)	1.194 (4.153)	-0.718 (4.779)	0.264 (4.852)	1.477 (4.565)	-0.126 (4.051)	0.823 (4.400)
Week 4, n	96	51	89	53	105	51	53	107	99
	-0.148 (4.791)	0.192 (4.529)	1.303 (5.922)	1.681 (5.577)	0.224 (4.446)	0.730 (5.560)	1.088 (5.092)	0.730 (5.097)	1.080 (5.246)
Week 12, n	88	48	47	79	97	49	52	102	91
	0.255 (5.316)	1.231 (4.823)	2.089 (5.085)	2.263 (5.363)	0.042 (4.881)	0.691 (5.020)	0.190 (6.758)	0.721 (5.655)	1.792 (5.910)
<b>Heart Rate (bpm)</b>									
Week 1, n	23	25	22	24	35	17	17	38	35
	0.02 (6.366)	0.34 (3.180)	1.74 (5.748)	3.44 (7.199)	-1.34 (4.877)	0.78 (5.125)	0.18 (6.045)	1.84 (6.898)	1.97 (6.669)
Week 4, n	96	51	89	53	105	51	53	107	99
	0.34 (5.804)	0.12 (6.450)	1.86 (6.366)	4.32 (7.406)	0.39 (5.783)	0.85 (5.604)	1.74 (5.208)	1.68 (6.963)	2.72 (6.339)
Week 12, n	88	48	47	79	97	49	52	102	91
	1.15 (6.306)	0.90 (6.847)	2.73 (5.249)	3.67 (7.459)	0.12 (5.271)	0.61 (7.294)	0.81 (5.333)	2.33 (6.511)	3.28 (5.614)

A larger number of observations were obtained using 24-hour ABPM on two occasions in Studies 14-002 and 14-003, at baseline and after eight weeks of treatment but the analyses once again relied upon overall means by dosage and did not look at changes within individual subjects. From the Statistical Analysis Plan:

For the ABPM BP and HR data obtained during Screening and Week 8 at 30 minute interval during a 24 hour period, the overall mean, mean during the daytime period from 7:00 to 22:00 and mean during the nighttime period from 22:00 to 7:00 will be summarized by treatment group.

ABPM provides many readings in a short period of time but cannot control the conditions under which the measurements are obtained such as with position, exercise or emotion. In this case, data assessed in this manner can possibly give a general impression of impact on vital signs but provide no insight into either statistical uncertainty or comparability (because there is no attempt to account for variability due to measurement variability among studies and time points and variability within and between subjects).

The analysis of drug effects on QT is complicated by the relationship between the length of the QT interval and heart rate (RR interval). Hence the measured length of the QT interval must be adjusted for heart rate. The Fridericia correction is based on the formula:

$$QTc = QT / RR^{1/3}$$

which means  $QT = QTc * RR^{1/3}$ ,  $\ln(QT) = \ln(QTc) + \ln(RR)/3$  and  $\ln(QTc) = \ln(QT) - \ln(RR)/3$ . However, the relationship between QT and RR is frequently different than what is given by the Fridericia correction. The Bazett correction uses an exponent of 0.5. These analyses also assume that there is no variation among subjects in the relationship between QT and RR.

### Methods used in this review

#### *Clinic Vital Signs*

I assembled all data on heart rate and blood pressure collected in the Advs files for 15 studies conducted in human subjects in this NDA submission. Studies were not included if they only obtained baseline or pre-dose measurements.

<i>Study</i>	<i>Subjects</i>	<i>BP Measurements</i>	<i>Pulse Measurements</i>
14-001	107	4,219	4,219
14-002	239	19,763	13,196
14-003	476	38,866	25,972
14-004	174	12,170	8,178
14-005	645	10,541	8,969
15-001	31	348	348
15-009	32	365	365
ADX-N05-201	36	463	465
ADX-N05-202	93	3,148	3,146
(b) (4) NED-1	123	4,407	4,407
(b) (4) P01-101	4	32	32
(b) (4) SAB-101	26	2,654	2,654
(b) (4) USA-10	110	1,249	1,249

(b) (4)	-9603-01	24	1,230	1,230
(b) (4)	-9702-01	50	347	347
<b>Total</b>		<b>1,531*</b>	<b>99,802</b>	<b>74,777</b>

\*639 subjects in 14-005 were recruited from other studies

Statistical analyses were performed using hierarchical mixed models for repeated measurements (MMRM). This method allows for the difference in observed values when exposed to different drug dosages compared to no drug exposure (the fixed effect) to be estimated under a variety of different circumstances (random effects), estimating the variance due to the variety of circumstances and separating that variance from that seen in the fixed effect. The random effects used in the models include:

- **Study:** Studies are assumed to involve different populations and each population has a different mean value for each vital sign exclusive of drug effect. The variability among studies is assumed to follow a random normal distribution.
- **Subject:** Within study populations, each individual subject also has a different mean value exclusive of drug effect. It is also assumed to follow a random normal distribution. Inter-subject variability is nested within study.
- **Position:** For studies that made observations at different positions (i.e., standing or supine), individual subjects maintain the same orthostatic differences over time, but this difference can vary among subjects.
- **Study day:** Mean values for vital signs for subjects exclusive of drug effect vary from day to day and are assumed to follow a random normal distribution. Day to day variability is nested within position, subject and study.
- **Time:** Vital sign values exclusive of drug effects vary in general over the course of the day and similarly for all subjects. This also stratifies calculations so that the observed drug effect at each time point is given similar weight in the overall mean calculation.

For assessment of general trend in dose-response, dosage was treated as a continuous variable. To look for non-linearity, a model was fit using multivariate adaptive regression splines, but little difference was found between linear models and spline-based models.

For threshold effects the mixed model calculated odds ratios but because of computational difficulties, the model was simplified to use just subjects nested in time as random effects.

#### *Ambulatory Blood Pressure Monitoring*

The data provided by the Sponsor consisted of an average of up to four measurements obtained over 2-hour intervals. The combined dataset for the two ABPM studies consisted of 87,650 observations for each parameter in 705 subjects. I analyzed this dataset with a similar hierarchical MMRM but with only, study, subject and time as random effects. To compare ABPM results to results from clinic readings I considered the 8 am to 8 pm period for ABPM to correspond to the maximum twelve-hour observation period used with clinic measurements.

#### *Thorough QT Study*

Because there are multiple baseline ECGs for each subject and additional ECGs with negligible or no drug exposure (when the measured plasma solriamfetol concentration is zero (and the subject has not received moxifloxacin)), the individual relationship between QT and RR when patients are untreated can be estimated by linear regression

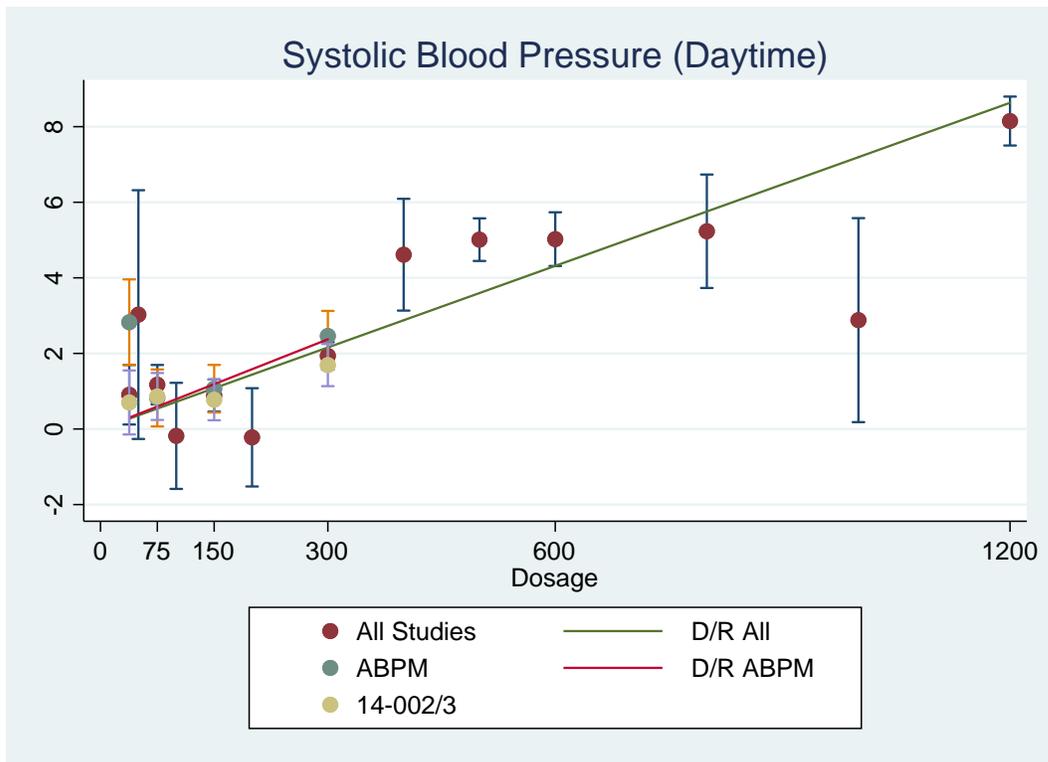
of  $\ln(RR)$  on  $\ln(QT)$  where the slope is the estimate of the power to which  $RR$  is raised (fixed at  $1/3$  by the Fridericia equation) and the intercept is the estimate of the logarithm of  $QT_c$  ( $QT$  when  $RR$  is one second). A simple linear regression for each subject would be imprecise as it would be based on very limited data. This noise can be reduced by using MMRM with  $\ln(RR)$  entered into the model as a random effect. Any drug effect is estimated by adding a dummy variable for drug exposure which would estimate a percentage change in  $QT_c$  due to drug effect or a continuous variable for plasma concentration which would estimate a percentage change in  $QT_c$  due to a given plasma concentration. Any drug effect is estimated as a fixed effect a continuous variable for drug concentration. This model can be refined further by avoiding the assumptions that the relationships between  $\ln(QT)$  and  $\ln(RR)$  and drug concentration and  $QT$  effect, respectively, are linear by fitting a cubic spline model to derive population-averaged  $QT/RR$  and  $QT$  effect/concentration curves for unexposed subjects and treating the spline components for the  $QT/RR$  relationship as random effects. Overfitting to the untreated data is avoided by fitting a single model to drug exposed and non-exposed observations rather than using a corrected  $QT$  value in the analysis. Instead of producing a  $QT_c$  value that corresponds to the expected  $QT$  value if the  $RR$  interval were one second, it predicts the  $QT$  interval in the absence of drug effect for the observed  $RR$  interval.

## Results

### Average Effect

#### Systolic Blood Pressure (Daytime)

<i>Dosage</i>	<i>Study</i>	<i>Effect</i>	<i>95% CI</i>	<i>D/R Trend</i>	
37.5	all	0.9	0.1	1.7	0.3
37.5	14-002/3	0.7	(0.1)	1.5	0.2
37.5	ABPM	2.8	1.7	4.0	0.3
50	all	3.0	(0.3)	6.3	0.4
75	all	1.2	0.6	1.7	0.5
75	14-002/3	0.9	0.2	1.5	0.4
75	ABPM	0.8	0.1	1.6	0.6
100	all	(0.2)	(1.6)	1.2	0.7
150	all	0.9	0.5	1.3	1.1
150	14-002/3	0.8	0.2	1.3	0.8
150	ABPM	1.1	0.4	1.7	1.2
200	all	(0.2)	(1.5)	1.1	1.4
300	all	1.9	1.6	2.3	2.2
300	14-002/3	1.7	1.1	2.2	1.6
300	ABPM	2.5	1.8	3.1	2.4
400	all	4.6	3.1	6.1	2.9
500	all	5.0	4.4	5.6	3.6
600	all	5.0	4.3	5.7	4.3
800	all	5.2	3.7	6.7	5.8
1000	all	2.9	0.2	5.6	7.2
1200	all	8.1	7.5	8.8	8.6



**A technical problem with the graphics software prevents inclusion of the dose/response line for 14-002/3**

**ABPM Nighttime SBP**

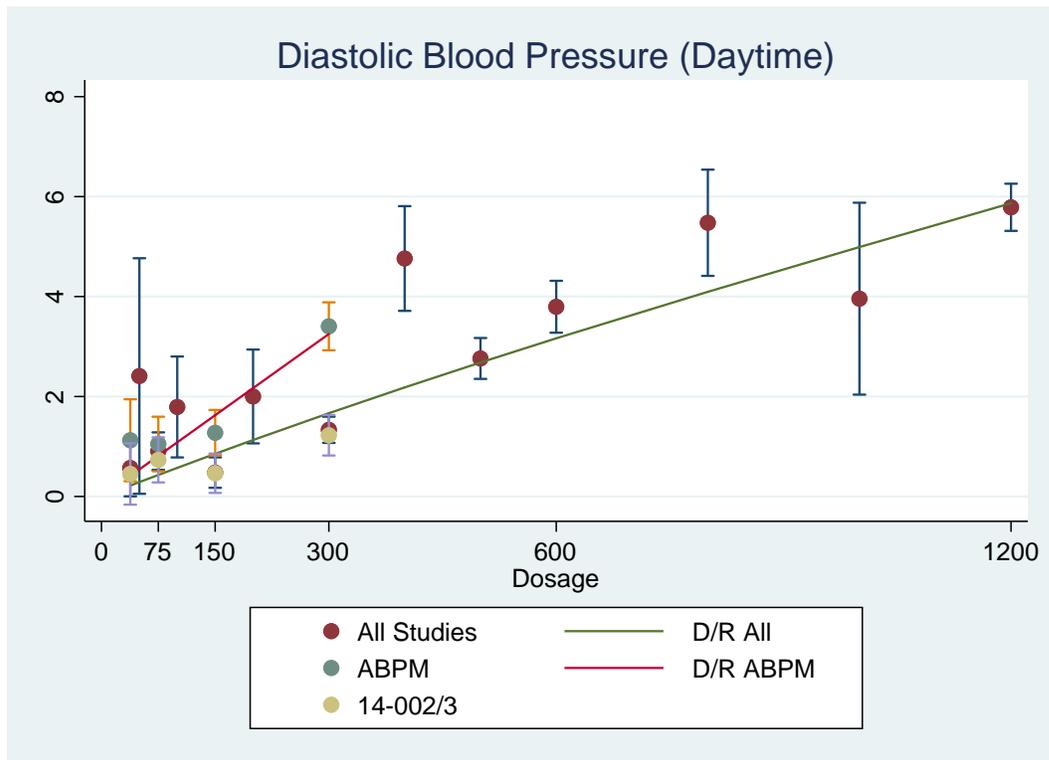
Dosage	Effect	95% CI		D/R Trend
37.5	1.6	0.4	2.9	0.2
75	(0.7)	(1.6)	0.1	0.3
150	(0.2)	(0.9)	0.4	0.6
300	1.0	0.3	1.7	1.2

The overall picture shows a clear dose-response relationship that is a bit muddled by an apparently larger increase off-trend for 37.5 mg in the ABPM studies but with relatively large confidence intervals. The dose-response trend lines (which are strongly statistically significant) do a good job of narrowing the differences among the estimates from daytime ABPM, clinic measurements in the same studies and when all studies are combined. Overall the average daytime increase for the 300mg dose appears to be about 2 mmHg and proportional for the other dosages used in phase 3 studies. The ABPM data suggest that the nighttime effect is about half of that seen during the day.

**Diastolic Blood Pressure (Daytime)**

Dosage	Study	Effect	95% CI	D/R Trend	
37.5	all	0.6	0.0	1.1	0.2
37.5	14-002/3	0.5	(0.2)	1.1	0.1
37.5	ABPM	1.1	0.3	1.9	0.4
50	all	2.4	0.1	4.8	0.3

75	all	0.9	0.5	1.3	0.4
75	14-002/3	0.7	0.3	1.2	0.3
75	ABPM	1.0	0.5	1.6	0.8
100	all	1.8	0.8	2.8	0.6
150	all	0.5	0.2	0.8	0.9
150	14-002/3	0.5	0.1	0.9	0.6
150	ABPM	1.3	0.8	1.7	1.6
200	all	2.0	1.1	2.9	1.1
300	all	1.3	1.1	1.6	1.7
300	14-002/3	1.2	0.8	1.6	1.1
300	ABPM	3.4	2.9	3.9	3.3
400	all	4.8	3.7	5.8	2.2
500	all	2.8	2.4	3.2	2.7
600	all	3.8	3.3	4.3	3.2
800	all	5.5	4.4	6.5	4.1
1000	all	4.0	2.0	5.9	5.0
1200	all	5.8	5.3	6.3	5.9



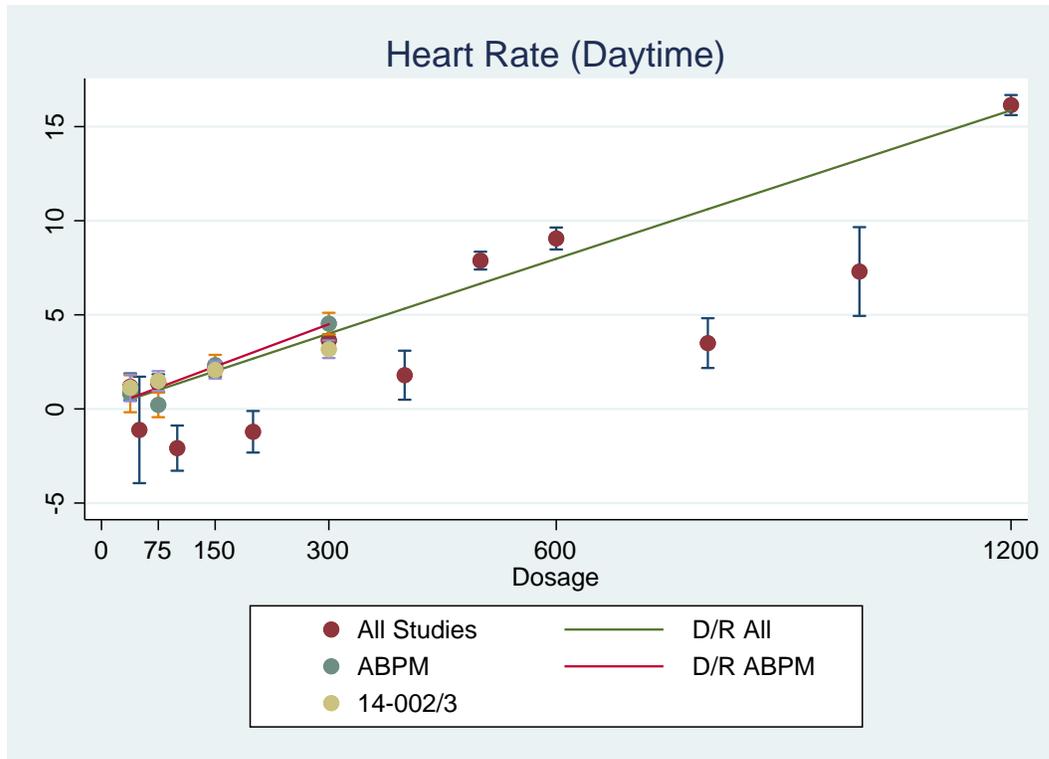
#### ABPM Nighttime DBP

Dosage	Effect	95% CI	D/R Trend
75	0.9	0.5 - 1.3	0.4
150	0.5	0.2 - 0.8	0.9
300	1.3	0.8 - 1.7	1.6
600	3.8	3.3 - 4.3	3.2
1200	5.8	5.3 - 6.3	5.9

37.5	0.4	(0.5)	1.3	0.2
75	(0.4)	(0.9)	0.2	0.4
150	0.8	0.3	1.3	0.8
300	1.7	1.1	2.2	1.6

For diastolic blood pressure, the data for dosages less than 300 mg are less muddled than for SBP but there is a substantial difference for the 300 mg for the ABPM data compared to clinic measurements. The dose-response relationship is still apparent and strongly statistically significant. Overall, the average daytime increase for the 300mg dose appears to be about 2 mmHg and proportional for the other dosages. The ABPM data again suggest that the nighttime effect is about half of that seen during the day.

Heart Rate (Daytime)					
<i>Dosage</i>	<i>Study</i>	<i>Effect</i>	<i>95% CI</i>		<i>D/R Trend</i>
37.5	all	1.2	0.5	1.9	0.5
37.5	14-002/3	1.1	0.4	1.8	0.4
37.5	ABPM	0.8	(0.2)	1.8	0.6
50	all	(1.1)	(3.9)	1.7	0.7
75	all	1.4	0.9	1.8	1.0
75	14-002/3	1.5	1.0	2.0	0.8
75	ABPM	0.2	(0.4)	0.9	1.1
100	all	(2.1)	(3.3)	(0.9)	1.3
150	all	2.1	1.7	2.5	2.0
150	14-002/3	2.1	1.6	2.5	1.6
150	ABPM	2.3	1.8	2.9	2.3
200	all	(1.2)	(2.3)	(0.1)	2.7
300	all	3.6	3.3	4.0	4.0
300	14-002/3	3.2	2.7	3.6	3.1
300	ABPM	4.5	4.0	5.1	4.5
400	all	1.8	0.5	3.1	5.3
500	all	7.9	7.4	8.4	6.7
600	all	9.1	8.5	9.6	8.0
800	all	3.5	2.2	4.8	10.6
1000	all	7.3	4.9	9.7	13.2
1200	all	16.1	15.6	16.7	15.9



#### ABPM Nighttime Heart Rate

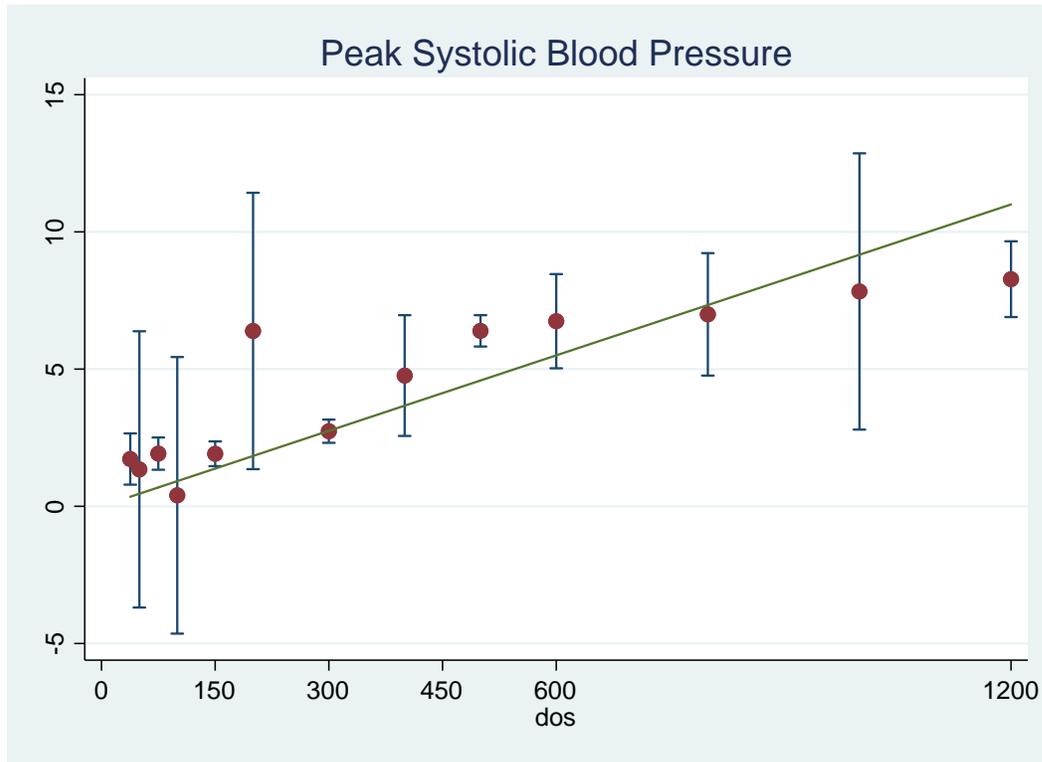
<i>Dosage</i>	<i>Effect</i>	<i>95% CI</i>		<i>D/R Trend</i>
37.5	(1.1)	(2.1)	(0.2)	0.2
75	1.1	0.5	1.7	0.4
150	(0.0)	(0.5)	0.5	0.7
300	2.4	1.9	3.0	1.5

For heart rate, the aberrant observations all come from small studies that tested unusual dosages; the ABPM data and the clinic data appear to agree for the 37.5 mg, 150 mg and 300 mg dosages. The dose-response relationship is quite clear and strongly statistically significant. Overall the average daytime increase for the 300mg dose appears to be about 4 bpm and proportional for the other dosages. In the thorough QT study, the average increase in heart rate was 8.2 bpm (95% CI 7.5 to 8.8) for the 300 mg dosage and 14.6 bpm (95% CI 13.8 to 15.3) for the 900 mg dosage. The ABPM data suggest that the nighttime effect is about one-third of that seen during the day.

#### Peak (2 HR) Effects SBP

<i>Dosage</i>	<i>Effect</i>	<i>95% CI</i>		<i>D/R Trend</i>
37.5	1.7	0.8	2.7	0.3
50	1.3	(3.7)	6.4	0.5
75	1.9	1.3	2.5	0.7
100	0.4	(4.6)	5.4	0.9
150	1.9	1.5	2.4	1.4

200	6.4	1.4	11.4	1.8
300	2.7	2.3	3.2	2.8
400	4.8	2.6	7.0	3.7
500	6.4	5.8	7.0	4.6
600	6.7	5.0	8.5	5.5
800	7.0	4.8	9.2	7.3
1000	7.8	2.8	12.9	9.2
1200	8.3	6.9	9.7	11.0

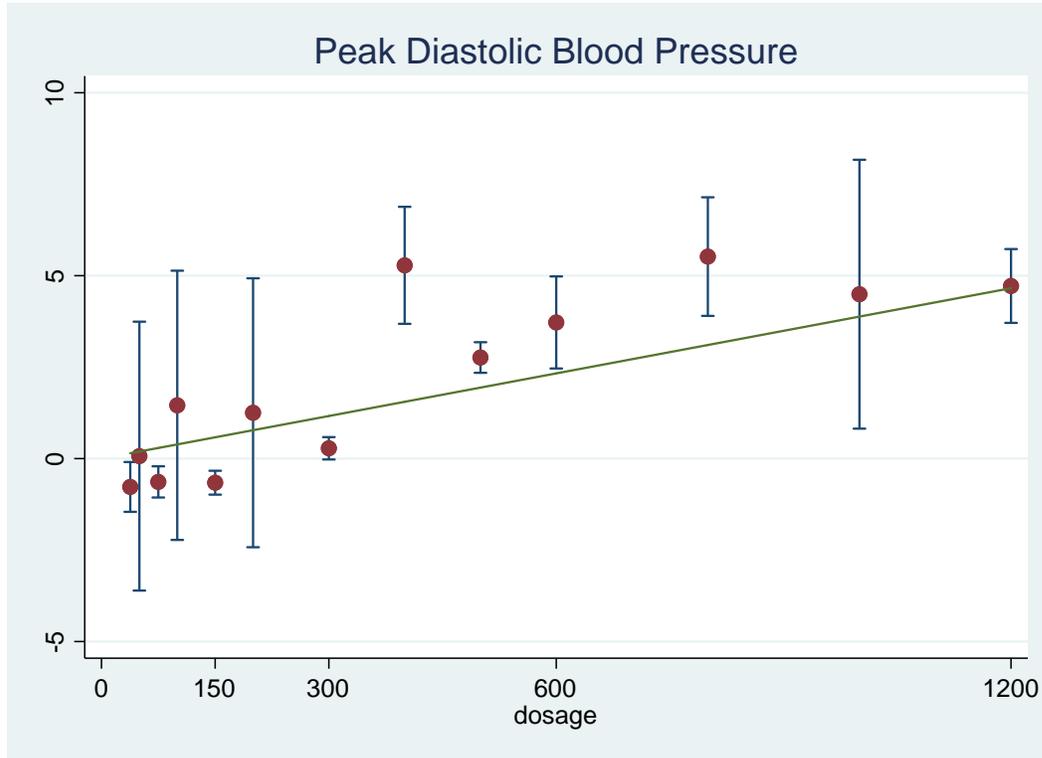


A clear dose-response trend can be seen, consistent with an increase of about 3 mmHg for the 300 mg dosage with proportionately lower estimates for lower dosages.

*Peak (2 HR) Effects DBP*

<i>Dosage</i>	<i>Effect</i>	<i>95% CI</i>		<i>D/R Trend</i>
37.5	(0.8)	(1.5)	(0.1)	0.3
50	0.1	(3.6)	3.7	0.3
75	(0.6)	(1.1)	(0.2)	0.5
100	1.5	(2.2)	5.1	0.7
150	(0.7)	(1.0)	(0.3)	1.0
200	1.3	(2.4)	4.9	1.4
300	0.3	(0.0)	0.6	2.0
400	5.3	3.7	6.9	2.7
500	2.8	2.3	3.2	3.4
600	3.7	2.5	5.0	4.1

800	5.5	3.9	7.1	5.4
1000	4.5	0.8	8.2	6.8
1200	4.7	3.7	5.7	8.1

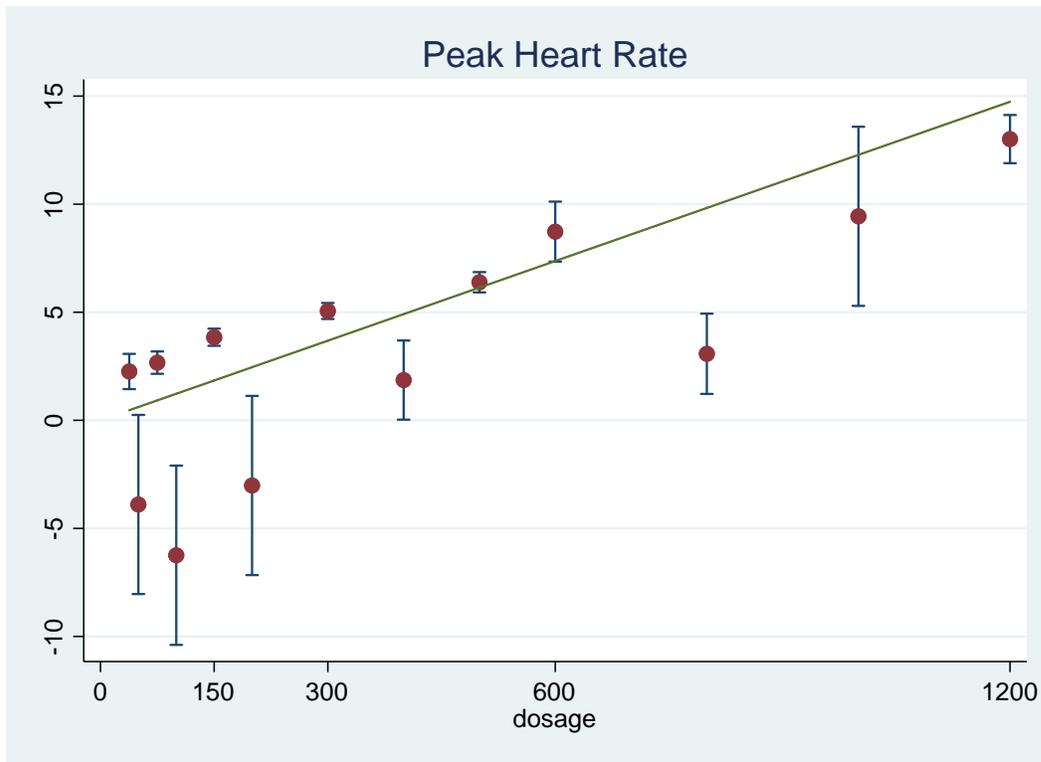


The observed mean peak increases in diastolic BP were negligible for the principal dosages (37.5, 75, 150 & 300 mg) but the dose-response pattern remains and is consistent with a 2 mmHg elevation with 300mg and proportionate increases for other dosages.

*Peak (2 HR) Effects Heart rate*

Dosage	Effect	95% CI		D/R Trend
37.5	2.3	1.4	3.1	0.5
50	(3.9)	(8.0)	0.2	0.6
75	2.7	2.2	3.2	0.9
100	(6.2)	(10.4)	(2.1)	1.2
150	3.8	3.4	4.2	1.8
200	(3.0)	(7.2)	1.1	2.5
300	5.1	4.7	5.4	3.7
400	1.9	0.0	3.7	4.9
500	6.4	5.9	6.9	6.1
600	8.7	7.3	10.1	7.4
800	3.1	1.2	4.9	9.8

1000	9.4	5.3	13.6	12.3
1200	13.0	11.9	14.1	14.7



For heart rate, the peak measurements differ little from the average measurements. In the thorough QT study, heart rate was increased by 7.8 bpm (95% CI 6.1 to 9.6) at C<sub>max</sub> and 7.6 bpm (95% CI 5.9 to 9.4) at two hours compared to no drug for the 300mg dosage and 14.2 bpm (95% CI 12.5 to 15.9) at C<sub>max</sub> and 12.7 bpm (95% CI 10.9 to 14.4) at two hours for the 900 mg dosage, again little different from the overall average.

*Threshold Effect*

Systolic Blood Pressure

Odds ratios for SBP>140 mmHg

Dosage	Study	Odds Ratio	95% CI		D/R Trend
38	all	1.3	1.0	1.5	1.0
38	14-002/3	1.1	0.8	1.6	1.0
38	ABPM	1.1	0.9	1.4	1.0
50	all	3.2	0.6	17.5	1.0
75	all	1.4	1.2	1.7	1.1
75	14-002/3	1.2	0.9	1.6	1.1
75	ABPM	1.3	1.1	1.5	1.1
100	all	1.3	0.7	2.3	1.1
150	all	1.1	1.0	1.2	1.2
150	14-002/3	0.9	0.7	1.2	1.1

150	ABPM	1.0	0.9	1.1	1.2
200	all	0.7	0.3	1.5	1.2
300	all	1.1	1.0	1.2	1.3
300	14-002/3	1.4	1.1	1.8	1.3
300	ABPM	1.5	1.3	1.7	1.4
400	all	2.0	1.2	3.5	1.5
500	all	2.3	1.7	3.1	1.6
600	all	1.4	0.8	2.6	1.8
800	all	1.9	1.1	3.4	2.2
1000	all	5.5	1.7	18.3	2.6
1200	all	5.0	3.4	7.1	3.2

#### Odds ratios for SBP>160 mmHg

<i>Dosage</i>	<i>Study</i>	<i>Effect</i>	<i>95% CI</i>		<i>D/R Trend</i>
38	all	3.5	1.2	10.3	1.0
38	14-002/3	3.2	0.9	10.5	1.0
38	ABPM	1.0	0.6	1.8	1.0
75	all	2.4	1.3	4.4	1.0
75	14-002/3	1.1	0.4	2.7	0.9
75	ABPM	1.3	0.9	1.9	1.1
100	all	2.9	0.3	29.0	0.9
150	all	1.3	0.8	2.2	0.9
150	14-002/3	1.1	0.5	2.4	0.9
150	ABPM	0.8	0.6	1.1	1.2
300	all	0.9	0.6	1.5	0.8
300	14-002/3	0.8	0.4	1.8	0.8
300	ABPM	1.7	1.3	2.3	1.5
400	all	0.6	-	5.7	0.8
500	all	0.4	0.1	1.4	0.8
600	all	0.4	0.0	4.6	0.7
800	all	0.3	-	2.5	0.6
1200	all	1.1	0.3	3.9	0.5

#### Odds ratios for DBP>90 mmHg

<i>Dosage</i>	<i>Study</i>	<i>Effect</i>	<i>95% CI</i>		<i>D/R Trend</i>
38	all	0.9	0.7	1.2	1.0
38	14-002/3	1.0	0.7	1.3	1.0
38	ABPM	1.2	0.9	1.6	1.1

50	all	0.9	-	5.9	1.0
75	all	1.1	0.9	1.3	1.0
75	14-002/3	1.4	1.1	1.7	1.0
75	ABPM	1.3	1.1	1.6	1.2
100	all	1.9	0.9	4.2	1.0
150	all	1.0	0.9	1.2	1.1
150	14-002/3	1.0	0.9	1.2	1.0
150	ABPM	1.1	0.9	1.2	1.4
200	all	0.9	0.3	2.6	1.1
300	all	0.8	0.7	1.0	1.2
300	14-002/3	1.0	0.8	1.2	1.0
300	ABPM	2.3	1.9	2.7	2.0
400	all	1.4	0.9	2.3	1.2
500	all	1.2	0.8	1.9	1.3
600	all	4.8	2.5	9.2	1.3
800	all	1.9	1.3	3.0	1.5
1000	all	4.6	1.4	15.2	1.6
1200	all	2.7	1.8	3.9	1.8

#### Odds ratios for DBP>105 mmHg

<i>Dosage</i>	<i>Study</i>	<i>Effect</i>	<i>95% CI</i>		<i>D/R Trend</i>
38	all	1.8	0.5	6.6	1.0
38	14-002/3	1.6	0.4	6.2	1.0
38	ABPM	1.1	0.5	2.4	1.1
75	all	0.7	0.2	2.0	1.0
75	14-002/3	0.5	0.1	2.2	1.0
75	ABPM	1.2	0.7	1.9	1.2
100	all	7.3	0.7	74.9	1.0
150	all	1.0	0.5	2.2	1.0
150	14-002/3	0.7	0.2	1.9	1.0
150	ABPM	0.7	0.4	1.1	1.6
300	all	0.8	0.4	1.7	1.1
300	14-002/3	1.0	0.4	2.7	0.9
300	ABPM	2.9	2.1	4.0	2.4
400	all	4.3	0.8	23.7	1.1
500	all	0.3	0.0	2.7	1.1
600	all	2.6	0.4	15.0	1.1
800	all	4.4	0.8	24.3	1.2
1200	all	0.9	0.1	7.4	1.3

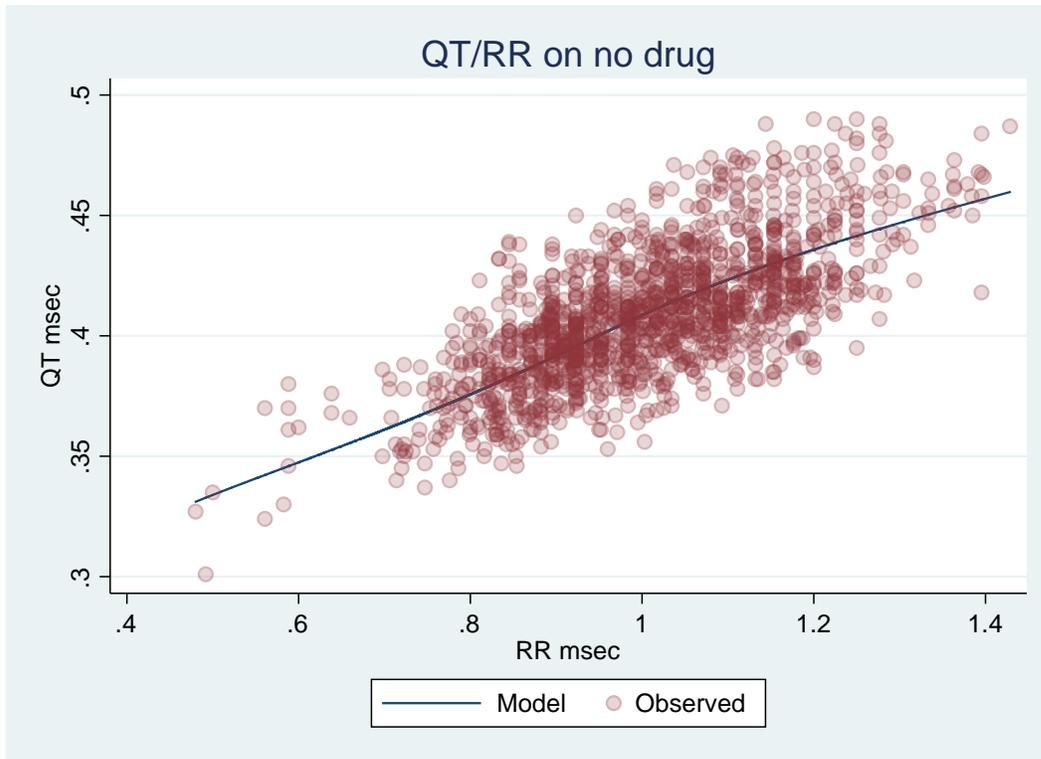
Odds ratios for HR>100 bpm

<i>Dosage</i>	<i>Study</i>	<i>Effect</i>	<i>95% CI</i>		<i>D/R Trend</i>
38	all	0.1	0.0	1.0	1.1
38	14-002/3	0.3	0.0	2.7	1.4
38	ABPM	1.4	1.0	2.1	1.1
75	all	0.7	0.4	1.3	1.3
75	14-002/3	1.6	0.6	4.3	1.8
75	ABPM	1.0	0.8	1.3	1.2
100	all	7.4	2.2	24.7	1.4
150	all	1.4	0.9	2.1	1.6
150	14-002/3	6.2	2.7	14.2	3.3
150	ABPM	1.7	1.4	2.0	1.5
200	all	2.9	0.8	10.4	1.9
300	all	2.0	1.4	2.8	2.6
300	14-002/3	8.9	3.9	20.4	10.8
300	ABPM	2.2	1.8	2.7	2.3
400	all	14.8	7.9	27.8	3.7
500	all	129.6	79.1	212.3	5.1
600	all	8.3	4.4	15.5	7.0
800	all	14.9	8.0	28.1	13.4
1200	all	35.9	23.4	55.1	49.2

At the threshold of systolic blood pressure over 140 mmHg, there is good agreement with the clinic and ABPM data for an odds ratio of 1.2-1.3 for the 150 mg dosage compared to no active drug treatment. For a threshold of 160 mmHg, only the ABPM data show evidence for dose-response, with an odds ratio similar to the 140 mmHg threshold. For diastolic BP, dose-response is again only seen with the ABPM data and suggest a greater effect with an interpolated odds ratio of 1.4-1.6 for the 150 mg dosage. For heart rate more than 100 beats per minute, there is agreement between the clinic data as a whole and the ABPM findings but the effect as measured by clinic readings in the phase 3 studies appears larger. The thorough QT study showed similar findings: the 300 mg dosage was associated with an odds ratio of 2.6 (95% CI 1.0 to 6.9); for the 900 mg dosage the odds ratio was 7.5 (95% CI 3.3 to 16.8).

*Solriamfetol Effects on QTc*

The relationship between QT and RR intervals in the absence of drug effect, along with the modeled population-averaged curve at shown in the following graph:



The distribution of Cmax (the maximum measured concentration) for the 300 mg and 900 mg dosages are shown in the next tables:

**Cmax for the 300 mg Dosage**

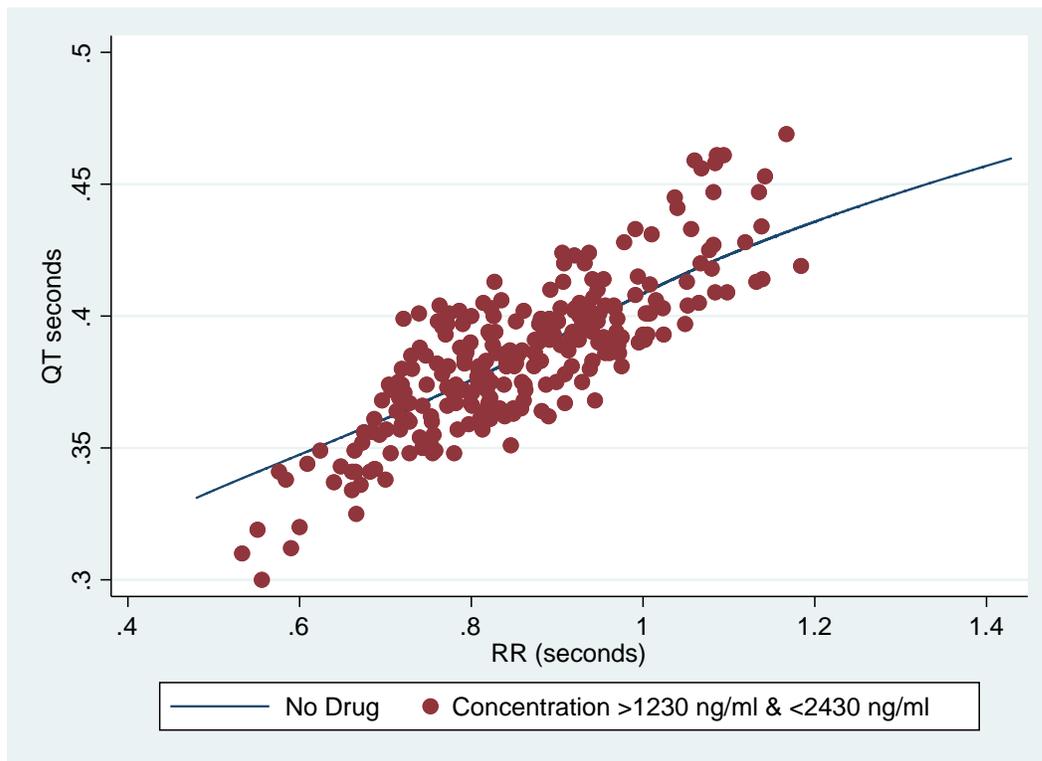
Percentiles		Smallest		
1%	1040	1040		
5%	1230	1150		
10%	1320	1230	N	56
25%	1565	1260		
50%	1785		Mean	1774.464
		Largest	Std. Dev.	342.4825
75%	1985	2180		
90%	2120	2430		
95%	2430	2480		
99%	2990	2990		

**Cmax for the 900 mg Dosage**

Percentiles		Smallest		
1%	3220	3220		
5%	4020	3730		
10%	4200	3760	N	61
25%	4590	4020		

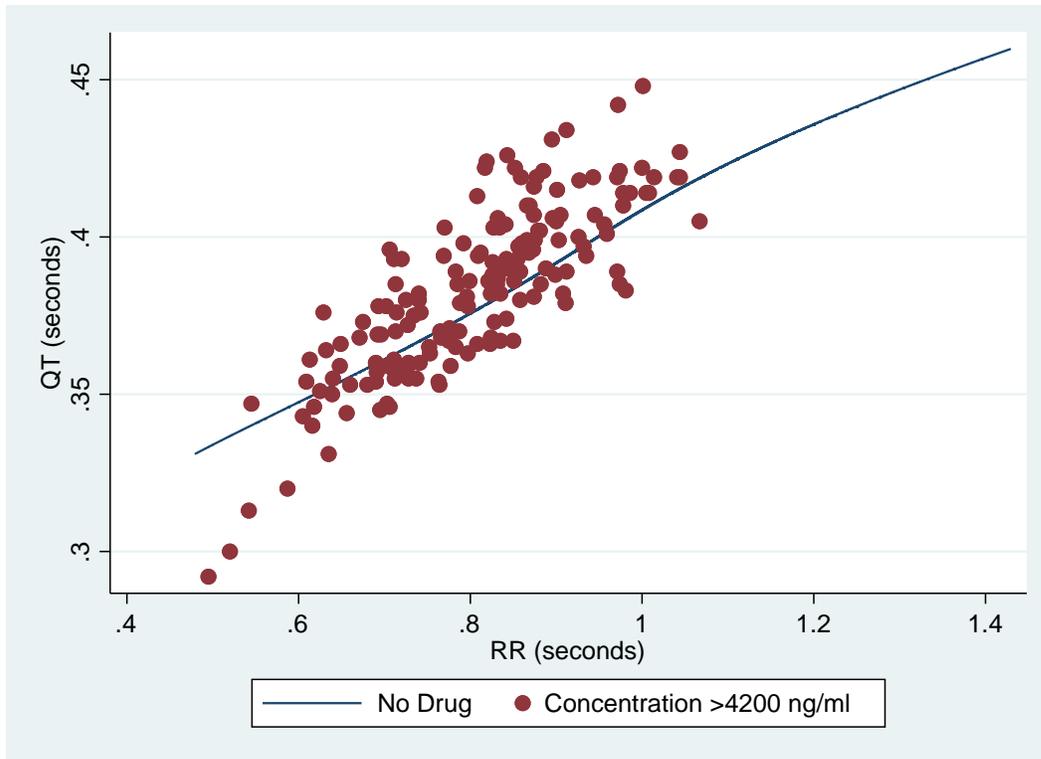
50%	5290		Mean	5301.967
		Largest	Std. Dev.	932.457
75%	5940	6640		
90%	6460	6780		
95%	6640	6860		
99%	8290	8290		

For plasma concentrations associated with the 300 mg dosage there appears to be little effect on the QT intervals:



Using the concentration range for Cmax between the 5<sup>th</sup> and 95<sup>th</sup> percentiles, the median difference between the observed QT and the expected QT (represented by the curve of the QT/RR relationship with no drug effect) is a reduction of 1.5 msec. Just over half of observations (52.9%) lie below the curve (p=0.38).

Using the tenth percentile for the 900 mg dosage (4200 ng/ml) as a representative cut-off point for maximum drug exposure, the QT/RR relationship for all concentration >4200 ng/ml is shown in the next graph and compared to the population-averaged curve for a concentration of zero.

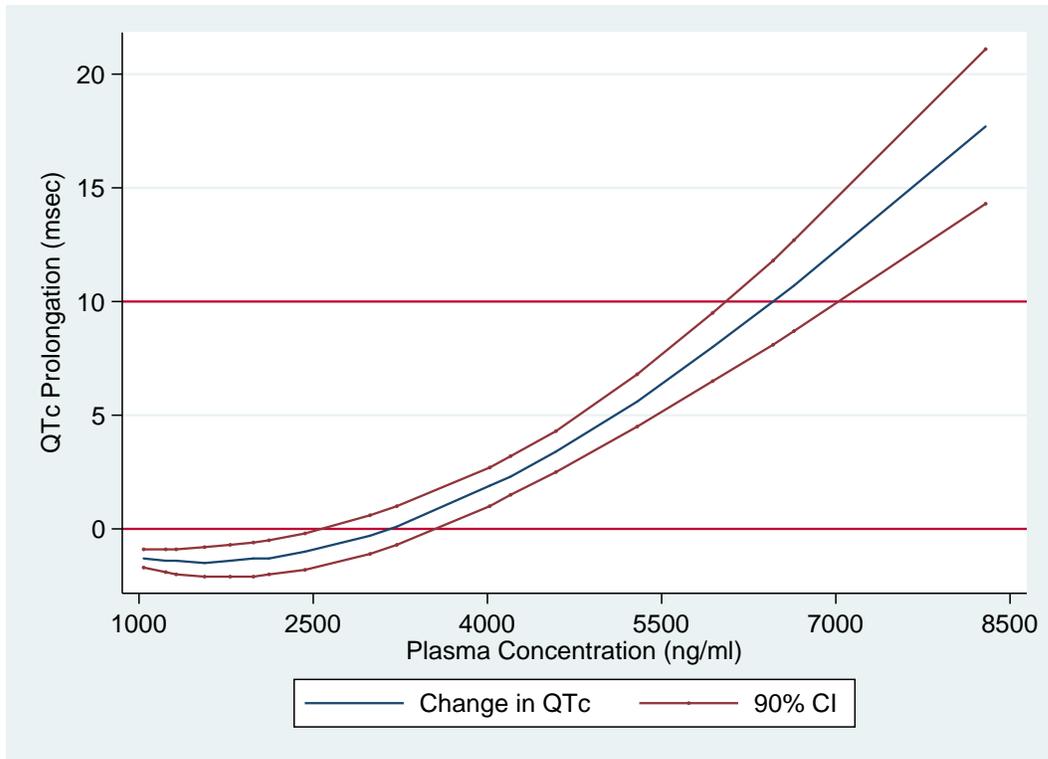


There is a definite shift indicating prolongation of the QT interval relative to RR. Two thirds (66.9%) of the QT/RR observations for concentrations >4200 ng/ml lie above the curve representing observations with no exposure to active drug ( $p=0.00001$ ). The median difference between the observed QT and the expected QT (represented by the curve) is 6.9 msec.

The next table compares the results reported in the IRT/QT consult using QTcF with the results obtained with the modeled QT/RR relationship at three hours after drug administration:

Dosage	QTc Method	QT Effect	90% CI	
300 mg	QTcF	2.8	0.3	5.3
	Model	1.1	(1.1)	3.3
1200 mg	QTcF	7.0	4.6	9.5
	Model	4.2	1.8	6.5

The next graph shows estimates from the model using plasma concentration rather than dosage:



At plasma concentrations associated with the 300 mg dosage (1000-3000 ng/ml), there is no effect (or a slight shortening) on QTc. A lengthening effect is seen with concentrations associated with the 900 mg dosage (>3000 ng/ml). The model estimates that the upper end of the 90% confidence interval crosses 10 msec at about 6000 ng/ml, about the 80th percentile for Cmax. The 90<sup>th</sup> percentile for Cmax (6460 ng/ml) has an estimated QTc prolongation effect of 10.0 msec (90% CI 8.1 to 11.8 msec).

### Conclusions

Looking at individual studies, it has been difficult to find consistent and reasonable estimates for effects of solriamfetol on heart rate and blood pressure. This analysis shows these effects with greater clarity. For the expected maximum recommended dosage, 150 mg, the average daytime effect appears to be about 1 mmHg for both systolic and diastolic blood pressure with an increase of 2 bpm in heart rate; these values decline overnight. At peak blood levels the effects are only slightly higher. It is prudent to draw attention to these effects in labeling through a Warning which would be of greater importance for patients in the Obstructive Sleep Apnea population who are likely to have other cardiac risk factors.

There do not appear to be QT prolongation effects at plasma concentrations associated with the 300 mg dosage, so none should be expected at the expected maximum recommended dosage of 150 mg. The 900 mg dosage does show QT prolongation effects at about the 10 msec level, the conventional cutoff for clinical significance.

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Clinical Review  
 David H. Millis, MD  
 NDA-211230  
 Solriamfetol / Sunosi

### CLINICAL REVIEW

<b>Application Type</b>	NDA
<b>Application Number(s)</b>	211230
<b>Priority or Standard</b>	Standard
<b>Submit Date(s)</b>	December 20, 2017
<b>Received Date(s)</b>	December 20, 2017
<b>PDUFA Goal Date</b>	December 20, 2018
<b>Division/Office</b>	Division of Psychiatry Products
<b>Reviewer Name(s)</b>	David H. Millis, MD
<b>Review Completion Date</b>	December 20, 2018
<b>Established/Proper Name</b>	solriamfetol
<b>(Proposed) Trade Name</b>	Sunosi
<b>Applicant</b>	Jazz Pharmaceuticals
<b>Dosage Form(s)</b>	oral tablet
<b>Applicant Proposed Dosing Regimen(s)</b>	37.5 mg, 75 mg, 150 mg (b) (4)
<b>Applicant Proposed Indication(s)/Population(s)</b>	excessive daytime sleepiness in patients with narcolepsy; excessive daytime sleepiness in patients with obstructive sleep apnea
<b>Recommendation on Regulatory Action</b>	Approve
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	excessive daytime sleepiness in patients with narcolepsy; excessive daytime sleepiness in patients with obstructive sleep apnea

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## Glossary

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AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
iPSP	Initial Pediatric Study Plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

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NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSA	obstructive sleep apnea
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SLFTOL	solriamfetol
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

## 1. Executive Summary

---

### 1.1. Product Introduction

Solriamfetol (JZP-110, ADX-N05, [*R*]-2-amino-3-phenylpropylcarbamate hydrochloride, proposed proprietary name “Sunosi”) is a new molecular entity developed by Jazz Pharmaceuticals (hereby known as the “Applicant”). It is a derivative of the amino acid phenylalanine, and is a dopamine and norepinephrine reuptake inhibitor (DNRI). The proposed mechanism of action of solriamfetol’s wake-promoting properties is enhancement of dopamine and norepinephrine signaling in the brainstem arousal systems.

With this submission, the Applicant is seeking claims for treatment of excessive daytime sleepiness (EDS) in narcolepsy and treatment of EDS in obstructive sleep apnea (OSA). The product will be available as tablets for oral administration, for which the Applicant has proposed 75 mg, 150 mg (b) (4) dose strengths. The dosing regimen originally proposed by the Applicant (b) (4)

However, the final product labeling will recommend a starting dose of 37.5 mg daily for patients with OSA and 75 mg daily for patients with narcolepsy.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

**Note:** *The information below reflects the review as of the original PDUFA date (12/20/2018). The Applicant submitted a Major Amendment on 12/19/2018. Any changes to the conclusions below will be addressed in a separate addendum.*

The data submitted by the Applicant demonstrate a statistically significant effect of solriamfetol compared to placebo on tests of maintenance of wakefulness and reduction in sleepiness in patients with narcolepsy and in patients with OSA. However, effectiveness has not been demonstrated for both indications at all proposed dosages. For the narcolepsy indication, solriamfetol 75 mg/day did not demonstrate statistically significant improvement over placebo on one of the prespecified co-primary endpoints in Study 14-002. For the OSA indication, solriamfetol 75 mg/day showed a statistically significant difference from placebo on both prespecified co-primary endpoints in Study 14-003.

The results of Study 14-002 raise the possibility that patients with narcolepsy could be started on the 150 mg dose of solriamfetol at the time of initiation of therapy for EDS. While Study 14-002 does not fully support approval of the 75 mg dose for treatment of EDS in narcolepsy, there are several reasons to approve this dose. First, the results of Study 14-005, the long-term open-label study, showed that a small number of patients with narcolepsy can be maintained on the

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75 mg dose. Second, initiating therapy with the 75 mg dose allows the clinician to assess for adverse events at a dose that may be more tolerable for some patients than the 150 mg dose.

Review of the clinical trial results indicate that solriamfetol can cause increases in systolic blood pressure, diastolic blood pressure, and heart rate, both in patients with narcolepsy and patients with OSA. The magnitude of the increases is dose related. These findings do not preclude approval of this NDA. (b) (4)

his issue is discussed in more detail in Section 8.4.7, Vital Signs, and Section 10.1, Prescription Drug Labeling.

The Applicant recommended (b) (4)

However, solriamfetol 37.5 mg/day showed a statistically significant difference from placebo on both prespecified co-primary endpoints in Study 14-003. While the 37.5 mg dose did not succeed on the key secondary endpoint in this study, the success on the co-primary endpoints indicates that some patients with OSA might benefit from this dose. Initiating therapy at this lower dose would allow clinicians to assess patients both for efficacy and for any changes in blood pressure or heart rate before advancing to a higher dose. Starting at the lower dose for patients with OSA is advisable in light of the high rate of cardiovascular co-morbidities in patients with OSA. For these reasons, the product labeling will recommend a starting dose of 37.5 mg/day for patients with OSA.

The 37.5 mg/day dose has not been tested in any studies of patients with narcolepsy. The lowest dosage tested in the narcolepsy trials was 75 mg/day. The product labeling will recommend a starting dosage of 75 mg/day for patients with narcolepsy.

### 1.3. **Benefit-Risk Assessment**

The Benefit-Risk Integrated Assessment is presented in Table 1, beginning on the following page.

### Benefit-Risk Integrated Assessment

Solriamfetol is a new molecular entity proposed for the treatment of excessive daytime sleepiness in patients with narcolepsy and in patients with OSA. Excessive daytime sleepiness is a prominent symptom of both narcolepsy and OSA. While mild sleepiness secondary to insufficient sleep can occur in healthy individuals, the EDS occurring in narcolepsy and OSA is of greater magnitude and poses significant burden on patients and on society. Patients with narcolepsy have reported that daytime sleepiness was the narcolepsy symptom that had the most significant impact on their daily lives. Potential consequences of EDS include reduced attention, cognitive impairment, compromised performance on psychomotor tasks, increased accident rates, decreased productivity, interference with social and occupational function, and decreased quality of life. Limitations of existing treatments for EDS include abuse potential, short duration of action, and possible development of tolerance to the wake-promoting effect. The significant impact of EDS on the lives of patients with narcolepsy and OSA and the limitations of available treatments support the need for additional treatment options for these patient populations.

Solriamfetol is not a treatment for obstructive sleep apnea and is not a substitute for continuous positive airway pressure (CPAP). It is intended to treat only the sleepiness associated with OSA. The product labeling will state that, (b) (4) (b) (4) for at least one month should be made prior to initiating solriamfetol for excessive daytime sleepiness. This will clarify that solriamfetol should be initiated only if the patient's daytime sleepiness does not improve following standard-of-care treatment for the underlying OSA.

Three placebo-controlled trials were positive on measures of maintenance of wakefulness and reduction in sleepiness for patients with narcolepsy and patients with OSA. The two placebo-controlled randomized-withdrawal trials demonstrated long-term effectiveness in each population, in that patients who showed initial improvement when treated with solriamfetol showed continued improvement if solriamfetol was continued, while subjects randomized to placebo during the randomized withdrawal showed a loss of effect.

In the solriamfetol clinical trials, the most common treatment-emergent adverse events (TEAEs) were insomnia, headache, nausea, decreased appetite, (b) (4) anxiety, (b) (4). These common AEs are described in the product labeling.

Solriamfetol caused increases in systolic blood pressure, diastolic blood pressure, and heart rate in some patients with narcolepsy and in some patients with OSA. The increases were dose related and sustained throughout much of the day. Solriamfetol will likely be administered chronically in patients for whom it is effective. The increases in blood pressure and heart rate can increase the risk of major adverse

cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death. The risk is higher with a drug that increases both blood pressure and heart rate than it is with a drug that increases one or the other, but not both. The level of cardiovascular risk is increased in patients with pre-existing cardiovascular disease. Patients with OSA often have multiple risk factors for MACE at baseline, including hypertension, diabetes, hyperlipidemia, and high body mass index. Obesity is also a common co-morbidity for patients with narcolepsy. (b) (4)

(b) (4). Blood pressure should be adequately controlled, and the patient should be monitored (b) (4) for new-onset hypertension or exacerbation of pre-existing hypertension. For patients with OSA, the recommended starting dose will be 37.5 mg, to ensure that patients with high pre-existing cardiovascular risk are given a trial on the lowest dose that might be efficacious. In Study 14-003, the 37.5 mg/day dosage showed a statistically significant improvement compared to placebo on the two co-primary endpoints. Initiating therapy at this lower dose would allow clinicians to assess patients both for efficacy and for any changes in blood pressure or heart rate before advancing to a higher dose.

Based on the evidence of efficacy in treating a debilitating symptom occurring in these two chronic illnesses and potential advantages over available treatments, I recommend approval of this product for the treatment of EDS in narcolepsy and OSA. The recommended starting dose is 75 mg daily for patients with narcolepsy and 37.5 mg daily for patients with OSA. The recommended maximum dose is (b) (4) mg daily. Because elimination of the drug is primarily through the renal system, the product labeling will include recommended adjustments in dosing and in the titration schedule for patients with renal impairment.

### Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#">Analysis of Condition</a>	<ul style="list-style-type: none"> <li>Excessive daytime sleepiness is a disabling symptom of both narcolepsy and OSA.</li> <li>While mild sleepiness secondary to insufficient sleep can occur in healthy individuals, the EDS occurring in narcolepsy and OSA is of greater magnitude and poses significant burden on patients and on society.</li> </ul>	<p>The EDS associated with narcolepsy and OSA can compromise the safety of the patient and of other individuals, and can reduce the patient's quality of life.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>• A 2013 survey of patients with narcolepsy indicated that daytime sleepiness was the narcolepsy symptom that had the most significant impact on their daily lives.</li> <li>• Potential consequences of EDS include reduced attention, cognitive impairment, compromised performance on psychomotor tasks, increased accident rates, decreased productivity, interference with social and occupational functioning, and decreased quality of life.</li> </ul>	
<p><u>Current Treatment Options</u></p>	<ul style="list-style-type: none"> <li>• For EDS in narcolepsy: sodium oxybate, modafinil, armodafinil, methylphenidate, amphetamine</li> <li>• For EDS in OSA: modafinil and armodafinil</li> <li>• Methylphenidate and amphetamine: limited by tolerance and abuse potential; Schedule II</li> <li>• Sodium oxybate: limited by abuse potential and possible diversion for use in drug-facilitated sexual assault; Schedule III, with Schedule I penalties for illicit use; requires a REMS</li> <li>• Modafinil, armodafinil: wake-promoting effect often does not last throughout the day</li> <li>• Modafinil and armodafinil are substrates, inducers, and inhibitors of CYP450 isoenzymes, raising possibility of drug interactions</li> <li>• Modafinil and armodafinil have label warnings for Stevens-Johnson Syndrome, angioedema, anaphylactoid reactions, and multi-organ hypersensitivity reactions</li> </ul>	<p>Limitations of existing treatment options, including tolerance and abuse potential for some agents and short duration of action for others, support the need for additional treatment options.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><u>Benefit</u></p>	<p>The Applicant conducted five adequate and well-controlled trials to assess the efficacy of solriamfetol for the treatment of EDS in narcolepsy and OSA.</p> <ul style="list-style-type: none"> <li>• Study ADX-N05-202 (narcolepsy): The co-primary endpoints were the change in MWT and CGI-C scores. For both endpoints, the difference in mean change from baseline compared to placebo was statistically significant.</li> <li>• Study 14-002 (narcolepsy): On the co-primary endpoint of change in MWT, the difference in mean change from baseline was statistically significant for the 75 mg, 150 mg, and 300 mg doses. On the co-primary endpoint of change in ESS, the difference in mean change was statistically significant for the 150 mg and 300 mg doses, but not for the 75 mg dose.</li> <li>• Study 14-003 (OSA): The co-primary endpoints were the change in MWT and ESS scores. For both endpoints, the difference in mean change from baseline compared to placebo was statistically significant for all solriamfetol dose groups (37.5 mg, 75 mg, 150 mg, and 300 mg).</li> <li>• Study 14-004 (OSA): The co-primary endpoints were change in MWT and ESS scores. For both endpoints, the difference in mean change compared to placebo during the randomized withdrawal period was statistically significant.</li> <li>• Study 14-005 (narcolepsy, OSA): The primary endpoint for the randomized withdrawal period was the change in ESS. For both subjects with narcolepsy and subjects with OSA, the mean ESS score</li> </ul>	<p>Solriamfetol demonstrated statistically significant efficacy compared to placebo on all five trials. There is adequate evidence of efficacy to approve solriamfetol for the treatment of EDS in narcolepsy and for the treatment of EDS in OSA.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>increased significantly more for the placebo group than for the solriamfetol group, indicating better control of daytime sleepiness for subjects who remained on solriamfetol during the randomized withdrawal.</p> <p>Additional favorable characteristics of solriamfetol:</p> <ul style="list-style-type: none"> <li>• onset of effect as early as one hour after dosing</li> <li>• duration of effect is about nine hours, supporting once-daily dosing</li> <li>• no signs of tolerance or rebound hypersomnia after discontinuation</li> <li>• not metabolized by CYP450 isoenzymes, and no inhibition or induction of CYP450 isoenzymes, so drug interactions are expected to be minimal</li> <li>• no pattern of hypersensitivity reactions observed during short-term or long-term clinical trials</li> </ul>	
<p><a href="#">Risk and Risk Management</a></p>	<p><b>Cardiovascular Risk</b></p> <ul style="list-style-type: none"> <li>• Increases in both blood pressure and heart rate observed in both patients with narcolepsy and patients with OSA</li> <li>• Increases were dose related</li> <li>• Increases were sustained throughout most of the day</li> <li>• Chronic administration is likely</li> <li>• Increased risk of MACE events is a concern</li> <li>• Level of cardiovascular risk is increased in patients with pre-existing cardiovascular disease</li> <li>• For narcolepsy patients, obesity is a common pre-existing risk factor for cardiovascular disease</li> </ul>	<p>(b) (4)</p> <p>For patients with OSA, the recommended starting dose will be 37.5 mg, to ensure that patients with high pre-existing cardiovascular risk are given a trial on the lowest dose that might be efficacious.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>OSA patients often have multiple pre-existing risk factors for cardiovascular disease, including hypertension, hyperlipidemia, obesity, and diabetes</li> </ul>	
	<p><b>Common TEAEs</b></p> <ul style="list-style-type: none"> <li>Most common TEAEs: insomnia, headache, nausea, decreased appetite, (b) (4) anxiety, (b) (4)</li> <li>All of the most common TEAEs are dose-dependent, with the exception of nasopharyngitis</li> </ul>	<p>The product labeling lists the TEAEs that occurred most frequently in the placebo-controlled trials, the less common TEAEs that occurred more frequently than in placebo, and the TEAEs that were dose-related.</p>
	<p><b>Dosing in Renal Insufficiency</b></p> <ul style="list-style-type: none"> <li>Because excretion is primarily through the renal system, patients with decreased renal function may be more susceptible to adverse events.</li> </ul>	<p>The product labeling will include recommended adjustments in dosing and in the titration schedule for patients with renal impairment.</p>
	<p><b>Treatment of EDS vs. Treatment of OSA</b></p> <ul style="list-style-type: none"> <li>Clinicians should be made aware that solriamfetol is not a treatment for obstructive sleep apnea and is not a substitute for CPAP.</li> </ul>	<p>The product labeling will state that, (b) (4) to treat the OSA (b) (4) for at least one month should be made prior to initiating solriamfetol for EDS.</p>

#### 1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

<input checked="" type="checkbox"/>	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
<input checked="" type="checkbox"/>	Clinical outcome assessment (COA) data, such as	
<input checked="" type="checkbox"/>	Patient reported outcome (PRO)	PGI-C, FOSQ-10, SF-36v2, EuroQol, WPA:SHP; all described in Chapter 6
<input type="checkbox"/>	Observer reported outcome (ObsRO)	
<input checked="" type="checkbox"/>	Clinician reported outcome (ClinRO)	CGI-C
<input type="checkbox"/>	Performance outcome (PerfO)	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications)	
<input type="checkbox"/>	Other: (Please specify)	
<input type="checkbox"/>	Patient experience data that were not submitted in the application, but were considered in this review:	
<input type="checkbox"/>	Input informed from participation in meetings with patient stakeholders	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Other: (Please specify)	
<input type="checkbox"/>	Patient experience data was not submitted as part of this application.	

## 2. Therapeutic Context

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### 2.1. Analysis of Condition

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

Narcolepsy is a rare, lifelong disease without an identified cure. In adults, narcolepsy affects an estimated 0.02% to 0.067% of the population worldwide and approximately one in 2000 individuals in the United States. Excessive sleepiness is a defining characteristic of narcolepsy, with the first criterion for the diagnosis of narcolepsy in the DSM-5 being “recurrent periods of an irrepressible need to sleep, lapsing into sleep, or napping occurring within the same day,” occurring at least three times per week. The excessive daytime sleepiness occurring in narcolepsy cannot be addressed through increasing the amount of nighttime sleep. Patients with narcolepsy experience impaired psychosocial functioning, decreased work performance, increased susceptibility to accidents while working or driving, and decreased quality of life. Respondents to a 2013 survey of patients with narcolepsy indicated that daytime sleepiness was the narcolepsy symptom that had the most significant impact on their daily lives.

Obstructive sleep apnea is caused by partial or complete obstruction of the upper airway during sleep. This results in repeated arousals and sleep fragmentation. Prevalence estimates range from 10% to 17% of the United States population. Obesity is a risk factor for OSA and a frequent comorbidity. Persistent excessive daytime sleepiness is a presenting complaint in many patients later diagnosed with obstructive sleep apnea. Increasing the number of hours of nighttime sleep does not improve the daytime sleepiness that occurs in OSA. As in patients with narcolepsy, patients with OSA experienced impaired psychosocial functioning, decreased work performance, increased susceptibility to accidents while working or driving, and decreased quality of life because of excessive daytime sleepiness.

### 2.2. Analysis of Current Treatment Options

For patients with narcolepsy, there are five drug treatments approved to treat excessive sleepiness: sodium oxybate, modafinil, armodafinil, methylphenidate, and amphetamine. For patients with OSA, continuous positive airway pressure (CPAP) is part of the standard of care. CPAP aims to stabilize the upper airway with a constant flow of air, preventing collapse of the airway during sleep. However, EDS may persist despite CPAP treatment. Modafinil and

armodafinil are the only drugs approved to treat EDS in OSA. There is little evidence to support the use of amphetamine or methylphenidate for the treatment of EDS in OSA.

The currently available options for treating EDS in narcolepsy and OSA have limitations. Stimulants such as amphetamines and methylphenidate have wake-promoting effects, but patients often develop tolerance to the wake-promoting effect. Amphetamines and methylphenidate have high abuse potential, and they are listed as Schedule II controlled substances. Sodium oxybate is the sodium salt of gamma-hydroxybutyric acid (GHB), which has been misused to commit drug-facilitated sexual assault and date rape. It is listed as a Schedule III controlled substance because of its abuse potential, but illicit use is subject to Schedule I penalties. It is available in the United States only through a risk evaluation and mitigation strategy (REMS) program. Modafinil and armodafinil have lower abuse potential and are listed as Schedule IV controlled substances. However, for many patients they do not adequately promote wakefulness throughout the day. In addition, modafinil and armodafinil are substrates, inducers, and inhibitors of CYP450 isoenzymes, raising the possibility of interactions with medications that subjects may be prescribed for other illnesses. Finally, modafinil and armodafinil both have label warnings for Stevens-Johnson Syndrome, angioedema, anaphylactoid reactions, and multi-organ hypersensitivity reactions. The significant impact of EDS on the lives of patients with narcolepsy and OSA and the limitations of available treatments support the need for additional treatment options for these patient populations.

### 3. Regulatory Background

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#### 3.1. U.S. Regulatory Actions and Marketing History

To date, solriamfetol is not approved for marketing in the United States. The Agency has not placed any specific limitations on the current or future development of solriamfetol on the basis of safety information.

#### 3.2. Summary of Presubmission/Submission Regulatory Activity

Regarding the narcolepsy indication, the Applicant has orphan drug designation for use of an (b) (4) phenylalanine derivative for treatment of narcolepsy. Because of the orphan drug designation, the development program will be exempt from the Pediatric Research Equity Act (PREA) requirement for pediatric studies. During a pre-NDA meeting held on October 17, 2017, DPP encouraged the Applicant to consider a pediatric program in children with narcolepsy, provided that no safety concerns preclude it.

Regarding the OSA indication, the Applicant has filed an initial Pediatric Study Plan (iPSP), and it has been accepted by the Agency. The Applicant will submit a request for a waiver from all

PREA requirements for the OSA indication, on the following basis: [1] the primary treatment of OSA in pediatric patients is surgical management, and professional treatment guidelines do not recommend pharmaceutical therapy; [2] the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; [3] the product is not likely to be used in a substantial number of pediatric patients; and [4] pediatric studies would be impossible or highly impractical to conduct.

### 3.3. Foreign Regulatory Actions and Marketing History

To date, solriamfetol is not approved for marketing in any foreign country.

## 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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### 4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations completed five clinical site investigations. The OSI compliance classifications were “no action indicated” for four sites and “voluntary action indicated” for one site. OSI concluded that the studies appear to have been conducted adequately, and the data generated from these sites appear to be acceptable.

### 4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) has reviewed the application. The findings of their review are as follows:

- Score lines were originally proposed by the Applicant (b) (4)  
The score line for the 75 mg tablet was approved, allowing the tablet to be split in half to achieve a 37.5 mg dose for patients (b) (4). Tablet breakability and split tablet stability were demonstrated per FDA’s guidance on scored tablets.
- The specification for solriamfetol includes tests and acceptance criteria for appearance, identification, assay, related impurities, chiral purity, water content, related solvents, residue on ignition, and microbiological quality. None of the specified impurities exceeded the qualification limit in any of the batches used in the Phase 3 clinical studies. No significant changes or trends were observed in appearance, assay, related impurities, chiral purity, water content, or microbial contamination over (b) (4) months storage under long-term storage conditions or at six months storage under the accelerated storage condition. All results complied with the proposed specification. OPQ does not

recommend any special storage conditions.

- Based on the stability data provided, OPQ granted a 30-month shelf life for the drug product when stored at USP Controlled Room Temperature.
- Based on modeled and available data, OPQ expects a low environmental impact risk.
- OPQ assessed the manufacturing facilities named in the application as acceptable. There were no significant differences found between the overall manufacturing processes used for the clinical supply and those intended for the commercial supply. No inspections were scheduled.
- The application included a biowaiver request supporting the bridge between the Phase II to Phase III formulation and dosage form changes (from capsules to tablets). Data provided in the application demonstrated similarity between dissolution profiles of the capsules and tablets. OPQ granted the biowaiver.

OPQ has recommended approval of the application.

#### 4.3. **Clinical Microbiology**

No new clinical microbiology data were submitted with this application.

#### 4.4. **Nonclinical Pharmacology/Toxicology**

The findings of the Pharmacology/Toxicology review are as follows:

- The mechanism of action for solriamfetol is unknown. The results from the majority of pharmacology studies suggest that the CNS effects of solriamfetol are mediated by noradrenergic and dopaminergic transmissions. Solriamfetol has relatively low binding affinities for the dopamine transporter (DAT) and norepinephrine transporter (NET), and inhibits the reuptake of dopamine and norepinephrine with relatively low potency. At therapeutically relevant levels, solriamfetol showed negligible serotonergic activity, and had minimal effects on stimulating the release of dopamine, norepinephrine, or serotonin.
- The Applicant claims that solriamfetol is a non-amphetamine wake-promoter, and that the mechanisms of action are different from amphetamine. The Pharm/Tox reviewer does not agree, because [1] the proposed norepinephrine and dopamine reuptake inhibition are known mechanisms shared by amphetamine, and [2] when compared to different selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), or amphetamines, the neurobehavioral effects of solriamfetol were mostly similar to those of amphetamine or dextroamphetamine. In *in vivo* rodent models, the effects of solriamfetol on sleep-wake architecture were similar to those of amphetamine treatment.
  - *Reviewer's Comment:* while the proposed mechanism of action for solriamfetol is shared with amphetamines, there are some mechanistic differences between

solriamfetol and amphetamines. For example, solriamfetol has no known action in the trace amine-associated receptor 1 (TARR1), or in vesicular monoamine transporters (VMAT) 1 and 2. This could explain why solriamfetol does not appear to release dopamine and norepinephrine into the synaptic cleft, as amphetamines do. In addition, there are widely used drugs that inhibit dopamine and norepinephrine reuptake, such as bupropion, that are not considered amphetamines. I agree that solriamfetol is amphetamine-like, but I do not agree that it should be categorized as an amphetamine.

- The safety pharmacology of solriamfetol was evaluated in the cardiovascular, respiratory, and CNS systems in animal studies. No severe adverse effects were identified at clinically relevant doses.
- In pregnant rats, after oral administration, solriamfetol was present in non-reproductive and reproductive tissues as well as the fetus. The exposure in these tissues generally paralleled those in the blood.
- The *in vivo* metabolism profiles of solriamfetol are similar between dogs and humans. In both species, limited hepatic metabolism is observed, and the majority of drug is excreted unchanged in the urine. In rats, solriamfetol undergoes both renal excretion and hepatic metabolism. Compared to nonclinical animal species, there is no unique or major human metabolite. At clinically relevant doses, solriamfetol is unlikely to cause significant drug-drug interactions.
- In nonclinical toxicology studies in the mouse, rat, dog, and rabbit, the most prominent drug-related effects of solriamfetol are observed in the CNS. The severity of CNS clinical signs increased in a dose-dependent manner, from hyperactivity at lower doses to tremor, convulsion, and self-injury in rats at higher doses. Solriamfetol also caused dose-dependent decreases in food consumption and body weight gain, particularly during the first few weeks after initiation of treatment.
- The safety margins relative to the MRHD of 300 mg at the no observed adverse effect levels (NOAELs) in the pivotal general toxicology studies were approximately 1 in the dog and < 1 in the mouse and rat. However, many of the dose-limiting toxicities in animal studies were due to pharmacology-related CNS signs and/or body weight decreases, which are clinically monitorable and were reversible on cessation of treatment. The Pharm/Tox reviewer opines that the small safety margins do not impose unacceptable risks for the proposed indication and do not preclude approval of the application.
- Solriamfetol was non-genotoxic in an adequate battery of genotoxicity assays. Solriamfetol was not carcinogenic and did not induce tumors in rats or mice when administered orally at doses up to approximately 3.5 and 9 times the MRHD of 300 mg/day to rats and mice, respectively, based on AUC.
- Solriamfetol did not affect fertility or sperm parameters when administered orally to male rats for eight weeks at doses approximately 1 and 3.5 times the MRHD, based on body surface area. However, at approximately 11 times the MRHD, sperm count and

sperm concentration were decreased about 10%, without affecting fertility. Solriamfetol did not affect fertility when administered orally to female rats for two weeks pre-mating, during mating, and through gestation day seven at approximately 0.5, 2, and 9.5 times the MRHD.

- In embryo-fetal developmental studies, oral administration of solriamfetol during organogenesis caused maternal and fetal toxicities in rats and rabbits at doses  $\geq 2$  and 2.5 times MRHD, respectively, and was teratogenic at doses 9.5 and  $\geq 2.5$  times MRHD, respectively. The Pharm/Tox reviewer notes that the animal findings do not suggest the need for specific or additional monitoring recommendations in humans; however, the risk-to-benefit profile should be carefully considered when administering solriamfetol to pregnant or breastfeeding women, as fetal and infant exposure are likely to occur with a small safety margin.

The Pharm/Tox reviewer concludes that the nonclinical studies submitted support the approval of solriamfetol for the proposed indications.

#### 4.5. Clinical Pharmacology

The Applicant initially proposed

(b) (4)

The Office of Clinical Pharmacology (OCP) recommends a starting dose of 75 mg for all patients in the general population, and an interval of seven days for dose titration for all patients. This dosing schedule would allow sufficient time to observe for a clinical response at the lowest dose and would avoid raising the dose unnecessarily, minimizing the risks for cardiac adverse events associated with increased blood pressure. Using a seven-day titration interval for all patients would also simplify the titration instructions, possibly reducing the potential for medication errors.

The Applicant has proposed (b) (4) for patients with moderate renal impairment, and (b) (4) for patients with severe renal impairment.

In a study of patients with different levels of renal impairment, the  $AUC_{inf}$  and  $t_{1/2}$  values of a single dose of 75 mg solriamfetol increased with more severe levels of renal impairment.  $AUC_{inf}$  was higher by approximately 1.5-, 2.3-, and 4.4-fold, and  $t_{1/2}$  increased approximately 1.2-, 1.9-, and 3.9-fold in patients with mild (eGFR 60-89 mL/min/1.73 m<sup>2</sup>), moderate (eGFR 30-59 mL/min/1.73 m<sup>2</sup>), or severe (eGFR < 30 mL/min/1.73 m<sup>2</sup>) renal impairment, respectively, compared with patients with normal (eGFR  $\geq 90$  mL/min/1.73 m<sup>2</sup>) renal function. In patients with end-stage renal disease, solriamfetol  $AUC_t$  was nearly 6.2-fold higher than in subjects with normal renal function. The Applicant notes that solriamfetol is not recommended for patients with end-stage renal disease. OCP suggests that, due to the prolonged half-life of solriamfetol in patients with moderate or severe renal impairment, a higher risk for insomnia

and sustained increase in diastolic blood pressure, systolic blood pressure, and heart rate is likely, even after the Applicant's proposed dose adjustments. OCP recommends the addition of language to the label to communicate the increased risk of insomnia, increased systolic blood pressure, increased diastolic blood pressure, and increased heart rate in patients with moderate or severe renal impairment.

OCP reviewed the results of the Applicant's food effect study. Ingestion of solriamfetol with a high-fat meal resulted in minimal change in  $C_{max}$  and  $AUC_{inf}$ . A delay of approximately one hour was observed in  $T_{max}$ . These changes are not considered clinically significant. OCP concluded that solriamfetol can be taken either with or without food.

OCP reviewed the results of the thorough QT study conducted by the Applicant. Solriamfetol did not induce any significant QTc prolongation effect at a dose of 900 mg, which is three times the highest recommended dose.

Population PK analysis indicated that gender and race do not have clinically relevant effects on the pharmacokinetics of solriamfetol. Dose adjustments were not done in the clinical studies that enrolled patients age 65 years and above. While  $C_{max}$  in the clinical studies was higher in females than males after solriamfetol administration, either under fasting or fed conditions,  $C_{14hr}$  levels were comparable. OCP concludes that no dosage adjustment based on age, race, or gender is necessary.

#### **4.6. Devices and Companion Diagnostic Issues**

There are no device or companion diagnostic issues relevant to this application.

#### **4.7. Consumer Study Reviews**

No consumer study reviews were conducted in the course of this application.

### **5. Sources of Clinical Data and Review Strategy**

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#### **5.1. Table of Clinical Studies**

The Tables of Clinical Studies (Table 1 and Table 2) begin on the following page.

**Table 1: Table of Clinical Studies: EDS in Narcolepsy**

Study ID	Trial Design	Regimen / Schedule	Study Endpoints	Treatment Duration / Follow Up	Patients Enrolled	Study Population	Number of Centers and Countries
<b>Controlled Studies to Support Efficacy and Safety – EDS in Narcolepsy</b>							
ADX-N05-202	Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group	150 mg QD x 4 wks, then 300 mg QD x 8 wks; placebo	<i>Co-primary endpoints:</i> [1] Change in the mean sleep latency time from the first four test sessions of the MWT from baseline to last post-baseline assessment  [2] Percentage of patients with improvement in the CGI-C at last postbaseline assessment	12 weeks treatment + 2 weeks safety follow-up	93	Adults with narcolepsy, baseline EES $\geq$ 10, baseline mean sleep latency $\leq$ 10 minutes	28 centers 1 country (USA)
14-002	Phase 3, multicenter, double-blind, placebo-controlled, parallel-group	75 mg/day; 150 mg/day; 300 mg/day; placebo	<i>Co-primary endpoints:</i> [1] Change from baseline to Week 12 in mean sleep latency time from MWT  [2] Change from baseline to Week 12 in ESS score	12 weeks treatment + 2 weeks safety follow-up	239	Adults with narcolepsy, EES $\geq$ 10, baseline mean sleep latency < 25 minutes	59 centers 5 countries
14-005	Phase 3, multicenter, open-label, with double-blind, placebo-controlled, randomized withdrawal period	75 mg/day; 150 mg/day; 300 mg/day; continued drug vs placebo during randomized withdrawal	Change in ESS score from baseline to end of two-week randomized withdrawal period	approx. 52 weeks open-label treatment; 2 weeks randomized withdrawal after approx. 6 months of treatment; resume open-label treatment after randomized withdrawal	683	Adults with narcolepsy and adults with OSA; completion of a previous solriamfetol study	79 centers 7 countries

**Table 2: Table of Clinical Studies: EDS in Obstructive Sleep Apnea**

Study ID	Trial Design	Regimen / Schedule	Study Endpoints	Treatment Duration / Follow Up	Patients Enrolled	Study Population	Number of Centers and Countries
<b>Controlled Studies to Support Efficacy and Safety – EDS in OSA</b>							
14-003	Phase 3, multicenter, randomized, double-blind, placebo-controlled	37.5 mg/day; 75 mg/day; 150 mg/day; 300 mg/day; placebo	<i>Co-primary endpoints:</i>  [1] Change in mean sleep latency time from the first four test sessions of the MWT from baseline to Week 12  [2] Change in ESS score from baseline to Week 12	12 weeks treatment + 2 weeks safety follow-up	476	Adults with OSA; baseline ESS $\geq$ 10; baseline mean sleep latency < 30 minutes	59 centers 5 countries
14-004	Phase 3, multicenter, double-blind, placebo-controlled, randomized withdrawal	37.5 mg/day; 75 mg/day; 150 mg/day; 300 mg/day; continued drug vs placebo during randomized withdrawal	<i>Co-primary endpoints:</i>  [1] Change in mean sleep latency time from the first four test sessions of the MWT from Week 4 to Week 6  [2] Change in ESS score from Week 4 to Week 6	4 weeks treatment + 2 weeks randomized withdrawal + 2 weeks safety follow-up	174	Adults with OSA; baseline ESS $\geq$ 10; baseline mean sleep latency < 30 minutes	34 centers 5 countries
14-005	Phase 3, multicenter, open-label, with double-blind, placebo-controlled, randomized withdrawal period	75 mg/day; 150 mg/day; 300 mg/day; continued drug vs placebo during randomized withdrawal	Change in ESS score from baseline to end of two-week randomized withdrawal period	approx. 52 weeks open-label treatment; 2 weeks randomized withdrawal after approx. 6 months of treatment; resume open-label treatment after randomized withdrawal	683	Adults with narcolepsy and adults with OSA; completion of a previous solriamfetol study	79 centers 7 countries

## 5.2. Review Strategy

The review of efficacy will focus on Studies ADX-N05-202, 14-002, and 14-005 for treatment of EDS in narcolepsy, and Studies 14-003, 14-004, and 14-005 for treatment of EDS in OSA. The safety review will be based on the same studies used in the efficacy review. The Applicant has also submitted data from [REDACTED] (b) (4) major depressive disorder (MDD), from early phase pharmacokinetic studies in healthy subjects, from studies in subjects with a history of substance abuse, and from studies in subjects with renal impairment. The more serious adverse events occurring in these studies, including deaths, non-fatal serious adverse events, and adverse events that led to dropout, will be discussed. In addition, data from these studies will be discussed with regards to evaluation of the abuse potential for solriamfetol and the Applicant's suggested dosing adjustments for patients with renal impairment.

## 6. Review of Relevant Individual Trials Used to Support Efficacy

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The following assessment tools and efficacy endpoints were used in one or more of the solriamfetol clinical trials.

The **Epworth Sleepiness Scale (ESS)** measures a person's general level of daytime sleepiness. It is a self-administered questionnaire with eight questions. Respondents are asked to rate, on a four-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in eight different activities. The ESS score can range from 0 to 24. The higher the ESS score, the higher that person's daytime sleepiness.

The **Maintenance of Wakefulness Test (MWT)** is used to objectively assess daytime sleepiness. It measures a patient's ability to remain awake in a quiet, relaxing, stimulation-free environment. The test is conducted at a sleep center. The patient is given five test sessions of 40 minutes each in a quiet, dimly-lit bedroom. The patient is asked to sit still while looking forward, and not do anything to intentionally try to stay awake. The test sessions are spaced two hours apart. A sleep center technician monitors for the time of onset of sleep. Each test session ends either after the patient falls asleep, or after 40 minutes have passed and the patient has remained awake for the entire test session. The result reported for the MWT is the average of the time to fall asleep for the first four test sessions. The shorter the average time on the MWT, the more difficult it is for the patient to remain awake.

The **Multiple Sleep Latency Test (MSLT)** is used to measure the time it takes from the start of a daytime nap period to the first signs of sleep, called sleep latency. The test is based on the idea that the sleepier a person is, the faster they will fall asleep. The test is conducted at a sleep

center. The patient is scheduled for five naps at two-hour intervals. The patient lies in bed with the goal of falling asleep. A sleep center technician monitors for the time of onset of sleep. After 20 minutes, the patient is awakened. Interpretation of the test results includes assessing whether the patient enters rapid-eye movement (REM) sleep during the naps. Patients with narcolepsy often have two or more periods of REM sleep during the MSLT. Patients with idiopathic hypersomnia fall asleep easily but do not reach REM sleep during the nap sessions. The MSLT is used more commonly as a diagnostic tool than as an efficacy endpoint in clinical trials. For example, the MSLT was not used as an efficacy endpoint in any of the solriamfetol trials, but it was used during the screening period to confirm the diagnosis of narcolepsy.

The **Clinical Global Impression – Severity (CGI-S)** scale is a 7-point scale for rating symptom severity in patients with psychiatric disorders. The clinician rates the severity of the patient’s illness at the time of assessment, relative to the clinician’s past experience with patients who have the same diagnosis. Possible ratings are:

1. Normal; not at all ill
2. Borderline mentally ill
3. Mildly ill
4. Moderately ill
5. Markedly ill
6. Severely ill
7. Among the most extremely ill patients

The CGI-S was not used as an efficacy endpoint for any of the trials, but was an element of the inclusion criteria for several trials.

The **Clinical Global Impression – Improvement (CGI-I)** scale, also called the **Clinical Global Impression – Change (CGI-C)** scale, is a 7-point scale for rating symptom improvement in patients with psychiatric disorders. The clinician rates how much the patient’s illness has improved or worsened relative to a baseline state. Possible ratings are:

1. Very much improved
2. Much improved
3. Minimally improved
4. No change
5. Minimally worse
6. Much worse
7. Very much worse

The **Patient Global Impression of Change (PGI-C)** scale is a self-rated, 7-point scale for assessment of the patient’s overall treatment experience. The questionnaire presents the following single question to the patient: “Since the start of the study, my overall status is: (check one box only).” Possible ratings are:

1. Very much improved

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2. Much improved
3. Minimally improved
4. No change
5. Minimally worse
6. Much worse
7. Very much worse

The **FOSQ-10** is a short version of the 30-item Functional Outcomes of Sleep Questionnaire (FOSQ-30). The FOSQ-30 is an instrument designed to assess the impact of sleepiness on the ability of the patient to conduct daily activities. The FOSQ-10 was designed to have psychometric properties comparable to the FOSQ-30, while being more practical to administer both in clinical trials and in clinical practice. The FOSQ-10 uses a 4-point scale:

1. extreme difficulty
2. moderate difficulty
3. a little difficulty
4. no difficulty

The range of scores on the FOSQ-10 is from 10 (lowest functional ability) to 40 (highest functional ability). The FOSQ-10 was not used as a primary efficacy endpoint in any of the solriamfetol trials, but was used as an exploratory endpoint in several trials.

The **SF-36v2 Health Survey** includes 36 questions to measure functional health and well-being from the patient's perspective across eight domains: bodily pain, general health, physical functioning, physical role limitations, emotional role limitations, social functioning, vitality, and mental health. The number of possible answers presented for each question vary from two to six. The range of scores is from 0 to 100, with higher scores representing better health status. The SF-36v2 was not used as a primary efficacy endpoint in any of the solriamfetol trials, but was used as an exploratory endpoint in several trials.

The **EuroQol** is a self-reported instrument designed to measure health outcomes. Part I of the scale consists of five dimensions including mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has a 3-point response scale. The digits for the five dimensions are combined into a five-digit number describing the respondent's health status. The developers of the instrument note that the five-digit number has no arithmetic properties, is only descriptive, and should not be used as a cardinal score. Part II uses a visual analogue scale to measure health status, ranging from 0 (worst imaginable) to 100 (best imaginable). The EuroQol was not used as a primary efficacy endpoint in any of the solriamfetol trials, but was used as an exploratory endpoint in several trials.

The **Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)** is a patient-reported quantitative assessment of the amount of absenteeism and daily activity impairment attributable to a specific health problem. The instrument consists of

six questions about the respondent's ability to work, functioning at work, and ability to perform usual activities outside of work over the past seven days. Four questions ask the respondent about hours worked and hours missed from work, and two questions ask the respondent to rate their ability to perform work activities and activities outside of work on a scale from 0 (no difficulty performing) to 10 (unable to perform). Results are expressed as impairment percentages, with higher percentages indicating greater impairment and less productivity. The WPAI:SHP was not used as a primary efficacy endpoint in any of the solriamfetol trials, but was used as an exploratory endpoint in several trials.

## 6.1. Study ADX-N05-202 (Indication: Narcolepsy)

### 6.1.1. Study Design

#### Overview and Objective

Study Title: "A twelve-week, double-blind, placebo-controlled, randomized, parallel-group, multi-center study of the safety and efficacy of ADX-N05 in the treatment of excessive daytime sleepiness in subjects with narcolepsy."

*(Reviewer's Comment: ADX-N05 is a previous name for solriamfetol.)*

#### Primary Objectives:

1. To evaluate the efficacy of solriamfetol administered once daily for up to twelve weeks in a dose range of 150 mg to 300 mg, compared to placebo, in the treatment of excessive daytime sleepiness in adults with narcolepsy.
2. To evaluate the safety and tolerability of solriamfetol administered once daily for up to twelve weeks in a dose range of 150 mg to 300 mg, compared to placebo, in the treatment of excessive daytime sleepiness in adults with narcolepsy.

#### Secondary Objective:

- To perform an exploratory analysis of the potential efficacy of solriamfetol in the subset of subjects with narcolepsy who also have cataplexy.

#### Trial Design

##### Study Design Overview:

Study ADX-N05-202 was a twelve-week, double-blind, flexible target-dose, placebo-controlled, multi-center, randomized, parallel-group study. Subjects completed a Screening Phase of up to 28 days, including screening assessments and discontinuation of any current narcolepsy treatments, and a Baseline Phase, including an overnight stay for baseline efficacy and safety

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measurements. Subjects who continued to meet eligibility requirements were randomly assigned to two treatment groups:

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

Follow-up assessments were scheduled for Week 14.

Trial Location:

The study was conducted at 28 study centers in the United States.

Diagnostic Criteria:

The source of the definition for narcolepsy used in the screening of subjects was The International Classification of Sleep Disorders, Second Edition (ICSD-2).

Key Inclusion Criteria:

1. Age between 18 and 65 years, inclusive.
2. If female, surgically sterile, post-menopausal, or using an acceptable method of contraception.
3. Current diagnosis of narcolepsy as defined by ICSD-2. Subjects without a clear documented history of cataplexy must have had a Multiple Sleep Latency Test (MSLT) which confirmed the diagnosis of narcolepsy.
4. Baseline Epworth Sleepiness Scale (ESS) score  $\geq 10$ .
5. Baseline mean sleep latency time of  $\leq 10$  minutes, as documented by the average of the first four test sessions of the five-session Maintenance of Wakefulness Test (MWT) during the Baseline Phase.

Key Exclusion Criteria:

1. If female, pregnant or lactating.
2. Customary bedtime later than midnight.
3. History or presence of any clinically significant medical condition, behavior or psychiatric disorder (including suicidal ideation), or surgical history that could affect the safety of the subject or interfere with study assessments.
4. History of phenylketonuria (PKU) or history of hypersensitivity to phenylalanine-derived products.
5. Any other clinically relevant medical, behavioral, or psychiatric disorder other than narcolepsy that is associated with excessive sleepiness.
6. History of moderate to severe sleep apnea (apnea hypopnea index  $\geq 15$  per hour).
7. Occupation requiring routine night work or variable shifts.

8. Presence of a clinically significant abnormality on physical examination or ECG, including a QTcF interval > 450 msec for males and > 470 msec for females.
9. Presence or history of significant cardiovascular disease including: myocardial infarction, uncontrolled hypertension (defined as consistent systolic blood pressure  $\geq$  160 mmHg or consistent diastolic blood pressure  $\geq$  90 mmHg despite present therapy), angina pectoris, life threatening or symptomatic arrhythmias, clinically significant valvular heart disease, history of any revascularization procedures, second or third degree heart block with or without a pacemaker, or symptomatic heart failure.
10. Body mass index (BMI) > 34.
11. Serum creatinine concentration  $\geq$  1.5 times the upper limit of normal.
12. Laboratory value(s) (clinical chemistry, hematology, or urinalysis) outside the laboratory reference range that are considered to be clinically significant.
13. Excessive caffeine use one week prior to baseline assessments, or anticipated excessive use during the study, defined as > 600 mg of caffeine per day or > 6 cups of coffee per day.
14. Reported use of any medications for the treatment of narcolepsy including any over the counter (OTC) sleep aids or stimulants, within a time period prior to baseline assessments corresponding to at least five half-lives of the narcolepsy or sleep aid in question. Sodium oxybate should be sufficiently washed out until the subject has returned to their baseline level of excessive daytime sleepiness.
15. Reported use of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), or anti-convulsant agents within 14 days prior to dosing, or any investigational drug use within 30 days prior to dosing.
16. Reported use of any other product with stimulating or sedating effects on the subject. If a subject has been regularly taking a medication with stimulating or sedating properties for any medical condition other than a sleep disorder (e.g. antihistamines for seasonal allergies) and the medication does not cause stimulating or sedating side effects in the subject, the subject may continue use of the medication as long as the dose remains stable throughout the study.
17. Previous exposure to solriamfetol.
18. History of repeated alcohol or drug abuse within the past two years.
19. Nicotine dependence that has an effect on sleep (e.g., the subject routinely awakens at night to smoke).
20. Urine drug screen positive for suspected substance of abuse.

#### Study Treatments:

The study treatments were solriamfetol or matching placebo given as an oral capsule at a dose of 150 mg/day for the first four weeks and 300 mg/day for the remaining eight weeks.

#### **Study Endpoints**

Primary Efficacy Endpoints:

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

Secondary Efficacy Endpoints:

1. Change from baseline in the average sleep latency time (in minutes) as determined from the MWT (average of the first four test sessions) following four weeks of treatment with solriamfetol 150 mg vs. placebo.
2. Change from baseline in sleep latency time (in minutes) as determined from each of the five individual MWT trials for solriamfetol vs. placebo at Week 4 and at last assessment.
3. Change from baseline in ESS scores for solriamfetol vs. placebo at Week 4 and at last assessment.
4. Clinical Global Impression-Change (CGI-C) scores for solriamfetol vs. placebo at Week 4.
5. Patient Global Impression-Change (PGI-C) scores for solriamfetol vs. placebo at Week 4 and at last assessment.

Exploratory Endpoints:

1. Change from Baseline in the median number of cataplectic attacks per week for the subset of subjects with cataplexy for solriamfetol vs. placebo at Week 4 and at last post-Baseline assessment.
2. Primary and secondary efficacy endpoints assessed for the subset of subjects with cataplexy.

**Statistical Analysis Plan**

When comparisons between groups were performed, two-sided tests at a 0.05 level of significance ( $\alpha=0.05$ ) were used. The null hypothesis for all analyses is that there is no difference between the solriamfetol treatment and placebo. No adjustment of multiplicity was made for the co-primary endpoints.

*Maintenance of Wakefulness Test:* The primary analysis was a comparison of treatment vs. placebo groups on change from Baseline to last available post-Baseline assessment (Week 12/Last Assessment) in the average sleep latency time (in minutes) averaged across the first four test sessions of the MWT using a two-sample t-test. Secondary analyses repeated this primary analysis for effects at the end of Week 4 and for the five MWT trials analyzed separately at Week 4 and the last available post-Baseline assessment (Week 12/Last

Assessment), also using independent two-sample t-tests. Exploratory analyses repeated the primary and secondary analyses for the subset of subjects with cataplexy.

*Clinical Global Impression-Change:* The proportion of subjects experiencing at least minimal improvement on the CGI-C was calculated and summarized for each of the treatment groups at Week 4 and the last available post-Baseline assessment (Week 12/Last Assessment). Improvement was defined as a CGI-C score of 1 (very much improved), 2 (much improved), or 3 (minimally improved). Comparisons were performed between groups using Fisher's Exact Test. These analyses were repeated for the subset of subjects with cataplexy.

*Epworth Sleepiness Scale:* The mean change in ESS scores from Baseline to Week 4 and from Baseline to last available post-Baseline assessment (Week 12/Last Assessment) in each of the treatment groups was calculated and compared using a two-sample t-test. These analyses were repeated for the subset of subjects with cataplexy.

*Patient Global Impression-Change:* The proportion of subjects experiencing at least minimal improvement on the PGI-C was calculated and summarized for each of the treatment groups at Week 4 and at last available post-Baseline assessment (Week 12/Last Assessment). Improvement was defined as a PGI-C score of 1 (very much improved), 2 (much improved), or 3 (minimally improved). Comparisons were made using a Fisher's Exact Test. These analyses were repeated for the subset of subjects with cataplexy.

*Cataplexy Diary:* The change from Baseline in median number of cataplectic attacks per week for treatment vs. controls at Week 4 and at last available post-Baseline assessment (Week 12/Last Assessment) was calculated for the subset of subjects with cataplexy in each of the treatment groups. A Wilcoxon rank-sum test was used to compare the groups.

## **Protocol Amendments**

*Original protocol date: August 13, 2012*

*Amendment #1: February 28, 2013*

- Upper limit of age of subjects was increased from 65 years to 70 years.
- Planned number of study sites increased from 30 centers to 50 centers.
- Inclusion criterion #4 updated to require polysomnography to confirm diagnosis of narcolepsy in subjects without a clear documented history of cataplexy.
- Exclusion criterion #6 updated. Replaced "History of moderate to severe sleep apnea" with "Presence of moderate to severe sleep apnea unless, in the documented opinion of the investigator, such apnea has been controlled by current treatment for at least two months prior to screening."
- Time window of  $\pm 3$  days added to the schedule of weekly phone contacts between

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study visits.

### **Data Quality and Integrity: Sponsor's Assurance**

Study ADX-N05-202 was conducted while the product was owned by Aerial BioPharma. Steps taken by Aerial BioPharma to ensure data integrity included training of study personnel at each study center on the protocol and central laboratory procedures, eCRF completion, AE and SAE reporting, handling of study drug, and GCP compliance. Site staff responsible for conducting the MWT were required to be tested and certified in the procedure. Source document verification review was performed by the study monitors for all eCRF data entries. Data were verified by direct inspection of source records and data. Each Investigator electronically signed the eCRF for each subject to confirm that the data were complete and accurate. Urinalysis, clinical hematology, and chemistry analyses were conducted by a central laboratory ( (b) (4) ). Electrocardiogram data were collected and interpreted by (b) (4). A comprehensive data management plan was developed.

#### **6.1.2. Study Results**

##### **Compliance with Good Clinical Practices**

The cover page of the Clinical Study Report states: "This study was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents." Page 249 of the Clinical Study Report states: "This study will be conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of the ICH Guidelines and all applicable regulations, including current United States Code of Federal Regulations (CFR), Title 21, Parts 50, 54, 56, and 312 and Title 45, Part 164."

##### **Financial Disclosure**

Financial disclosures for each of the five pivotal trials under this NDA were reviewed at the time the NDA was filed. See Appendix 13.2 for details. For Study ADX-N05-202, no investigators had disclosable financial interests.

##### **Patient Disposition**

213 subjects were screened. 93 were randomly assigned to a treatment group; 44 to solriamfetol and 49 to placebo. Of the 93 subjects randomized, all subjects received at least one dose of study drug (Safety Population). 90 subjects (43 on solriamfetol and 47 on placebo) had at least one post-Baseline efficacy assessment (Intent-to-Treat [ITT] Population). Details of subject dispositions is presented in Table 3.

**Table 3: Study ADX-N05-202, Patient Disposition**

	Solriamfetol N (%)	Placebo N (%)	Total N (%)
<b>Subjects Screened</b>			213
Screen Failures			120
<b>Subjects Randomized</b>	44	49	93
<b>Subjects Completing Study</b>	36 (81.8)	38 (77.6)	74 (79.6)
<b>Subjects Discontinued Prematurely</b>	8 (18.2)	11 (22.4)	19 (20.4)
<b>Reason for Discontinuation</b>			
Withdrawal by Subject	3 (6.8)	5 (10.2)	8 (8.6)
Protocol Violation	1 (2.3)	0	1 (1.1)
Lack of Efficacy	0	3 (6.1)	3 (3.2)
Adverse Event	3 (6.8)	2 (4.1)	5 (5.4)
Withdrawn by Investigator	0	0	0
Lost to Follow-Up	0	1 (2.0)	1 (1.1)
Other	1 (2.3)	0	1 (1.1)
<b>Analysis Populations</b>			
Safety Population	44	49	93
ITT Population	43	47	90
Per Protocol Population	36	38	74
Cataplexy Population	17	15	32

Source: ADX-N05-202 Clinical Study Report, Table 6, page 57.

### Protocol Violations/Deviations

Overall, the number of protocol deviations was similar across treatment groups, with deviations occurring in 42 subjects in the solriamfetol group and 43 subjects in the placebo group. The majority of protocol deviations involved completion of study visits or assessments outside the specified time window, and non-fasting lab collections. Deviations outside of those categories included the following:

- Subject (b) (6) (solriamfetol) was randomized despite not meeting inclusion criterion #6 (baseline mean sleep latency ≤ 10 minutes, as documented by the average of the first four test sessions of the baseline five-session Maintenance of Wakefulness Test). The Applicant determined that this subject should be withdrawn from the study early due to not meeting this inclusion criterion. The subject was discontinued following approximately three weeks of dosing. An early discontinuation visit was conducted.
- Subject (b) (6) (placebo) was randomized and administered a dose of study drug prior to completing all baseline assessments.
- Subjects (b) (6) and (b) (6) (solriamfetol) and Subjects (b) (6) and (b) (6) (placebo) were one to two days short of the full washout period for their narcolepsy/cataplexy medications prior to completing the seven-day baseline cataplexy diary.
- Subject (b) (6) (placebo) completed a seven-day washout (five half-lives) of escitalopram

prior to dosing, instead of the protocol-specified 14-day washout.

- Subject (b) (6) (placebo) did not return 22 capsules of study drug at the Week 12 visit. The subject denied taking any additional doses of study drug, and reported that the capsules were possibly lost.
- Subject (b) (6) (placebo), Subject (b) (6) (solriamfetol), and Subject (b) (6) (placebo) took two capsules of study drug instead of one on one day during Weeks 1-4 of the treatment period. Subject (b) (6) (placebo) missed ten doses of study drug between the Week 4 and Week 6 visits.
- Seven solriamfetol subjects and twelve placebo subjects took a prohibited medication on one or more days during the treatment or follow-up period.
- Five solriamfetol subjects, three placebo subjects, and five screen failure subjects had consent deviations primarily involving signing an outdated version of the IRB-approved consent or not being re-consented with the most recent IRB-approved version of the consent. In each case, there were no differences in the risks to the subject or study procedures in the version of the consent signed versus the appropriate version.

#### Table of Demographic Characteristics

The majority of subjects were female (65 %) and White (74%). Mean (SD) age was 38.7 (12.1) years, and the range was from 18 to 70 years. Mean body weight was 76.1 (16.4) kg. Mean body mass index was 26.6 (4.5) kg/m<sup>2</sup>. Table 4 presents the demographic characteristics of the safety population.

**Table 4: Study ADX-N05-202, Demographic Characteristics at Screening, Safety Population**

	Solriamfetol (N = 44)	Placebo (N = 49)	Total (N = 93)
<b>Age (years)</b>			
N	44	49	93
Mean (SD)	41.0 (12.3)	36.7 (11.7)	38.7 (12.1)
Median	39.5	32.0	36.0
Min, Max	19, 70	18, 66	18, 70
<b>Gender</b>			
Female	30 (68%)	30 (61%)	60 (65%)
Male	14 (32%)	19 (39%)	33 (35%)
<b>Race</b>			
American Indian or Alaska Native	0	0	0
Black or African American	12 (28%)	10 (20%)	22 (24%)
Native Hawaiian or Other Pacific Islander	1 (2%)	0	1 (1%)
Asian	1 (2%)	0	1 (1%)
White	30 (68%)	39 (80%)	69 (74%)
<b>Ethnicity</b>			
Hispanic or Latino	1 (2%)	3 (6%)	4 (4%)

Not Hispanic or Latino	43 (98%)	46 (94%)	89 (96%)
<b>Height (cm)</b>			
N	44	49	93
Mean (SD)	168.7 (7.9)	168.3 (10.3)	168.5 (9.2)
Median	168.8	167.6	167.6
Min, Max	155, 185	145, 197	150, 197
<b>Weight (kg)</b>			
N	44	49	93
Mean (SD)	76.8 (16.1)	75.4 (16.9)	76.1 (16.4)
Median	77.7	78.0	78.0
Min, Max	37, 113	47, 114	37, 114

Source: ADX-N05-202 Clinical Study Report, Table 14.1.2, page 96.

### Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The study protocol included plans for an exploratory analysis of the potential efficacy of solriamfetol in the subset of narcolepsy patients who also have cataplexy. Of the 90 subjects in the ITT Population, 32 had cataplexy (Cataplexy Population). Study subjects with cataplexy were dispensed a cataplexy diary at screening, and were instructed to record the total number of cataplectic attacks each day for at least seven days prior to the baseline visit date. This study did not specifically recruit for cataplexy subjects. While it is possible for individuals with cataplexy to have several cataplectic episodes per day, subjects in the Cataplexy Population in this study were predominantly mildly ill, with a median of four cataplectic events per week at baseline.

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study site personnel reviewed treatment compliance with subjects at each study visit by performing a study drug accountability review. Subjects were also reminded of treatment compliance during scheduled telephone contacts. Missed doses were reported in the eCRF. Any unaccounted study drug was documented in the site's study drug accountability records.

Compliance with study drug dosing was calculated based on the average daily compliance of subjects during the study period. Subjects were considered to be 100% compliant on days where the dose taken was equal to the dose prescribed, and 0% compliant on days where the dose taken differed from the dose prescribed. The compliance rate was similar across the two treatment groups: 99.4% for the solriamfetol group and 99.3% for the placebo group. With the exception of one subject who mistakenly took one extra 150 mg capsule on one day during Week 2, all solriamfetol subjects took a daily dose of 150 mg during Weeks 1-4. 38 of 40 solriamfetol subjects (95%) escalated to the 300 mg dose following the Week 4 visit. Between 87% and 89% of subjects remained at the 300 mg dose each week during Weeks 5-12.

Table 5 lists the prohibited concomitant medications used by subjects during the treatment period of Study ADX-N05-202. These occurrences were reported as protocol deviations.

**Table 5: Study ADX-N05-202, Use of Prohibited Concomitant Medications**

Subject	Prohibited Concomitant Medication
(b) (6)	clonazepam
(b) (6)	acetaminophen + oxycodone; acetaminophen + codeine
(b) (6)	acetaminophen + hydrocodone bitartrate
(b) (6)	diphenhydramine
(b) (6)	diphenhydramine
(b) (6)	diphenhydramine
(b) (6)	sumatriptan + naproxen sodium
(b) (6)	guaifenesin + codeine phosphate liquid
(b) (6)	escitalopram
(b) (6)	phenylephrine
(b) (6)	pregabalin (approved by Sponsor)
(b) (6)	melatonin; acetaminophen + phenylephrine + dextromethorphan
(b) (6)	dextromethorphan + guaifenesin
(b) (6)	hydroxyzine (single dose)
(b) (6)	cyclobenzaprine

Subjects (b) (6) re-started anti-narcoleptic medications following the Week 12 visit and prior to the Week13/Follow-up visit.

**Efficacy Results – Primary Endpoint**

*Maintenance of Wakefulness Test:* Table 6 summarizes the change from Baseline in average sleep latency from the first four MWT trials at Week 12/Last Assessment for the ITT population. At Baseline, the average sleep latency was similar in the two treatment groups: 5.66 minutes for the solriamfetol group and 5.70 for the placebo group. At Week 12/Last Assessment, the average sleep latency increased by 12.8 minutes for the solriamfetol group and by 2.1 minutes for the placebo group. The difference in mean change from Baseline was statistically significantly higher in the solriamfetol group (two-sample t-test,  $p < 0.0001$ ).

**Table 6: Study ADX-N05-202, Change in Average Sleep Latency, First Four MWT Test Sessions, Week 12/Last Assessment, ITT Population**

	Observed Values: Mean (SD)	Change from Baseline: Mean (SD)	p-value
<b>Baseline</b>			
solriamfetol (N=43)	5.7 (5.9)	---	---
Placebo (N=47)	5.7 (2.8)	---	---
<b>Week 12/Last Assessment</b>			
solriamfetol (N=40)	17.6 (11.4)	12.8 (10.3)	< 0.0001
Placebo (N=45)	7.9 (8.6)	2.1 (7.9)	

Source: ADX-N05-202 Clinical Study Report, Table 1, page 6.

**Clinical Global Impression-Change:** Table 7 provides a summary of CGI mean scores and the proportion of subjects experiencing improvement at Week 12/Last Assessment for the ITT population. At Baseline, the mean Clinical Global Impression-Severity (CGI-S) scores were 5.00 for the solriamfetol group and 5.04 for the placebo group. At Week 12/Last Assessment, subjects in the solriamfetol group had a mean CGI-C score of 2.2 (much improved), while subjects in the placebo group had a mean CGI-C score of 3.5 (minimal to no improvement). While 86.0% of subjects in the solriamfetol group experienced improvement, 38.3% of subjects in the placebo group experienced improvement. The difference in the proportion of subjects experiencing improvement was statistically significant in favor of the solriamfetol group (Fisher’s Exact Test,  $p < 0.0001$ ).

**Table 7: Study ADX-N05-202, Change in Clinical Global Impression-Change, Week 12/Last Assessment, ITT Population**

	Observed Values: Mean (SD)	Subjects Experiencing Improvement: N (%)	p-value
<b>Baseline</b>			
solriamfetol (N=43)	5.0 (0.8)	---	---
Placebo (N=47)	5.0 (1.0)	---	---
<b>Week 12/Last Assessment</b>			
solriamfetol (N=43)	2.2 (1.2)	37 (86.0)	< 0.0001
Placebo (N=47)	3.5 (1.1)	18 (38.3)	

Source: ADX-N05-202 Clinical Study Report, Table 2, page 7.

**Efficacy Results – Secondary and other relevant endpoints**

**Maintenance of Wakefulness Test:** At Week 4, the average sleep latency increased by 9.5 minutes for the solriamfetol group versus 1.4 minutes for the placebo group. The difference in mean change from Baseline was statistically significant in favor of the solriamfetol group (from Applicant: two-sample t-test,  $p < 0.0001$ ). At Week 12/Last Assessment, 77.5% of solriamfetol subjects had an increase of four or more minutes in average sleep latency, while 53.3% of placebo subjects showed no response. For each of the five individual MWT trials at Week 12/Last Assessment, mean changes from Baseline for the solriamfetol group ranged from 8.2 to 15.5 minutes, versus changes of -1.6 to 2.7 minutes for the placebo group.

**Clinical Global Impression-Change:** The percentage of subjects experiencing at least minimal improvement was greater for the solriamfetol group at all time points. The greatest difference between treatment groups was seen at Week 12/Last Assessment, when 86.0% of solriamfetol subjects showed improvement, versus 38.3% of placebo-treated subjects (from Applicant: Fisher’s Exact Test,  $p < 0.0001$ ).

*Epworth Sleepiness Scale:* The average ESS total score at Baseline was 17.3 for the solriamfetol group and 17.4 for the placebo group. After four weeks of treatment, the average EES score decreased by 5.6 points for the solriamfetol group and 2.4 points for the placebo group, a statistically significant difference (from Applicant: two-sample t-test,  $p=0.0038$ ). At Week 12/Last Assessment, the average ESS total score decreased by 8.5 points for the solriamfetol group and 2.5 points for the placebo group (from Applicant:  $p < 0.0001$ ).

*Patient Global Impression-Change:* At Week 4, 82.5% of solriamfetol subjects reported experiencing improvement, versus 44.4% of placebo subjects (from Applicant: Fisher's Exact Test,  $p=0.0003$ ). The greatest different between treatment groups was seen at Week 12/Last Assessment, when 93.0% of solriamfetol subjects reported improvement versus 38.3% of the placebo group (from Applicant: Fisher's Exact Test,  $p < 0.0001$ ).

*Cataplexy:* The subset of subjects with cataplexy showed similar results to the overall ITT population for change from Baseline in sleep latency on the average of the first four test sessions of the MWT, change in sleep latency for the five individual MWT trials at both Week 4 and Week 12/Last Assessment, improvement on the CGI-C, improvement on the PGI-C, and decrease in mean ESS total scores. Treatment with solriamfetol did not result in a noticeable difference from placebo in the median change from Baseline in weekly cataplectic events. However, the study did not specifically recruit for cataplexy subjects, resulting in a cataplexy population predominantly having mild symptoms (median of four cataplectic events per week at Baseline). A post-hoc analysis including only subjects with three or more cataplectic events per week showed a median reduction of seven cataplectic events per week for the solriamfetol group, versus a median reduction of 1.5 events per week for the placebo group.

### **Dose/Dose Response**

This trial does not provide data on dose response. The protocol compared placebo treatment to a single drug treatment arm, in which all subjects were started on the 150 mg dose and titrated to the 300 mg dose. Even though the study included two doses during different parts of the treatment phase, no formal analyses were planned or completed to investigate a potential dose-response relationship.

### **Durability of Response**

Subjects treated with solriamfetol showed statistically significant improvement compared to placebo on several efficacy endpoints that were measured at multiple time points across the course of the trial. On the MWT, change from baseline compared to placebo in the average sleep latency from the first four MWT trials was statistically significant at Week 4 (150 mg/day) and at Week 12 (300 mg/day).

## **Persistence of Effect**

This trial did not include investigation of persistence of effect after discontinuation of the drug.

## **6.2. Study 14-002 (Indication: Narcolepsy)**

### **6.2.1. Study Design**

#### **Overview and Objective**

Study Title: “A twelve-week, double-blind, placebo-controlled, randomized, parallel-group, multicenter study of the safety and efficacy of solriamfetol [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the treatment of excessive sleepiness in subjects with narcolepsy.”

#### Primary Objective:

- To evaluate the efficacy of solriamfetol administered once daily (QD) for up to 12 weeks in doses of 75 mg/day, 150 mg/day, and 300 mg/day compared to placebo in the treatment of excessive sleepiness in adult subjects with narcolepsy.

#### Secondary Objectives:

1. To evaluate the safety and tolerability of solriamfetol administered once daily for up to 12 weeks in doses of 75 mg/day, 150 mg/day, and 300 mg/day compared to placebo in the treatment of excessive sleepiness in adult subjects with narcolepsy.
2. To characterize the pharmacokinetics (PK) of solriamfetol in subjects with narcolepsy using sparse sampling methods.

#### **Trial Design**

##### Study Design Overview:

This was a 12-week, randomized, double-blind, placebo-controlled, multicenter, four-arm parallel group study of the safety and efficacy of solriamfetol in the treatment of excessive sleepiness in adult subjects with narcolepsy. Following Screening and Baseline visits, subjects were randomized to one of four treatment arms for the Treatment Phase: solriamfetol 75 mg/day, 150 mg/day, 300 mg/day, or placebo.

##### Trial Location:

The trial was conducted at 59 study centers: 50 in North America and nine in Europe.

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Diagnostic Criteria:

Subjects had to have a documented diagnosis of narcolepsy according to criteria of either the International Classification of Sleep Disorders, Third Edition (ICSD-3) or Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

Key Inclusion Criteria:

1. Age between 18 and 75 years, inclusive.
2. Diagnosis of narcolepsy according to ICSD-3 or DSM-5.
3. Baseline mean sleep latency < 25 minutes as documented by the mean of the first four test sessions of the Baseline five-session MWT.
4. Baseline Epworth Sleepiness Scale (ESS) score  $\geq 10$ .
5. Usual nightly total sleep time of at least six hours.
6. Body mass index (BMI) from 18 to < 45 kg/m<sup>2</sup>.
7. Consent to use a medically acceptable method of contraception for at least two months prior to the first dose of study drug, throughout the entire study period, and for 30 days after the study is completed.

Key Exclusion Criteria:

1. Female subjects who are pregnant, nursing, or lactating.
2. Usual bedtime later than 1:00 am (0100 hours).
3. Occupation requiring nighttime or variable shift work.
4. Moderate or severe obstructive sleep apnea on the baseline PSG.
5. Any other clinically relevant medical, behavioral, or psychiatric disorder other than narcolepsy that is associated with excessive sleepiness.
6. History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria.
7. History or presence of any acutely unstable medical condition, behavioral or psychiatric disorder (including active suicidal ideation), or surgical history that could affect the safety of the subject or interfere with study efficacy, safety, PK assessments, or the ability of the subject to complete the trial per the judgment of the Investigator.
8. History of bariatric surgery within the past year or a history of any gastric bypass procedure.
9. Presence of renal impairment or calculated creatinine clearance < 60 mL/min.
10. Clinically significant cardiovascular disease, electrocardiogram (ECG), or laboratory abnormality in the opinion of the Investigator.
11. Excessive caffeine use (defined as > 600 mg caffeine per day) one week prior to Baseline assessments or anticipated excessive use during the study.
12. Use of any over-the-counter (OTC) or prescription medication that could affect the evaluation of excessive sleepiness within a time period prior to the Baseline visit corresponding to at least five half-lives of the drug, or planned use of such drugs at

some point throughout the duration of the study. Medications should be discontinued such that the subject has returned to his/her baseline level of daytime sleepiness at least seven days prior to the Baseline visit.

13. Use of any medications that could affect the evaluation of cataplexy within a time period prior to the Baseline visit corresponding to at least five half-lives of the drug or planned use of such drugs at some point throughout the duration of the study. Medications should be discontinued such that the subject has returned to his/her baseline level of cataplexy at least seven days prior to the Baseline visit.
14. Received an investigational drug in the past 30 days or five half-lives (whichever is longer) prior to the Baseline visit, or planned to use an investigational drug (other than the study drug) during the study.
15. Previous exposure to solriamfetol, or participation in a previous clinical trial of solriamfetol.
16. Current or past (within the past two years) diagnosis of a moderate or severe substance use disorder, or seeking treatment for a substance related disorder.
17. Urine drug screen positive for an illicit drug of abuse at screening or at any point throughout the duration of the study, except for a prescribed drug (e.g., amphetamine) at screening.
18. Nicotine dependence that has an effect on sleep (e.g., a subject who routinely awakens at night to smoke).
19. History of phenylketonuria or history of hypersensitivity to phenylalanine-derived products.

#### Study Treatments:

Study treatments were solriamfetol 75 mg, 150 mg, 300 mg, or placebo, administered daily by mouth. Subjects randomized to the 75-mg dose did not undergo dose titration. Subjects randomized to the 150-mg dose received 75 mg from Day 1 through Day 3 of the Treatment Phase, then received 150 mg daily starting on Day 4. Subjects randomized to the 300-mg dose received 150 mg from Day 1 through Day 3, then received 300 mg daily starting on Day 4.

#### Assignment to Treatment:

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

#### Procedures and Schedule:

Subjects returned to the study site for efficacy and safety assessments at the end of Weeks 1, 4, 8, and 12. The Week 4 and Week 12 visits included an overnight stay at the study site for nocturnal polysomnography (PSG) followed by a Maintenance of Wakefulness Test (MWT). The Week 8 visit included 24-hour ambulatory blood pressure monitoring (ABPM). Four blood samples were collected from each subject for PK evaluations: one sample at Week 1, one

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sample at Week 4 within 8-12 hours after dosing on the day subjects checked in for the overnight PSG, and two samples at Week 8. Subjects received their final dose of study drug at the final clinic visit at Week 12. A safety follow-up visit was scheduled for Week 14. Subjects interested in enrolling in the open-label safety study (Study 14-005) did not have a safety follow-up visit.

Prohibited Concurrent Medications:

- Medications that could affect the evaluation of excessive sleepiness. Examples:
  - OTC sleep aids or stimulants
  - pseudoephedrine
  - methylphenidate
  - amphetamines
  - modafinil
  - armodafinil
  - sodium oxybate
  - pemoline
  - trazodone
  - hypnotics
  - benzodiazepines
  - barbiturates
  - opioids
- Medications that could affect the evaluation of cataplexy. Examples:
  - selective serotonin reuptake inhibitors
  - serotonin-norepinephrine reuptake inhibitors
  - tricyclic antidepressants
  - monoamine oxidase inhibitors
  - anti-convulsant agents
  - sodium oxybate

**Study Endpoints**

Co-primary Study Endpoints:

1. *MWT*: Change in the mean sleep latency time (in minutes) as determined from the first four test sessions of a 40-minute MWT from Baseline to Week 12.
2. *ESS*: Change in ESS score from Baseline to Week 12 (range [best to worst] 0 to 24).

Pharmacokinetic Measures:

Concentration data for solriamfetol were tabulated by sampling time point, and were included in a population PK analysis to characterize the solriamfetol PK profile in narcolepsy patients and to explore exposure-efficacy correlations.

Key Secondary Efficacy Endpoint:

*Patient Global Impression of Change (PGI-C)*: Percentage of subjects reported as improved (minimally, much, or very much) on the PGI-C at Week 12.

Other Secondary Efficacy Endpoints:

1. *Time course of efficacy on the MTW*: Change in sleep latency time (in minutes) on each of the five MWT trials at Week 4 and Week 12.
2. *Clinical Global Impression of Change (CGI-C)*: Percentage of subjects reported as improved (minimally, much, or very much) at Week 12.
3. *MWT*: Change in the mean sleep latency time (in minutes) as determined from the first four test sessions of a 40-minute MWT from Baseline to Week 4.
4. *ESS*: Change in ESS score from Baseline to Week 1, Week 4, and Week 8.
5. *PGI-C*: Percentage of subjects reported as improved at Week 1, Week 4, and Week 8.
6. *CGI-C*: Percentage of subjects reported as improved at Week 1, Week 4, and Week 8.

Functional Outcomes and Quality of Life Endpoints:

1. *Functional Outcomes of Sleep Questionnaire Short Version (FOSQ-10)*: Change in the total score from Baseline to Week 1, Week 4, Week 8, and Week 12.
2. *36-Item Short Form Health Survey Version 2 (SF-36v2)*: Change in the 8-domain scores, physical component summary (PCS) score, and mental component summary (MCS) score from Baseline to Week 4, Week 8, and Week 12.
3. *EuroQol (EQ-5D-5L)*:
  - a. *EQ-5D Dimensions*:
    - i. Number and percentage of subjects in each of the five levels (e.g. no problem, slight problem, moderate problem, severe problem, unable) for each dimension (e.g., mobility, self-care) over time
    - ii. Number and percentage of subjects reporting any problems (levels 2-5) for each dimension (e.g., mobility, self-care) over time
  - b. *EQ-Visual Analogue Scale (EQ VAS)*: Mean and standard deviation (SD) or median with 25<sup>th</sup> and 75<sup>th</sup> percentiles for the visual analog scale (VAS) at baseline, Week 1, Week 4, Week 8, and Week 12. Change in the mean VAS scores from Baseline to Week 1, Week 4, Week 8, and Week 12.
  - c. *EQ-5D-5L Index*: Index value at Baseline, to Week 1, Week 4, Week 8, and Week 12.
4. *Work Productivity and Activity Impairment Questionnaire; Specific Health Problems (WPAI:SHP)*: Percent work time missed due to problem over time, percent impairment while working due to problem over time, percent overall work impairment due to problem over time, and percent activity impairment due to problem over time.

Exploratory Endpoints:

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NDA-211230  
Solriamfetol / Sunosi

1. Number of cataplexy attacks: Change in the mean and median weekly number of cataplexy attacks in the subgroup of subjects who reported the presence of cataplexy at screening from Baseline to Week 1, Weeks 2-4, Weeks 5-8, and Weeks 9-12.
2. Change in PSG parameters including total sleep time (TST), time in Stages N1, N2, N3, wake after sleep onset (WASO), number of awakenings, apnea index, apnea hypopnea index, number of central apneas, oxygen saturation (SaO<sub>2</sub>) nadir, and SaO<sub>2</sub> mean from Baseline to Week 4 and Week 12.

### Statistical Analysis Plan

For the analysis of the co-primary efficacy endpoints, a mixed-effect model with repeated measures (MMRM) was used as the primary method of analysis. This model included fixed effects for treatment (i.e., dose group), visit, treatment-by-time interaction, baseline value of the efficacy endpoint, and randomization stratification factor. All available data were included in the model. An unstructured covariance matrix was used to model the correlation among repeated measurements. The estimates of treatment difference versus placebo and their 95% confidence intervals were presented. In addition to the MMRM, an analysis of covariance (ANCOVA) model was used to analyze MWT and ESS to provide sensitivity analyses. This ANCOVA model included the effect for treatment (i.e., dose group) as a fixed effect, and baseline value of the efficacy endpoint and randomization stratification factor as the covariate.

A time course analysis of MWT sleep latency (in minutes) was performed for the solriamfetol dose(s) that were shown to be efficacious i.e., showed a significant difference versus placebo in the primary analysis of both co-primary endpoints of MWT and ESS. The chi-squared test was used to test the hypotheses associated with the analysis of PGI-C (key secondary endpoint) and the secondary efficacy endpoint of CGI-C at Week 12. For the other MWT and ESS endpoints and the FOSQ-10, SF-36v2, EQ VAS, EQ-5D-5L Index, and WPAI:SHP endpoints, a similar MMRM to that used in the primary analysis of the co-primary endpoints was used; the other PGI-C and CGI-C endpoints, and EQ-5D-5L: EQ 5D Dimensions endpoints were analyzed using the chi-squared test.

Concentration data were tabulated by sampling time point. Scatter plots and spaghetti plots of solriamfetol concentrations over time were provided, sorted by solriamfetol treatment groups.

### Protocol Amendments

*Original protocol date: December 18, 2014*

*Amendment #1: February 18, 2015*

- update to exposure data to include subjects from a Phase 1 human abuse liability study;

- update to the Introduction to include safety information on the number of patients who reported palpitations or chest pain or who had a T-wave inversion in study MDD-201;
- a new section, “End of Trial,” to satisfy EU regulatory requirements on defining the end of the trial;
- a clarification was made that the Safety Follow-up Visit was not required for subjects who enrolled in the open-label safety study (14-005) at the final clinic visit;
- deletion of “documented aspermia” as a criterion for subjects whose method of contraception is vasectomy;
- updated descriptions of solriamfetol and placebo excipients;
- clarification of the use of vital signs measurements to meet entrance criteria;
- replacement of the C-SSRS version at the screening visit by the Baseline/Screening Version;
- revision of the pregnancy information section to clarify following of pregnant partners;
- text describing collection of the two pharmacokinetic blood samples at the Week 8 visit was modified for clarity.
- Changes to the exclusion criteria:
  - Exclusion Criterion #4 was clarified to indicate that this criterion pertained to the baseline PSG in the study, and modified from a strict Apnea-Hypopnea Index (AHI) cutoff to exclude subjects with moderate or severe OSA to allow investigators to exclude subjects who might not meet the AHI threshold but demonstrated findings on the baseline PSG that were highly suggestive of moderate or severe OSA.
  - Exclusion Criterion #7 was revised to align with text in Section 6.9, which states that the presence of *active* suicidal ideation would exclude a subject from participation in the study.
  - In Exclusion Criterion #9, calculated creatinine clearance was changed from < 70 mL/min to < 60 mL/min to correspond with the standard categories of renal impairment.
  - In Exclusion Criterion #11, ondansetron, which has a known risk of torsade de pointes, was added to the list of excluded concomitant medications.
  - In Exclusion Criterion #12, systolic blood pressure level was changed from 140 mmHg to 150 mmHg, in response to FDA feedback to recruit a more inclusive patient population. In addition, blood pressure measures were clarified to indicate that the criterion applied when consistently observed across the multiple baseline measures.
  - In Exclusion Criteria #15 and #16, the timing of discontinuation of the use of excluded medications that might affect evaluation of excessive sleepiness was modified.

*Amendment #2: September 10, 2015*

- Changes to the inclusion criteria:

- In Inclusion Criterion #1, the upper age limit was changed from 70 to 75 years old.
- Changes to the exclusion criteria:
  - Exclusion Criterion #7 was changed to limit subjects who had acutely unstable conditions vs. those with clinically significant conditions. Individuals who were unlikely to be able to complete the study were also excluded.
  - Exclusion Criterion #12 was changed to exclude myocardial infarction and history of revascularization procedures if these occurred within the past year; to increase the blood pressure cutoff values from 150/90 mmHg to 155/95 mmHg; to exclude chronic ventricular arrhythmias (rather than all clinically significant arrhythmias); to exclude angina pectoris only if it is unstable; to exclude congestive heart failure specifically; and to remove the wording regarding exclusion of second or third degree heart block and clinically significant valvular disease, as these conditions were either already excluded in this criterion or addressed in another exclusion criterion.
- Information on the following of pregnancy in cases of live birth was made consistent with the Pregnant Partner Informed Consent Form.

*Amendment #3: February 8, 2016*

- Changes to inclusion criteria:
  - In Inclusion Criterion #3, the requirement for the baseline mean sleep latency, as documented by the mean of the first four test sessions of the MWT, was changed to < 25 minutes because the criterion of ≤ 10 minutes excluded subjects who were otherwise eligible and are representative of the sleepy narcolepsy population.
  - In Inclusion Criterion #6, the upper limit of the eligible range of BMI was raised from < 40 kg/m<sup>2</sup> to < 45 kg/m<sup>2</sup> based on feedback from investigators in the United States who reported that the BMI cutoff of 40 kg/m<sup>2</sup> was excluding otherwise healthy potential subjects. Obesity is a well-characterized comorbidity of narcolepsy, and this change allowed the enrollment of a representative patient population with minimal change to risk of participation.
- Changes to exclusion criteria:
  - Exclusion Criterion #8, which dealt with bariatric surgery, was clarified to state that a history of any gastric bypass procedure was exclusionary because of its potential to affect the absorption and PK of SOLRIAMFETOL. Other bariatric surgery procedures, such as a gastric band procedure, are exclusionary only if performed within the past year.
  - Cardiac Exclusion Criteria #10, #11, and #12 were changed as follows:
    - A thorough QT/QTc (TQT) study with SOLRIAMFETOL had not been completed when Study 14-002 was initiated; therefore, as a precaution, subjects with a history or presence of a risk factor for torsade de pointes

(Exclusion Criterion #10) and subjects who used and could not safely discontinue medication with known risk for torsade de pointes (Exclusion Criterion #11) were excluded from this study. However, the findings from the completed TQT Study 15-002 showed no QTcF prolongation reaching the threshold of regulatory concerns with SOLRIAMFETOL at the proposed therapeutic dose of 300 mg or at the supratherapeutic dose of 900 mg. Therefore, Exclusion Criterion #10 was changed to exclude only subjects with a clinically significant ECG abnormality, and Exclusion Criterion #11 was removed (no changes was made in the extent or frequency of assessments of cardiovascular safety).

- Exclusion Criterion #12 was revised to more clearly specify which types of congestive heart failure and cardiac arrhythmias were excluded.
- Rescreening of subjects who had not met previous eligibility requirements, but who were likely to meet the revised eligibility requirements, was not addressed in the protocol. This amendment clarified that those subjects would be allowed to be rescreened with approval by the Medical Monitor.
- The statistical analyses described in the protocol were updated to incorporate feedback from the FDA about the previously planned analyses.
- A change was made to the Week 1 procedures such that the overnight PSG and the MWT that followed would no longer be done at Week 1. Data from those assessments was not essential, and this change would not affect the primary efficacy analyses.
- The length of time during which screening labs could be repeated was extended.

### Country-Specific Amendments

Amendments 2FR, 3FR, 4FR, 5FR, and 6FR were country-specific amendments that applied only to clinical sites in France.

#### *Amendment 2FR: August 17, 2015*

- added a safety follow-up phone contact for further assessment of adverse events after discontinuation of study drug;
- added further specifications to Inclusion Criterion #1 (affiliation with a Social Security regime) and Inclusion Criterion #9 (that a subject not be a vulnerable person or legally protected adult);
- added the exclusion of individuals with a current or past diagnosis of mild substance use disorder, in addition to individuals with moderate or severe substance use disorders.

#### *Amendment 3FR: October 9, 2015*

- consisted of the changes specified in Amendment #2 (September 10, 2015).

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*Amendment 4FR: December 1, 2015*

- changed the time for following a live birth as the outcome of pregnancy during the study from six months to a minimum of six months.

*Amendment 5FR: March 11, 2016*

- consisted of the changes specified in Amendment #3 (February 8, 2016)

*Amendment 6FR: June 1, 2016*

- added three drugs to the list of drugs included in the urine drug screen in Table 1 of the protocol: buprenorphine, 3,4-methylenedioxymethamphetamine, and nortriptyline. Although urine drug screening for these drugs was not required by the protocol, the testing kit being used at the sites did screen for those substances. The addition of these drugs to the list of laboratory tests did not change the conduct of the trial.

### **Changes in the Planned Analyses**

The following two endpoints, initially described in the original protocol, were modified:

- SF-36v2
  - original: Change in the total score and change in the eight subscales from baseline to Week 4, Week 8, and Week 12.
  - modification: Change in the eight Domain Scores, the Physical Component Summary (PCS) Score, and the Mental Component Summary (MCS) Score from baseline to Weeks 4, 8, and 12.
- Number of cataplexy attacks
  - original: Change in the mean and median weekly number of cataplexy attacks in the subgroup of subjects who report the presence of cataplexy at screening, from baseline to Weeks 1 to 12.
  - modification: Change in the mean and median weekly number of cataplexy attacks in the subgroup of subjects who reported the presence of cataplexy at screening, from baseline to Week 1, Weeks 2-4, Weeks 5-8, and Weeks 9-12.

### **Data Quality and Integrity: Sponsor's Assurance**

Steps to assure the accuracy and reliability of data included the selection of qualified investigators and an appropriate study site, review of protocol procedures with the investigator and associated personnel prior to the study, and periodic monitoring visits by Jazz Pharmaceuticals or its designee. Data were reviewed for accuracy and completeness by Jazz Pharmaceuticals or its designee during and after onsite monitoring visits, and any discrepancies were resolved with the investigator or designees as appropriate. Quality control audits could be performed at the discretion of the Sponsor. Electronic CRFs (eCRFs) were used for the recording of all trial data with the exception of MWT, PSG, ECG, laboratory, and PK data. The principal investigator reviewed the eCRFs and the MWT, PSG, ECG, and laboratory results and provided

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his signature certifying that he reviewed the data and considered the data accurate to the best of his knowledge and provided his signature certifying that he reviewed the data and considered the data accurate to the best of his knowledge. A comprehensive Data Management Plan was developed. A central laboratory ( (b) (4) ) reviewed all sleep study data.

#### *Reporting of Serum Direct Bilirubin Values*

A technical issue was identified regarding serum direct bilirubin values reported from laboratory testing. Between January 2, 2016 and November 21, 2016, serum direct bilirubin values levels assayed by (b) (4) for this study were assigned a positive proportional bias due to a calibrator issue (calibrator manufactured by Siemens Healthcare Diagnostics). Calibrator values were reassigned by the manufacturer and were placed into effect by (b) (4) as of November 21, 2016. (b) (4) conducted an internal correlation between results obtained using the old calibrator set point and the new reassigned calibrator set point. A positive shift in direct bilirubin results was observed that was proportional in nature. An average bias of 30% was seen when direct bilirubin was more than three times the upper limit of normal (ULN). Differences for results that were in the normal range and up to three times the ULN were within the total allowable error of the assay. Siemens estimated the average bias to be approximately 40%. A correction factor could not be provided and previously tested samples could not be re-assayed. Results from 385 samples collected from 197 subjects during the affected period are in the clinical database uncorrected. Upon analysis by Jazz and (b) (4) (CRO) of the direct bilirubin outliers, the clinical significance of the positive bias was considered to be minimal.

#### *Adjustment for Errors Noted After Database Lock*

Errata in the protocol deviations log were discovered after database lock for four subjects:

1. Subject (b) (6) (75 mg/day solriamfetol) was incorrectly listed as having a major protocol deviation in enrollment criterion (did not meet inclusion criterion #3) in that there was a discrepancy between the site and central lab scoring in the subject's baseline MWT that was > 20% variance; however, the discrepant MWT was for Subject (b) (6).
2. Subject (b) (6) (150 mg/day solriamfetol) was listed incorrectly as meeting inclusion criterion #2 for ICSD-3; however, the listing was not based on updated information showing that the subject had cataplexy.
3. Subject (b) (6) was incorrectly listed as meeting exclusion criterion #3, with a discrepancy noted between the site and central laboratory scoring of baseline MWT; however, the scores were within the allowable 20% variance and should not have been reported as a deviation.

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4. Subject (b) (6) was incorrectly listed as not meeting inclusion criterion #6 (BMI was outside the protocol-specified range); however, the subject's BMI was within protocol-specified limits at study entry.

One subject was enrolled in the study despite having met exclusion criterion #18 (Subject (b) (6) participated in Study ADX-N05-202). This was not reported as a protocol deviation. The subject completed the study.

Subject (b) (6) experienced a TEAE of right bundle branch block which was incorrectly reported as leading to study drug interruption. Study drug was not interrupted as the onset day of the TEAE was Day 86, which was the Week 12 MWT day, and the subject had received the final dose of study drug on that day as scheduled.

No adjustments were made in the data as a result of these errors.

## 6.2.2. Study Results

### Compliance with Good Clinical Practices

The Clinical Study Report for Study 14-002, Section 9.6.1, Study Administration and Conduct (page 60), states: "The study was conducted according to GCP guidelines and according to national law." Section 9.6.2, Data Generation and Analysis, (page 61) states: "The standard procedures for handling and processing records were followed in compliance with 21 CFR 11, Good Clinical Practices, ICH Guidelines, and the Standard Operating Procedures of Jazz Pharmaceuticals or the CRO ( (b) (4) )."

### Financial Disclosure

Financial disclosures for each of the five pivotal trials under this NDA were reviewed at the time the NDA was filed. For Study 14-002, (b) (6) and (b) (6) had disclosable financial interests. See Appendix 13.2 for details.

### Patient Disposition

239 subjects were enrolled in the study. Three subjects who either did not meet inclusion criteria or met exclusion criteria were randomized in error. These subjects did not receive study medication. The Safety Population was comprised of the remaining 236 subjects; the Modified Intent-to-Treat (mITT) population, 231 subjects; the Per Protocol (PP) population, 195 subjects; and the Pharmacokinetic (PK) population, 172 subjects. The most frequent reasons for withdrawal from the study were lack of efficacy and adverse events. Cataplexy was the most

frequent TEAE leading to withdrawal, occurring in one subject in the placebo group and two subjects in the solriamfetol 300 mg group, and was the only TEAE that led to withdrawal of more than one subject. Each of the three subjects had a previous history of cataplexy, and as per protocol had washed out of prohibited cataplexy medications prior to starting on study drug. There were no deaths during the study. Details of patient disposition for the Safety Population are presented in Table 8.

**Table 8: Study 14-002, Patient Disposition, Safety Population**

	Placebo (N=59)	Solriamfetol 75 mg (N=59)	Solriamfetol 150 mg (N=59)	Solriamfetol 300 mg (N=59)	Combined Solriamfetol (N=177)
Completed: n (%)					
Yes	52 (88.1)	49 (83.1)	51 (86.4)	43 (72.9)	143 (80.8)
No	7 (11.9)	10 (16.9)	8 (13.6)	16 (27.1)	34 (19.2)
If No, Primary Reason: n (%)					
Lack of Efficacy	1 (1.7)	4 (6.8)	1 (1.7)	6 (10.2)	11 (6.2)
Protocol Violation	0	0	1 (1.7)	1 (1.7)	2 (1.1)
Adverse Event	1 (1.7)	2 (3.4)	4 (6.8)	5 (8.5)	11 (6.2)
Withdrawal of Consent	1 (1.7)	1 (1.7)	1 (1.7)	2 (3.4)	4 (2.3)
Lost to Follow-up	1 (1.7)	1 (1.7)	0	0	1 (0.6)
Sponsor Decision	1 (1.7)	0	0	0	0
Other <sup>a</sup>	2 (3.4)	2 (3.4)	1 (1.7)	2 (3.4)	5 (2.8)

<sup>a</sup> Other reasons included randomization in error due to not meeting inclusion criteria or meeting exclusion criteria, and unplanned pregnancy for one subject.

Source: Study 14-002 Clinical Study Report, Table 3, page 79.

### Protocol Violations/Deviations

Major protocol deviations were reported for 72 subjects in the Safety Population, including 18 (30.5%) of subjects in the placebo group and 54 (30.5%) of subjects in the solriamfetol group. The majority of major protocol deviations in both the placebo group and the solriamfetol group were related to informed consent. The percentage of subjects with major protocol deviations was similar across the solriamfetol dose groups. Major protocol deviations are summarized in Table 9.

**Table 9: Study 14-002, Major Protocol Deviations, Safety Population**

Deviation Category, n (%)	Placebo (N=59)	Solriamfetol 75 mg (N=59)	Solriamfetol 150 mg (N=59)	Solriamfetol 300 mg (N=59)	Combined Solriamfetol (N=177)
Any Major Protocol Deviation	18 (30.5)	22 (37.3)	17 (28.8)	15 (25.4)	54 (30.5)
Concomitant Medications	1 (1.7)	1 (1.7)	3 (5.1)	2 (3.4)	6 (3.4)
Dosing	1 (1.7)	2 (3.4)	0	1 (1.7)	3 (1.7)
Enrollment Criteria	1 (1.7)	4 (6.8)	3 (5.1)	4 (6.8)	11 (6.2)
Informed Consent	10 (16.9)	9 (15.3)	9 (15.3)	6 (10.2)	24 (13.6)
Laboratory	3 (5.1)	1 (1.7)	1 (1.7)	0	2 (1.1)
Non-compliance	1 (1.7)	4 (6.8)	3 (5.1)	5 (8.5)	12 (6.8)
Visit/Procedure Required	2 (3.4)	4 (6.8)	1 (1.7)	1 (1.7)	6 (3.4)

Source: Study 14-002 Clinical Study Report, Table 5, page 84.

### Table of Demographic Characteristics

The majority of subjects were white females, and the majority of subjects in each treatment group were enrolled at sites in North America. Demographic characteristics were balanced across treatment groups with the exception of a higher percentage of black or African American subjects in the placebo and solriamfetol 75 mg groups compared with the 150 mg and 300 mg groups. A higher percentage of subjects in the 75 mg treatment group were from European sites compared with the other treatment groups. Demographics of the safety population are presented in Table 10.

**Table 10: Study 14-002, Patient Demographics, Safety Population**

Characteristic	Placebo (N=59)	Solriamfetol 75 mg (N=59)	Solriamfetol 150 mg (N=59)	Solriamfetol 300 mg (N=59)	Combined Solriamfetol (N=177)
Age (years)					
n	59	59	59	59	177
Mean (SD)	36.0 (15.2)	36.5 (12.8)	38.1 (13.0)	34.3 (11.5)	36.3 (12.5)
Median	32	36	38	32	35
Range	18, 70	18, 68	20, 68	18, 64	18, 68
Sex, n (%)					
Male	24 (40.7)	22 (37.3)	17 (28.8)	19 (32.2)	58 (32.8)
Female	35 (59.3)	37 (62.7)	42 (71.2)	40 (67.8)	119 (67.2)
Race, n (%)					
American Indian or Alaska Native	0	0	1 (1.7)	1 (1.7)	2 (1.1)
Asian	0	0	3 (5.1)	3 (5.1)	6 (3.4)
Black or African American	10 (16.9)	12 (20.3)	6 (10.2)	5 (8.5)	23 (13.0)
Native Hawaiian or Other Pacific Islander	0	0	0	1 (1.7)	1 (0.6)
White	47 (79.7)	46 (78.0)	48 (81.4)	48 (81.4)	142 (80.2)
Multiple	2 (3.4)	1 (1.7)	1 (1.7)	1 (1.7)	3 (1.7)
Ethnicity, n (%)					
Hispanic or Latino	1 (1.7)	4 (6.8)	7 (11.9)	1 (1.7)	12 (6.8)
Not Hispanic or Latino	58 (98.3)	55 (93.2)	52 (88.1)	58 (98.3)	165 (93.2)
Region, n (%)					
North America	52 (88.1)	43 (72.9)	49 (83.1)	48 (81.4)	140 (79.1)
Europe	7 (11.9)	16 (27.1)	10 (16.9)	11 (18.6)	37 (20.9)
Body Mass Index (kg/m <sup>2</sup> )					
n	59	59	59	59	177
Mean (SD)	29.1 (6.0)	27.9 (5.4)	27.9 (5.8)	28.1 (6.3)	28.0 (5.8)
Median	28.4	26.6	28.3	26.9	27.3
Range	18.9, 43.4	18.4, 40.0	18.0, 40.4	18.0, 44.6	18.0, 44.6

Source: Study 14-002 Clinical Study Report, Table 7, page 86.

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Baseline CGIs 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 percentage of subjects with the presence or absence of cataplexy was similar across all treatment groups. Baseline MWT sleep latency and baseline ESS scores were similar across treatment groups. The incidence of sleep apnea was higher in the 150 mg solriamfetol group compared with the other treatment groups. The incidence of hypertension was relatively low (10.2%) in the 75 mg solriamfetol group compared to the other treatment groups. Baseline characteristics for the safety population are presented in Table 11.

**Table 11: Study 14-002, Baseline Characteristics, Safety Population**

Characteristic	Placebo (N=59)	Solriamfetol 75 mg (N=59)	Solriamfetol 150 mg (N=59)	Solriamfetol 300 mg (N=59)	Combined Solriamfetol (N=177)
Baseline Mean Sleep Latency Time (min), n	58	58	57	59	174
Mean (SD)	6.1 (5.6)	7.5 (5.4)	7.7 (5.6)	8.7 (6.2)	8.0 (5.7)
Baseline ESS Total Score, n	59	59	59	59	177
Mean (SD)	17.3 (2.8)	17.3 (3.5)	16.9 (3.7)	17.2 (2.8)	17.1 (3.3)
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
Presence of Sleep Apnea	9 (15.3)	11 (18.6)	15 (25.4)	7 (11.9)	33 (18.6)
Presence of Hypertension	12 (20.3)	6 (10.2)	13 (22.0)	11 (18.6)	30 (16.9)
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)

Sources: Study 14-002 Clinical Study Report, Table 8, page 88, and Table 9, page 90.

### Treatment Compliance

Compliance with study drug was defined as:

$$100 * \frac{\text{total number of capsules dispensed} - \text{total number of capsules returned}}{\text{total number of capsules expected to be taken}}$$

Treatment compliance was high across all treatment groups. Mean overall compliance was 97.5%, with 89% of subjects receiving between 80% and 100% of study drug doses. One subject, in the placebo group, had 36% compliance. This was reported as a major protocol deviation.

### Efficacy Results - Primary Endpoint

MWT: solriamfetol at 150-mg and 300-mg doses met both co-primary efficacy endpoints of increasing MWT mean sleep latency time and reducing ESS score compared with placebo. The 75-mg dose of solriamfetol did not achieve a statistically significant difference from placebo on the MWT. The results for the MWT are summarized in Table 12.

**Table 12: Study 14-002, MWT Results**

Endpoint	Placebo (N=58)	solriamfetol		
		75 mg (N=59)	150 mg (N=55)	300 mg (N=59)
<b>Change in MWT from Baseline to Week 12</b>				
LS Mean (SE)	2.1 (1.3)	4.7 (1.3)	9.8 (1.3)	12.3 (1.4)
LS Mean Difference	---	2.6	7.7	10.1
95% CI	---	(-1.0, 6.3)	(4.0, 11.3)	(6.4, 13.9)
p-value	---	0.1595	< 0.0001	< 0.0001

*Adapted from ISE, Table 6, page 41.*

solriamfetol at doses of 150 mg and 300 mg improved maintenance of wakefulness in a dose-related manner as measured by increased duration of MWT mean sleep latency (minutes) in subjects with narcolepsy. MWT mean sleep latency (minutes) progressively increased with solriamfetol doses, with a statistically significant improvement relative to placebo observed at the two higher solriamfetol doses at Week 12. Least squares mean differences in duration of MWT mean sleep latency relative to placebo were 2.62 ( $p = 0.1595$ ), 7.65 ( $p < 0.0001$ ), and 10.14 ( $p < 0.0001$ ) minutes for solriamfetol 75 mg, 150 mg, and 300 mg, respectively.

Improvement in maintenance of wakefulness as measured by increased duration of MWT sleep latency (minutes) with solriamfetol 150 mg and 300 mg compared with placebo was comparable in subjects with and without cataplexy. However, baseline MWT mean sleep latency was higher in subjects with cataplexy. For subjects with cataplexy, least squares mean differences in the increase in duration of MWT mean sleep latency relative to placebo were 1.63 ( $p = 0.5383$ ), 6.07 ( $p = 0.0261$ ), and 8.87 ( $p = 0.0014$ ) minutes for solriamfetol 75 mg, 150 mg, and 300 mg, respectively, at Week 12. For subjects without cataplexy, least squares mean differences in the increase in duration of MWT mean sleep latency relative to placebo were 3.43 ( $p = 0.2010$ ), 9.05 ( $p = 0.0008$ ), 11.20 ( $p < 0.0001$ ) minutes for solriamfetol 75 mg, 150 mg, and 300 mg, respectively, at Week 12.

*ESS:* solriamfetol at 75 mg, 150 mg, and 300 mg doses reduced sleepiness in a dose-related manner in subjects with narcolepsy as assessed by reduction in ESS score. ESS scores decreased with larger doses of solriamfetol, and a statistically significant reduction in ESS scores relative to placebo was observed at Week 12 at all three solriamfetol doses. The ESS results for Study 14-002 are summarized in Table 13.

**Table 13: Study 14-002, ESS Results**

Endpoint	Placebo (N=58)	solriamfetol		
		75 mg (N=59)	150 mg (N=55)	300 mg (N=59)
<b>Change in ESS Score from Baseline to Week 12</b>				
LS Mean (SE)	-1.6 (0.7)	-3.8 (0.7)	-5.4 (0.7)	-6.4 (0.7)
LS Mean Difference	---	-2.2	-3.8	-4.7
95% CI	---	(-4.0, -0.3)	(-5.6, -2.0)	(-6.6, -2.9)
p-value	---	0.0211	< 0.0001	< 0.0001

*Adapted from ISE, Table 6, page 41.*

Least squares mean differences in ESS scores relative to placebo were -2.2 ( $p = 0.0211$ ), -3.8 ( $p < 0.0001$ ), and -4.7 ( $p < 0.0001$ ) for solriamfetol 75 mg, 150 mg, and 300 mg, respectively. The mean ESS (SD) score at Week 12 was 15.7 (4.61) in placebo and 13.8 (5.59), 11.5 (5.45), and 11.1 (5.26) in the solriamfetol 75 mg, 150 mg, and 300 mg treatment groups.

In subjects with and without cataplexy, solriamfetol effects in reducing sleepiness as measured by the total ESS score were generally comparable. For subjects with cataplexy, least squares mean differences in reduction in ESS scores relative to placebo were -1.3 ( $p = 0.3392$ ), -3.7 ( $p = 0.0057$ ), and -4.5 ( $p = 0.0010$ ) for solriamfetol 75 mg, 150 mg, and 300 mg, respectively. For subjects without cataplexy, least squares mean differences in reduction ESS scores relative to placebo were -3.0 ( $p = 0.0241$ ), -3.7 ( $p = 0.0050$ ), and -4.9 ( $p = 0.0005$ ) for solriamfetol 75 mg, 150 mg, and 300 mg, respectively.

#### **Data Quality and Integrity - Reviewers' Assessment**

The Office of Scientific Investigations inspected two sites participating in this study, Site #100 and Site #104. Each site enrolled eight subjects. For each site, the primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events for either site. The assessment of OSI was that the inspection results did not indicate the need for any regulatory action.

#### **Efficacy Results - Secondary and other relevant endpoints**

*Improvement on the PGI-C (key secondary endpoint):* solriamfetol at 75 mg, 150 mg, and 300 mg doses increased the percentage of subjects reporting improvement (minimally, much, or very much) in their overall condition in a dose-related manner as measured using the PGI-C at Week 12. Based on the fixed hierarchical testing sequence, solriamfetol doses of 150 mg and 300 mg met the key secondary endpoint. The percentage of subjects reported as improved on the PGI-C was increased relative to placebo at Week 12, with larger increased observed with higher doses of solriamfetol. The increase in the percentage of subjects reporting improvement

on the PGI-C relative to placebo was 28.1% ( $p = 0.0023$ ), 38.5% ( $p < 0.0001$ ), and 45.1% ( $p < 0.0001$ ) for solriamfetol 75 mg, 150 mg, and 300 mg, respectively.

In subjects with and without cataplexy, the percentage of subjects reporting improvement on the PGI-C at Week 12 was generally comparable. The magnitude of the effect relative to placebo was numerically higher in subjects without cataplexy. For subjects with cataplexy, the percentage of subjects reporting improvement on the PGI-C relative to placebo was 10.0% ( $p = 0.4383$ ), 33.0% ( $p = 0.0116$ ), and 38.5% ( $p = 0.0020$ ) for solriamfetol 75 mg, 150 mg, and 300 mg, respectively. For subjects without cataplexy, the percentage of subjects reporting improvement on the PGI-C relative to placebo was 47.7% ( $p = 0.0003$ ), 44.1% ( $p = 0.0008$ ), and 51.7% ( $p < 0.0001$ ) for solriamfetol 75 mg, 150 mg, and 300 mg, respectively.

*Duration of effect, as measured by change in sleep latency over the course of a sequence of MWT trials:* The duration of the effect of solriamfetol at doses of 150 mg and 300 mg showed a dose-related improvement on the MWT mean sleep latency time for each of the five MWT trials, spanning approximately nine hours after dosing. The onset of the effect of solriamfetol on improvement in MWT mean sleep latency was observed as early as one hour after dosing.

*Change in mean sleep latency on the MWT:* The effect of solriamfetol 150 mg and 300 mg doses on improvement in MWT mean sleep latency was observed by Week 1, and the improvement was durable over 12 weeks.

*Change in ESS score:* The effect of solriamfetol in reducing excessive sleepiness as measured by ESS scores was observed by Week 1 and persisted over the 12 weeks of the study for solriamfetol doses of 150 mg and 300 mg.

*Percentage of subjects improved on the PGI-C:* solriamfetol at doses of 150 mg and 300 mg increased the percentage of subjects reporting improvement on the PGI-C by Week 1. The increase was maintained through Week 12.

*Improvement on the CGI-C:* solriamfetol at doses of 150 mg and 300 mg increased the percentage of subjects with clinician-reported improvement in their overall condition at Weeks 1, 4, 8, and 12.

*Percentage of subjects improved on the CGI-C, stratified by presence/absence of cataplexy:* The percentage of subjects demonstrating improvement on the CGI-C at Week 12 was comparable for subjects with and without cataplexy.

### **Efficacy Results – Functional Outcomes and Quality of Life Endpoints**

*FOSQ-10*: Subjects treated with solriamfetol 75 mg, 150 mg, or 300 mg showed numerical increases over placebo from baseline to Week 12.

*WPAI:SHP*: Subjects treated with solriamfetol 150 mg or 300 mg demonstrated a decrease compared to placebo on all four endpoint scores (percent impairment while working due to narcolepsy; percent overall work impairment due to narcolepsy; percent activity impairment due to narcolepsy; percent work time missed due to narcolepsy).

*SF-36v2*: solriamfetol produced numerical improvement over placebo; this effect was driven by improvement in the role physical, general health, and vitality scores.

### **Efficacy Results – Exploratory Endpoints**

*Cataplexy attacks*: No change in the number of cataplexy attacks was observed in subjects reporting cataplexy.

*Change in PSG parameters*: No change in PSG parameters was observed. solriamfetol did not have an effect on sleep architecture. No clinically significant changes were observed for TST, time in Stage N1, Stage N2, Stage N3, or WASO.

### **Dose/Dose Response**

Dose response was demonstrated for solriamfetol in this study. Solriamfetol 75 mg met only one of the co-primary efficacy endpoints, change in ESS score from baseline to Week 12. It did not meet the endpoint of change in MWT from baseline to Week 12. Solriamfetol 150 mg and 300 mg each met both of the co-primary endpoints. The LS mean difference from placebo increased with increasing dose on both co-primary endpoints, with the greatest separation from placebo seen with the 300 mg dose (see Table 12 and Table 13).

### **Durability of Response**

The time course of efficacy on the MWT was assessed for the 150 mg and 300 mg solriamfetol doses, as these were the doses that showed statistically significant differences relative to placebo on the endpoint of change in MWT mean sleep latency from baseline to Week 12. For both the 150 mg and 300 mg treatment groups, pairwise comparison versus placebo for each of the five MWT sessions at Week 12 showed significant improvement in the MWT mean sleep latency time for all five trials. The magnitude of improvement in MWT mean sleep latency was dose-related, with the largest increases observed in the 300 mg solriamfetol group.

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Changes from baseline in ESS scores compared with placebo were observed at solriamfetol doses of 75 mg, 150 mg, and 300 mg by Week 1, and were maintained at Week 4 and Week 8. The changes were dose-dependent, with the smallest changes in the 75 mg group and largest changes in the 300 mg group.

### 6.3. Study 14-003 (Indication: Obstructive Sleep Apnea)

#### 6.3.1. Study Design

##### Overview and Objective

Study Title: “A twelve-week, double-blind, placebo-controlled, randomized, parallel-group, multicenter study of the safety and efficacy of solriamfetol [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the treatment of excessive sleepiness in subjects with obstructive sleep apnea (OSA).”

Primary Objective:

- To evaluate the efficacy of solriamfetol administered once daily (QD) for up to 12 weeks in doses of 37.5 mg, 75 mg, 150 mg, and 300 mg compared to placebo in the treatment of excessive sleepiness in adult subjects with OSA.

Secondary Objectives:

1. To evaluate the safety and tolerability of solriamfetol administered once daily (QD) for up to 12 weeks in doses of 37.5 mg, 75 mg, 150 mg, and 300 mg compared to placebo in the treatment of excessive sleepiness in adult subjects with OSA.
2. To characterize the pharmacokinetics (PK) of solriamfetol in subjects with OSA using sparse sampling methods.

##### Trial Design

Study Design Overview:

This was a 12-week, randomized, double-blind, placebo-controlled, multicenter, five-arm parallel group study of the safety and efficacy of solriamfetol in the treatment of excessive sleepiness in adult subjects with OSA. Following Screening and Baseline visits, subjects were randomized to one of five treatment arms for the Treatment Phase: solriamfetol 37.5 mg, 75 mg, 150 mg, 300 mg, or placebo.

Trial Location:

The trial was conducted at 59 study centers: 50 in North America and nine in Europe.

Diagnostic Criteria:

Subjects had to have a documented diagnosis of obstructive sleep apnea according to criteria of the International Classification of Sleep Disorders, Third Edition (ICSD-3).

Key Inclusion Criteria:

1. Age between 18 and 75 years, inclusive.
2. Diagnosis of OSA according to ICSD-3 criteria.
3. At least minimal use of a primary therapy for OSA or an attempt to use a primary therapy for OSA, as evidenced by any one of the following:
  - a. Use of a primary therapy for OSA (positive airway pressure, oral pressure therapy, oral appliance, or upper airway stimulator) on at least one night per week;
  - b. History of at least one month of an attempt to use one or more primary OSA therapies with at least one documented adjustment that was made in an attempt to optimize the primary OSA therapy;
  - c. History of a surgical intervention intended to treat OSA symptoms.
4. Stable level of compliance with a primary OSA therapy for at least one month prior to Baseline, as evidenced by any one of the following:
  - a. A stable level of use of a primary OSA therapy;
  - b. A lack of use of a primary OSA therapy following a history of attempted use;
  - c. A history of a surgical intervention intended to treat OSA symptoms.
5. Baseline Epworth Sleepiness Scale (ESS)  $\geq 10$ .
6. Baseline mean sleep latency  $< 30$  minutes, calculated as the mean of the first four test sessions of the MWT.
7. Usual nightly total sleep time (TST) of at least six hours.
8. Body mass index (BMI) of at least  $18 \text{ kg/m}^2$  and less than  $45 \text{ kg/m}^2$ .
9. Consent to use a medically acceptable method of contraception for at least two months prior to the first dose of study drug, throughout the entire study period, and for 30 days after the study is completed.

Key Exclusion Criteria:

1. Unwilling to attempt to use one or more primary OSA therapies.
2. Female subjects who are pregnant, nursing, or lactating.
3. Usual bedtime later than 1:00 am (0100 hours).
4. Occupation requiring nighttime or variable shift work.
5. Any other clinically relevant medical, behavioral, or psychiatric disorder other than OSA that is associated with excessive sleepiness.
6. History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria.

7. History or presence of any acutely unstable medical condition, behavioral or psychiatric disorder (including active suicidal ideation), or surgical history that could affect the safety of the subject or interfere with study efficacy, safety, PK assessments, or the ability of the subject to complete the trial per the judgment of the Investigator.
8. History of bariatric surgery within the past year or a history of any gastric bypass procedure.
9. Presence of renal impairment or calculated creatinine clearance < 60 mL/min.
10. Clinically significant cardiovascular disease, electrocardiogram (ECG), or laboratory abnormality in the opinion of the Investigator.
11. Excessive caffeine use (defined as > 600 mg caffeine per day) one week prior to Baseline assessments or anticipated excessive use during the study.
12. Use of any over-the-counter (OTC) or prescription medication that could affect the evaluation of excessive sleepiness within a time period prior to the Baseline visit corresponding to at least five half-lives of the drug, or planned use of such drugs at some point throughout the duration of the study. Medications should be discontinued such that the subject has returned to his/her baseline level of daytime sleepiness at least seven days prior to the Baseline visit.
13. Received an investigational drug in the past 30 days or five half-lives (whichever is longer) prior to the Baseline visit, or planned to use an investigational drug (other than the study drug) during the study.
14. Previous exposure to solriamfetol, or participation in a previous clinical trial of solriamfetol.
15. Current or past (within the past two years) diagnosis of a moderate or severe substance use disorder, or seeking treatment for a substance related disorder.
16. Urine drug screen positive for an illicit drug of abuse at screening or at any point throughout the duration of the study, except for a prescribed drug (e.g., amphetamine) at screening.
17. Nicotine dependence that has an effect on sleep (e.g., a subject who routinely awakens at night to smoke).
18. History of phenylketonuria or history of hypersensitivity to phenylalanine-derived products.

Study Treatments:

Study treatments were solriamfetol 37.5 mg, 75 mg, 150 mg, 300 mg, or placebo, administered daily by mouth. Subjects randomized to the 37.5-mg dose or the 75-mg dose did not undergo dose titration. Subjects randomized to the 150-mg dose received 75 mg from Day 1 through Day 3 of the Treatment Phase, then received 150 mg daily starting on Day 4. Subjects randomized to the 300-mg dose received 150 mg from Day 1 through Day 3, then received 300 mg daily starting on Day 4.

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Assignment to Treatment:

Subjects were stratified on the basis of their compliance with their primary OSA therapy. Stratified subjects were randomized in a 1:1:2:2:2 ratio to receive solriamfetol 37.5 mg, 75 mg, 150 mg, 300 mg, or placebo QD over the 12-week treatment phase.

Procedures and Schedule:

During the Treatment Phase, subjects returned to the study site to complete efficacy and safety assessments at the end of Weeks 1, 4, 8, and 12. The Week 4 and 12 visits included an overnight stay at the study site for nocturnal PSG followed by a MWT. The Week 8 visit included 24-hour ABPM. Four blood samples were collected from each subject for PK evaluations: one sample at Week 1, two samples at Week 8, and one sample at Week 4. Subjects received their final dose of study drug at the Week 12 visit. Subjects returned at the end of Week 14 for follow-up assessments.

**Study Endpoints**

Co-Primary Efficacy Endpoints:

1. *MWT*: Change in the mean sleep latency time (in minutes) as determined from the first four test sessions of a 40-minute MWT from Baseline to Week 12.
2. *ESS*: Change in ESS score from Baseline to Week 12.

Key Secondary Efficacy Endpoint:

*Patient Global Impression of Change (PGI-C)*: Percentage of subjects reported as improved (minimally, much, or very much) on the PGI-C at Week 12.

Other Secondary Efficacy Endpoints:

1. *Time course of efficacy on the MTW*: Change in sleep latency time (in minutes) on each of the five MWT test sessions.
2. *MWT*: Change in the mean sleep latency time (in minutes) as determined from the first four test sessions of a 40-minute MWT from Baseline to Week 4.
3. *ESS*: Change in ESS score from Baseline to Week 1, Week 4, and Week 8.
4. *PGI-C*: Percentage of subjects reported as improved at Week 1, Week 4, and Week 8.
5. *Clinical Global Impression of Change (CGI-C)*: Percentage of subjects reported as improved (minimally, much, or very much) at Week 12.
6. *CGI-C*: Percentage of subjects reported as improved at Week 1, Week 4, and Week 8.

Functional Outcomes and Quality of Life Endpoints:

1. *Functional Outcomes of Sleep Questionnaire Short Version (FOSQ-10)*: Change in the total score from Baseline to Week 1, Week 4, Week 8, and Week 12.
2. *36-Item Short Form Health Survey Version 2 (SF-36v2)*: Change in the 8-domain scores, physical component summary (PCS) score, and mental component summary (MCS) score from Baseline to Week 4, Week 8, and Week 12.

3. *EuroQol (EQ-5D-5L)*:
  - a. *EQ-5D Dimensions*:
    - i. Number and percentage of subjects in each of the five levels (e.g. no problem, slight problem, moderate problem, severe problem, unable) for each dimension (e.g., mobility, self-care) over time
    - ii. Number and percentage of subjects reporting any problems (levels 2-5) for each dimension (e.g., mobility, self-care) over time
  - b. *EQ-Visual Analogue Scale (EQ VAS)*: Mean and standard deviation (SD) or median with 25<sup>th</sup> and 75<sup>th</sup> percentiles for the visual analog scale (VAS) at baseline, Week 1, Week 4, Week 8, and Week 12. Change in the mean VAS scores from Baseline to Week 1, Week 4, Week 8, and Week 12.
  - c. *EQ-5D-5L Index*: Index value at Baseline, to Week 1, Week 4, Week 8, and Week 12.
4. *Work Productivity and Activity Impairment Questionnaire; Specific Health Problems (WPAI:SHP)*: Percent work time missed due to problem over time, percent impairment while working due to problem over time, percent overall work impairment due to problem over time, and percent activity impairment due to problem over time.

Exploratory Endpoints:

1. Change in frequency of use of primary OSA therapy from Baseline to Week 12.
2. Change in PSG parameters including total sleep time (TST), time in Stages N1, N2, N3, wake after sleep onset (WASO), number of awakenings, apnea index, apnea hypopnea index, number of central apneas, oxygen saturation (SaO<sub>2</sub>) nadir, and SaO<sub>2</sub> mean from Baseline to Week 4 and Week 12.

**Statistical Analysis Plan**

For the analysis of the co-primary efficacy endpoints, a mixed-effect model with repeated measures (MMRM) was used as the primary method of analysis. This model included fixed effects for treatment (i.e., dose group), visit (as a discrete and repeated factor), treatment-by-time interaction, baseline value of the efficacy endpoint, and randomization stratification factor. All available data were included in the model. An unstructured covariance matrix was used to model the correlation among repeated measurements. The estimates of treatment difference versus placebo and their 95% confidence intervals were presented. In addition to the MMRM, an analysis of covariance (ANCOVA) model was used to analyze MWT and ESS to provide sensitivity analyses. This ANCOVA model included the effect for treatment (i.e., dose group) as a fixed effect, and baseline value of the efficacy endpoint and randomization stratification factor as the covariate.

A time course analysis of MWT sleep latency (in minutes) was performed for the solriamfetol dose(s) that showed a significant difference versus placebo in the primary analysis of both co-primary endpoints of MWT and ESS. The chi-squared test was used to test the hypotheses

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associated with the analysis of PGI-C (key secondary endpoint) and the secondary efficacy endpoint of CGI-C at Week 12. For the other MWT and ESS endpoints and the FOSQ-10, SF-36v2, EQ VAS, EQ-5D-5L Index, and WPAI:SHP endpoints, a similar MMRM to that used in the primary analysis of the co-primary endpoints was used; the other PGI-C and CGI-C endpoints, and EQ-5D-5L: EQ 5D Dimensions endpoints were analyzed using the chi-squared test.

Concentration data were tabulated by sampling time point. Scatter plots and spaghetti plots of solriamfetol concentrations over time were provided, sorted by solriamfetol treatment groups.

## Protocol Amendments

*Original protocol date: December 17, 2014*

*Amendment #1: February 18, 2015*

- update to exposure data to include subjects from a Phase 1 human abuse liability study;
- update to the Introduction to include safety information on the number of patients who reported palpitations or chest pain or who had a T-wave inversion in study MDD-201;
- a new section, “End of Trial,” to satisfy EU regulatory requirements on defining the end of the trial;
- a clarification was made that the Safety Follow-up Visit was not required for subjects who enrolled in the open-label safety study (14-005) at the final clinic visit;
- deletion of “documented aspermia” as a criterion for subjects whose method of contraception is vasectomy;
- updated descriptions of solriamfetol and placebo excipients;
- clarification of the use of vital signs measurements to meet entrance criteria;
- replacement of the C-SSRS version at the screening visit by the Baseline/Screening Version;
- revision of the pregnancy information section to clarify following of pregnant partners;
- text describing collection of the two pharmacokinetic blood samples at the Week 8 visit was modified for clarity;
- for consistency across PSG assessments in the study it was clarified that subjects who are compliant with their PAP device use at the beginning of the study should use their PAP device for each PSG assessment and that subjects who use a PAP device, but who are not fully compliant, should decide with the investigator whether they will use their PAP device during all or none of the PSG assessments;
- the instructions for the collection of primary OSA therapy usage were revised to allow a subject who uses a PAP device for which usage data cannot be retrieved to report their primary OSA therapy usage and the estimated duration of use on a daily basis using the same diary-based method that subjects who do not use PAP therapy will employ.

- Changes to the exclusion criteria:
  - Exclusion Criterion #7 was revised to align with text in Section 6.9, which states that the presence of *active* suicidal ideation would exclude a subject from participation in the study.
  - In Exclusion Criterion #9, calculated creatinine clearance was changed from < 70 mL/min to < 60 mL/min to correspond with the standard categories of renal impairment.
  - In Exclusion Criterion #11, ondansetron, which has a known risk of torsade de pointes, was added to the list of excluded concomitant medications.
  - In Exclusion Criterion #12, systolic blood pressure level was changed from 140 mmHg to 150 mmHg, in response to FDA feedback to recruit a more inclusive patient population. In addition, blood pressure measures were clarified to indicate that the criterion applied when consistently observed across the multiple baseline measures.
  - Exclusion Criterion #15 was changed to specify that the use of excluded medications that might affect evaluation of excessive sleepiness should be discontinued such that the baseline level of symptoms is present for at least seven days prior to the baseline visit, because the baseline measures will assess these symptoms over the past seven days.

*Amendment #2: September 10, 2015*

- Changes to the inclusion criteria:
  - In Inclusion Criterion #1, the upper age limit was changed from 70 to 75 years old.
- Changes to the exclusion criteria:
  - Exclusion Criterion #7 was changed to limit subjects who had acutely unstable conditions vs. those with clinically significant conditions. Individuals who were unlikely to be able to complete the study were also excluded.
  - Exclusion Criterion #12 was changed to exclude myocardial infarction and history of revascularization procedures if these occurred within the past year; to increase the blood pressure cutoff values from 150/90 mmHg to 155/95 mmHg; to exclude chronic ventricular arrhythmias (rather than all clinically significant arrhythmias); to exclude angina pectoris only if it is unstable; to exclude congestive heart failure specifically; and to remove the wording regarding exclusion of second or third degree heart block and clinically significant valvular disease, as these conditions were either already excluded in this criterion or addressed in another exclusion criterion.
- Information on the following of pregnancy in cases of live birth was made consistent with the Pregnant Partner Informed Consent Form.

*Amendment #3: February 8, 2016*

- Changes to inclusion criteria:
  - Inclusion Criterion #3 was changed to specify that primary OSA therapy may include oral pressure therapy or use of an upper airway stimulator, in addition to the already specified therapies of positive airway pressure and oral appliances.
  - In Inclusion Criterion #6, the upper limit of the eligible range of BMI was raised from  $< 40 \text{ kg/m}^2$  to  $< 45 \text{ kg/m}^2$  based on feedback from investigators in the United States who reported that the BMI cutoff of  $40 \text{ kg/m}^2$  was excluding otherwise healthy potential subjects. Obesity is a well-characterized comorbidity of the OSA population, and this change allowed the enrollment of a representative patient population with minimal change to risk of participation.
  - In Inclusion Criterion #6, the requirement for the baseline mean sleep latency, as documented by the mean of the first four test sessions of the MWT, was changed to  $< 30$  minutes because the criterion of  $\leq 20$  minutes was excluding subjects who were otherwise eligible and are representative of the OSA population with excessive daytime sleepiness.
- Changes to exclusion criteria:
  - Exclusion Criterion #8, which dealt with bariatric surgery, was clarified to state that a history of any gastric bypass procedure was exclusionary because of its potential to affect the absorption and PK of solriamfetol. Other bariatric surgery procedures, such as a gastric band procedure, are exclusionary only if performed within the past year.
  - Cardiac Exclusion Criteria #10, #11, and #12 were changed as follows:
    - A thorough QT/QTc (TQT) study with solriamfetol had not been completed when Study 14-003 was initiated; therefore, as a precaution, subjects with a history or presence of a risk factor for torsade de pointes (Exclusion Criterion #10) and subjects who used and could not safely discontinue medication with known risk for torsade de pointes (Exclusion Criterion #11) were excluded from this study. However, the findings from the completed TQT Study 15-002 showed no QTcF prolongation reaching the threshold of regulatory concerns with solriamfetol at the proposed therapeutic dose of 300 mg or at the suprathreshold dose of 900 mg. Therefore, Exclusion Criterion #10 was changed to exclude only subjects with a clinically significant ECG abnormality, and Exclusion Criterion #11 was removed (no changes were made in the extent or frequency of assessments of cardiovascular safety).
    - Exclusion Criterion #12 was revised to more clearly specify which types of congestive heart failure and cardiac arrhythmias were excluded.
  - Rescreening of subjects who had not met previous eligibility requirements, but who were likely to meet the revised eligibility requirements, was not addressed

in the protocol. This amendment clarified that those subjects would be allowed to be rescreened with approval by the Medical Monitor.

- The statistical analyses described in the protocol were updated to incorporate feedback from the FDA about the previously planned analyses.
- A change was made to the Week 1 procedures such that the overnight PSG and the MWT that followed would no longer be done at Week 1. Data from those assessments was not essential, and this change would not affect the primary efficacy analyses.
- The length of time during which screening labs could be repeated was extended.

### **Country-Specific Amendments**

Amendments 2FR, 3FR, 4FR, 5FR, and 6FR were country-specific amendments that applied only to clinical sites in France.

#### *Amendment 2FR: August 17, 2015*

- added a safety follow-up phone contact for further assessment of adverse events after discontinuation of study drug;
- added further specifications to Inclusion Criterion #1 (affiliation with a Social Security regime) and Inclusion Criterion #11 (that a subject not be a vulnerable person or legally protected adult);
- added the exclusion of individuals with a current or past diagnosis of mild substance use disorder, in addition to individuals with moderate or severe substance use disorders.

#### *Amendment 3FR: October 9, 2015*

- consisted of the changes specified in Amendment #2 (September 10, 2015).

#### *Amendment 4FR: December 1, 2015*

- changed the time for following a live birth as the outcome of pregnancy during the study from six months to a minimum of six months.

#### *Amendment 5FR: March 11, 2016*

- consisted of the changes specified in Amendment #3 (February 8, 2016)

#### *Amendment 6FR: June 1, 2016*

- added three drugs to the list of drugs included in the urine drug screen in Table 1 of the protocol: buprenorphine, 3,4-methylenedioxymethamphetamine, and nortriptyline. Although urine drug screening for these drugs was not required by the protocol, the testing kit being used at the sites did screen for those substances. The addition of these drugs to the list of laboratory tests did not change the conduct of the trial.

### Changes in the Planned Analyses

The following two endpoints, initially described in the original protocol, were modified:

- SF-36v2
  - original: Change in the total score and change in the eight subscales from baseline to Week 4, Week 8, and Week 12.
  - modification: Change in the eight Domain Scores, the Physical Component Summary (PCS) Score, and the Mental Component Summary (MCS) Score from baseline to Weeks 4, 8, and 12.
- Change in frequency of use of primary OSA therapy
  - original: Change in frequency of use of primary OSA therapy from baseline to Week 12.
  - modification: Change in frequency of use of primary OSA therapy from baseline to each subsequent analysis period (i.e., Weeks 1-4, 5-8, and 9-12).

### Data Quality and Integrity: Sponsor's Assurance

Steps to assure the accuracy and reliability of data included the selection of qualified investigators and an appropriate study site, review of protocol procedures with the investigator and associated personnel prior to the study, and periodic monitoring visits by Jazz Pharmaceuticals or its designee. Data were reviewed for accuracy and completeness by Jazz Pharmaceuticals or its designee during and after onsite monitoring visits, and any discrepancies were resolved with the investigator or designees as appropriate. Quality control audits could be performed at the discretion of the Sponsor. Electronic CRFs (eCRFs) were used for the recording of all trial data not recorded in subject diaries, obtained by ECG recording, or generated by laboratory report. The principal investigator reviewed the eCRFs and provided his signature certifying that he reviewed the data and considered the data accurate to the best of his knowledge and provided his signature certifying that he reviewed the data and considered the data accurate to the best of his knowledge. A comprehensive Data Management Plan was developed. A central laboratory ( (b) (4) ) reviewed all sleep study data.

### Reporting of Serum Direct Bilirubin Values

A technical issue was identified regarding serum direct bilirubin values reported from laboratory testing. Between January 2, 2016 and November 21, 2016, serum direct bilirubin values levels assayed by (b) (4) for this study were assigned a positive proportional bias due to a calibrator issue (calibrator manufactured by Siemens Healthcare Diagnostics). Calibrator values were reassigned by the manufacturer and were placed into effect by (b) (4) as of November 21, 2016. (b) (4) conducted an internal correlation between results obtained using the old calibrator set point and the new reassigned calibrator set point. A positive shift in direct bilirubin results was observed that was proportional in nature. An average bias of 30% was seen when direct bilirubin was more than three times the upper limit

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of normal (ULN). Differences for results that were in the normal range and up to three times the ULN were within the total allowable error of the assay. Siemens estimated the average bias to be approximately 40%. A correction factor could not be provided and previously tested samples could not be re-assayed. Results from 924 samples collected from 420 subjects during the affected period are in the clinical database uncorrected. Upon analysis by Jazz and (b) (4) (CRO) of the direct bilirubin outliers, the clinical significance of the positive bias was considered to be minimal.

### 6.3.2. Study Results

#### Compliance with Good Clinical Practices

The Clinical Study Report for Study 14-003, Section 9.6.1, Study Administration and Conduct (page 54), states: "The study was conducted according to GCP guidelines and according to national law." Section 9.6.2, Data Generation and Analysis, (page 54) states: "The standard procedures for handling and processing records were followed in compliance with 21 CFR 11, Good Clinical Practices, ICH Guidelines, and the Standard Operating Procedures of Jazz Pharmaceuticals or the CRO ( (b) (4) )."

#### Financial Disclosure

Financial disclosures for each of the five pivotal trials under this NDA were reviewed at the time the NDA was filed. For Study 14-003, (b) (6) and (b) (6) had disclosable financial interests. See Appendix 13.2 for details.

#### Patient Disposition

A total of 476 subjects were enrolled in the study. Of these, 474 subjects received at least one dose of study medication and comprised the Safety Population. The Modified Intent-to-Treat (mITT) population was comprised of 459 subjects; the Per Protocol population, 392 subjects; and the Pharmacokinetic population, 343 subjects. The majority of subjects in the Safety Population who were randomized to receive placebo (84.9%) or solriamfetol (85.4%) completed the study. Overall, a greater percentage of subjects in the 300 mg solriamfetol group (13.6%) relative to all other treatment groups did not complete the study due to one or more adverse events. Details of patient disposition for the Safety Population are presented in Table 14.

**Table 14: Study 14-003, Patient Disposition, Safety Population**

	Placebo (N=119)	Solriamfetol 37.5 mg (N=58)	Solriamfetol 75 mg (N=62)	Solriamfetol 150 mg (N=117)	Solriamfetol 300 mg (N=118)	Combined Solriamfetol (N=355)
Completed: n (%)						
Yes	101 (84.9)	49 (84.5)	54 (87.1)	106 (90.6)	94 (79.7)	303 (85.4)
No	18 (15.1)	9 (15.5)	8 (12.9)	11 (9.4)	24 (20.3)	52 (14.6)
If No, Primary Reason: n (%)						
Lack of Efficacy	0	0	0	0	0	0
Protocol Violation	2 (1.7)	0	0	2 (1.7)	0	2 (0.6)
Adverse Event	4 (3.4)	3 (5.2)	2 (3.2)	5 (4.3)	16 (13.6)	26 (7.3)
Withdrawal of Consent	4 (3.4)	2 (3.4)	2 (3.2)	1 (0.9)	4 (3.4)	9 (2.5)
Lost to Follow-up	0	1 (1.7)	0	0	2 (1.7)	3 (0.8)
Treatment Non-compliant	2 (1.7)	0	0	0	1 (0.8)	1 (0.3)
Other <sup>a</sup>	6 (5.0)	3 (5.2)	4 (6.5)	3 (2.6)	1 (0.8)	11 (3.1)

<sup>a</sup> Other reasons included randomization in error, noncompliance with study protocol due to immigration detention, total sleep time criterion not met, baseline MWT criterion not met, baseline MWT scores between local and central sites not in agreement and Sponsor advised to withdraw subject, MWT mean sleep latency could not be scored by the central laboratory, noncompliant with study procedures, not eligible by PSG criteria, and protocol deviation of MWT trial terminated before sleep onset observed.

Source: Study 14-003 Clinical Study Report, Table 4, page 72.

### Protocol Violations/Deviations

Major protocol deviations were reported for 85 subjects in the Safety Population, with 27 (22.7%) and 58 (16.3%) of these subjects randomized to placebo or solriamfetol, respectively. The percentage of subjects with major protocol deviations was similar across solriamfetol dose groups. For both placebo and solriamfetol dose groups, most protocol deviations were related to informed consent and/or enrollment criteria. Major protocol deviations are summarized in Table 15.

**Table 15: Study 14-003, Major Protocol Deviations, Safety Population**

Deviation Category, n (%)	Placebo (N=119)	Solriamfetol 37.5 mg (N=58)	Solriamfetol 75 mg (N=62)	Solriamfetol 150 mg (N=117)	Solriamfetol 300 mg (N=118)	Combined Solriamfetol (N=355)
Any Major Protocol Deviation	27 (22.7)	10 (17.2)	7 (11.3)	23 (19.7)	18 (15.3)	58 (16.3)
Concomitant Medications	1 (0.8)	0	2 (3.2)	2 (1.7)	1 (0.8)	5 (1.4)
Dosing	4 (3.4)	2 (3.4)	0	1 (0.9)	5 (4.2)	8 (2.3)
Enrollment Criteria	10 (8.4)	8 (13.8)	1 (1.6)	9 (7.7)	4 (3.4)	22 (6.2)
Informed Consent	10 (8.4)	0	3 (4.8)	11 (9.4)	2 (1.7)	16 (4.5)
Laboratory <sup>a</sup>	4 (3.4)	0	0	1 (0.9)	4 (3.4)	5 (1.4)
Non-compliance	1 (0.8)	0	0	4 (3.4)	1 (0.8)	5 (1.4)
Visit/Procedure Required	1 (0.8)	0	1 (1.6)	4 (3.4)	2 (1.7)	7 (2.0)

<sup>a</sup> Deviation in this category generally refers to having not performed a laboratory procedure at the specified time point or having a laboratory test abnormality (such as positive urine screen) that precluded study continuation.  
*Source: Study 14-003 Clinical Study Report, Table 5, page 73.*

Subject (b) (6), randomized to the placebo group, should have been listed with a major protocol deviation based on violation of Exclusionary Criterion #18 (previous exposure to solriamfetol in a clinical trial). The subject had previously enrolled in Study 14-004 under ID (b) (6) and had received solriamfetol 300 mg.

Two subjects had protocol violations that resulted in duplicate subject information for this study:

- Subject (b) (6) was randomized to the placebo group, but should have been excluded based on Exclusionary Criterion #18 (previous exposure to solriamfetol in a clinical trial). This subject was enrolled a second time in Study 14-003 at a different site. The second ID number given to this subjects was (b) (6). Under this ID, the subject was randomized to the solriamfetol 75 mg dose group.
- Subject (b) (6) was randomized to the solriamfetol 37.5 mg group, but should have been excluded based on Exclusionary Criterion #18 (previous exposure to solriamfetol in a clinical trial). This subject was enrolled a second time in Study 14-003 at a different site. The second ID number given to this subjects was (b) (6). Under this ID, the subject was randomized to the solriamfetol 150 mg dose group.

Data from participation of the two duplicate subjects was included in the Study 14-003 database and analyses without correction. The Sponsor performed sensitivity analyses removing all data from the four subject IDs associated with the two duplicate subjects. The sensitivity analyses showed that the effect on demographic data, baseline characteristics, exposure, efficacy, and safety data was minimal and would not have an impact on the overall study conclusions.

### **Table of Demographic Characteristics**

In the Safety Population, the majority of subjects were white males, and the majority of subjects in each treatment group were enrolled at sites in North America. Demographic characteristics were balanced across treatment groups. Demographics of the safety population are presented in Table 16.

**Table 16: Study 14-003, Patient Demographics, Safety Population**

Characteristic	Placebo (N=119)	Solriamfetol 37.5 mg (N=58)	Solriamfetol 75 mg (N=62)	Solriamfetol 150 mg (N=117)	Solriamfetol 300 mg (N=118)	Combined Solriamfetol (N=355)
Age (years)						
n	119	58	62	117	118	355
Mean (SD)	54.1 (11.4)	57.1 (10.2)	54.4 (11.5)	52.7 (10.6)	53.2 (10.6)	53.9 (10.8)
Median	55.0	59.5	56.5	53.0	54.0	55.0
Range	20, 74	33, 72	29, 74	21, 75	24, 72	21, 75
Sex, n (%)						
Male	77 (64.7)	39 (67.2)	35 (56.5)	72 (61.5)	74 (62.7)	220 (62.0)
Female	42 (35.3)	19 (32.8)	27 (43.5)	45 (38.5)	44 (37.3)	135 (38.0)
Race, n (%)						
American Indian or Alaska Native	1 (0.8)	0	0	0	0	0
Asian	4 (3.4)	3 (5.2)	1 (1.6)	3 (2.6)	6 (5.1)	13 (3.7)
Black or African American	26 (21.8)	10 (17.2)	14 (22.6)	18 (15.4)	21 (17.8)	63 (17.7)
Native Hawaiian or Other Pacific Islander	1 (0.8)	0	0	1 (0.9)	0	1 (0.3)
White	87 (73.1)	45 (77.6)	46 (74.2)	93 (79.5)	90 (76.3)	274 (77.2)
Multiple	0	0	1 (1.6)	2 (1.7)	1 (0.8)	4 (1.1)
Ethnicity, n (%)						
Hispanic or Latino	13 (10.9)	6 (10.3)	5 (8.1)	11 (9.4)	11 (9.3)	33 (9.3)
Not Hispanic or Latino	106 (89.1)	52 (89.7)	57 (91.9)	106 (90.6)	107 (90.7)	322 (90.7)
Region, n (%)						
North America	115 (96.6)	55 (94.8)	62 (100)	115 (98.3)	111 (94.1)	343 (96.6)
Europe	4 (3.4)	3 (5.2)	0	2 (1.7)	7 (5.9)	12 (3.4)
Body Mass Index (kg/m <sup>2</sup> )						
n	119	58	62	117	118	355
Mean (SD)	33.1 (5.2)	34.1 (5.3)	33.4 (5.7)	33.3 (4.8)	32.9 (5.6)	33.3 (5.3)
Median	33.5	34.5	33.2	33.2	33.2	33.3
Range	13.6, 44.4	20.5, 45.0	21.8, 44.3	23.8, 45.4	21.4, 45.2	20.5, 45.4

Source: Study 14-003 Clinical Study Report, Table 7, page 77.

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Baseline CGI evaluations categorized most subjects as moderately or markedly ill. Across treatment groups, compliance with use of primary OSA therapy ranged from 68% to 73%. The baseline MWT mean sleep latency in minutes was 12.4 minutes for subjects randomized to placebo, and 12.6 minutes for subjects randomized to solriamfetol. Baseline mean ESS score was 15.6 for subjects randomized to placebo and 15.1 for subjects randomized to solriamfetol. The incidence of hypertension was highest in patients randomized to the solriamfetol 37.5 mg group (58.6%), compared to 50.4% in the placebo group and less than 50% in each of the other

solriamfetol dose groups. Baseline characteristics for the safety population are presented in Table 17.

**Table 17: Study 14-003, Baseline Characteristics, Safety Population**

Characteristic	Placebo (N=119)	Solriamfetol 37.5 mg (N=58)	Solriamfetol 75 mg (N=62)	Solriamfetol 150 mg (N=117)	Solriamfetol 300 mg (N=119)	Combined Solriamfetol (N=355)
Baseline Mean Sleep Latency Time (min), n	114	55	61	116	116	348
Mean (SD)	12.4 (7.2)	13.6 (8.1)	13.1 (7.2)	12.5 (7.2)	12.0 (7.4)	12.6 (7.4)
Baseline ESS Total Score, n	119	58	62	117	118	355
Mean (SD)	15.6 (3.3)	15.1 (3.5)	14.8 (3.5)	15.1 (3.4)	15.2 (3.1)	15.1 (3.3)
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)
Presence of Hypertension	60 (50.4)	34 (58.6)	30 (48.4)	56 (47.9)	53 (44.9)	173 (48.7)

Sources: Study 14-003 Clinical Study Report, Table 8, page 79, and Table 9, page 80.

## Treatment Compliance

Compliance with study drug was defined as:

$$100 * \frac{\text{total number of capsules dispensed} - \text{total number of capsules returned}}{\text{total number of capsules expected to be taken}}$$

Treatment compliance was high across all treatment groups. Mean overall compliance was 97.2%, with 88% of subjects receiving between 80% and 100% of study drug doses. Two subjects had calculated treatment compliance > 120% due to leaving the study without returning dispensed doses of study drug. One subject was withdrawn from the study due to a severe TEAE of streptococcal endocarditis, and the other subject failed to return after the Week 1 visit. Both subjects were excluded from the Per Protocol population.

## Efficacy Results - Primary Endpoint

*MWT*: solriamfetol improved maintenance of wakefulness at each dose as measured by increased duration of MWT sleep latency (in minutes) in OSA patients compared with placebo.

MWT mean sleep latency increased with solriamfetol dose. The least square (LS) mean differences in duration of sleep latency increased by 4.53 minutes ( $p = 0.0086$ ), 8.87 minutes ( $p < 0.0001$ ), 10.74 minutes ( $p < 0.0001$ ), and 12.77 minutes ( $p < 0.0001$ ) for each of the 37.5 mg, 75 mg, 150 mg, and 300 mg solriamfetol dose groups relative to placebo. Improvement in maintenance of wakefulness with solriamfetol relative to placebo was comparable in subjects compliant and noncompliant with their primary OSA therapy. The LS mean differences from baseline in comparison to placebo for both the compliant and noncompliant subgroups were numerically in favor of active treatment. See Table 18.

**Table 18: Study 14-003, Change in Mean Sleep Latency from Baseline, mITT Population**

Visit	Placebo (N = 114)	solriamfetol			
		37.5 mg (N = 56)	75 mg (N = 58)	150 mg (N = 116)	300 mg (N = 115)
<b>Baseline</b>					
n	111	54	57	115	113
Mean (SD)	12.6 (7.1)	13.6 (8.2)	12.4 (6.9)	12.5 (7.2)	12.1 (7.4)
<b>Week 12</b>					
n	100	49	54	105	93
Mean (SD)	13.4 (10.3)	18.6 (12.3)	21.8 (11.3)	23.6 (11.0)	25.3 (11.3)
LS Mean (SE)	0.2 (1.0)	4.7 (1.4)	9.1 (1.4)	11.0 (1.0)	13.0 (1.0)
LS Mean Difference	---	4.5	8.9	10.7	12.8
95% CI	---	(1.2, 7.9)	(5.6, 12.1)	(8.1, 13.4)	(10.0, 15.6)
p-value	---	0.0086	< 0.0001	< 0.0001	< 0.0001

*Adapted from Study 14-003 Clinical Study Report, Table 14, page 88.*

*ESS*: solriamfetol reduced sleepiness compared to placebo as measured by the ESS score in OSA patients. LS mean changes from Baseline to Week 12 were -3.3 for the placebo group and -5.1, -5.0, 07.7, and -7.9 for the 37.5 mg, 75 mg, 150 mg, and 300 mg solriamfetol groups, respectively. The LS mean changes from Baseline to Week 12 resulted in LS mean differences of -1.9 ( $p = 0.0161$ ), -1.7 ( $p = 0.0233$ ), -4.5 ( $p \leq 0.0001$ ), and -4.7 ( $p \leq 0.0001$ ) for 37.5 mg, 75 mg, 150 mg, and 300 mg solriamfetol relative to placebo, respectively. solriamfetol effects in reducing sleepiness compared to placebo were comparable in subjects compliant and those noncompliant with their primary OSA therapy. See Table 19.

**Table 19: Study 14-003, Change in ESS Scores, mITT Population**

Visit	Placebo (N = 114)	solriamfetol			
		37.5 mg (N = 56)	75 mg (N = 58)	150 mg (N = 116)	300 mg (N = 115)
<b>Baseline</b>					
n	114	56	58	116	115
Mean (SD)	15.6 (3.3)	15.1 (3.5)	15.0 (3.5)	15.1 (3.4)	15.1 (3.1)
<b>Week 12</b>					
n	102	49	54	106	94
Mean (SD)	12.2 (4.5)	9.7 (5.3)	10.0 (5.2)	7.5 (4.7)	7.1 (4.8)
LS Mean (SE)	-3.3 (0.5)	-5.1 (0.6)	-5.0 (0.6)	-7.7 (0.4)	-7.9 (0.5)
LS Mean Difference	---	-1.9	-1.7	-4.5	-4.7
95% CI	---	(-3.4, -0.3)	(-3.2, -0.2)	(-5.7, -3.2)	(-5.9, -3.4)
p-value	---	0.0161	0.0233	< 0.0001	< 0.0001

*Adapted from Study 14-003 Clinical Study Report, Table 15, page 89.*

The magnitude of the solriamfetol effect on wakefulness (MWT) and sleepiness (ESS) relative to placebo was durable over 12 weeks.

### **Efficacy Results – Secondary Endpoints**

*Improvement on the PGI-C (key secondary endpoint):* solriamfetol increased the percentage of OSA patients reporting improvement in their overall condition as measured by the PGI-C. Improvement in the PGI-C at Week 12 was reported for 49.1% of placebo subjects and 55.4%, 72.4%, 89.7%, and 88.7% of subjects in each of the 37.5 mg, 75 mg, 150 mg, and 300 mg solriamfetol dose groups, respectively. Percentage differences relative to placebo were 6.2% (p = 0.4447), 23.3% (p=0.0035), 40.5% (p<0.0001), and 39.6% (p<0.0001), respectively.

*Duration of effect, as measured by change in sleep latency over the course of a sequence of MWT trials:* The duration of MWT mean sleep latency was consistent and statistically significant relative to placebo through nine hours post-dose with daily dosing at 75 mg, 150 mg, and 300 mg solriamfetol.

*Percentage of subjects improved on the PGI-C:* The effect of solriamfetol on the PGI-C was observed early and was sustained through the course of the study. At each of Weeks 1, 4, and 8, the percentage of subjects reported as improved on the PGI-C was statistically significantly increased with solriamfetol dose relative to placebo for each of the 75 mg, 150 mg, and 300 mg dose groups.

*Percentage of subjects improved on the CGI-C:* solriamfetol increased the percentage of OSA patients for which their clinician reported improvement in their overall condition as measured using the CGI-C. Dose-related increases in the percentage of subjects with overall improvement

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on the CGI-C were observed with solriamfetol treatment relative to placebo at each of Weeks 1, 4, 8, and 12.

### **Efficacy Results – Functional Outcomes and Quality of Life Endpoints**

*FOSQ-10*: solriamfetol 150 mg and 300 mg showed dose-dependent improvements in patient-reported functioning and activities on the FOSQ-10.

*WPAI:SHP*: solriamfetol 150 mg and 300 mg had lower absenteeism and lower overall work impairment at Week 12 compared to placebo.

*SF-36v2*: Treatment with solriamfetol was associated with improvements in health-related quality of life as measured on the SF-36v2. solriamfetol 150 mg had the greatest impact on the SF-36v2 subscales with improvements on the Physical and Mental Component Summary Scales and on the Role Physical, General Health, Vitality, Social Functioning, and Role Emotional domains. solriamfetol 300 mg showed improvement relative to placebo on the Role Physical and Vitality domains and on the Physical Component Summary Scale of the SF-36v2.

*EuroQoL EQ-5D-5L*: solriamfetol had limited effects on the EuroQoL EQ-5D-5L.

### **Efficacy Results – Exploratory Endpoints**

*Use of primary OSA therapy*: No clinically meaningful change in the frequency of use of primary OSA therapy was observed with solriamfetol treatment.

*Change in PSG parameters*: No change in PSG parameters was observed. solriamfetol did not affect sleep architecture. No clinically significant changes were observed for TST, time in Stage N1, Stage N2, Stage N3, or WASO.

### **Data Quality and Integrity - Reviewers' Assessment**

The Office of Scientific Investigations inspected three sites participating in this study: Site #102 (enrolled 15 subjects), Site #111 (enrolled 22 subjects), and Site #164 (enrolled 21 subjects). For each site, the primary efficacy endpoint data were verifiable. For Site #164, OSI provided a finding of Voluntary Action Indicated due to failure to follow protocol in the randomization of a subject whose diastolic blood pressure at screening and at baseline met exclusionary criteria. OSI states that the principal investigator submitted a letter that adequately responded to the inspection finding. OSI felt that the isolated violation did not appear to impact the study outcome. The assessment of OSI was that the inspection results did not indicate the need for any regulatory action against any of the inspected sites.

### **Dose/Dose Response**

Dose response was demonstrated on both of the co-primary efficacy endpoints in this study. For the change in mean sleep latency on the MWT, the difference from placebo increased with increasing dose, with LS mean differences of 4.5, 8.9, 10.7, and 12.8 minutes for the 37.5 mg, 75 mg, 150 mg, and 300 mg solriamfetol doses, respectively (see Table 18). For the change in ESS score, the difference from placebo generally decreased with increasing dose, with LS mean differences of -1.9, -1.7, -4.5, and -4.7 points for the 37.5 mg, 75 mg, 150 mg, and 300 mg solriamfetol doses, respectively (see Table 19).

### **Durability of Response**

The ability of solriamfetol to improve wakefulness throughout the day relative to placebo was assessed in each of the five trials of the MWT at Week 12. At baseline, MWT mean sleep latency in minutes was similar across treatment groups at each of trials 1 through 5. At Week 12, for the 75 mg, 150 mg, and 300 mg solriamfetol dose groups, pairwise comparison to placebo showed statistically significant improvement of the MWT mean sleep latency in trials 1 through 5, spanning approximately nine hours following single dose administration. For the 37.5 mg solriamfetol group, improvement in MWT mean sleep latency relative to placebo was not statistically significant at the first MWT trial at Week 12, and no two consecutive trials showed statistically significant differences from placebo. However, the magnitude of change for the 37.5 mg dose was greater than that of the placebo group at each of the five MWT trials.

## **6.4. Study 14-004 (Indication: Obstructive Sleep Apnea)**

### **6.4.1. Study Design**

#### **Overview and Objective**

Study Title: "A six-week, double-blind, placebo-controlled, randomized-withdrawal, multicenter study of the safety and efficacy of solriamfetol [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the treatment of excessive sleepiness in subjects with obstructive sleep apnea (OSA)."

Primary Objective:

- To evaluate the efficacy of solriamfetol administered once daily (QD) compared to placebo in the treatment of excessive sleepiness in adult subjects with OSA.

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Secondary Objective:

- To evaluate the safety and tolerability of solriamfetol administered QD for up to six weeks in doses of 75 mg, 150 mg, and 300 mg compared to placebo in the treatment of excessive sleepiness in adult subjects with OSA.

**Trial Design**

Study Design Overview:

The study had four phases: a Screening phase, a Titration phase, a Stable-Dose phase, and a Double-Blind Withdrawal phase. Following screening (up to 28 days), subjects entered the two-week, open-label Titration Phase. Dosing started at solriamfetol 75 mg daily, and was titrated to identify the most efficacious and tolerable dose. The maximum dose studied was 300 mg daily. Subjects who were titrated to an efficacious and tolerable dose entered the two-week, open-label Stable-Dose phase, and remained on that dose.

Subjects who completed the Week 4 visit of the Stable-Dose phase were eligible to enter the two-week Double-Blind Withdrawal phase if they met the following criteria:

1. reported much or very much improvement on the Patient Global Impression of Change (PGI-C) scale;
2. showed a numerical improvement in mean sleep latency on the Maintenance of Wakefulness Test (MWT) from the beginning of the Titration phase to Week 4;
3. showed a numerical improvement in Epworth Sleepiness Scale (ESS) score from the beginning of the Titration phase to Week 4.

Subjects who did not meet these criteria were discontinued from the study.

Trial Location:

The trial was conducted at 34 study centers: 25 in the United States and nine in Europe (Finland, France, Germany, and Sweden).

Diagnostic Criteria:

Subjects had to have a documented diagnosis of obstructive sleep apnea according to criteria of the International Classification of Sleep Disorders, Third Edition (ICSD-3).

Key Inclusion Criteria:

1. Age between 18 and 75 years, inclusive.
2. Diagnosis of OSA according to ICSD-3 criteria.
3. At least minimal use of a primary therapy for OSA or an attempt to use a primary therapy for OSA, as evidenced by any one of the following:
  - a. Use of a primary therapy for OSA (positive airway pressure, oral pressure therapy, oral appliance, or upper airway stimulator) on at least one night per week;

- b. History of at least one month of an attempt to use one or more primary OSA therapies with at least one documented adjustment that was made in an attempt to optimize the primary OSA therapy;
  - c. History of a surgical intervention intended to treat OSA symptoms.
4. Stable level of compliance with a primary OSA therapy for at least one month prior to the Titration phase, as evidenced by any one of the following:
  - a. A stable level of use of a primary OSA therapy;
  - b. A lack of use of a primary OSA therapy following a history of attempted use;
  - c. A history of a surgical intervention intended to treat OSA symptoms.
5. Epworth Sleepiness Scale (ESS)  $\geq$  10 at the beginning of the Titration phase.
6. Baseline mean sleep latency  $<$  30 minutes, calculated as the mean of the first four test sessions of the MWT at the beginning of the Titration phase.
7. Usual nightly total sleep time (TST) of at least six hours.
8. Body mass index (BMI) of at least 18 kg/m<sup>2</sup> and less than 45 kg/m<sup>2</sup>.
9. Consent to use a medically acceptable method of contraception for at least two months prior to the first dose of study drug, throughout the entire study period, and for 30 days after the study is completed.

Key Exclusion Criteria:

1. Unwilling to attempt to use one or more primary OSA therapies.
2. Female subjects who are pregnant, nursing, or lactating.
3. Usual bedtime later than 1:00 am (0100 hours).
4. Occupation requiring nighttime or variable shift work.
5. Any other clinically relevant medical, behavioral, or psychiatric disorder other than OSA that is associated with excessive sleepiness.
6. History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria.
7. History or presence of any acutely unstable medical condition, behavioral or psychiatric disorder (including active suicidal ideation), or surgical history that could affect the safety of the subject or interfere with study efficacy or safety assessments or the ability of the subject to complete the trial per the judgment of the Investigator.
8. History of bariatric surgery within the past year or a history of any gastric bypass procedure.
9. Presence of renal impairment or calculated creatinine clearance  $<$  60 mL/min.
10. Clinically significant cardiovascular disease, electrocardiogram (ECG), or laboratory abnormality in the opinion of the Investigator.
11. Excessive caffeine use (defined as  $>$  600 mg caffeine per day) one week prior to Baseline assessments or anticipated excessive use during the study.
12. Use of any over-the-counter (OTC) or prescription medication that could affect the evaluation of excessive sleepiness within a time period prior to the Titration phase

corresponding to at least five half-lives of the drug, or planned use of such drugs at some point throughout the duration of the study. Medications should be discontinued such that the subject has returned to his/her baseline level of daytime sleepiness at least seven days prior to the Titration phase.

13. Received an investigational drug in the past 30 days or five half-lives (whichever is longer) prior to the Titration phase, or planned to use an investigational drug (other than the study drug) during the study.
14. Previous exposure to solriamfetol, or participation in a previous clinical trial of solriamfetol.
15. Current or past (within the past two years) diagnosis of a moderate or severe substance use disorder, or seeking treatment for a substance related disorder.
16. Urine drug screen positive for an illicit drug of abuse at screening or at any point throughout the duration of the study, except for a prescribed drug (e.g., amphetamine) at screening.
17. Nicotine dependence that has an effect on sleep (e.g., a subject who routinely awakens at night to smoke).
18. History of phenylketonuria or history of hypersensitivity to phenylalanine-derived products.

Study Treatments:

Study treatments were solriamfetol 75 mg, 150 mg, 300 mg, or placebo, administered daily by mouth.

Assignment to Treatment:

For the Double-Blind Withdrawal phase, randomization was stratified on the basis of subjects' compliant or noncompliant use of their primary OSA therapy. Subjects were assigned in a 1:1 ratio to continue solriamfetol at the dose received in the Stable-Dose phase or to receive placebo for two weeks.

Dose Modification or Discontinuation:

During the Titration phase, study drug dosing started at 75 mg daily and was titrated up once every three days, to either 150 mg daily or the maximum dose of 300 mg daily. Subjects could also be titrated down to 75 mg or 150 mg at any time following consultation with investigative site staff.

Procedures and Schedule:

The study phases and duration for each phase are presented in Table 20.

**Table 20: Study 14-004, Study Phases and Duration**

<b>Study Phase</b>	<b>Duration</b>
Screening	up to 28 days
Titration	two weeks
Stable-Dose	two weeks
Double-Blind Withdrawal	two weeks

At the conclusion of the Double-Blind Withdrawal phase (end of Week 6), subjects returned to the study site for a nocturnal polysomnogram (PSG) and MWT in addition to other efficacy and safety assessments. The final dose of study medication was taken prior to the initiation of the Week 6 MWT.

At the end of Week 8, two weeks after the final dose of study medication, subjects returned for follow-up safety assessments, and were then discharged from the study unless there were any outstanding safety issues that required further follow-up.

### **Study Endpoints**

#### Co-Primary Efficacy Endpoints:

1. *MWT*: Change in mean sleep latency time as determined from the first four test sessions of a 40-minute MWT from the end of the Stable-Dose phase (Week 4) to the end of the Double-Blind Withdrawal phase (Week 6).
2. *ESS*: Change in ESS score from the end of the Stable-Dose phase (Week 4) to the end of the Double-Blind Withdrawal phase (Week 6).

#### Key Secondary Endpoint:

- *PGI-C*: Percentage of subjects reported as worse (minimally, much, or very much) on the PGI-C at the end of the Double-Blind Withdrawal phase (Week 6).

#### Other Secondary Endpoints:

1. *CGI-C*: Percentage of subjects reported as worse (minimally, much, or very much) on the CGI-C at the end of the Double-Blind Withdrawal phase (Week 6).
2. *FOSQ-10*: Change in the total score from the beginning of the Titration phase (Day -1) to the end of the Stable-Dose phase (Week 4) and from the end of the Stable-Dose phase (Week 4) to the end of the Double-Blind Withdrawal phase (Week 6).

### **Statistical Analysis Plan**

For the analysis of the co-primary efficacy endpoints, an analysis of covariance (ANCOVA) model was used. This model included treatment group, the measurement at the end of Week 4,

and randomization stratification factor as fixed effects. The estimates of treatment difference versus placebo and their 95% confidence intervals (CIs) were presented. The last-observation carried forward (LOCF) approach was used for subjects who discontinued early in the Double-Blind Withdrawal phase. Estimates of the least squares (LS) mean treatment difference versus placebo and their 95% CIs were presented. Secondary analyses of the co-primary endpoints were performed using the same statistical method as the primary analysis based on the PP population. Sensitivity analyses, using the ANCOVA model with both a single imputation (SI) and a multiple imputation approach, were conducted to test the potential impact of missing data and to qualitatively evaluate the robustness of the primary analysis method.

For comparisons between solriamfetol and placebo, subjects who were randomized to continue solriamfetol in the Double-Blind Withdrawal phase were treated as a single group regardless of the dose of solriamfetol that they received. Thus, there were no multiplicity issues with respect to multiple doses in the hypothesis testing. A fixed sequential testing strategy was used to address the multiplicity issues in testing multiple endpoints.

For the primary analysis of the key secondary endpoint PGI-C, a comparison between combined solriamfetol and placebo was performed using a chi-square test and 95% CIs for the difference in proportions were calculated based on the mITT population. Missing data at Week 6 were imputed using LOCF. The secondary analysis of the PGI-C used the same statistical method as the primary analysis based on the PP population. In the sensitivity analyses for PGI-C, missing data at the end of the Double-Blind Withdrawal Phase (Week 6) were imputed using two SI approaches. The chi-squared test was used to test the hypotheses associated with the analysis of the secondary endpoint CGI-C. For the FOSQ-10 endpoints, an ANCOVA model similar to that used for the primary analysis was used.

## Protocol Amendments

*Original protocol date: December 17, 2014*

*Amendment #1: February 18, 2015*

- update to exposure data to include subjects from a Phase 1 human abuse liability study;
- update to the Introduction to include safety information on the number of patients who reported palpitations or chest pain or who had a T-wave inversion in study MDD-201;
- a new section, "End of Trial," to satisfy EU regulatory requirements on defining the end of the trial;
- a clarification was made that the Safety Follow-up Visit was not required for subjects who enrolled in the open-label safety study (14-005) at the final clinic visit;
- deletion of "documented aspermia" as a criterion for subjects whose method of contraception is vasectomy;
- updated descriptions of solriamfetol and placebo excipients;

- clarification of the use of vital signs measurements to meet entrance criteria;
- replacement of the C-SSRS version at the screening visit by the Baseline/Screening Version;
- revision of the pregnancy information section to clarify following of pregnant partners;
- for consistency across PSG assessments in the study it was clarified that subjects who are compliant with their PAP device use at the beginning of the study should use their PAP device for each PSG assessment and that subjects who use a PAP device, but who are not fully compliant, should decide with the investigator whether they will use their PAP device during all or none of the PSG assessments;
- the instructions for the collection of primary OSA therapy usage were revised to allow a subject who uses a PAP device for which usage data cannot be retrieved to report their primary OSA therapy usage and the estimated duration of use on a daily basis using the same diary-based method that subjects who do not use PAP therapy will employ.
- Changes to the exclusion criteria:
  - Exclusion Criterion #7 was revised to align with text in Section 6.9, which states that the presence of *active* suicidal ideation would exclude a subject from participation in the study.
  - In Exclusion Criterion #9, calculated creatinine clearance was changed from < 70 mL/min to < 60 mL/min to correspond with the standard categories of renal impairment.
  - In Exclusion Criterion #11, ondansetron, which has a known risk of torsade de pointes, was added to the list of excluded concomitant medications.
  - In Exclusion Criterion #12, systolic blood pressure level was changed from 140 mmHg to 150 mmHg, in response to FDA feedback to recruit a more inclusive patient population. In addition, blood pressure measures were clarified to indicate that the criterion applied when consistently observed across the multiple baseline measures.
  - Exclusion Criterion #15 was changed to specify that the use of excluded medications that might affect evaluation of excessive sleepiness should be discontinued such that the baseline level of symptoms is present for at least seven days prior to the baseline visit, because the baseline measures will assess these symptoms over the past seven days.

*Amendment #2: September 10, 2015*

- Changes to the inclusion criteria:
  - In Inclusion Criterion #1, the upper age limit was changed from 70 to 75 years old.
- Changes to the exclusion criteria:
  - Exclusion Criterion #7 was changed to limit subjects who had acutely unstable conditions vs. those with clinically significant conditions. Individuals who were unlikely to be able to complete the study were also excluded.

- Exclusion Criterion #12 was changed to exclude myocardial infarction and history of revascularization procedures if these occurred within the past year; to increase the blood pressure cutoff values from 150/90 mmHg to 155/95 mmHg; to exclude chronic ventricular arrhythmias (rather than all clinically significant arrhythmias); to exclude angina pectoris only if it is unstable; to exclude congestive heart failure specifically; and to remove the wording regarding exclusion of second or third degree heart block and clinically significant valvular disease, as these conditions were either already excluded in this criterion or addressed in another exclusion criterion.
- Information on the following of pregnancy in cases of live birth was made consistent with the Pregnant Partner Informed Consent Form.

*Amendment #3: February 8, 2016*

- Changes to inclusion criteria:
  - Inclusion Criterion #3 was changed to specify that primary OSA therapy may include oral pressure therapy or use of an upper airway stimulator, in addition to the already specified therapies of positive airway pressure and oral appliances.
  - In Inclusion Criterion #6, the upper limit of the eligible range of BMI was raised from  $< 40 \text{ kg/m}^2$  to  $< 45 \text{ kg/m}^2$  based on feedback from investigators in the United States who reported that the BMI cutoff of  $40 \text{ kg/m}^2$  was excluding otherwise healthy potential subjects. Obesity is a well-characterized comorbidity of the OSA population, and this change allowed the enrollment of a representative patient population with minimal change to risk of participation.
  - In Inclusion Criterion #6, the requirement for the baseline mean sleep latency, as documented by the mean of the first four test sessions of the MWT, was changed to  $< 30$  minutes because the criterion of  $\leq 20$  minutes was excluding subjects who were otherwise eligible and are representative of the OSA population with excessive daytime sleepiness.
- Changes to exclusion criteria:
  - Exclusion Criterion #8, which dealt with bariatric surgery, was clarified to state that a history of any gastric bypass procedure was exclusionary because of its potential to affect the absorption and PK of solriamfetol. Other bariatric surgery procedures, such as a gastric band procedure, are exclusionary only if performed within the past year.
  - Cardiac Exclusion Criteria #10, #11, and #12 were changed as follows:
    - A thorough QT/QTc (TQT) study with solriamfetol had not been completed when Study 14-004 was initiated; therefore, as a precaution, subjects with a history or presence of a risk factor for torsade de pointes (Exclusion Criterion #10) and subjects who used and could not safely discontinue medication with known risk for torsade de pointes (Exclusion Criterion #11) were excluded from this study. However, the findings from

the completed TQT Study 15-002 showed no QTcF prolongation reaching the threshold of regulatory concerns with solriamfetol at the proposed therapeutic dose of 300 mg or at the suprathreshold dose of 900 mg. Therefore, Exclusion Criterion #10 was changed to exclude only subjects with a clinically significant ECG abnormality, and Exclusion Criterion #11 was removed (no changes were made in the extent or frequency of assessments of cardiovascular safety).

- Exclusion Criterion #12 was revised to more clearly specify which types of congestive heart failure and cardiac arrhythmias were excluded.
- Rescreening of subjects who had not met previous eligibility requirements, but who were likely to meet the revised eligibility requirements, was not addressed in the protocol. This amendment clarified that those subjects would be allowed to be rescreened with approval by the Medical Monitor.
- The statistical analyses described in the protocol were updated to incorporate feedback from the FDA about the previously planned analyses.
- The length of time during which screening labs could be repeated was extended.

### **Country-Specific Amendments**

Amendments 2FR, 3FR, 4FR, 5FR, and 6FR were country-specific amendments that applied only to clinical sites in France.

#### *Amendment 2FR: August 17, 2015*

- added a safety follow-up phone contact for further assessment of adverse events after discontinuation of study drug;
- added further specifications to Inclusion Criterion #1 (affiliation with a Social Security regime) and Inclusion Criterion #11 (that a subject not be a vulnerable person or legally protected adult);
- added the exclusion of individuals with a current or past diagnosis of mild substance use disorder, in addition to individuals with moderate or severe substance use disorders.

#### *Amendment 3FR: October 9, 2015*

- consisted of the changes specified in Amendment #2 (September 10, 2015).

#### *Amendment 4FR: December 1, 2015*

- changed the time for following a live birth as the outcome of pregnancy during the study from six months to a minimum of six months.

#### *Amendment 5FR: March 11, 2016*

- consisted of the changes specified in Amendment #3 (February 8, 2016)

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*Amendment 6FR: June 1, 2016*

added three drugs to the list of drugs included in the urine drug screen in Table 1 of the protocol: buprenorphine, 3,4-methylenedioxymethamphetamine, and nortriptyline. Although urine drug screening for these drugs was not required by the protocol, the testing kit being used at the sites did screen for those substances. The addition of these drugs to the list of laboratory tests did not change the conduct of the trial.

**Data Quality and Integrity: Sponsor's Assurance**

Steps to assure the accuracy and reliability of data included the selection of qualified investigators and an appropriate study site, review of protocol procedures with the investigator and associated personnel prior to the study, and periodic monitoring visits by Jazz Pharmaceuticals or its designee. Data were reviewed for accuracy and completeness by Jazz Pharmaceuticals or its designee during and after onsite monitoring visits, and any discrepancies were resolved with the investigator or designees as appropriate. Quality control audits could be performed at the discretion of the Sponsor. Electronic CRFs (eCRFs) were used for the recording of all trial data not recorded in subject diaries, obtained by ECG recording, or generated by laboratory report. The principal investigator reviewed the eCRFs and provided his signature certifying that he reviewed the data and considered the data accurate to the best of his knowledge and provided his signature certifying that he reviewed the data and considered the data accurate to the best of his knowledge. A comprehensive Data Management Plan was developed. A central laboratory ( (b)(4) ) reviewed all sleep study data.

*Reporting of Serum Direct Bilirubin Values*

A technical issue was identified regarding serum direct bilirubin values reported from laboratory testing. Between January 2, 2016 and November 21, 2016, serum direct bilirubin values levels assayed by (b)(4) for this study were assigned a positive proportional bias due to a calibrator issue (calibrator manufactured by Siemens Healthcare Diagnostics). Calibrator values were reassigned by the manufacturer and were placed into effect by (b)(4) as of November 21, 2016. (b)(4) conducted an internal correlation between results obtained using the old calibrator set point and the new reassigned calibrator set point. A positive shift in direct bilirubin results was observed that was proportional in nature. An average bias of 30% was seen when direct bilirubin was more than three times the upper limit of normal (ULN). Differences for results that were in the normal range and up to three times the ULN were within the total allowable error of the assay. Siemens estimated the average bias to be approximately 40%. A correction factor could not be provided and previously tested samples could not be re-assayed. Results from 332 samples collected from 146 subjects during the affected period are in the clinical database uncorrected. Upon analysis by Jazz and (b)(4) (CRO) of the direct bilirubin outliers, the clinical significance of the positive bias was considered to be minimal.

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## 6.4.2. Study Results

### Compliance with Good Clinical Practices

The Clinical Study Report for Study 14-004, Section 9.6.1, Study Administration and Conduct (page 47), states: “The study was conducted according to GCP guidelines and according to national law.” Section 9.6.2, Data Generation and Analysis, (page 47) states: “The standard procedures for handling and processing records were followed in compliance with 21 CFR 11, Good Clinical Practices, ICH Guidelines, and the Standard Operating Procedures of Jazz Pharmaceuticals or the CRO ( (b) (4) ).”

### Financial Disclosure

Financial disclosures for each of the five pivotal trials under this NDA were reviewed at the time the NDA was filed. For Study 14-004, (b) (6) . See Appendix 13.2 for details.

### Patient Disposition

174 subjects were enrolled in the study. Of these, 124 were randomized into the Double-Blind Withdrawal phase and comprised the Safety population for that phase. Two of these subjects prematurely discontinued the study and did not have a post-efficacy baseline observation to be considered for LOCF. The remaining 122 subjects comprised the modified intent-to-treat (mITT) population. The most frequent reason for withdrawal from the Titration phase was MWT criteria not met. This occurred in seven subjects and was related to a discrepancy between site and central scoring of the MWT leading to enrollment of some subjects who did not meet the protocol-defined MWT criteria at baseline. One subject who did not meet Inclusion Criterion #6 was randomized in error. Details of patient disposition for the Safety Population are presented in Table 21 (Titration and Stable-Dose Phases) and Table 22 (Double-Blind Randomized Withdrawal Period).

**Table 21: Study 14-004, Patient Disposition, Titration and Stable-Dose Phases, Safety Population**

Completed Phase, n (%)	Titration Phase				Stable-Dose Phase			
	75 mg (N=28)	150 mg (N=52)	300 mg (N=94)	All (N=174)	75 mg (N=23)	150 mg (N=50)	300 mg (N=84)	All (N=157)
Yes	23 (82.1)	47 (90.4)	88 (93.6)	158 (90.8)	23 (100)	48 (96.0)	77 (91.7)	148 (94.3)
Yes, but Early Termination Before Next Phase	0	1 (1.9)	0	1 (0.6)	5 (21.7)	8 (16.0)	11 (13.1)	24 (15.3)
Protocol Violation	0	0	0	0	0	1 (2.0)	0	1 (0.6)
Adverse Event	0	0	0	0	0	1 (2.0)	0	1 (.06)
Withdrawal of Consent	0	0	0	0	0	1 (2.0)	0	1 (0.6)
Other	0	0	0	0	1 (4.3)	0	0	1 (0.6)
Randomization Criteria Not Met								
Not Much or Not Very Much Improved on PGI-C					3 (13.0)	4 (8.0)	10 (11.9)	17 (10.8)
No Improvement on MWT					1 (4.3)	2 (4.0)	1 (1.2)	4 (2.5)
No Improvement on ESS					1 (4.3)	1 (2.0)	3 (3.6)	5 (3.2)
No	5 (17.9)	5 (9.6)	6 (6.4)	16 (9.2)	0	2 (4.0)	7 (8.3)	9 (5.7)
If No, Primary Reason, n (%)								
Lack of Efficacy	0	0	0	0	0	0	1 (1.2)	1 (0.6)
Protocol Violation	0	0	1 (1.1)	1 (0.6)	0	0	0	0
Adverse Event	0	3 (5.8)	2 (2.1)	5 (2.9)	0	0	0	0
Withdrawal by Subject	1 (3.6)	0	0	1 (0.6)	0	0	3 (3.6)	3 (1.9)
Lost to Follow-up	0	0	1 (1.1)	1 (0.6)	0	2 (4.0)	1 (1.2)	3 (1.9)
Treatment Non-Compliant	1 (3.6)	0	0	1 (0.6)	0	0	0	0
Diary Non-Compliant	0	0	0	0	0	0	0	0
Sponsor Decision	0	0	0	0	0	0	1 (1.2)	1 (0.6)
Investigator Decision	0	0	0	0	0	0	0	0
Other <sup>a</sup>	3 (10.7)	2 (3.8)	2 (2.1)	7 (4.0)	0	0	0	0

<sup>a</sup> Subjects did not meet criteria for MWT (due to a discrepancy between site and central scoring of MWT).

Source: Study 14-004 Clinical Study Report, Table 14.1.2.1a, page 171.

**Table 22: Study 14-004, Patient Disposition, Double-Blind Randomized Withdrawal Period, Safety Population**

	Placebo (N=62)	Solriamfetol 75 mg (N=9)	Solriamfetol 150 mg (N=26)	Solriamfetol 300 mg (N=27)	Combined Solriamfetol (N=62)
Completed Phase, n (%)					
Yes	62 (100)	9 (100)	25 (96.2)	26 (96.3)	60 (96.8)
No	0	0	1 (3.8)	1 (3.7)	2 (3.2)
If No, Primary Reason, n (%)					
Withdrawal by Subject	0	0	1 (3.8)	0	1 (1.6)
Failure to Meet Randomization Criteria <sup>a</sup>	0	0	0	1 (3.7)	1 (1.6)

<sup>a</sup> Subject randomized in error; did not meet Inclusion Criterion #6.

Source: Study 14-004 Clinical Study Report, Table 14.1.2.1b, page 176.

### Protocol Violations/Deviations

Major protocol deviations in the Safety Population were recorded for 28 subjects (16.1%) in the Titration phase, eight subjects (5.1%) in the Stable-Dose phase, and six subjects in the Double-

Blind Withdrawal phase: two (3.2%) in the placebo group and four (6.5%) in the solriamfetol groups. The most common deviations were in dosing, enrollment criteria, and informed consent. Protocol deviations for the Safety Population are presented in Table 23 (Titration and Stable-Dose Phases) and Table 24 (Double-Blind Randomized Withdrawal Period).

**Table 23: Study 14-004, Protocol Deviations, Titration and Stable-Dose Phases**

Deviation Category, n (%)	Titration Phase				Stable-Dose Phase			
	75 mg (N=28)	150 mg (N=52)	300 mg (N=94)	All (N=174)	75 mg (N=23)	150 mg (N=50)	300 mg (N=84)	All (N=157)
Any Major Protocol Deviation	8 (28.6)	7 (13.5)	13 (13.8)	28 (16.1)	1 (4.3)	5 (10.0)	2 (2.4)	8 (5.1)
Concomitant Medications	0	0	1 (1.1)	1 (0.6)	0	0	0	0
Dosing	4 (14.3)	3 (5.8)	9 (9.6)	16 (9.2)	0	0	0	0
Enrollment Criteria	3 (10.7)	2 (3.8)	4 (4.3)	9 (5.2)	1 (4.3)	4 (8.0)	1 (1.2)	6 (3.8)
Informed Consent	2 (7.1)	2 (3.8)	2 (2.1)	6 (3.4)	0	0	0	0
Visit Schedule	0	1 (1.9)	0	1 (0.6)	0	0	0	0
Visit/Procedure Required	0	0	1 (1.1)	1 (0.6)	0	1 (2.0)	0	1 (0.6)
Other	3 (10.7)	1 (1.9)	0	4 (2.3)	0	1 (2.0)	1 (1.2)	2 (1.3)

Percentages are subject incidences. A subject can have multiple protocol deviations.

Source: Study 14-004 Clinical Study Report, Table 14.1.4.1a, page 190.

**Table 24: Study 14-004, Protocol Deviations, Double-Blind Randomized Withdrawal Period**

Deviation Category, n (%)	Placebo (N=62)	Solriamfetol 75 mg (N=9)	Solriamfetol 150 mg (N=26)	Solriamfetol 300 mg (N=27)	Combined Solriamfetol (N=62)
Any Major Protocol Deviation	2 (3.2)	1 (11.1)	0	3 (11.1)	4 (6.5)
Dosing	1 (1.6)	0	0	0	0
Enrollment Criteria	0	0	0	1 (3.7)	1 (1.6)
Informed Consent	1 (1.6)	1 (11.1)	0	2 (7.4)	3 (4.8)

Percentages are subject incidences. A subject can have multiple protocol deviations.

Source: Study 14-004 Clinical Study Report, Table 14.1.4.1b, page 191.

### Table of Demographic Characteristics

For the Safety Population randomized to the Double-Blind Randomized Withdrawal Period, the majority of subjects were white, male, and located in North America. Mean age was 56 years, and mean BMI was 33 kg/m<sup>2</sup>. Demographics of the Safety Population randomized to the Randomized Withdrawal Period are presented in Table 25.

**Table 25: Study 14-004, Patient Demographics, Double-Blind Randomized Withdrawal Period, Safety Population**

Characteristic	Placebo (N=62)	Solriamfetol 75 mg (N=9)	Solriamfetol 150 mg (N=26)	Solriamfetol 300 mg (N=27)	Combined Solriamfetol (N=62)
<b>Age (years)</b>					
n	62	9	26	27	62
Mean (SD)	56.2 (9.8)	59.9 (12.0)	57.8 (10.6)	53.6 (11.7)	56.3 (11.4)
Median	59	62	59	56	58
Range	30, 72	35, 72	38, 74	30, 74	30, 74
<b>Sex, n (%)</b>					
Male	41 (66.1)	4 (44.4)	15 (57.7)	17 (63.0)	36 (58.1)
Female	21 (33.9)	5 (55.6)	11 (42.3)	10 (37.0)	26 (41.9)
<b>Race, n (%)</b>					
American Indian or Alaska Native	0	0	0	0	0
Asian	2 (3.2)	0	0	0	0
Black or African American	15 (24.2)	3 (33.3)	5 (19.2)	4 (14.8)	12 (19.4)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
White	45 (72.6)	6 (66.7)	21 (80.8)	23 (84.2)	50 (80.6)
Other	0	0	0	0	0
Multiple	0	0	0	0	0
<b>Ethnicity, n (%)</b>					
Hispanic or Latino	4 (6.5)	2 (22.2)	4 (15.4)	3 (11.1)	9 (14.5)
Not Hispanic or Latino	58 (93.5)	7 (77.8)	22 (84.6)	24 (88.9)	53 (85.5)
<b>Region, n (%)</b>					
North America	51 (82.3)	7 (77.8)	23 (88.5)	20 (74.1)	50 (80.6)
Europe	11 (17.7)	2 (22.2)	3 (11.5)	7 (25.9)	12 (19.4)
<b>Country, n (%)</b>					
USA	51 (82.3)	7 (77.8)	23 (88.5)	20 (74.1)	50 (80.6)
Canada	0	0	0	0	0
France	1 (1.6)	0	0	0	0
Germany	1 (1.6)	0	2 (7.7)	0	2 (3.2)
Finland	8 (12.9)	1 (11.1)	0	6 (22.2)	7 (11.3)
Sweden	1 (1.6)	1 (11.1)	1 (3.8)	1 (3.7)	3 (4.8)
<b>Body Mass Index (kg/m<sup>2</sup>)</b>					
n	62	9	26	27	62
Mean (SD)	33.3 (5.5)	34.0 (4.6)	32.1 (5.0)	33.3 (5.2)	32.9 (5.0)
Median	32.7	36.3	32.2	34.7	33.1
Range	22.0, 44.4	26.4, 38.5	23.2, 43.1	24.5, 42.2	23.2, 43.1

Source: Study 14-004 Clinical Study Report, Table 14.1.5.1b, page 202.

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Baseline characteristics were similar across solriamfetol treatment groups and between the solriamfetol groups and the placebo group. The majority of subjects were classified as either moderately ill or markedly ill on the CGI. Baseline disease characteristics are presented in Table 26.

**Table 26: Study 14-004, Baseline Characteristics, Safety Population**

	Titration Phase, Combined Solriamfetol (N=174)	Stable-Dose Phase, Combined Solriamfetol (N=157)	Double-Blind Withdrawal Phase	
			Placebo (N=62)	Combined Solriamfetol (N=62)
Baseline Mean Sleep Latency Time (min)				
n	171	157	62	62
Mean (SD)	13.2 (7.5)	12.9 (7.1)	12.3 (7.9)	13.0 (6.7)
Median	11.4	11.1	9.7	11.0
Range	1.1, 40.0	1.1, 31.0	1.1, 28.1	2.5, 31.0
Baseline ESS Total Score				
n	174	157	62	62
Mean (SD)	15.4 (3.4)	15.5 (3.5)	16.0 (3.5)	15.3 (3.5)
Median	15.0	15.0	16.0	15.0
Range	10, 23	10, 23	10, 23	10, 23
Baseline CGIs, n (%)				
1=Normal, not at all ill	0	0	0	0
2=Borderline ill	6 (3.4)	6 (3.8)	3 (4.8)	2 (3.2)
3=Mildly ill	21 (12.1)	18 (11.5)	7 (11.3)	6 (9.7)
4=Moderately ill	71 (40.8)	61 (38.9)	23 (37.1)	23 (37.1)
5=Markedly ill	43 (24.7)	41 (26.1)	15 (24.2)	20 (32.3)
6=Severely ill	28 (16.1)	26 (16.6)	11 (17.7)	10 (16.1)
7=Among the most extremely ill patients	5 (2.9)	5 (3.2)	3 (4.8)	1 (1.6)

Source: Study 14-004 Clinical Study Report, Table 7, page 71.

The medical conditions reported most frequently in the histories of study subjects were hypertension, gastroesophageal reflux disease, obesity, and depression. The medical conditions reported by at least 10% of subjects in the Safety Population are presented in Table 27.

**Table 27: Study 14-004, Medical History, Conditions Reported by ≥ 10% of Subjects, Safety Population**

System Organ Class Preferred Term, n (%)	Titration Phase, Combined Solriamfetol (N=174)	Stable-Dose Phase, Combined Solriamfetol (N=157)	Double-Blind Withdrawal Phase	
			Placebo (N=62)	Combined Solriamfetol (N=62)
Hypertension	72 (41.4)	66 (42.0)	28 (45.2)	28 (45.2)
Gastroesophageal reflux disease	36 (20.7)	35 (22.3)	14 (22.6)	9 (14.5)
Obesity	34 (19.5)	27 (17.2)	13 (21.0)	11 (17.7)
Depression	33 (19.0)	30 (19.1)	14 (22.6)	9 (14.5)
Seasonal allergy	32 (18.4)	30 (19.1)	12 (19.4)	12 (19.4)
Osteoarthritis	30 (17.2)	27 (17.2)	10 (16.1)	11 (17.7)
Hyperlipidemia	27 (15.5)	24 (15.3)	9 (14.5)	9 (14.5)
Type 2 diabetes	26 (14.9)	24 (15.3)	7 (11.3)	9 (14.5)
Hypercholesterolaemia	25 (14.4)	24 (15.3)	7 (11.3)	10 (16.1)
Drug hypersensitivity	23 (13.2)	23 (14.6)	9 (14.5)	9 (14.5)
Anxiety	22 (12.6)	20 (12.7)	5 (8.1)	10 (16.1)
Hysterectomy	21 (12.1)	20 (12.7)	5 (8.1)	9 (14.5)
Hypothyroidism	20 (11.5)	17 (10.8)	5 (8.1)	9 (14.5)
Tonsillectomy	20 (11.5)	8 (9.5)	6 (9.7)	7 (11.3)

Source: Study 14-004 Clinical Study Report, Table 9, page 74.

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance with study drug was defined as:

$$100 * \frac{\text{total number of capsules dispensed} - \text{total number of capsules returned}}{\text{total number of capsules expected to be taken}}$$

Three subjects with compliance rates < 70% discontinued from the study; one due to her personal schedule (overall compliance 60%), one who was mistakenly randomized into the Double-Blind Withdrawal Phase (overall compliance 53%), and one who was lost to follow-up (overall compliance 37%).

Two subjects had compliance rates > 120%. For one subject, an error was found in the drug return log. It was determined that the subject had been compliant, but the compliance data in the study was not corrected because the error was found after the database lock. For the other subject, it was found that the subject did not meet the enrollment criterion for mean sleep latency. The site was advised to discontinue the subject, but the subject continued to take study drug for two days. The subject was then withdrawn from the study. For both of these subjects, dosing was considered a major protocol deviation.

Treatment compliance by study phase is presented in Table 28.

**Table 28: Study 14-004, Treatment Compliance by Study Phase, Safety Population**

	Titration Phase, Combined Solriamfetol (N=174)	Stable-Dose Phase, Combined Solriamfetol (N=157)	Double-Blind Withdrawal Phase	
			Placebo (N=62)	Combined Solriamfetol (N=62)
Compliance (%)				
n	169	152	61	62
Mean (SD)	97.8 (10.1)	98.0 (10.7)	99.8 (3.9)	98.6 (5.7)
Median	100	100	100	100
Range	35.3, 142.9	35.3, 154.5	85.7, 115.4	73.3, 114.3
Compliance Category, n (%)				
< 80%	5 (3.0)	7 (4.6)	0	1 (1.6)
80% - 100%	158 (93.5)	132 (86.8)	57 (93.4)	57 (91.9)
> 100%	6 (3.6)	13 (8.6)	4 (6.6)	4 (6.5)
> 120%	2 (1.2)	2 (1.3)	0	0

Source: Study 14-004 Clinical Study Report, Table 12, page 80.

### Efficacy Results – Co-Primary Endpoints

Subjects who continued receiving solriamfetol in the randomized withdrawal period maintained the treatment benefits observed at Week 4, with little change in MWT mean sleep latency (-0.96 (SE 1.350) minutes) and minimal change in EES score (-0.1 (SE 0.73)). In contrast, the placebo group showed a mean reduction of 12.11 (SE 1.316) minutes in mean sleep latency and a 4.5 (SE 0.71) increase in ESS score at Week 6. The difference between the solriamfetol group and the placebo group was statistically significant ( $p \leq 0.0001$ ) for both endpoints. See Table 29.

**Table 29: Study 14-004, Change in MWT Mean Sleep Latency and ESS Score from Beginning to End of Randomized Withdrawal Period**

	MWT Mean Sleep Latency		ESS Score	
	Placebo (N = 62)	Combined solriamfetol (N = 60)	Placebo (N = 62)	Combined solriamfetol (N = 60)
<b>Week 4 (Efficacy Baseline)</b>				
n	60	59	62	60
Mean (SD)	29.0 (9.9)	31.7 (9.2)	5.9 (3.8)	6.4 (4.4)
<b>Week 6 (End of Rand Withdrawal)</b>				
n	61	58	62	60
Mean (SD)	17.6 (10.7)	29.7 (9.9)	10.8 (5.3)	6.4 (5.1)
LS Mean (SE)	-12.1 (1.3)	-1.0 (1.4)	4.5 (0.7)	-0.1 (0.7)
LS Mean Difference	---	11.2	---	-4.6
95% CI	---	(7.8, 14.6)	---	(-6.4, -2.8)
p-value	---	< 0.0001	---	< 0.0001

*Adapted from Study 14-004 Clinical Study Report, Table 15, page 83; Table 14.2.1.2.1, page 502; and Table 14.2.2.2.1, page 583.*

### **Efficacy Results – Key Secondary Endpoint**

On the PIGc, a higher percentage of subjects in the placebo group rated their condition as worse compared to subjects in the solriamfetol group (50% vs. 20%, respectively), resulting in a LS mean difference of -30.0 ( $p = 0.0005$ ).

### **Efficacy Results – Other Secondary Endpoints**

On the CGI-C, a greater percentage of subjects in the Placebo group had their condition rated as worse by the clinician at the end of the two-week randomized withdrawal period compared to solriamfetol subjects. The difference was statistically significant in favor of the solriamfetol group ( $p < 0.0001$ ).

On the FOSQ-10, there was a statistically significant difference between solriamfetol and placebo at Week 6, with poorer functioning in the placebo group at the end of the two-week randomized withdrawal period ( $p = 0.02$ ).

### **Dose/Dose Response**

Dose response was not explicitly assessed in this study. Each subject was individually titrated to identify the most efficacious and tolerable dose for that subject.

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## **Durability of Response**

Maintenance of effect for patients with OSA was demonstrated. Following four weeks of open-label, subjects were randomized to either placebo or continued treatment with solriamfetol. Subjects randomized to placebo showed a decline in wakefulness on the MWT, greater subjective sleepiness on the ESS, and evaluation of their overall condition as worsened on the PGI-C compared with subjects who continued solriamfetol.

## **6.5. Study 14-005 (Indications: Narcolepsy and Obstructive Sleep Apnea)**

### **6.5.1. Study Design**

#### **Overview and Objective**

Study Title: “A long-term safety and maintenance of efficacy study of solriamfetol [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the treatment of excessive sleepiness in subjects with narcolepsy or obstructive sleep apnea.”

#### Primary Objective of Overall Study:

- To evaluate the safety and tolerability of solriamfetol administered once daily (QD) for up to 52 weeks in doses of 75 mg, 150 mg, and 300 mg.

#### Primary Objective of Randomized Withdrawal Period:

- To evaluate the maintenance of efficacy of solriamfetol compared to placebo in the treatment of excessive sleepiness in adult subjects with narcolepsy or obstructive sleep apnea (OSA) after at least 26 weeks of daily administration of solriamfetol.

#### Key Secondary Objective:

- To evaluate the maintenance of efficacy of open-label solriamfetol administered QD for up to 52 weeks in doses of 75 mg, 150 mg, and 300 mg in the treatment of excessive sleepiness in adult subjects with narcolepsy or OSA.

#### Additional Secondary Objective:

- To evaluate the safety and tolerability of solriamfetol compared to placebo during the Randomized Withdrawal Period in the Maintenance Phase.

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## **Trial Design**

### Study Design Overview:

Subjects were recruited from among subjects who had completed a previous study of solriamfetol for treatment of either narcolepsy or OSA. The study consisted of a two-week Titration phase for all subjects, followed by a Maintenance phase of 38 weeks for subjects who completed Study 14-002 or 14-003 (Group A) or 50 weeks for subjects who completed Study 14-004, 15-004, 15-005, ADX-N05-201, or ADX-N05-202 (Group B).

During the Titration phase, subjects began treatment with solriamfetol 75 mg QD. Following a telephone consultation with site staff, they could then titrate up one dose level once every three days, to a maximum dose of 300 mg/day. Subjects could also titrate down to 75 mg or 150 mg. Investigators were instructed to titrate subjects to the maximal dose that was tolerated. After the Titration phase, subjects entered the Maintenance phase at the stable dose that was reached at the end of the Titration phase.

In the Maintenance phase, only three dose adjustments (to doses of 75 mg, 150 mg, or 300 mg daily) were allowed during the first 12 weeks of that phase, after which no further dose adjustments were permitted. If the dose could not be successfully adjusted within these parameters, the subject discontinued treatment and was withdrawn from the study.

During the Maintenance phase, a two-weeks 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 randomized in a 1:1 ratio to continue to receive solriamfetol at the dose they were currently receiving or to receive placebo for two weeks. At the end of the Randomized Withdrawal period, subjects resumed solriamfetol treatment at the same dose they had received at the beginning of the Randomized Withdrawal period for the remainder of the study. After completion of the Maintenance phase, all subjects entered a two-week Safety Follow-Up period.

### Trial Location:

The study was conducted at 79 study centers; 63 in North America and 16 in Europe.

### Diagnostic Criteria:

Subjects who had completed Study 14-002, 14-003, 14-004, 15-004, 15-005, ADX-N05-201, or ADX-N05-202 and met the screening criteria were eligible to enroll.

### Key Inclusion Criteria:

1. Subject met one of the following:
  - a. Completed Study 14-002 or 14-003 (Group A);

- b. Completed Study 14-004, 15-004, 15-005, ADX-N05-201, or ADX-N05-202 (Group B)
2. Subject would be able, in the opinion of the investigator, to take solriamfetol for 40 weeks if continuing from Group A, or for 52 weeks if continuing from Group B, and would be able to complete all tests and visits.
3. Usual nightly total sleep time of at least six hours.
4. Body mass index (BMI) of at least 18 kg/m<sup>2</sup> and less than 45 kg/m<sup>2</sup>.
5. Willing to use a medically acceptable method of contraception for at least two months prior to the first dose of study drug, throughout the entire study period, and for 30 days after completion of the study.

Key Exclusion Criteria:

1. Female subjects who were pregnant, nursing, or lactating.
2. Usual bedtime later than 1:00 AM (0100 hours).
3. Occupation requiring nighttime or variable shift work.
4. Experienced any serious adverse event (SAE) in a previous study that was deemed related to solriamfetol, or experienced an adverse event (AE) in a previous study that might prevent him/her from safely participating in and completing the current study.
5. Any other clinically relevant medical, behavioral, or psychiatric disorder other than narcolepsy or OSA that is associated with excessive sleepiness.
6. History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria.
7. History or presence of any acutely unstable medical condition, behavioral or psychiatric disorder (including active suicidal ideation), or surgical history that could affect the safety of the subject or interfere with study efficacy or safety assessments or the ability of the subject to complete the trial per the judgment of the Investigator.
8. History of bariatric surgery within the past year or a history of any gastric bypass procedure.
9. Presence of renal impairment or calculated creatinine clearance < 60 mL/min.
10. Clinically significant cardiovascular disease, electrocardiogram (ECG), or laboratory abnormality in the opinion of the Investigator.
11. Excessive caffeine use (defined as > 600 mg caffeine per day) one week prior to Baseline visit or anticipated excessive use during the study.
12. Received an investigational drug other than solriamfetol in the past 30 days or five half-lives (whichever is longer) before the Baseline visit, or planned to use an investigational drug (other than the study drug) during the study.
13. Current or past (within the past two years) diagnosis of a moderate or severe substance use disorder, or seeking treatment for a substance related disorder.
14. Nicotine dependence that has an effect on sleep (e.g., subject routinely awakens at night to smoke).

15. Urine drug screen positive for an illicit drug of abuse at screening or at any point throughout the duration of the study, except for a prescribed drug (e.g., amphetamine) at screening.
16. History of phenylketonuria or history of hypersensitivity to phenylalanine-derived products.
17. Use of other medications affecting sleep:
  - a. Group A: Planned use of any OTC or prescription medications that could affect the evaluation of excessive sleepiness at any time during the study.
  - b. Group B: Use of any 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 five half-lives of the drug(s) or planned use of such drugs(s) at some point throughout the duration of the study. Medications were to be discontinued such that the subject had returned to his/her baseline level of daytime sleepiness at least seven days prior to the Baseline visit, in the opinion of the investigator.

Study Treatments:

Subjects all entered Study 14-005 from a previous study, and were continued on the dose of study drug that they were taking at the end of the previous study.

Prohibited Concurrent Medications:

- Monoamine oxidase inhibitors (MAOIs)
- Medications that could affect the evaluation of excessive sleepiness. Examples:
  - OTC sleep aids or stimulants
  - pseudoephedrine
  - methylphenidate
  - amphetamines
  - modafinil
  - armodafinil
  - sodium oxybate
  - pemoline
  - trazodone
  - hypnotics
  - benzodiazepines
  - barbiturates
  - opioids

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### **Study Endpoints: Randomized Withdrawal Period**

#### Randomized Withdrawal: Primary Efficacy Endpoint

- Change in Epworth Sleepiness Scale (ESS) score from the beginning to the end of the two-week Randomized Withdrawal Period

#### Randomized Withdrawal: Secondary Endpoints

- Patient Global Impression of Change (PGI-C) at the end of the two-week Randomized Withdrawal Period
- Clinical Global Impression of Change (CGI-C) at the end of the two-week Randomized Withdrawal Period

#### Randomized Withdrawal: Other Endpoints

- Functional Outcomes of Sleep Questionnaire Short Version (FOSQ-10) at the end of the Randomized Withdrawal Period
- Compliance with primary OSA therapy during the Randomized Withdrawal Period

### **Study Endpoints: Open-Label Phase**

#### Open-Label Phase: Efficacy Endpoints

- Change in ESS score over time
- Percentage of subjects assessed by the investigator as improved (minimally, much, or very much) on the CGI-C
- Percentage of subjects reported as improved (minimally, much, or very much) on the PGI-C

#### Open-Label Phase: Functional Outcome and Quality of Life Endpoints

- FOSQ-10
- 36-Item Short Form Health Survey Version 2 (SF-36v2)
- EuroQoL (EQ-5D-5L)
- Work Productivity Activity Impairment Questionnaire (WPAI:SHP)
- Resource Utilization Questionnaire

#### Open-Label Phase: Other Endpoints

- Compliance with primary OSA therapy during the open-label phase

### **Statistical Analysis Plan**

For Group A, changes in each endpoint were provided both relative to baseline of the parent study and relative to the final assessment in the parent study. For Group B, changes were summarized relative to baseline in the current study (Study 14-005).

Efficacy and safety data were summarized using descriptive statistics. For comparisons between solriamfetol and placebo at the end of the Randomized Withdrawal Period in the Maintenance Phase, subjects who were randomized to continue on solriamfetol in the Randomized Withdrawal Period of the Maintenance Phase were treated as a single group regardless of their diagnosis (narcolepsy or OSA) or the dose of solriamfetol received. Thus, there were no multiplicity issues with respect to multiple doses in the hypothesis testing. A fixed sequential testing strategy was employed to address the multiplicity issues in testing the primary and secondary endpoints in the Randomized Withdrawal Period.

For the analysis of the primary efficacy endpoint of the ESS in the Randomized Withdrawal Period, an analysis of covariance (ANCOVA) model was used. This model included treatment group and randomization stratification factor (narcolepsy vs. OSA) as fixed effects. The ESS score at the beginning of the Randomized Withdrawal Period was used as the covariate. The response variable was the change in ESS score from the beginning to the end of the 2-week Randomized Withdrawal Period. The estimates of treatment difference versus placebo and their 95% confidence intervals (CIs) were presented.

The chi-squared test was used to test the hypotheses associated with the analysis of the secondary endpoints of PGI-C and CGI-C at the end of the 2-week Randomized Withdrawal Period. Efficacy data from the open-label phase were summarized using descriptive statistics. No formal hypotheses were tested for the open-label efficacy data.

## **Protocol Amendments**

*Original protocol date: December 18, 2014*

*Amendment #1: February 18, 2015*

- update to exposure data to include subjects from a Phase 1 human abuse liability study;
- update to the Introduction to include safety information on the number of patients who reported palpitations or chest pain or who had a T-wave inversion in study MDD-201;
- a new section, "End of Trial," to satisfy EU regulatory requirements on defining the end of the trial;
- a clarification was made that the Safety Follow-up Visit was not required for subjects who enrolled in the open-label safety study (14-005) at the final clinic visit;
- deletion of "documented aspermia" as a criterion for subjects whose method of contraception is vasectomy;
- updated descriptions of solriamfetol and placebo excipients;
- clarification of the use of vital signs measurements to meet entrance criteria;

- replacement of the C-SSRS version at the screening visit by the Baseline/Screening Version;
- corrections to delete baseline CGI-C and PGI-C for Group B subjects, as these measurements are not performed at baseline for this group;
- revision of the pregnancy information section to clarify following of pregnant partners;
- for consistency across PSG assessments in the study it was clarified that subjects who are compliant with their PAP device use at the beginning of the study should use their PAP device for each PSG assessment and that subjects who use a PAP device, but who are not fully compliant, should decide with the investigator whether they will use their PAP device during all or none of the PSG assessments;
- the instructions for the collection of primary OSA therapy usage were revised to allow a subject who uses a PAP device for which usage data cannot be retrieved to report their primary OSA therapy usage and the estimated duration of use on a daily basis using the same diary-based method that subjects who do not use PAP therapy will employ.
- Changes to the exclusion criteria:
  - Exclusion Criterion #7 was revised to align with text in Section 6.9, which states that the presence of *active* suicidal ideation would exclude a subject from participation in the study.
  - In Exclusion Criterion #9, calculated creatinine clearance was changed from < 70 mL/min to < 60 mL/min to correspond with the standard categories of renal impairment.
  - In Exclusion Criterion #11, ondansetron, which has a known risk of torsade de pointes, was added to the list of excluded concomitant medications.
  - In Exclusion Criterion #12, systolic blood pressure level was changed from 140 mmHg to 150 mmHg, in response to FDA feedback to recruit a more inclusive patient population. In addition, blood pressure measures were clarified to indicate that the criterion applied when consistently observed across the multiple baseline measures.
  - Exclusion Criterion #15 was changed to state that Group A and Group B subjects will be excluded if there is a planned use of any over the counter (OTC) or prescription medications that could affect the evaluation of excessive sleepiness at any time during the study, but that only Group B subjects (who are not enrolling directly from another study) should discontinue the use of any OTC or prescription medications such that the baseline level of symptoms are present for at least seven days prior to the baseline visit (because the baseline measures will assess these symptoms over the past seven days, and Group A subjects will not be on other medications).

*Amendment #2: September 11, 2015*

- Changes to the exclusion criteria:

- Exclusion Criterion #7 was changed to limit subjects who had acutely unstable conditions vs. those with clinically significant conditions. Individuals who were unlikely to be able to complete the study were also excluded.
- Exclusion Criterion #12 was changed to exclude myocardial infarction and history of revascularization procedures if these occurred within the past year; to increase the blood pressure cutoff values from 150/90 mmHg to 155/95 mmHg; to exclude chronic ventricular arrhythmias (rather than all clinically significant arrhythmias); to exclude angina pectoris only if it is unstable; to exclude congestive heart failure specifically; and to remove the wording regarding exclusion of second or third degree heart block and clinically significant valvular disease, as these conditions were either already excluded in this criterion or addressed in another exclusion criterion.
- Number of subjects planned for enrollment was changed from “approximately 450” to “up to 500” to ensure meeting the regulatory requirements for the number of required subject exposures of at least 300 subjects for six months and at least 100 subjects for one year.
- Information on the following of pregnancy in cases of live birth was made consistent with the Pregnant Partner Informed Consent Form.
- Clarified that the parallel one-year comparisons for Group A and Group B are changes in ESS relative to the initial baseline from the previous trial and baseline in this study, respectively. This is a clarification and not a change in the previously planned analyses.
- Added that an interim analysis (for the purpose of a regulatory submission) would be planned when approximately 50 subjects with narcolepsy and 50 subjects with OSA have an exposure to solriamfetol of 52 weeks, and 100 subjects with narcolepsy and 200 subjects with OSA have an exposure to solriamfetol of 26 weeks.

*Amendment #3: February 2, 2016*

- This amendment includes the addition of a two-week double-blind, placebo-controlled, randomized withdrawal period at the six-month time point in the Maintenance Phase of the study. The change will require one additional clinic visit at the end of the two-week randomized withdrawal period, and will not extend the duration of the study. The purpose of the change is to provide data to support the maintenance of efficacy of solriamfetol, and to do so in a way that minimizes additional burden to subjects.
- Protocol changes specific to the additional of the randomized withdrawal period:
  - To ensure that enough subjects complete the study and to provide appropriate power for the randomized withdrawal portion of the study, the maximum enrollment into the study was increased from 500 to 600 subjects.
  - Subjects with OSA who have completed the six-week Study 14-004 and subjects with narcolepsy or OSA who have completed Studies 15-004 or 15-005 may enroll in this study if they meet the entry criteria. As a result, the anticipated duration of enrollment in the study was increased from 15 to 18 months.

- Random assignment (in a 1:1 ratio) at the Week 27 visit for Group A or the Week 26 visit for Group B will occur such that approximately half of the subjects will continue to receive solriamfetol at the dose that they are currently receiving and half will receive placebo for two weeks in a double-blind manner.
- After the two-week randomized withdrawal period, subjects will receive the same dose that they had been receiving at the beginning of the randomized withdrawal period for the remainder of the study. Given that approximately half of the subjects will have been randomized to receive placebo during the two-week randomized withdrawal period, a fixed titration of three days at a lower dose will be included for subjects who were on the 150 mg or 300 mg doses.
- Additional versions of the CGI-C and PGI-C questionnaires were included to assess change in clinical condition over the two-week randomized withdrawal period.
- Changes to inclusion criteria:
  - Inclusion Criterion #3 was changed to specify that primary OSA therapy may include oral pressure therapy or use of an upper airway stimulator, in addition to the already specified therapies of positive airway pressure and oral appliances.
  - In Inclusion Criterion #6, the upper limit of the eligible range of BMI was raised from  $< 40 \text{ kg/m}^2$  to  $< 45 \text{ kg/m}^2$  based on feedback from investigators in the United States who reported that the BMI cutoff of  $40 \text{ kg/m}^2$  was excluding otherwise healthy potential subjects. Obesity is a well-characterized comorbidity of the OSA population, and this change allowed the enrollment of a representative patient population with minimal change to risk of participation.
  - In Inclusion Criterion #6, the requirement for the baseline mean sleep latency, as documented by the mean of the first four test sessions of the MWT, was changed to  $< 30$  minutes because the criterion of  $\leq 20$  minutes was excluding subjects who were otherwise eligible and are representative of the OSA population with excessive daytime sleepiness.
- Changes to exclusion criteria:
  - Exclusion Criterion #8, which dealt with bariatric surgery, was clarified to state that a history of any gastric bypass procedure was exclusionary because of its potential to affect the absorption and PK of solriamfetol. Other bariatric surgery procedures, such as a gastric band procedure, are exclusionary only if performed within the past year.
  - Cardiac Exclusion Criteria #10, #11, and #12 were changed as follows:
    - A thorough QT/QTc (TQT) study with solriamfetol had not been completed when Study 14-004 was initiated; therefore, as a precaution, subjects with a history or presence of a risk factor for torsade de pointes (Exclusion Criterion #10) and subjects who used and could not safely discontinue medication with known risk for torsade de pointes (Exclusion Criterion #11) were excluded from this study. However, the findings from

the completed TQT Study 15-002 showed no QTcF prolongation reaching the threshold of regulatory concerns with solriamfetol at the proposed therapeutic dose of 300 mg or at the suprathreshold dose of 900 mg. Therefore, Exclusion Criterion #10 was changed to exclude only subjects with a clinically significant ECG abnormality, and Exclusion Criterion #11 was removed (no changes were made in the extent or frequency of assessments of cardiovascular safety).

- Exclusion Criterion #12 was revised to more clearly specify which types of congestive heart failure and cardiac arrhythmias were excluded.
  - Rescreening of subjects who had not met previous eligibility requirements, but who were likely to meet the revised eligibility requirements, was not addressed in the protocol. This amendment clarified that those subjects would be allowed to be rescreened with approval by the Medical Monitor.
  - The statistical analyses described in the protocol were updated to incorporate feedback from the FDA about the previously planned analyses.
  - The length of time during which screening labs could be repeated was extended.

*Amendment #4: November 17, 2016*

- The primary change in this amendment is a clarification of the randomized withdrawal period at the six-month time point in the Maintenance Phase of the study. The amendment clarifies that when approximately 300 subjects are randomized into the randomized withdrawal period, no more subjects will be randomized into the randomized withdrawal period. All subjects who have not entered the randomized withdrawal period at that time will receive open-label solriamfetol for the remainder of the study.
- The synopsis, study activities, study schema, and other sections were updated to indicate alternative procedures for subjects who will not be randomized into the randomized withdrawal period after approximately 300 subjects are randomized.
- The total enrollment was changed from “up to 600” to “approximately 600” to ensure that all eligible subjects from prior studies will be able to enroll in this study.
- The frequency of lab assessments was changed to assess labs every three months instead of only at the beginning and end of the study to provide more routine monitoring of patient safety. This added two more safety lab assessments for Group A and three more safety lab assessments for Group B.
- The length of time during which screening labs (serum chemistry, hematology, urinalysis) would not need to be repeated was extended from 14 days to 28 days for Group B to cover the entire screening period so that the sites and subjects are not unduly burdened by having to repeat the screening labs within the screening period.
- Exclusion criterion #8 regarding bariatric surgery was clarified to state that a history of any gastric bypass procedure is exclusionary because of its potential to affect the absorption and pharmacokinetics of solriamfetol. Other bariatric surgery procedures,

such as a gastric band procedure, are exclusionary only if performed within the past year.

### **Country-Specific Amendments**

Amendments 2FR, 3FR, 4FR, 5FR, and 6FR were country-specific amendments that applied only to clinical sites in France.

#### *Amendment 2FR: August 17, 2015*

- added a safety follow-up phone contact for further assessment of adverse events after discontinuation of study drug;
- added further specifications to Inclusion Criterion #1 (affiliation with a Social Security regime) and Inclusion Criterion #11 (that a subject not be a vulnerable person or legally protected adult);
- added the exclusion of individuals with a current or past diagnosis of mild substance use disorder, in addition to individuals with moderate or severe substance use disorders;
- added that subjects participating in the Maintenance Phase of the study will be provided no more than a 28-day supply of study drug at a time.

#### *Amendment 3FR: October 12, 2015*

- consisted of the changes specified in Amendment #2 (September 10, 2015).

#### *Amendment 4FR: December 1, 2015*

- changed the time for following a live birth as the outcome of pregnancy during the study from six months to a minimum of six months.

#### *Amendment 5FR: March 13, 2016*

- consisted of the changes specified in Amendment #3 (February 8, 2016)

#### *Amendment 6FR: June 1, 2016*

- added three drugs to the list of drugs included in the urine drug screen in Table 1 of the protocol: buprenorphine, 3,4-methylenedioxymethamphetamine, and nortriptyline. Although urine drug screening for these drugs was not required by the protocol, the testing kit being used at the sites did screen for those substances. The addition of these drugs to the list of laboratory tests did not change the conduct of the trial.

#### *Amendment 7FR: December 2, 2016*

- consisted of the changes specified in Amendment #4 (November 17, 2016)

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### **Data Quality and Integrity: Sponsor's Assurance**

Steps to assure the accuracy and reliability of data included the selection of qualified investigators and an appropriate study site, review of protocol procedures with the investigator and associated personnel prior to the study, and periodic monitoring visits by Jazz Pharmaceuticals or its designee. Data were reviewed for accuracy and completeness by Jazz Pharmaceuticals or its designee during and after onsite monitoring visits, and any discrepancies were resolved with the investigator or designees as appropriate. Quality control audits could be performed at the discretion of the Sponsor. Electronic CRFs (eCRFs) were used for the recording of all trial data not recorded in subject diaries, obtained by ECG recording, or generated by laboratory report. The principal investigator reviewed the eCRFs and provided his signature certifying that he reviewed the data and considered the data accurate to the best of his knowledge and provided his signature certifying that he reviewed the data and considered the data accurate to the best of his knowledge. A comprehensive Data Management Plan was developed.

#### *Reporting of Serum Direct Bilirubin Values*

A technical issue was identified regarding serum direct bilirubin values reported from laboratory testing. Between January 2, 2016 and November 21, 2016, serum direct bilirubin values levels assayed by (b) (4) for this study were assigned a positive proportional bias due to a calibrator issue (calibrator manufactured by Siemens Healthcare Diagnostics). Calibrator values were reassigned by the manufacturer and were placed into effect by (b) (4) as of November 21, 2016. (b) (4) conducted an internal correlation between results obtained using the old calibrator set point and the new reassigned calibrator set point. A positive shift in direct bilirubin results was observed that was proportional in nature. An average bias of 30% was seen when direct bilirubin was more than three times the upper limit of normal (ULN). Differences for results that were in the normal range and up to three times the ULN were within the total allowable error of the assay. Siemens estimated the average bias to be approximately 40%. A correction factor could not be provided and previously tested samples could not be re-assayed. Results from 247 samples collected from 220 subjects during the affected period are in the clinical database uncorrected. Upon analysis by Jazz and (b) (4) (CRO) of the direct bilirubin outliers, the clinical significance of the positive bias was considered to be minimal.

### **6.5.2. Study Results**

#### **Compliance with Good Clinical Practices**

The Clinical Study Report for Study 14-005, Section 9.6.1, Study Administration and Conduct (page 63), states: "The study was conducted according to GCP guidelines and according to national law." Section 9.6.2, Data Generation and Analysis, (page 63) states: "The standard

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procedures for handling and processing records were followed in compliance with 21 CFR 11, Good Clinical Practices, ICH Guidelines, and the Standard Operating Procedures of Jazz Pharmaceuticals or the CRO ( (b) (4) ).”

### Financial Disclosure

Financial disclosures for each of the five pivotal trials under this NDA were reviewed at the time the NDA was filed. For Study 14-005, (b) (6) and (b) (6) had disclosable financial interests. See Appendix 13.2 for details.

### Patient Disposition

A total of 640 subjects were enrolled: 227 with narcolepsy and 413 with OSA. The majority (521 subjects) previously completed Studies 14-002 or 14-003 (Group A). Two subjects withdrew from the study prior to receiving study drug, one for “other reasons” and one due to withdrawal of consent. A total of 638 subjects, including 226 with narcolepsy and 412 with OSA, received at least one dose of solriamfetol in the open-label phase and were included in the Safety Population. Patient disposition for the open label phase is presented in Table 30.

**Table 30: Study 14-005, Patient Disposition, Open Label Phase, By Indication, Safety Population**

Completed Phase, n (%)	Indication: Narcolepsy				Indication: OSA			
	75 mg (N=15)	150 mg (N=66)	300 mg (N=145)	All SLFTOL* (N=226)	75 mg (N=49)	150 mg (N=142)	300 mg (N=221)	All SLFTOL* (N=412)
Yes	3 (20.0)	16 (24.2)	53 (36.6)	72 (31.9)	8 (16.3)	32 (22.5)	47 (21.3)	87 (21.1)
No	10 (66.7)	21 (31.8)	34 (23.4)	65 (28.8)	19 (38.8)	29 (20.4)	31 (14.0)	79 (19.2)
Ongoing	2 (13.3)	29 (43.9)	58 (40.0)	89 (39.4)	22 (44.9)	81 (57.0)	143 (64.7)	246 (59.7)
If No, Primary Reason, n (%)								
Lack of Efficacy	4 (26.7)	14 (21.2)	17 (11.7)	35 (15.5)	4 (8.2)	2 (1.4)	9 (4.1)	15 (3.6)
Protocol Violation	0	1 (1.5)	1 (0.7)	2 (0.9)	1 (2.0)	2 (1.4)	1 (0.5)	4 (1.0)
Adverse Event	5 (33.3)	6 (9.1)	9 (6.2)	20 (8.8)	11 (22.4)	10 (7.0)	9 (4.1)	30 (7.3)
Withdrawal by Subject	0	0	2 (1.4)	2 (0.9)	2 (4.1)	9 (6.3)	8 (3.6)	19 (4.6)
Lost to Follow-up	0	0	4 (2.8)	4 (1.8)	0	3 (2.1)	1 (0.9)	5 (1.2)
Treatment Non-Compliant	1 (6.7)	0	1 (0.7)	2 (0.9)	1 (2.0)	2 (1.4)	1 (0.5)	4 (1.0)
Other	0	0	0	0	0	1 (0.7)	1 (0.5)	2 (0.5)

SLFTOL = solriamfetol.

Source: Study 14-005 Clinical Study Report, Table 14.1.2.1a, page 314-315.

The safety population for the randomized withdrawal period was comprised of 282 subjects: 79 with narcolepsy and 203 with OSA. Patient disposition for the randomized withdrawal period is presented in Table 31.

**Table 31: Study 14-005, Patient Disposition, Randomized Withdrawal Period, By Indication, Safety Population**

Completed Phase, n (%)	Indication: Narcolepsy					Indication: OSA				
	PBO (N=40)	75 mg (N=1)	150 mg (N=12)	300 mg (N=26)	All SLFTOL (N=39)	PBO (N=102)	75 mg (N=12)	150 mg (N=34)	300 mg (N=55)	All SLFTOL (N=101)
Completed RW but ongoing in study	40 (100.0)	1 (100.0)	12 (100.0)	25 (96.2)	38 (97.4)	101 (99.0)	12 (100.0)	34 (100.0)	53 (96.4)	99 (98.0)
Ongoing during RW period	0	0	0	0	0	1 (1.0)	0	0	1 (1.8)	1 (1.0)
ET during RW period	0	0	0	1 (3.8)	1 (2.6)	0	0	0	1 (1.8)	1 (1.0)
If Withdrawn, Primary Reason, n (%)										
Withdrawal by Subject	0	0	0	0	0	0	0	0	1 (1.8)	1 (1.0)
Treatment Non-Compliant	0	0	0	1 (3.8)	1 (2.6)	0	0	0	0	0

Source: Study 14-005 Clinical Study Report, Table 14.1.2.1b, page 325-326.

### Protocol Violations/Deviations

Major protocol deviations were reported for 120 subjects (18.8%) in the open-label phase and seven subjects in the randomized withdrawal period; three subjects (2.1%) in the placebo group and four subjects (2.9%) in the combined solriamfetol groups. In the open-label phase, the most frequently reported major deviations were related to informed consent violations, non-compliance with study procedures, concomitant medication violations, and laboratory violations. In the randomized withdrawal period, concomitant medication violations and study drug dosing violations were the only major deviations reported in more than one subject.

The majority of informed consent violations were due to subjects not being provided the latest version of the informed consent form for signature and/or failure to obtain new signatures on the most recent informed consent form after protocol amendments. Deviations related to noncompliance included taking less study drug than specified by protocol, assessment of the CGIs and/or CGI-C by site personnel who did not have the protocol-required credentials, not returning study drug and/or a study drug bottle to the study site, taking study drug at an incorrect time of day, positive urine drug screen results, failure to complete the OSA diary, and taking a prohibited medication concomitantly with study drug. Protocol deviations for the open-label phase are presented in Table 32, and for the randomized-withdrawal phase in Table 33.

**Table 32: Study 14-005, Major Protocol Deviations, Open Label Phase, By Indication, Safety Population**

Deviation Category, n (%)	Indication: Narcolepsy				Indication: OSA			
	75 mg (N=15)	150 mg (N=66)	300 mg (N=145)	All SLFTOL (N=226)	75 mg (N=49)	150 mg (N=142)	300 mg (N=221)	All SLFTOL (N=412)
Any Major Protocol Deviation	2 (13.3)	10 (15.2)	29 (20.0)	41 (18.1)	4 (8.2)	24 (16.9)	51 (23.1)	79 (19.2)
Informed Consent	1 (6.7)	5 (7.6)	16 (11.0)	22 (9.7)	2 (4.1)	11 (7.7)	17 (7.7)	30 (7.3)
Non-compliance	0	5 (7.6)	11 (7.6)	16 (7.1)	0	6 (4.2)	22 (10.0)	28 (6.8)
Concomitant Medications	1 (6.7)	1 (1.5)	4 (2.8)	6 (2.7)	1 (2.0)	4 (2.8)	3 (1.4)	8 (1.9)
Enrollment Criteria	0	2 (3.0)	0	2 (0.9)	0	3 (2.1)	3 (1.4)	6 (1.5)
Laboratory	0	0	2 (1.4)	2 (0.9)	1 (2.0)	2 (1.4)	9 (4.1)	12 (2.9)
Dosing	0	1 (1.5)	0	1 (0.4)	0	0	2 (0.9)	2 (0.5)
Visit/Procedure Required	0	1 (1.5)	0	1 (0.4)	0	1 (0.7)	1 (0.5)	2 (0.5)
Regulatory	0	0	0	0	0	0	1 (0.5)	1 (0.2)

Source: Study 14-005 Clinical Study Report, Table 14.1.4.1a, page 401-402.

**Table 33: Study 14-005, Major Protocol Deviations, Randomized Withdrawal Period, By Indication, Safety Population**

Deviation Category, n (%)	Indication: Narcolepsy					Indication: OSA				
	PBO (N=40)	75 mg (N=1)	150 mg (N=12)	300 mg (N=26)	All SLFTOL (N=39)	PBO (N=102)	75 mg (N=12)	150 mg (N=34)	300 mg (N=55)	All SLFTOL (N=101)
Any Major Protocol Deviation	2 (5.0)	0	1 (8.3)	1 (3.8)	2 (5.1)	1 (1.0)	0	0	2 (3.6)	2 (2.0)
Concomitant Medications	1 (2.5)	0	1 (8.3)	0	1 (2.6)	1 (1.0)	0	0	1 (1.8)	1 (1.0)
Dosing	1 (2.5)	0	1 (8.3)	0	1 (2.6)	0	0	0	1 (1.8)	1 (1.0)
Laboratory	0	0	1 (8.3)	0	1 (2.6)	0	0	0	0	0
Visit Schedule	0	0	0	1 (3.8)	1 (2.6)	0	0	0	0	0
Informed Consent	0	0	0	0	0	0	0	0	1 (1.8)	1 (1.0)

Source: Study 14-005 Clinical Study Report, Table 14.1.4.1b, page 404-405.

Three subjects were each enrolled and treated twice in Study 14-005, which resulted in duplicate subject information for this study. Major protocol deviations were reported for two of the three subjects. For one subject, the duplicate enrollment was not discovered until after the database lock. All analyses were performed including the duplicate subjects, without correction. The Applicant performed sensitivity analyses in which these subjects were removed. These analyses indicated that the multiple enrollments did not have a substantial effect on patient demographics, ESS scores during the open-label phase and randomized withdrawal period for the safety and mITT populations, or frequency of TEAEs for the safety population.

### Table of Demographic Characteristics

Demographics and baseline characteristics for Safety Population subjects are presented in Table 34 (Open-Label Phase) and Table 35 (Randomized Withdrawal Period).

**Table 34: Study 14-005, Patient Demographics, Open-Label Phase, Safety Population**

	Indication: Narcolepsy				Indication: OSA			
	75 mg (N=15)	150 mg (N=66)	300 mg (N=145)	All SLFTOL (N=226)	75 mg (N=49)	150 mg (N=142)	300 mg (N=221)	All SLFTOL (N=412)
Age (years)								
n	15	66	145	226	49	142	221	412
Mean (SD)	33.4 (11.9)	39.0 (12.3)	39.0 (14.2)	38.7 (13.5)	58.2 (10.0)	55.6 (11.0)	53.8 (10.6)	55.1 (10.8)
Median	29	38	40	38	59	57	55	56
Range	18, 60	19, 68	18, 69	18, 69	35, 75	21, 76	21, 74	21, 76
Sex, n (%)								
Male	5 (33.3)	25 (37.9)	50 (34.5)	80 (35.4)	28 (57.1)	83 (58.5)	142 (64.3)	253 (61.4)
Female	10 (66.7)	41 (62.1)	95 (65.5)	146 (64.6)	21 (42.9)	59 (41.5)	79 (35.7)	159 (38.6)
Race, n (%)								
American Indian or Alaska Native	0	1 (1.5)	0	1 (0.4)	1 (2.0)	0	0	1 (0.2)
Asian	0	2 (3.0)	2 (1.4)	4 (1.8)	1 (2.0)	6 (4.2)	4 (1.8)	11 (2.7)
Black or African American	1 (6.7)	10 (15.2)	22 (15.2)	33 (14.6)	11 (22.4)	26 (18.3)	39 (17.6)	76 (18.4)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.7)	1 (0.4)	0	2 (1.4)	0	2 (0.5)
White	13 (86.7)	53 (80.3)	116 (80.0)	182 (80.5)	36 (73.5)	107 (75.4)	177 (80.1)	320 (77.7)
Multiple	1 (6.7)	0	4 (2.8)	5 (2.2)	0	1 (0.7)	1 (0.5)	2 (0.5)
Ethnicity, n (%)								
Hispanic or Latino	0	2 (3.0)	8 (5.5)	10 (4.4)	5 (10.2)	8 (5.6)	16 (7.2)	29 (7.0)
Not Hispanic or Latino	15 (100.0)	64 (97.0)	137 (94.5)	216 (95.6)	44 (89.8)	134 (94.4)	205 (92.8)	383 (93.0)
Region, n (%)								
North America	13 (86.7)	55 (83.3)	116 (80.0)	184 (81.4)	43 (87.8)	135 (95.1)	211 (95.5)	389 (94.4)
Europe	2 (13.3)	11 (16.7)	29 (20.0)	42 (18.6)	6 (12.2)	7 (4.9)	10 (4.5)	23 (5.6)
Country, n (%)								
USA	11 (73.3)	49 (74.2)	106 (73.1)	166 (73.5)	43 (87.8)	133 (93.7)	203 (91.9)	379 (92.0)
Canada	2 (13.3)	6 (9.1)	10 (6.9)	18 (8.0)	0	2 (1.4)	8 (3.6)	10 (2.4)
France	0	3 (4.5)	8 (5.5)	11 (4.9)	0	0	1 (0.5)	1 (0.2)
Germany	2 (13.3)	7 (10.6)	11 (7.6)	20 (8.8)	2 (4.1)	6 (4.2)	3 (1.4)	11 (2.7)
Finland	0	0	6 (4.1)	6 (2.7)	4 (8.2)	1 (0.7)	6 (2.7)	11 (2.7)
Italy	0	0	4 (2.8)	4 (1.8)	0	0	0	0
Netherlands	0	1 (1.5)	0	1 (0.4)	0	0	0	0
Body Mass Index (kg/m <sup>2</sup> )								
n	15	66	145	226	49	142	220	411
Mean (SD)	25.0 (4.2)	28.7 (5.9)	28.5 (5.8)	28.3 (5.8)	32.6 (5.3)	33.5 (5.3)	33.8 (5.1)	33.5 (5.2)
Median	23.6	28.5	27.6	27.6	32.8	33.6	33.6	33.5
Range	19.7, 34.4	18.0, 44.6	18.0, 43.4	18.0, 44.6	13.6, 43.5	20.5, 45.4	23.1, 45.2	13.6, 45.4

Source: Study 14-005 Clinical Study Report, Table 14.1.5.1a, pages 418-423.

**Table 35: Study 14-005, Patient Demographics, Randomized Withdrawal Period, Safety Population**

	Indication: Narcolepsy					Indication: OSA				
	PBO (N=40)	75 mg (N=1)	150 mg (N=12)	300 mg (N=26)	All SLFTOL (N=39)	PBO (N=101)	75 mg (N=12)	150 mg (N=34)	300 mg (N=55)	All SLFTOL (N=101)
Age (years)										
n	40	1	12	26	39	101	12	34	55	101
Mean (SD)	41.4 (12.6)	34.0 (n/a)	40.0 (15.1)	40.4 (15.3)	40.1 (14.9)	54.4 (9.9)	58.3 (9.7)	52.2 (11.7)	54.3 (9.1)	54.1 (10.2)
Median	40	34	35	39	37	55	59	52	55	55
Range	22, 69	34, 34	24, 66	20, 68	20, 68	30, 74	36, 72	31, 71	36, 74	31, 74
Sex, n (%)										
Male	12 (30.0)	0	5 (41.7)	9 (34.6)	14 (35.9)	72 (71.3)	7 (58.3)	19 (55.9)	36 (65.5)	62 (61.4)
Female	28 (70.0)	1 (100.0)	7 (58.3)	17 (65.4)	25 (64.1)	29 (28.7)	5 (41.7)	15 (44.1)	19 (34.5)	39 (38.6)
Race, n (%)										
American Indian or Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	2 (5.0)	0	1 (8.3)	1 (3.8)	2 (5.1)	3 (3.0)	1 (8.3)	0	0	1 (1.0)
Black or African American	5 (12.5)	1 (100.0)	2 (16.7)	6 (23.1)	9 (23.1)	20 (19.8)	3 (25.0)	5 (14.7)	8 (14.5)	16 (15.8)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
White	32 (80.0)	0	9 (75.0)	19 (73.1)	28 (71.8)	78 (77.2)	8 (66.7)	29 (85.3)	47 (85.5)	84 (83.2)
Multiple	1 (2.5)	0	0	0	0	0	0	0	0	0
Ethnicity, n (%)										
Hispanic or Latino	2 (5.0)	0	0	1 (3.8)	1 (2.6)	5 (5.0)	1 (8.3)	1 (2.9)	1 (1.8)	3 (3.0)
Not Hispanic or Latino	38 (95.0)	1 (100.0)	12 (100.0)	25 (96.2)	38 (97.4)	96 (95.0)	11 (91.7)	33 (97.1)	54 (98.2)	98 (97.0)
Region, n (%)										
North America	33 (82.5)	1 (100.0)	9 (75.0)	21 (80.8)	31 (79.5)	96 (95.0)	8 (66.7)	31 (91.2)	54 (98.2)	93 (92.1)
Europe	7 (17.5)	0	3 (25.0)	5 (19.2)	8 (20.5)	5 (5.0)	4 (33.3)	3 (8.8)	1 (1.8)	8 (7.9)
Country, n (%)										
USA	29 (72.5)	1 (100.0)	9 (75.0)	19 (73.1)	29 (74.4)	93 (92.1)	8 (66.7)	31 (91.2)	52 (94.5)	91 (90.1)
Canada	4 (10.0)	0	0	2 (7.7)	1 (5.1)	3 (3.0)	0	0	2 (3.6)	2 (2.0)
France	2 (5.0)	0	2 (16.7)	1 (3.8)	3 (7.7)	1 (1.0)	0	0	0	0
Germany	5 (12.5)	0	1 (8.3)	2 (7.7)	3 (7.7)	2 (2.0)	1 (8.3)	3 (8.8)	0	4 (4.0)
Finland	0	0	0	2 (7.7)	2 (5.1)	2 (2.0)	3 (25.0)	0	1 (1.8)	4 (4.0)
Italy	0	0	0	0	0	0	0	0	0	0
Netherlands	0	0	0	0	0	0	0	0	0	0
Body Mass Index (kg/m <sup>2</sup> )										
n	40	1	12	26	39	101	12	34	55	101
Mean (SD)	27.6 (5.6)	29.8 (n/a)	27.2 (7.7)	28.6 (5.9)	28.2 (6.4)	33.4 (5.4)	32.7 (4.3)	33.1 (5.3)	33.7 (4.4)	33.4 (4.7)
Median	26.8	29.8	26.1	28.5	28.4	33.4	32.6	33.4	33.5	33.3
Range	18.0, 39.5	29.8, 29.8	18.0, 43.3	20.1, 40.0	18.0, 43.3	23.3, 43.9	21.8, 39.2	20.5, 41.2	23.7, 44.0	20.5, 44.0

Source: Study 14-005 Clinical Study Report, Table 14.1.4.1b, pages 10331-10336.

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

For subjects in Group A, because subjects were permitted to enroll directly from the parent study without a washout period, baseline for efficacy measures was defined as the baseline from the parent study. For subjects in Group B, study drug dosing was interrupted between the parent study and Study 14-005. For those subjects, baseline for efficacy measures was defined as the baseline at the start of Study 14-005. Subjects in Group A and in Group B both had mean total ESS scores of 15.9. For both groups, scores were on average higher for subjects with

narcolepsy than for subjects with OSA. The majority of subjects in both diagnostic categories were classified as moderately, markedly, or severely ill, based on CGI scores. Baseline disease characteristics for subjects entering the open-label phase of Study 14-005 are presented in Table 36.

**Table 36: Study 14-005, Baseline Disease Characteristics, Open-Label Phase, Safety Population**

	Combined Solriamfetol, Overall (N=638)	Combined Solriamfetol, OSA (N=412)	Combined Solriamfetol, Narcolepsy (N=226)
Presence of cataplexy			
Yes	114 (17.9)	N/A	114 (50.4)
No	112 (17.6)	N/A	112 (49.6)
Primary OSA Therapy Use			
Compliant	319 (50.0)	319 (77.4)	N/A
Non-compliant	93 (14.6)	93 (22.6)	N/A
Baseline ESS Total Score, Group A			
n	519	333	186
Mean (SD)	15.9 (3.4)	15.2 (3.3)	17.3 (3.1)
Median	16	15	17
Range	10, 24	10, 24	10, 24
Baseline ESS Total Score, Group B			
n	119	79	40
Mean (SD)	15.9 (4.2)	14.9 (3.9)	17.9 (4.0)
Median	16	15	19
Range	4, 24	4, 24	6, 24
Baseline CGIs, n (%)			
1 = Normal, not at all ill	2 (0.3)	2 (0.5)	0
2 = Borderline ill	9 (1.4)	9 (2.2)	0
3 = Mildly ill	37 (5.8)	29 (7.0)	8 (3.5)
4 = Moderately ill	220 (34.5)	164 (39.8)	56 (24.8)
5 = Markedly ill	231 (36.2)	138 (33.5)	93 (41.2)
6 = Severely ill	112 (17.6)	58 (14.1)	54 (23.9)
7 = Among the most extremely ill	23 (3.6)	9 (2.2)	14 (6.2)
Missing	4 (0.6)	3 (0.7)	1 (0.4)

Source: Study 14-005 Clinical Study Report, Table 12, page 94.

The medical conditions reported most frequently in the histories of study subjects (beyond the expected diagnoses of sleep apnea syndrome, narcolepsy, and continuous positive airway pressure) were hypertension, seasonal allergy, depression, and gastroesophageal reflux

disease. The medical conditions reported by at least 10% of subjects in the Safety Population are presented in Table 37.

**Table 37: Study 14-005, Elements of Medical History in ≥ 10% of All Subjects, Subjects with OSA, or Subjects with Narcolepsy; Open-Label Phase, Safety Population**

<b>Preferred Term, n (%)</b>	<b>Combined Solriamfetol, Overall (N=638)</b>	<b>Combined Solriamfetol, OSA (N=412)</b>	<b>Combined Solriamfetol, Narcolepsy (N = 226)</b>
Sleep apnea syndrome	455 (71.3)	412 (100.0)	43 (19.0)
Continuous positive airway pressure	374 (58.6)	354 (85.9)	20 (8.8)
Hypertension	239 (37.5)	200 (48.5)	39 (17.3)
Narcolepsy	225 (35.3)	0 (0.0)	225 (99.6)
Seasonal allergy	175 (27.4)	117 (28.4)	58 (25.7)
Depression	153 (24.0)	93 (22.6)	60 (26.5)
Gastroesophageal reflux disease	134 (21.0)	102 (24.8)	32 (14.2)
Drug hypersensitivity	120 (18.8)	77 (18.7)	43 (19.0)
Cataplexy	115 (18.0)	0 (0.0)	115 (50.9)
Hyperlipidemia	96 (15.0)	88 (21.4)	8 (3.5)
Headache	88 (13.8)	54 (13.1)	34 (15.0)
Type 2 diabetes mellitus	88 (13.8)	81 (19.7)	7 (3.1)
Hypercholesterolemia	81 (12.7)	69 (16.7)	12 (5.3)
Tonsillectomy	81 (12.7)	55 (13.3)	26 (11.5)
Anxiety	79 (12.4)	50 (12.1)	29 (12.8)
Obesity	79 (12.4)	62 (15.0)	17 (7.5)
Asthma	76 (11.9)	48 (11.7)	28 (12.4)
Osteoarthritis	72 (11.3)	62 (15.0)	10 (4.4)
Hysterectomy	69 (10.8)	53 (12.9)	16 (7.1)
Middle insomnia	69 (10.8)	3 (0.7)	66 (29.2)
Migraine	66 (10.3)	37 (9.0)	29 (12.8)
Sleep paralysis	66 (10.3)	0 (0.0)	66 (29.2)
Postmenopause	65 (10.2)	52 (12.6)	13 (5.8)
Back pain	62 (9.7)	39 (9.5)	23 (10.2)
Hypothyroidism	53 (8.3)	43 (10.4)	10 (4.4)
Hypnagogic hallucination	52 (8.2)	0 (0.0)	52 (23.0)
Hypnopompic hallucination	33 (5.2)	0 (0.0)	33 (14.6)

Source: Study 14-005 Clinical Study Report, Table 14, page 102.

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Compliance with study drug was defined as:

$$100 * \frac{\text{total number of capsules dispensed} - \text{total number of capsules returned}}{\text{total number of capsules expected to be taken}}$$

Subjects with narcolepsy had higher mean compliance rates (94.1%) than subjects with OSA (89.7%). Seven subjects had a compliance rate > 120%. These were generally subjects who withdrew early from the study or were lost to follow-up and did not return all the dispensed study drug. Compliance rates for across the entire study (combined open-label and randomized withdrawal periods) are presented in Table 38. Compliance rates for the randomized withdrawal period only are presented in Table 39.

**Table 38: Study 14-005, Treatment Compliance, Entire Study Duration, Safety Population**

	<b>Full Safety Pop (N=638)</b>	<b>OSA (N=412)</b>	<b>Narcolepsy (N=226)</b>
Compliance (%)			
n	635	411	224
Mean (SD)	91.3 (27.2)	89.7 (19.8)	94.1 (37.0)
Median	98.0	97.4	99.0
Range	0, 438	0, 200	18, 438
Compliance Category, n (%)			
< 80%	114 (18.0)	78 (19.0)	36 (16.1)
80-100%	425 (66.9)	275 (66.9)	150 (67.0)
> 100%	96 (15.1)	58 (14.1)	38 (17.0)
> 120%	7 (1.1)	3 (0.7)	4 (1.8)

Source: Study 14-005 Clinical Study Report, Table 17, page 109.

**Table 39: Study 14-005, Treatment Compliance, Randomized Withdrawal Period, Safety Population**

	Full Safety Pop		OSA		Narcolepsy	
	PBO (N=142)	All SLFTOL (N=140)	PBO (N=102)	All SLFTOL (N=101)	PBO (N=40)	All SLFTOL (N=39)
Compliance (%)						
n	139	137	100	100	39	37
Mean (SD)	96.3 (12.0)	97.5 (7.3)	96.5 (11.2)	98.1 (6.5)	95.7 (14.0)	95.7 (9.1)
Median	100.0	100.0	100.0	100.0	100.0	100.0
Range	20, 143	68, 114	33, 143	71, 114	20, 107	68, 100
Compliance Category, n (%)						
< 80%	9 (6.5)	8 (5.8)	7 (7.0)	4 (4.0)	2 (5.1)	4 (10.8)
80-100%	121 (87.1)	122 (89.1)	86 (86.0)	89 (89.0)	35 (89.7)	33 (89.2)
> 100%	9 (6.5)	7 (5.1)	7 (7.0)	7 (7.0)	2 (5.1)	0
> 120%	1 (0.7)	0	1 (1.0)	0	0	0

Source: Study 14-005 Clinical Study Report, Table 18, page 112.

**Efficacy Results – Randomized Withdrawal Period**

Primary Endpoint: Change in ESS Score

For the mITT Population, subjects who continued to receive solriamfetol during the randomized withdrawal period experienced a mean increase of 1.3 in ESS score. In comparison, subjects randomized to placebo showed a mean increase of 4.8 in ESS score. The changes represent a statistically significant difference in least square means of -3.7 points between the solriamfetol and placebo groups ( $p < 0.0001$ ). The difference in LS means was statistically significant for both the subgroup of narcolepsy patients and the subgroup of OSA patients. See Table 40.

**Table 40: Study 14-005, Change in ESS Score from Efficacy Baseline to End of Randomized Withdrawal Period, mITT Population**

	Overall		OSA		Narcolepsy	
	Placebo (N = 141)	Combined solriamfetol (N = 139)	Placebo (N = 101)	Combined solriamfetol (N = 101)	Placebo (N = 40)	Combined solriamfetol (N = 38)
<b>Efficacy Baseline</b>						
n	141	139	101	101	40	38
Mean (SD)	7.8 (5.0)	7.3 (5.3)	6.5 (4.3)	5.9 (4.3)	11.0 (5.1)	10.9 (6.0)
<b>End of Randomized Withdrawal</b>						
n	141	139	101	101	40	38
Mean (SD)	12.6 (5.7)	8.5 (5.8)	11.2 (5.5)	7.2 (5.2)	15.9 (4.7)	12.0 (5.8)
LS Mean (SE)	5.3 (0.4)	1.6 (0.4)	4.9 (0.5)	1.1 (0.5)	4.9 (0.6)	1.1 (0.6)
LS Mean Difference	---	-3.7	---	-3.7	---	-3.8
95% CI	---	(-4.8, -2.7)	---	(-5.1, -2.4)	---	(-5.5, -2.2)
p-value	---	< 0.0001	---	< 0.0001	---	< 0.0001

*Adapted from Study 14-005 Clinical Study Report, Table 20, page 115.*

**Secondary Endpoint: Percentage of Subjects Assessed as Worse on PGI-C**

At the end of the randomized withdrawal period, a higher percentage of subjects who received placebo rated their condition as worse on the PGI-C compared to subjects who received solriamfetol (64.5% vs. 28.2%, respectively), resulting in a statistically significant difference in the percentage of subjects who experienced worsening. The difference was statistically significant for both the subgroup of narcolepsy patients and the subgroup of OSA patients. See Table 41.

**Table 41: Study 14-005, Percentage of Subjects Reported as Worse on PGI-C, mITT Population**

	Overall		OSA		Narcolepsy	
	Placebo (N = 141)	Combined solriamfetol (N = 139)	Placebo (N = 101)	Combined solriamfetol (N = 101)	Placebo (N = 40)	Combined solriamfetol (N = 38)
<b>Subjects Reported Worse on PGI-C</b>						
n	138	131	100	94	38	37
Yes, n (%)	89 (64.5)	37 (28.2)	59 (59.0)	26 (27.7)	30 (78.9)	11 (29.7)
No, n (%)	49 (35.5)	94 (71.8)	41 (41.0)	68 (72.3)	8 (21.1)	26 (70.3)
% Difference from Placebo	---	-36.2	---	-31.3	---	-49.2
95% CI	---	[-47.4, -25.2]	---	[-44.6, -18.1]	---	[-68.8, -29.6]
p-value	---	<0.0001	---	<0.0001	---	<0.0001

*Source: Study 14-005 Clinical Study Report, Table 22, page 120.*

**Secondary Endpoint: Percentage of Subjects Assessed as Worse on CGI-C**

At the end of the randomized withdrawal period, a higher percentage of subjects who received placebo had their condition rated by their clinician as worse on the CGI-C compared to subjects who received solriamfetol (63.8% vs. 28.7%, respectively), resulting in a statistically significant difference in the percentage of subjects described as worse by their clinician. The difference was statistically significant for both the subgroup of narcolepsy patients and the subgroup of OSA patients.

**Other Endpoints**

- At the beginning of the randomized withdrawal period, mean FOSQ-10 total scores were comparable for the placebo and solriamfetol treatment groups (17.14 and 17.40, respectively). At the end of the randomized withdrawal period, subjects in the placebo group had a mean FOSQ-10 score of 14.60, compared with a mean score of 16.60 for subjects who continued to receive solriamfetol. The resulting LS mean difference of 1.7

between the placebo and solriamfetol groups was statistically significant in favor of solriamfetol ( $p < 0.0001$ ). The LS mean difference between placebo and solriamfetol was also statistically significant for subjects with narcolepsy and subjects with OSA.

- For both the placebo and solriamfetol groups, minimal changes in OSA therapy were noted from the beginning to the end of the randomized withdrawal period. The difference between treatment groups for change in percentage of nights therapy was used was not statistically significant ( $p = 0.5040$ ).

### **Efficacy Results – Open-Label Phase**

- For the combined OSA and narcolepsy groups, mean and median ESS scores remained below 10 at all timepoints assessed in the open-label phase. For subjects with narcolepsy, most mean ESS scores remained at or below 11 postbaseline.
- On both the CGI-C and PGI-C, the majority of subjects had improvement at every postbaseline assessment.
- Improvement was noted in functional outcome assessment measures over the course of the study.

### **Use of the 75 mg Dose of Solriamfetol in Study 14-005**

Because the 75 mg/day dose of solriamfetol did not separate from placebo on one of the co-primary endpoints in Study 14-002, the use of the 75 mg dose in Study 14-005 was reviewed. Of the 227 subjects with narcolepsy in Study 14-005, 15 subjects were stabilized on the 75 mg dose during the open-label phase (7%), while 66 were stabilized on the 150 mg dose (29%) and 145 were stabilized on the 300 mg dose (64%). Of the 15 subjects on the 75 mg dose, four discontinued the study for lack of efficacy. Five discontinued due to an adverse event, and one was discontinued because of treatment non-compliance. Five subjects on the 75 mg dose either completed the study or were still in the study at the cutoff date of April 21, 2017. The small number of subjects who were stabilized on the 75 mg dose, and the smaller number of subjects who remained on this dose through either a completion date or the study cutoff date, brings into question the usefulness of the 75 mg dose for the general population of patients with EDS and narcolepsy.

### **Dose/Dose Response**

Dose response was not explicitly assessed in this study. Each subject was individually titrated to identify the most efficacious and tolerable dose for that subject.

### **Durability of Response**

Maintenance of effect was demonstrated for both patients with narcolepsy and patients with OSA. Following six months of open-label treatment, subjects were randomized to either

placebo or continued treatment with solriamfetol. Subjects randomized to placebo showed greater subjective sleepiness on the ESS and evaluation of their overall condition as worsened on the PGI-C compared with subjects who continued solriamfetol. See Table 40 and Table 41.

## 7. Integrated Review of Effectiveness

### 7.1. Assessment of Efficacy Across Trials – EDS in Narcolepsy

#### 7.1.1. Primary Endpoints

The solriamfetol clinical development program for treatment of EDS in narcolepsy included two 12-week placebo-controlled trials and an open-label, long-term trial with a randomized-withdrawal period. For all studies, the efficacy population is the same as the modified Intent-to-Treat (mITT) population, and is defined as all subjects who were randomized, received at least one dose of study drug after randomization, and had a baseline assessment and at least one post-baseline assessment on the primary efficacy endpoint or on both co-primary endpoints.

The MWT, ESS, CGI-C, and PGI-C were classified differently as endpoints in the three studies.

- In Study ADX-N05-202, the MWT and CGI-C were co-primary endpoints, and the ESS and PGI-C were secondary endpoints.
- In Study 14-002, the MWT and ESS were co-primary endpoints, and the PGI-C and CGI-C were secondary endpoints.
- In Study 14-005, the MWT was not performed. The ESS was the primary endpoint, and the PGI-C and CGI-C were secondary endpoints.

A summary of the key features across these trials is provided in Table 42.

**Table 42: Key Features Across Narcolepsy Trials in the Solriamfetol Development Program**

Trial	ADX-N05-202	14-002	14-005
<b>Trial Phase</b>	Phase 2	Phase 3	Phase 3
<b>Design</b>	Multicenter, randomized, double-blind, placebo-controlled, parallel-group	Multicenter, double-blind, placebo-controlled, parallel-group	Multicenter, open-label, with double-blind, placebo-controlled, randomized withdrawal period
<b>Number of Study Centers; Locations (n)</b>	28 United States (28)	59 Canada (5) France (3) Germany (5) Netherlands (1) United States (45)	79 Canada (6) Finland (3) France (4) Germany (6) Italy (1)

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			Netherlands (2) United States (57)
<b>Study Population</b>	Narcolepsy Total solriamfetol: 44 Total PBO: 49	Narcolepsy Total solriamfetol: 177 Total PBO: 59	Narcolepsy and OSA Total narcolepsy: 80
<b>Treatment Dose/Duration</b>	solriamfetol 150 mg QD x 4 wks, then 300 mg QD x 8 wks  PBO QD x 12 wks	solriamfetol QD x 12 wks, three dose groups: 75 mg, 150 mg, 300 mg  PBO QD x 12 wks	solriamfetol QD x 52 wks, three dose groups: 75 mg, 150 mg, 300 mg  Randomized withdrawal: continue drug x 2 wks vs PBO x 2 wks
<b>Total Enrollment (Enrolled/Efficacy Population)</b>	Total: 93/90  solriamfetol: 44/43  PBO: 49/47	Total: 239/231  solriamfetol: 179/174 75 mg: 59/59 150 mg: 60/55 300 mg: 60/59  PBO: 60/58	Total: 638/282  Narcolepsy: 203/79
<b>Primary Efficacy Endpoint</b>	<i>Co-primary endpoints:</i>  [1] Change in the mean sleep latency time from the first four test sessions of the MWT from baseline to last post-baseline assessment  [2] Percentage of patients with improvement in the CGI-C at last postbaseline assessment	<i>Co-primary endpoints:</i>  [1] Change from baseline to Week 12 in mean sleep latency time from MWT  [2] Change from baseline to Week 12 in ESS score	Change in ESS score from baseline to end of two-week randomized withdrawal period
<b>Key Secondary Efficacy Assessments</b>	[1] Change in mean sleep latency time from MWT (average of the first four test sessions) from baseline to Week 4  [2] Change in ESS score from baseline to Week 4 and at last post-baseline assessment  [3] Percentage of subjects reported as improved on the CGI-C scores at Week 4  [4] Percentage of subjects	Percentage of subjects with improvement on PGI-C at Week 12 and at last post-baseline assessment	[1] PGI-C from beginning to end of the two-week randomized-withdrawal period  [2] CGI-C from beginning to end of the two-week randomized-withdrawal period

	with improvement on PGI-C at Week 4 and at last post-baseline assessment		
<b>Other Secondary Efficacy Assessments</b>	Change in mean sleep latency time from each of five individual MWT trials from baseline to Week 4 and at last post-baseline assessment	<p>[1] Change in mean sleep latency time from MWT (average of the first four test sessions) from baseline to Week 4</p> <p>[2] Change in mean sleep latency time from each of five individual MWT trials from baseline to Week 4 and at last post-baseline assessment</p> <p>[3] Change in ESS score from baseline to Week 4 and at last post-baseline assessment</p> <p>[4] Percentage of subjects with improvement on PGI-C score at Week 4</p> <p>[5] Percentage of subjects with improvement on CGI-C score at Week 4</p>	-----

*Adapted from NDA-211230 Integrated Summary of Efficacy, Table 1, page 19.*

**Primary Endpoint Results: Study ADX-N05-202**

For both primary endpoints, change in mean sleep latency on MWT and change from baseline in CGI-C score, the difference in mean change from baseline was statistically significant in favor of the solriamfetol group compared to placebo. The results on primary endpoints are summarized in Table 43.

**Table 43: Study ADX-N05-202, Primary Endpoint Results**

Endpoint	Placebo (N=47)	solriamfetol (N=43)
<b>Change in Mean Sleep Latency (min) from Baseline to Week 12</b>		
n	45	40
Mean change (SD)	2.1 (7.9)	12.8 (10.3)
p-value	---	< 0.0001
<b>Change in CGI-C Score from Baseline to Week 12</b>		
n	47	43
Observed values, mean (SD)	3.5 (1.1)	2.2 (1.2)
Proportion of subjects experiencing improvement, n (%)	18 (38.3)	37 (86.0)
p-value	---	< 0.0001

Adapted from ISE, Table 9, page 50.

**Primary Endpoint Results: Study 14-002**

The first primary endpoint was the change in MWT from baseline to Week 12. On this endpoint, the difference in mean change from baseline was statistically significant compared to placebo for the 75 mg, 150 mg, and 300 mg doses. The second primary endpoint was the change in ESS score from baseline to Week 12. On this endpoint, the difference in mean change from baseline was statistically significant compared to placebo for the 150 mg and 300 mg doses, but not for the 75 mg dose. The amount of improvement showed a dose-related effect for both endpoints, with subjects treated with the 300 mg dose showing the most improvement. The results on the primary endpoints are summarized in Table 44.

**Table 44: Study 14-002, Primary Endpoint Results**

Endpoint	Placebo (N=58)	solriamfetol		
		75 mg (N=59)	150 mg (N=55)	300 mg (N=59)
<b>Change in MWT from Baseline to Week 12</b>				
LS Mean (SE)	2.1 (1.3)	4.7 (1.3)	9.8 (1.3)	12.3 (1.4)
LS Mean Difference	---	2.6	7.7	10.1
95% CI	---	(-1.0, 6.3)	(4.0, 11.3)	(6.4, 13.9)
p-value	---	0.1595	< 0.0001	< 0.0001
<b>Change in ESS Score from Baseline to Week 12</b>				
LS Mean (SE)	-1.6 (0.7)	-3.8 (0.7)	-5.4 (0.7)	-6.4 (0.7)
LS Mean Difference	---	-2.2	-3.8	-4.7
95% CI	---	(-4.0, -0.3)	(-5.6, -2.0)	(-6.6, -2.9)
p-value	---	0.0211	< 0.0001	< 0.0001

Adapted from ISE, Table 6, page 41.

**Primary Endpoint Results: Study 14-005**

The long-term, open-label study enrolled subjects from previous solriamfetol studies who were diagnosed with either narcolepsy or OSA. The study included a two-week titration phase, followed by a maintenance phase of up to 50 weeks. During the maintenance phase, a two-week randomized withdrawal period was conducted. At the end of the randomized withdrawal period, subjects resumed solriamfetol treatment at the same dose that they had received at the beginning of that period. At the time of the data cutoff, 278 subjects who had entered the randomized withdrawal period had completed the study.

The primary endpoint for the randomized withdrawal period was the change in ESS score from the beginning to the end of this period. For subjects with narcolepsy, the mean ESS score during the randomized withdrawal period increased by a mean of 4.9 for the placebo group, compared with a mean increase of 1.1 for subjects who remained on solriamfetol, with a statistically significant LS mean difference of -3.8 ( $p < 0.0001$ ) in favor of solriamfetol. Efficacy results for the entire study population and for the narcolepsy group are shown in Table 45.

**Table 45: Study 14-005, Primary Endpoint Results, Entire Study Population and Narcolepsy Group**

Endpoint	Overall		Narcolepsy	
	Placebo (N=141)	Combined solriamfetol (N=139)	Placebo (N=40)	Combined solriamfetol (N=38)
<b>Change in ESS</b>				
LS mean (SE)	5.3 (0.4)	1.6 (0.4)	4.9 (0.6)	1.1 (0.6)
LS mean difference	---	-3.7	---	-3.8
95% CI	---	(-4.8, -2.7)	---	(-5.5, -2.2)
p-value	---	< 0.0001	---	< 0.0001

*Adapted from ISE, Table 9, page 50.*

**7.1.2. Secondary and Other Endpoints**

**Secondary Endpoint Results: Study ADX-N05-202**

The key secondary endpoint was the change in ESS score from baseline to Week 12. The mean change from baseline in ESS total score was statistically significant in favor of the solriamfetol treatment group. At Week 12, the average score decreased by 8.5 points for the solriamfetol group versus 2.5 points for the placebo group ( $p < 0.0001$ ).

**Secondary Endpoint Results: Study 14-002**

The key secondary endpoint was the percentage of subjects reporting improvement at Week 12 on the PGI-C. The percentage difference compared with placebo was statistically significant for

the 75 mg dose ( $p = 0.0023$ ), the 150 mg dose ( $p < 0.0001$ ) and the 300 mg dose ( $p < 0.0001$ ). The percentage of subjects reporting improvement showed a dose-related effect, with 28.1%, 38.5%, and 45.1% of subjects reporting improvement after treatment with the 75 mg, 150 mg, and 300 mg doses, respectively.

### **Secondary Endpoint Results: Study 14-005**

At the end of the randomized withdrawal period, 78.9% of subjects in the placebo group rated their condition as worse on the PGI-C, compared with 29.7% of subjects who continued solriamfetol treatment, resulting in a statistically significant LS mean difference of -49.2% ( $p < 0.001$ ).

#### **7.1.3. Subpopulations**

Among the subpopulation analyses conducted by the Applicant was one to assess the impact of baseline severity of sleepiness on the magnitude of drug response. The analysis was conducted on data from Study 14-003, which enrolled only patients diagnosed with OSA. This patient population was chosen because patients with OSA showed a wider range of levels of sleepiness than patients with narcolepsy. Details of this analysis are presented in Section 7.2.3. The Applicant concluded that OSA subjects with more severe levels of sleepiness may derive greater benefit from higher solriamfetol doses. An additional possible conclusion from this analysis is that patients with EDS and narcolepsy may in general require higher doses than 75 mg, since those patients are likely to have daytime sleepiness in the more severe range.

#### **7.1.4. Dose and Dose-Response**

Study 14-002 evaluated three doses of solriamfetol, and thus allows for dose-response evaluation. The co-primary endpoints were the MWT and the ESS. Subjects with narcolepsy were randomized 1:1:1:1 to receive solriamfetol 75 mg/day, 150 mg/day, 300 mg/day, or placebo. The 75-mg dose did not separate from placebo on the MWT, but did separate from placebo on the ESS. The 150-mg dose and the 300-mg dose both separated from placebo on both co-primary endpoints, with a more pronounced effect at the 300-mg dose.

Study 14-005 was an open-label study incorporating a randomized-withdrawal phase. In the open-label phase, subjects were titrated to an efficacious and tolerable dose in the Titration Phase and then entered an open-label Stable Dose Phase. For patients with narcolepsy in Study 14-005, the percentage of subjects stabilized at the 75 mg, 150 mg, and 300 mg doses were 7.0%, 29.2%, and 64.2%, respectively. Thus, a larger percentage of patients with narcolepsy were stabilized at the 300 mg dose than at any of the lower doses.

### 7.1.5. Onset, Duration, and Durability of Efficacy Effects

In the 12-week placebo-controlled studies ADX-N05-202 and 14-002, effects of solriamfetol on reducing excessive sleepiness as measured by the MWT, ESS, and PGI-C were observed by Week 1 and persisted through Week 12. In Study 14-002, improvements in ability to stay awake were maintained throughout the day at the 150 mg and 300 mg doses of solriamfetol, as shown by the difference from placebo in LS mean change of MWT sleep latency on the five trials.

Maintenance of effect for patients with narcolepsy was demonstrated in Study 14-005. Following six months of open-label treatment, subjects were randomized to either placebo or continued treatment with solriamfetol. Subjects randomized to placebo showed greater subjective sleepiness on the ESS and evaluation of their overall condition as worsened on the PGI-C compared with subjects who continued solriamfetol.

## 7.2. Assessment of Efficacy Across Trials – EDS in Obstructive Sleep Apnea

### 7.2.1. Primary Endpoints

The solriamfetol clinical development program for treatment of EDS in OSA included one 12-week placebo-controlled trial, a six-week randomized-withdrawal trial, and an open-label, long-term trial with a randomized-withdrawal phase. For all studies, the efficacy population is the same as the modified Intent-to-Treat (mITT) population, and is defined as all subjects who were randomized, received at least one dose of study drug after randomization, and had a baseline assessment and at least one post-baseline assessment on the primary efficacy endpoint or on both co-primary endpoints.

For both Study 14-003 and Study 14-004, the MWT and ESS were co-primary endpoints. The MWT was not performed in Study 14-005. In that study, the ESS was the primary endpoint. In all three studies, the PGI-C and CGI-C were secondary endpoints.

A summary of the key features across these trials is provided in Table 46.

**Table 46: Key Features Across OSA Trials in the Solriamfetol Development Program**

Trial	14-003	14-004	14-005
<b>Trial Phase</b>	Phase 3	Phase 3	Phase 3
<b>Design</b>	Multicenter, randomized, double-blind, placebo-controlled	Multicenter, double-blind, placebo-controlled, randomized withdrawal	Multicenter, open-label, with double-blind, placebo-controlled, randomized withdrawal period

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<b>Number of Study Centers; Locations (n)</b>	59 Canada (5) France (3) Germany (5) Netherlands (1) United States (45)	34 Finland (3) France (3) Germany (2) Sweden (1) United States (25)	79 Canada (6) Finland (3) France (4) Germany (6) Italy (1) Netherlands (2) United States (57)
<b>Study Population</b>	OSA Total solriamfetol: 355 Total PBO: 119	OSA Total solriamfetol: 174	Narcolepsy and OSA Total OSA: 412
<b>Treatment Dose/Duration</b>	solriamfetol QD x 12 wks, four dose groups: 37.5 mg, 75 mg, 150 mg, 300 mg  PBO QD x 12 wks	Open-label period: solriamfetol QD x 4 wks, three dose groups: 75 mg, 150 mg, 300 mg  Randomized withdrawal: continued drug x 2 wks vs PBO x 2 wks	solriamfetol QD x 52 wks, three dose groups: 75 mg, 150 mg, 300 mg  Randomized withdrawal: continue drug x 2 wks vs PBO x 2 wks
<b>Total Enrollment (Enrolled/Efficacy Population)</b>	Total: 476/459  solriamfetol: 357/345 37.5 mg: 59/56 75 mg: 61/58 150 mg: 118/116 300 mg: 119/115  PBO: 119/114	Total: 174/124  Randomized withdrawal: 62 solriamfetol 62 PBO	Total: 638/282  OSA: 412/226
<b>Primary Efficacy Endpoint</b>	<i>Co-primary endpoints:</i>  [1] Change in mean sleep latency time from the first four test sessions of the MWT from baseline to Week 12  [2] Change in ESS score from baseline to Week 12	<i>Co-primary endpoints:</i>  [1] Change in mean sleep latency time from the first four test sessions of the MWT from Week 4 to Week 6  [2] Change in ESS score from Week 4 to Week 6	Change in ESS score from baseline to end of two-week randomized withdrawal period
<b>Key Secondary Efficacy Assessments</b>	Percentage of patients improved on PGI-C scores at Week 12	Percentage of subjects with improvement on PGI-C at the end of the randomized-withdrawal period (Week 6)	[1] PGI-C from beginning to end of the two-week randomized-withdrawal period  [2] CGI-C from beginning to end of the two-week randomized-withdrawal period
<b>Other Secondary</b>	[1] Change in mean sleep	[1] Percentage of subjects	-----

<b>Efficacy Assessments</b>	latency time from MWT (avg of first four test sessions) from baseline to Week 4  [2] Change in mean sleep latency from each of five individual MWT trials  [3] Change in ESS score from baseline to Weeks 1, 4, and 8 and at last post-baseline assessment  [4] Percentage of subjects with improvement on PGI-C score at Weeks 1, 4, and 8  [5] Percentage of subjects with improvement on CGI-C score at Weeks 4 and 12	with improvement on CGI-C at the end of the randomized-withdrawal period (Week 6)  [2] Change in FOSQ-10 total score from beginning of the titration phase (Day -1) to the end of the stable-dose phase (Week 4), and from the end of the stable-dose phase (Week 4) to the end of the randomized-withdrawal period (Week 6)	
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*Adapted from NDA-211230 Integrated Summary of Efficacy, Table 1, page 19.*

### Primary Endpoint Results: Study 14-003

The two primary endpoints were the change in MWT from baseline to Week 12 and the change in ESS score from baseline to Week 12. The difference in mean change from baseline was statistically significant compared to placebo for both endpoints and for all four solriamfetol dose groups. The amount of improvement generally showed a dose-related effect, with the exception that LS mean difference for the 37.5 mg group (-1.9) was of slightly greater magnitude than the LS mean difference from placebo for the 75 mg group (-1.7). The results on the primary endpoints are summarized in Table 47.

**Table 47: Study 14-003, Primary Endpoint Results**

Endpoint	Placebo (N=114)	Solriamfetol			
		37.5 mg (N=56)	75 mg (N=58)	150 mg (N=116)	300 mg (N=115)
<b>Change in MWT from Baseline to Week 12</b>					
LS Mean (SE)	0.2 (1.0)	4.7 (1.4)	9.1 (1.4)	10.9 (1.0)	13.0 (1.0)
LS Mean Difference	---	4.5	8.9	10.7	12.8
95% CI	---	(1.2, 7.9)	(5.6, 12.1)	(8.1, 13.4)	(10.0, 15.6)
p-value	---	0.0086	< 0.0001	< 0.0001	< 0.0001
<b>Change in ESS Score from Baseline to Week 12</b>					
LS Mean (SE)	-3.3 (0.5)	-5.1 (0.6)	-5.0 (0.6)	-7.7 (0.4)	-7.9 (0.5)
LS Mean Difference	---	-1.9	-1.7	-4.5	-4.7
95% CI	---	(-3.4, -0.3)	(-3.2, -0.2)	(-5.7, -3.2)	(-5.9, -3.4)
p-value	---	0.0161	0.0233	< 0.0001	<0.0001

*Adapted from ISE, Table 7, page 44.*

**Primary Endpoint Results: Study 14-004**

This was a randomized-withdrawal study with three two-week treatment phases: a titration phase, a stable-dose phase, and a double-blind randomized-withdrawal phase. The two primary endpoints were the change in MWT from baseline at the end of open-label treatment (Week 4) to the end of the randomized-withdrawal period (Week 6) and the change in ESS score from Week 4 to Week 6.

At the beginning of the randomized withdrawal period, subjects who were randomized to continue treatment experienced a mean change from baseline to Week 4 in sleep latency of 17.6 minutes (from 12.7 to 30.3 minutes). Their mean change from baseline to Week 4 in ESS total score was -9.5 (15.6 to 6.1).

Subjects who continued to receive solriamfetol in the randomized period maintained the treatment benefits noted at Week 4, with little change in mean sleep latency and minimal change in ESS score. The placebo group showed a reduction in mean sleep latency and an increase in ESS score at the end of the randomized withdrawal period. The differences between the solriamfetol and placebo groups were statistically significant for both endpoints. The results on the primary endpoints are summarized in Table 48.

**Table 48: Study 14-004, Primary Endpoint Results**

Endpoint	Placebo (N=62)	Combined solriamfetol (N=60)
<b>Change in MWT from Week 4 to Week 6</b>		
LS Mean (SE)	-12.1 (1.3)	-0.97 (1.4)
LS Mean Difference	---	11.2
95% CI	---	(7.8, 14.6)
p-value	---	< 0.0001
<b>Change in ESS Score from Week 4 to Week 6</b>		
LS Mean (SE)	4.5 (0.7)	-0.1
LS Mean Difference	---	-4.6
95% CI	---	(-6.4, -2.8)
p-value	---	< 0.0001

*Adapted from ISE, Table 8, page 47.*

**Primary Endpoint Results: Study 14-005**

The long-term, open-label study enrolled subjects from previous solriamfetol studies who were diagnosed with either narcolepsy or OSA. The study included a two-week titration phase, followed by a maintenance phase of up to 50 weeks. During the maintenance phase, a two-week randomized withdrawal period was conducted. At the end of the randomized withdrawal period, subjects resumed solriamfetol treatment at the same dose that they had received at the beginning of that period. At the time of the data cutoff, 278 subjects who had entered the randomized withdrawal period had completed the study.

The primary endpoint for the randomized withdrawal period was the change in ESS score from the beginning to the end of this period. For subjects with OSA, the mean ESS score during the randomized withdrawal period increased by a mean of 4.9 for the placebo group, compared with a mean increase of 1.1 for subjects who remained on solriamfetol, with a statistically significant LS mean difference of -3.8 ( $p < 0.0001$ ) in favor of solriamfetol. Efficacy results for the entire study population and for the OSA group are shown in Table 49.

**Table 49: Study 14-005: Primary Endpoint Results, Entire Study Population and OSA Group**

Endpoint	Overall		OSA	
	Placebo (N=141)	Combined solriamfetol (N=139)	Placebo (N=101)	Combined solriamfetol (N=101)
<b>Change in ESS</b>				
<b>LS mean (SE)</b>	5.3 (0.4)	1.6 (0.4)	4.9 (0.5)	1.1 (0.5)
<b>LS mean difference</b>	---	-3.7	---	-3.8
<b>95% CI</b>	---	(-4.8, -2.7)	---	(-5.1, -2.4)
<b>p-value</b>	---	< 0.0001	---	< 0.0001

*Adapted from ISE, Table 9, page 50.*

### 7.2.2. Secondary and Other Endpoints

#### Secondary Endpoint Results: Study 14-003

The key secondary endpoint was the percentage of subjects reporting improvement at Week 12 on the PGI-C. The percentage difference compared with placebo was statistically significant for the 75 mg dose ( $p = 0.0035$ ), the 150 mg dose ( $p < 0.0001$ ) and the 300 mg dose ( $p < 0.0001$ ), but not for the 37.5 mg dose group ( $p = 0.4447$ ). The percentage of subjects reporting improvement showed a generally dose-related effect, with 6.2%, 23.3%, 40.5%, and 39.6% of subjects reporting improvement after treatment with the 37.5 mg, 75 mg, 150 mg, and 300 mg doses, respectively.

#### Secondary Endpoint Results: Study 14-004

At the beginning of the randomized withdrawal period, 63.1% of subjects who were randomized to continue treatment reported being “much improved,” and 33.6% reported being “very much improved.” After two weeks of treatment in the randomized withdrawal period, 12 subjects (20%) who continued treatment with solriamfetol reported being “minimally worse”, “much worse,” or “very much worse,” compared to 31 subjects (50%) who were randomized to placebo. The difference between the groups was statistically significant ( $p = 0.0005$ ).

#### Secondary Endpoint Results: Study 14-005

At the end of the randomized withdrawal period, 59.0% of subjects with OSA in the placebo group rated their condition as worse on the PGI-C, compared with 27.7% of subjects who continued solriamfetol treatment, resulting in a statistically significant LS mean difference of -31.3% ( $p < 0.0001$ ).

### 7.2.3. Subpopulations

Among the subpopulation analyses conducted by the Applicant was one to assess the impact of baseline severity of sleepiness on the magnitude of drug response. Subgroups of “more severe sleepiness” and “less severe sleepiness” were defined by calculating median values for MWT, ESS, and CGIs across all treatment groups in the Pool1 population of subjects participating in the 12-week placebo-controlled trials. The cutoff values for defining sleepiness as more severe were MWT ≤ 11.375, ESS > 15 (range = 0 to 24), and CGIs > 4 (range = 1 to 7). The narcolepsy population was found to have more severe excessive sleepiness overall.

The Applicant presented analysis results for the OSA population, which demonstrated a wider range of sleepiness. The results are based on data from Study 14-003, which enrolled only patients diagnosed with OSA. The magnitude of treatment effect as measured by change in MWT mean sleep latency was smaller in the more severe subgroup when treated with the 37.5 mg and 75 mg doses of solriamfetol. The magnitude of treatment effect as measured by change in ESS score was smaller in the more severe subgroup when treated with the 37.5 mg and 150 mg doses of solriamfetol. Summary results from the subgroup analysis are presented in Table 50 (MWT) and Table 51 (ESS).

**Table 50: Study 14-003, MWT Mean Sleep Latency (min) by Subgroups of Baseline Severity of Sleepiness (OSA Subjects)**

	Placebo (N=113)	Solriamfetol			
		37.5 mg (N=56)	75 mg (N=57)	150 mg (N=115)	300 mg (N=115)
MWT > 11.375 (less severe)					
n	54	31	28	60	50
Baseline mean (SD)	18.7 (4.8)	19.1 (6.1)	18.2 (5.0)	17.9 (5.6)	19.0 (5.3)
Week 12 mean (SD)	16.0 (10.2)	24.1 (12.2)	25.6 (10.0)	26.7 (10.1)	30.0 (10.5)
LS mean (SE)	-3.1 (1.4)	4.5 (1.9)	7.2 (2.0)	8.5 (1.4)	10.7 (1.6)
LS mean difference	---	7.6	10.3	11.6	13.8
p-value	---	0.0013	< 0.0001	< 0.0001	< 0.0001
MWT ≤ 11.375 (more severe)					
n	56	23	28	54	63
Baseline mean (SD)	10.7 (6.9)	9.7 (8.0)	10.2 (6.1)	11.6 (6.9)	10.9 (7.2)
Week 12 mean (SD)	11.0 (8.4)	12.3 (8.8)	19.1 (11.3)	23.4 (11.0)	25.0 (10.9)
LS mean (SE)	-0.2 (1.3)	2.04 (2.0)	8.4 (2.0)	11.7 (1.3)	14.3 (1.3)
LS mean difference	---	2.3	8.6	12.0	14.5
p-value	---	0.3414	0.0004	< 0.0001	< 0.0001

Source: adapted from NDA-211230 ISE, Table 40, page 154.

**Table 51: Study 14-003, ESS Scores by Subgroups of Baseline Severity of Sleepiness (OSA Subjects)**

ESS Score	Placebo (N=113)	Solriamfetol			
		37.5 mg (N=56)	75 mg (N=57)	150 mg (N=115)	300 mg (N=115)
ESS ≤ 15 (less severe)					
n	61	32	33	65	63
Baseline mean (SD)	13.0 (1.5)	12.5 (1.7)	12.4 (1.4)	12.7 (1.7)	12.8 (1.6)
Week 12 mean (SD)	10.7 (3.2)	8.0 (4.4)	9.3 (4.6)	6.0 (3.4)	6.6 (4.4)
LS mean (SE)	-2.1 (0.5)	-4.7 (0.7)	-3.1 (0.7)	-7.0 (0.5)	-6.3 (0.5)
LS mean difference		-2.6	-1.0	-4.9	-4.2
p-value		0.0028	0.2424	< 0.0001	< 0.0001
ESS > 15 (more severe)					
n	52	24	24	50	52
Baseline mean (SD)	18.4 (2.1)	18.5 (2.0)	18.3 (2.0)	18.3 (2.2)	17.9 (1.9)
Week 12 mean (SD)	14.2 (5.0)	12.6 (5.5)	10.7 (6.0)	9.7 (5.3)	7.8 (5.4)
LS mean (SE)	-4.4 (0.7)	-5.5 (1.2)	-7.6 (1.1)	-8.4 (0.8)	-9.8 (0.8)
LS mean difference		-1.1	-3.2	-4.0	-5.4
p-value		0.4351	0.0144	0.0002	< 0.0001

Source: adapted from NDA-211230 ISE, Table 41, page 157.

The Applicant concludes that OSA subjects with more severe levels of sleepiness may derive greater benefit from higher solriamfetol doses. An additional possible conclusion from this analysis is that patients with EDS and narcolepsy may in general require higher doses than 75 mg, since those patients are likely to have more severe excessive daytime sleepiness.

#### 7.2.4. Dose and Dose-Response

Study 14-003 evaluated four doses of solriamfetol, and thus allows for dose-response evaluation. The co-primary endpoints were the MWT and the ESS. Subjects with OSA were randomized 1:1:2:2:2 to receive solriamfetol 37.5 mg/day, 75 mg/day, 150 mg/day, 300 mg/day, or placebo. All four doses separated from placebo on both co-primary endpoints. An incremental dose-response effect was observed on the MWT. The magnitude of effect on ESS was more pronounced in the 150-mg and 300-mg dose groups than in the two lower dose groups. On the key secondary endpoint of PGI-C, changes compared to placebo were not statistically significant for the 37.5-mg dose, but were significant for the other three doses.

In both Studies 14-004 and 14-005, subjects were titrated to an efficacious and tolerable dose in the Titration Phase and then entered an open-label Stable Dose Phase. For Study 14-004, the percentage of subjects stabilized at the 75 mg, 150 mg, and 300 mg doses were 10.0%, 32.6%, and 57.4%, respectively. For patients with OSA in Study 14-005, the percentage of subjects stabilized at the 75 mg, 150 mg, and 300 mg doses were 11.9%, 34.5%, and 53.6%, respectively. Thus, in both studies, a larger percentage of patients with OSA were stabilized at the 300 mg

dose than at any of the lower doses.

### **7.2.5. Onset, Duration, and Durability of Efficacy Effects**

In the 12-week placebo-controlled study 14-003, effects of solriamfetol on reducing excessive sleepiness as measured by the MWT, ESS, and PGI-C were observed by Week 1 and persisted through Week 12. Improvements in ability to stay awake were maintained throughout the day at the 75-mg, 150-mg, and 300-mg doses of solriamfetol, as shown by the difference from placebo in LS mean change of MWT sleep latency on each of the five MWT trials.

Maintenance of effect for patients with OSA was demonstrated in Studies 14-004 and 14-005. Following four weeks of open-label treatment in Study 14-004 or six months of open-label treatment in Study 14-005, subjects were randomized to either placebo or continued treatment with solriamfetol. Subjects randomized to placebo showed a decline in wakefulness on the MWT (14-004 only), greater subjective sleepiness on the ESS, and evaluation of their overall condition as worsened on the PGI-C compared with subjects who continued solriamfetol.

## **7.3. Additional Efficacy Considerations**

### **7.3.1. Considerations on Benefit in the Postmarket Setting**

Subjects with work schedules characterized by a need to be alert at night, such as shift workers, were excluded from all five of the pivotal studies. Thus, the results of these studies cannot be used to assess the efficacy of solriamfetol for the maintenance of wakefulness at night.

## **7.4. Integrated Assessment of Effectiveness**

### **7.4.1. Treatment of EDS in Narcolepsy**

The Sponsor conducted three trials to assess the efficacy of solriamfetol in patients with narcolepsy. All three trials were positive, though not for all proposed doses. Study 14-002 was positive on both primary endpoints for the 150 mg and 300 mg doses, but not for the 75 mg dose. The use of the 75 mg dose in patients with narcolepsy was not evaluated in Study ADX-N05-202 or Study 14-005. The trials provide adequate evidence of efficacy to approve solriamfetol 150 mg/day and solriamfetol 300 mg/day for the treatment of EDS in narcolepsy.

#### 7.4.2. Treatment of EDS in Obstructive Sleep Apnea

The Sponsor conducted three trials to assess the efficacy of solriamfetol in subjects with OSA. All three trials were positive. Study 14-003 was positive on both primary endpoints for the 37.5 mg, 75 mg, 150 mg, and 300 mg doses. The trials provide adequate evidence of efficacy to approve solriamfetol for the treatment of EDS in narcolepsy.

## 8. Review of Safety

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### 8.1. Safety Review Approach

This safety review is based on analysis of data from three 12-week placebo-controlled trials (ADX-N05-202, a Phase 2 study in subjects with narcolepsy; 14-002, a Phase 3 study in subjects with narcolepsy; and 14-003, a Phase 3 study in subjects with OSA), one six-week Phase 3 randomized withdrawal study in subjects with OSA (14-004), and one Phase 3 long-term safety study enrolling subjects with either narcolepsy or OSA (14-005). The long-term study is still ongoing. The Applicant set a cutoff date of April 21, 2017, for inclusion of data from the long-term study in the NDA application.

The Applicant also submitted results from Phase 1 safety and pharmacokinetic studies, a thorough QT study, two abuse liability studies, and three Phase 2 studies in subjects with major depressive disorder. For these studies, this safety review will focus on deaths, non-fatal serious adverse events, and adverse events that resulted in dropout or withdrawal from the study.

For the Integrated Summary of Safety, the Applicant pooled studies of similar design and/or diagnosis. Pool 1 consists of the 12-week, placebo-controlled, parallel groups studies in subjects with narcolepsy or OSA (ADX-N05-202, 14-002, and 14-003). Pool 2 consists of all data from studies in narcolepsy and OSA, including short-term studies and studies with exposures considerably longer than the exposures in the placebo-controlled studies. Pool 2 results are presented by exposure duration regardless of dose, do not include events that occurred during placebo exposure, and do not display events that occurred during the safety follow-up period. Pool 3 combines data from three studies in subjects with major depressive disorder. Pool 4 combines data from six studies conducted in healthy subjects. This safety review will place the greatest emphasis on the data from Pool 1, as it allows comparison of drug-treated and placebo-treated subjects, as well as comparison of subjects who received different drug doses. The Pool 2 data will be analyzed to identify adverse events that may be related to longer-term drug exposure.

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In the Statistical Analysis Plan for the Integrated Summary of Safety, the Applicant defined treatment emergent adverse events (TEAEs) as those adverse events with onset date on or after the first dose date. An adverse event with a missing or partially missing start or stop date is treated as a TEAE if the available year or month does not allow determination of whether the event would have occurred before or after the first dose date. TEAEs in Pool 1 and Pool 2 may differ because the first dose dates may be different, given that placebo treatment is included in Pool 1 but not in Pool 2. This safety review will use the Applicant's definition for TEAEs, and will specify the pool used for each component of the analysis.

The Applicant has selected adverse events of interest for narcolepsy and OSA based on the pharmacology of solriamfetol, experience from clinical studies, comorbidities in the target patient population, safety issues associated with current available treatments, and regulatory considerations for new molecular entities. The adverse events of interest are in the areas of cardiovascular disorders, psychiatric disorders, neurologic disorders, hypersensitivity/skin reactions, renal and urinary disorders, muscle injury, and hepatic injury. To monitor for adverse events of interest, the Applicant included additional safety monitoring in the study protocols. The results of these assessments will be presented in Section 8.5, Analysis of Submission-Specific Safety Issues.

The Applicant has coded all AEs from verbatim terms into Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0 preferred terms. TEAEs are presented by System Organ Class (SOC) and Preferred Term (PT). This safety review will include analysis using queries designed to aggregate TEAEs coded with similar Preferred Terms.

## 8.2. Review of the Safety Database

### 8.2.1. Overall Exposure

Across the solriamfetol development program through April 21, 2017, approximately 1600 unique subjects have been exposed to solriamfetol. A total of 934 subjects comprise the all narcolepsy and OSA safety population. Of these subjects, 322 have narcolepsy and 612 have OSA. The ongoing open-label extension study contributes data from 638 subjects, 226 with narcolepsy and 412 with OSA, as of April 21, 2017. The MDD population is comprised of 468 subjects, 327 who received solriamfetol and 141 who received placebo. The healthy volunteer population includes 371 subjects, 251 who received solriamfetol and 120 who received placebo. The overall safety population includes 25 subjects with renal disease ranging in severity from mild to end-stage renal disease, and 61 subjects with a history of recreational drug use. 238 subjects were exposed to both solriamfetol and active comparators in Studies (b) (4) MDD-201 (paroxetine, n=122), (b) (4) SAB-101 (methylphenidate, n=18), 14-001 (phentermine, n=40), and 15-002 (moxifloxacin, n=58).

The Integrated Summary of Safety (ISS) submitted by the Applicant is based on data for 1508 subjects from the safety population of six narcolepsy or OSA studies, three studies in MDD, and six studies in healthy volunteers. The primary focus of the Integrated Summary of Safety is data from the 12-week placebo-controlled studies in narcolepsy and OSA. This includes 328 subjects with narcolepsy and 471 subjects with OSA, for a total of 799 subjects. Of these subjects, 573 received solriamfetol and 226 received placebo. The main focus of comparisons is among the five treatment groups, solriamfetol 37.5 mg, 75 mg, 150 mg, 300 mg, and placebo, and between the combined solriamfetol groups and placebo. Note that all subjects in the solriamfetol 37.5 mg group were subjects with OSA. The composition of the Pool 1 population is shown in Table 52.

**Table 52: Composition of the Pool 1 Population (Safety Population)**

	Placebo	Combined solriamfetol	37.5 mg	75 mg	150 mg	300 mg
Total no. of subjects	226	573	58	120	218	217
Narcolepsy subjects	108	220	N/A	59	102	99
OSA subjects	118	353	58	61	116	118
<b>Source</b>						
ADX-NO5-202 (N=93)	49	44	N/A	N/A	44 (4 weeks)	44 (8 weeks)
14-002 (N=240)	59	177	N/A	59	59	59
14-003 (N=440)	119	355	58	62	117	118

Source: NDA-211230 Integrated Summary of Safety, Table 3, page 45.

According to the ICH E1 Guideline, the safety database should include at least 1500 subjects with short-term exposure to the investigational drug, 300-600 subjects with exposure for at least six months, and 100 subjects with exposure for at least a year.

Table 53 depicts the duration of drug exposure for the short-term studies in the solriamfetol development program. A total of 1461 subjects were exposed to solriamfetol during short-term studies.

**Table 53: Duration of Drug Exposure for Short-Term Studies in the Solriamfetol Development Program**

Study ID	Population	Drug: Treated	Drug: Completed	Duration of Treatment
<b>Placebo-Controlled Studies in Narcolepsy and OSA</b>				
ADX-N05-201	Narcolepsy	33	33	4 weeks
ADX-N05-202 (pivotal)	Narcolepsy	44	36	12 weeks
14-002 (pivotal)	Narcolepsy	177	143	12 weeks
14-003 (pivotal)	OSA	355	303	12 weeks
14-004 (pivotal)	OSA	174	158	6 weeks
<b>Studies in MDD</b>				
(b) (4) -9801	MDD	27	14	8 weeks
(b) (4) USA-010	MDD	61	50	3 weeks
(b) (4) MDD-201	MDD	245	176	6 weeks
<b>Healthy Volunteer Studies</b>				
(b) (4) -9603-01	Healthy volunteers	24	24	9 weeks
(b) (4) P01-101	Health volunteers	4	4	16 days
(b) (4) -9702-01	Healthy volunteers	40	39	14 days
(b) (4) NED-1	Healthy volunteers	93	87	14 days
15-002	Healthy volunteers	60	55	61 days
15-009	Healthy volunteers	32	32	43 days
<b>Special Population Studies</b>				
(b) (4) SAB-101	Recreational drug users	18	18	6 days
14-001	Recreational drug users	43	37	6 weeks
15-001	Healthy volunteers and impaired renal function	31	30	33-41 days
<b>TOTALS</b>		<b>1461</b>	<b>1239</b>	

Source: adapted from NDA-211230 Integrated Summary of Safety, Table 1, page 34.

For Study 14-005, the long-term, open-label study, 638 subjects were exposed to solriamfetol as of April 21, 2017. This includes 255 subjects with exposures of less than six months, 365 subjects with exposures from six to twelve months, and 18 subjects with exposures of more than twelve months. While the number of subjects with exposures of at least a year is low, the original study design allowed for exposure to solriamfetol for only up to 52 weeks. The number of days of exposure beyond 52 weeks was within protocol-specified windows for the majority of subjects. Two subjects exceeded the protocol-specified windows between multiple visits, resulting in protocol violations.

*Reviewer's Comment:* The protocol design limited the number of subjects who would be

exposed to solriamfetol for more than one year. However, the safety database does meet the ICH E1 Guideline for short-term exposure and for exposure for at least six months.

### 8.2.2. **Relevant characteristics of the safety population:**

Demographics for the subjects in the 12-week placebo-controlled studies are shown in Table 54. The mean age, BMI, heart rate, and baseline systolic blood pressure of subjects was generally comparable across the solriamfetol dose groups and the placebo group, with the exception of the 37.5 mg dose group. This dose was used only in the OSA studies, and thus this dose group includes subjects who are older and have more underlying cardiovascular illness than the safety population as a whole. The 37.5 mg dose group also had a higher proportion of male subjects than the other dose groups or the placebo group. Baseline diastolic blood pressure was comparable across the dose groups.

The subjects enrolled in the three 12-week placebo-controlled trials of solriamfetol (Pool 1) were predominantly from US sites. Among the 573 Pool 1 subjects who were exposed to solriamfetol, 87.78 percent of those subjects were from US sites. The subpopulations of Pool 1 subjects broken down by diagnosis (narcolepsy or OSA) were also predominantly from US sites. Of the 220 subjects with a diagnosis of narcolepsy and exposed to solriamfetol, 77.27% were from US sites. Of the 353 subjects with a diagnosis of obstructive sleep apnea and exposed to solriamfetol, 94.33% were from US sites.

The subjects enrolled in all studies of solriamfetol (Pool 2) also were predominantly from US sites. Among the 930 Pool 2 subjects who were exposed to solriamfetol, 86.99% were from US sites. The subpopulations of Pool 2 subjects broken down by diagnosis (narcolepsy or OSA) were also predominantly from US sites. Of the 321 subjects with a diagnosis of narcolepsy and exposed to solriamfetol, 80.06% were from US sites. Of the 609 subjects with a diagnosis of obstructive sleep apnea and exposed to solriamfetol, 90.64% were from US sites.

The majority of subjects in the 12-week placebo-controlled studies were White and not Hispanic or Latino. The only difference in race among the dose groups was a higher proportion of Black or African American subjects in the 75 mg group compared with the other solriamfetol dose groups. However, the difference does not appear to be large enough to prevent comparisons across dose groups for African American subjects. In addition, the proportion of African American subjects in the 75 mg group was comparable to that of the placebo group. The numbers of subjects with racial classifications of American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander, and Multiple were all small, limiting the possibility of subgroup analysis on these racial groups.

**Table 54: 12-Week Placebo-Controlled Studies, Demographics and Baseline Characteristics, Safety Population**

Characteristic	Placebo N=226	Combined solriamfetol N=573	37.5 mg N=58	75 mg N=120	150 mg N=218	300 mg N=217
<b>Age (years)</b>						
n	226	573	58	120	218	217
Mean (SD)	45.6 (15.4)	47.4 (14.1)	57.1 (10.2)	45.5 (15.0)	46.4 (13.4)	45.8 (13.9)
Median	48.0	49.0	59.5	47.0	48.0	46.0
Range	18, 74	18, 75	33, 72	18, 74	19, 75	18, 72
<b>Sex, n (%)</b>						
Male	119 (52.7)	290 (50.6)	39 (67.2)	56 (46.7)	102 (46.8)	106 (48.9)
Female	107 (47.4)	283 (49.4)	19 (32.8)	64 (53.3)	116 (53.2)	111 (51.2)
<b>Race, n (%)</b>						
American Indian or Alaskan Native	1 (0.4)	2 (0.4)	0	0	1 (0.5)	1 (0.5)
Asian	4 (1.8)	20 (3.5)	3 (5.2)	1 (0.8)	7 (3.2)	10 (4.6)
Black or African American	45 (19.9)	95 (16.6)	10 (17.2)	25 (20.8)	34 (15.6)	37 (17.1)
Native Hawaiian or Other Pacific Islander	1 (0.4)	3 (0.5)	0	0	2 (0.9)	2 (0.9)
White	173 (76.6)	445 (77.7)	45 (77.6)	92 (76.7)	170 (78.0)	164 (75.6)
Multiple	2 (0.9)	8 (1.4)	0	2 (1.7)	4 (1.8)	3 (1.4)
<b>Ethnicity, n (%)</b>						
Hispanic or Latino	17 (7.5)	45 (7.9)	6 (10.3)	9 (7.5)	18 (8.3)	12 (5.5)
Not Hispanic or Latino	209 (92.5)	528 (92.2)	52 (89.7)	111 (92.5)	200 (91.7)	205 (94.5)
<b>Region, n (%)</b>						
North America	215 (95.1)	524 (91.5)	55 (94.8)	104 (86.7)	206 (94.5)	199 (91.7)
Europe	11 (4.9)	49 (8.6)	3 (5.2)	16 (13.3)	12 (5.5)	18 (8.3)
<b>Country, n (%)</b>						
USA	206 (91.2)	503 (87.8)	52 (89.7)	100 (83.3)	199 (91.3)	192 (88.5)
Germany	6 (2.7)	29 (5.1)	3 (5.2)	7 (5.8)	6 (2.8)	13 (6.0)
Canada	9 (4.0)	21 (3.7)	3 (5.2)	4 (3.3)	7 (3.2)	7 (3.2)
France	2 (0.9)	12 (2.1)	0	6 (5.00)	3 (1.4)	3 (1.4)
Finland	2 (0.9)	4 (0.7)	0	2 (1.7)	1 (0.5)	1 (0.5)
Italy	0	4 (0.7)	0	1 (0.8)	2 (0.9)	1 (0.5)
Netherlands	1 (0.44)	0	0	0	0	0
<b>Height (cm)</b>						

n	226	573	58	120	218	217
Mean (SD)	171.5 (9.5)	171.1 (9.6)	172.6 (10.9)	171.0 (9.6)	170.7 (9.0)	170.7 (9.7)
Median	170.2	171.5	174.7	172.6	170.2	170.2
Range	150, 200	144, 203	144, 191	150, 191	150, 193	146, 203
<b>Weight (kg)</b>						
n	226	573	58	120	218	217
Mean (SD)	90.3 (20.6)	91.6 (20.8)	101.7 (19.6)	89.9 (19.5)	89.5 (20.6)	89.4 (21.3)
Median	89.9	90.7	99.8	91.0	88.9	88.0
Range	47.4, 157.1	37.4, 153.3	52.4, 145.8	53.0, 143.8	37.4, 153.3	37.4, 152.5
<b>Body Mass Index (kg/m<sup>2</sup>)</b>						
n	226	573	58	120	218	217
Mean (SD)	30.6 (5.9)	31.2 (6.1)	34.1 (5.3)	30.8 (6.2)	30.5 (5.8)	30.5 (6.2)
Median	30.7	31.1	34.5	30.6	30.9	30.4
Range	13.6, 44.4	15.6, 45.4	20.5, 45.0	18.4, 44.3	15.6, 45.4	15.6, 45.2
<b>Baseline Heart Rate (beats/min)</b>						
n	226	573	58	120	218	217
Mean (SD)	73.5 (11.2)	75.4 (11.3)	77.0 (11.5)	75.6 (10.2)	74.0 (11.9)	74.9 (11.5)
Median	72.8	74.5	77.5	76.0	72.5	74.0
Range	49, 102	45, 111	50, 108	50, 106	45, 111	45, 107
<b>Baseline Systolic Blood Pressure (mmHg)</b>						
n	226	573	58	120	218	217
Mean (SD)	122.7 (14.0)	124.4 (13.5)	128.2 (14.2)	124.2 (12.7)	123.0 (14.7)	123.3 (12.7)
Median	123.0	123.0	129.9	122.5	122.0	122.5
Range	91, 160	89, 183	97, 170	94, 156	89, 183	89, 159
<b>Baseline Diastolic Blood Pressure (mmHg)</b>						
n	226	573	58	120	218	217
Mean (SD)	75.5 (8.8)	77.2 (8.6)	77.9 (9.6)	77.2 (9.3)	76.4 (8.8)	77.0 (8.0)
Median	75.8	77.5	77.5	77.5	77.2	77.0
Range	54, 108	51, 111	55, 102	51, 111	53, 103	59, 97

Source: NDA-211230 ISS, Table 5.3.5.3.1.2.1, page 520.

### 8.2.3. Adequacy of the safety database:

With the exception of the small number of subjects with drug exposures greater than one year, the safety database appears to meet the ICH E1 guidelines. Subjects in the safety population were predominantly from sites in the United States, so generalizability of results to the US population is not a concern. The small numbers of subjects in racial categories other than White or African American will limit the degree to which the safety analysis can be segmented by racial subgroups. Overall, the safety database appears adequate for assessment of the safety of solriamfetol for use in the United States population as a whole.

### 8.3. Adequacy of Applicant's Clinical Safety Assessments

#### 8.3.1. Issues Regarding Data Integrity and Submission Quality

The Applicant provided original Case Report Forms (CRFs) for all deaths, serious adverse events, and adverse events leading to discontinuation. It appears that adverse events were coded appropriately, based on review of the AE data files for each of the pivotal trials. The organizational structure of the submitted data allowed for adequate review of the safety data.

Table 55 shows the total number of Pool 1 subjects, the total number of Pool 1 TEAEs, and the average number of TEAEs reported per subject, by country. For the three countries with the largest enrollments (USA, Germany, and Canada), the number of TEAEs reported per subject is comparable (from 2.14 to 2.66). For countries with smaller enrollments, there is wider variation in the average number of TEAEs reported per subject. This variability may be related to the small sample sizes for those countries, which could cause the experiences of individual subjects to bias the statistics. For example, the one subject in the Netherlands with seven TEAEs reported, a subject in the placebo arm of Study 14-003, does not appear to be representative of the TEAE experiences of the Pool 1 population as a whole. Overall, there does not appear to be a clear pattern of over-reporting or under-reporting TEAEs for sites in any one country compared to the others.

**Table 55: Pool 1 TEAEs Per Subject, By Country**

Country	Pool 1 Subjects	TEAEs Reported	TEAEs per Subject
USA	709	1519	2.14
DEU	35	93	2.66
CAN	30	72	2.40
FRA	14	20	1.43
FIN	6	11	1.83
ITA	4	1	0.25
NLD	1	7	7.00
<b>TOTALS</b>	<b>799</b>	<b>1723</b>	<b>2.16</b>

Source: reviewer-generated table.

#### 8.3.2. Categorization of Adverse Events

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 to classify events under primary system organ class (SOC) and preferred

term (PT). Adverse Events of Interest (AEOIs) were defined by Standardized MedDRA Queries (SMQ, narrow and broad) from MedDRA version 18.0 and ad hoc queries (AHQ).

For Pool 1, treatment groups are the dose level of solriamfetol: 37.5 mg, 75 mg, 150 mg, 300 mg, or placebo. If a subject received multiple dose levels of solriamfetol either within a study or across studies, assignment of the subject's adverse event data to a treatment group is based on the subject's mean daily dose or by the modal daily dose received, and is not included in multiple dose levels. As the mean daily dose may not be a planned dose, it will be categorized as  $\leq 37.5$  mg,  $> 37.5$  mg and  $\leq 75$  mg,  $> 75$  mg and  $\leq 150$  mg, or  $> 150$  mg and  $\leq 300$  mg in the analysis.

For Pool 2, treatment groups are time periods of drug exposure, regardless of dose: Week 1, Week 2, Weeks 3-4, Weeks 5-12, Weeks 13-24, Weeks 25-36, and Week 37 or later. Exposure length is summarized both as a continuous variable and a categorical variable, using the categories  $< 2$  weeks,  $\geq 2$  weeks,  $\geq 1$  month,  $\geq 2$  months,  $\geq 3$  months,  $\geq 6$  months,  $\geq 9$  months, and  $\geq 12$  months. For subjects entering the extension study 14-005, total solriamfetol exposure length is defined as the sum of exposure in the parent study and in the extension study. If a subject received placebo during the randomized withdrawal period of either the parent study or the extension study, this time period is excluded from calculation of the duration of solriamfetol exposure.

The Applicant defines treatment-emergent adverse events (TEAEs) as adverse events with onset date on or after the first dose date. Events that occurred in the follow-up period are included, so TEAEs may occur after the last dose date. An adverse event with a completely or partially missing start or stop date (e.g., with only the year or month and year recorded) is treated as a TEAE if the relationship of the event to the first dose date cannot be determined from the available date information.

TEAE incidence is defined as the number of subjects having an event that began in a certain period divided by the total number of subjects at risk (i.e., exposed) at the beginning of the period. The denominator is based on the subject pool used for the analysis. For calculations of TEAE incidence, multiple events experienced by the same subject are counted only once in the numerator. For Pool 2, treatments are defined by time intervals rather than by dose. Treatments are considered independent. If a subject had an event that started in Week 1, and the same event started in Week 5, the subject is counted in the numerator of TEAE incidence for both periods.

### 8.3.3. Routine Clinical Tests

The clinical trials in the solriamfetol development program included routine laboratory assessments at regular intervals. Subjects were interviewed at each study visit to assess potential adverse events. The assessments completed are adequate to assess safety generally,

and to assess population-specific and drug class-specific safety issues.

For hematology and serum chemistry, subjects having markedly abnormal laboratory values are categorized as "markedly low" or "markedly high" using the criteria in Table 56. A positive urinalysis, including urine pregnancy test, is considered "markedly high" for analysis purposes.

**Table 56: Reference Ranges and Markedly Abnormal Values for Clinical Lab Tests**

Parameter	Conventional Unit	Reference Range ( <sup>(b) (4)</sup> Labs)	Markedly Abnormal Values	
			Low value	High value
<b>Hematology</b>				
Hemoglobin	g/dl	M: 13.0-17.5 F: 11.5-16.0	M: ≤ 12.0 F: ≤ 10.0	NA
WBC	10 <sup>3</sup> /μL	4.5-11.0	≤ 2.8	≥ 16
Platelets	10 <sup>3</sup> /μL	130-400	≤ 100	≥ 550
Neutrophils	10 <sup>3</sup> /μL	1.8-7.7	≤ 1.0	NA
Lymphocytes	10 <sup>3</sup> /μL	1.0-4.8	≤ 0.5	NA
Eosinophils	10 <sup>3</sup> /μL	0.0-0.5	NA	≥ 2.0
<b>Chemistry</b>				
Alkaline phosphatase	U/L	M: 53-129 F: 42-98	NA	≥ 3 x ULN
Total bilirubin	mg/dL	0.3-1.2	NA	≥ 2.0
AST (SGOT)	U/L	M: 14-39 F: 14-34	NA	≥ 3 x ULN
				≥ 5 x ULN
				≥ 10 x ULN
ALT (SGPT)	U/L	M: 0-44 F: 0-33	NA	≥ 3 x ULN
				≥ 5 x ULN
				≥ 10 x ULN
<b>Hy's Law Lab Criteria (patient must meet all three criteria below)</b>				
[1] Total bilirubin	mg/dL	0.3=1.2		> 2 x ULN
[2] AST (SGOT)	U/L	M: 14-39 F: 14-34		≥ 3 x ULN
[3] ALT (SGPT)	U/L	M: 0-44 F: 0-33		≥ 3 x ULN
Creatinine	mg/dL	M: 0.70-1.30	NA	≥ 2.0
eCreatinine clearance (Cockcroft-Gault calculation)	ml/Min	≥ 60	< 60	NA
Sodium	mmol/L	136-145	≤ 127	≥ 155
Potassium	mmol/L	3.5-5.1	≤ 3.0	≥ 6.0

Glucose, fasting	mg/dL	60-99	≤ 50	≥ 200
Calcium	mg/dL	8.6-10.2	≤ 7.6	≥ 11.5
Cholesterol, total	mg/dL	0-199	NA	≥ 300
CPK	U/L	M: 32-294 F: 33-211	NA	≥ 3 x ULN

Source: NDA-211230, Integrated Summary of Safety Statistical Analysis Plan, page 27.

## 8.4. Safety Results

### 8.4.1. Deaths

No deaths occurred during the 12-week placebo-controlled studies in narcolepsy and OSA, the studies in MDD, the studies in healthy volunteers, the studies in recreational drug users, or the studies in subjects with impaired renal function. One subject died during Study 14-005, the open-label extension study.

#### **Subject (b) (6), Study 14-005: Sepsis, Myocardial Infarction, Respiratory Failure**

The subject was a 70-year-old White male diagnosed with obstructive sleep apnea. He was treated with placebo during parent Study 14-004. On entering Study 14-005, he was started on solriamfetol 75 mg/day. The dose was titrated to 300 mg/day by Day 7. Concurrent medical illnesses included diabetes mellitus, rheumatoid arthritis, pulmonary fibrosis, coronary artery disease, and bipolar disorder. Concurrent medications included etanercept for rheumatoid arthritis, which has a black box warning regarding serious infections and sepsis. The diagnosis of bipolar disorder was not disclosed by the site in time to be included in the database for the interim lock date. The subject was hospitalized on Day 47 for a manic episode. Study drug was interrupted at an unknown date due to mania. The subject was discharged from the hospital on Day 51. Study drug was resumed at an unknown date following discharge. At some point after discharge, the subject developed weakness, fatigue, fever, and chills over the course of one to two weeks. He was rehospitalized on Day 72 for cellulitis, sepsis, and suspected pneumonia. A blood culture was positive for *Klebsiella pneumoniae*. The subject also developed *Clostridium difficile* colitis. On Day 76, the subject was diagnosed with an asymptomatic non-ST elevation myocardial infarction. This was believed to be related to demand ischemia secondary to bacteremia. On Day 94, the subject developed acute congestive heart failure, acute renal failure, progression of pulmonary fibrosis, and respiratory failure. The subject died on Day 95. The reported cause of death was sepsis. The death was assessed by the Investigator as not related to the study drug.

*Reviewer's Comment:* The investigator's assessment appears reasonable. The safety profile of solriamfetol has not revealed a pattern of an increased risk of bacteremia or sepsis.

#### 8.4.2. Serious Adverse Events

##### SAEs: Narcolepsy, Placebo-Controlled Trials

Among subjects with narcolepsy participating in the placebo-controlled trials, Studies ADX-N05-202 and 14-002, no subjects receiving placebo and three subjects (1.36%) receiving solriamfetol had SAEs.

##### **Subject (b) (6), Study ADX-N05-202: Conversion Disorder**

The subject was a 57-year-old White female with a diagnosis of narcolepsy with cataplexy, receiving solriamfetol 150 mg/day. On Day 10, the subject developed increased frequency of what she described as cataplexy attacks, with muscle weakness that prevented her from moving any of her extremities. The PI examined the subject on Day 11, and felt that there was a psychogenic cause for her symptoms. Study medication was discontinued, and she was admitted to the hospital for further evaluation, but signed herself out the following morning. CT scan, ECG, and labs were normal. PO<sub>2</sub> was low at 68 mmHg, but a pulmonary consult determined that she had no respiratory compromise. The hospital diagnosis was acute exacerbation of cataplexy, but the clinical site did not agree with this diagnosis. Symptoms were deemed to be resolved by Day 14. The subject returned to the clinical site on Day 20 after having resumed the study medication. The PI gave the diagnosis of conversion disorder, and considered the incident not to be related to the study medication.

*Reviewer's Comment:* The narrative does not indicate why the PI believed the subject's symptoms had a psychogenic cause as opposed to an exacerbation of cataplexy.

##### **Subject (b) (6), Study ADX-N05-202: Acute Cholecystitis**

The subject was a 36-year-old Black female with a diagnosis of narcolepsy without cataplexy, receiving solriamfetol 300 mg/day. The subject reported intermittent epigastric pain beginning about Day 57. She was evaluated in the emergency room four days later. X-ray revealed gallstones. The subject was referred to her primary care physician for follow-up. On Day 71 the subject returned to the emergency room with epigastric pain, nausea, and vomiting. She was admitted to the hospital, and study medication was discontinued. A cholecystectomy was performed on Day 72. The subject was discharged the following day. The surgeon's diagnosis was acute cholecystitis. The subject chose to withdraw from the study. The PI assessed the incident as probably not related to study medication.

*Reviewer's Comment:* The PI's assessment appears reasonable, considering the small number of gallbladder-related adverse events in the solriamfetol clinical development program.

##### **Subject (b) (6) Study 14-002: Non-Cardiac Chest Pain and Anxiety**

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The subject was a 63-year-old White female receiving solriamfetol 150 mg/day. On Day 52, subject had a study-scheduled ECG. She was told that some abnormalities were found, and she became anxious. The subject presented to the emergency room complaining of midsternal chest pain with left hand radiation, which had begun four hours earlier. She was no longer having chest pain by the time she was seen in the emergency room. Study drug was interrupted. ECG in the ER demonstrated sinus tachycardia at 100 bpm, ST-segment depression in inferior lead, normal axis, and normal intervals. These findings were a change from prior ECG results. Chest x-ray showed no active cardiopulmonary disease. Troponin T was <0.010 ng (reference range, 0.000 - 0.029 ng). The subject was given a single subcutaneous dose of enoxaprin 50 mg and of heparin 5000 units, and a single dose of short-acting metoprolol tartrate 50 mg. She was admitted for further evaluation. A myocardial perfusion stress test was normal with no evidence of infarction or ischemia. The subject was discharged on the same day as admission. Study drug was reintroduced on Day 53. The patient had no recurrence of chest pain after reintroducing the study drug. The subject completed the study, and entered the long-term, open-label extension study (14-005). The PI assessed the incident as not related to the study medication.

*Reviewer's Comment:* The PI's assessment appears reasonable, considering the onset of symptoms immediately after a stressful event, rapid resolution of symptoms, and negative rechallenge.

#### **SAEs: Narcolepsy, Long-Term Trial**

Among subjects with narcolepsy participating in the long-term, open-label solriamfetol trial, Study 14-005, four experienced SAEs.

#### **Subject (b) (6) Study 14-005: Suicide Attempt**

The subject was a 50-year-old White male with a diagnosis of narcolepsy with cataplexy. The subject had received solriamfetol 150 mg/day during parent Study 14-002. On entering Study 14-005, he was started on solriamfetol 75 mg/day. The dose was titrated to 300 mg/day by Day 7. On Day 189, after receiving upsetting personal news, the subject took an overdose of approximately 120 tablets of ibuprofen, 120 tablets of ephedrine, and one liter of alcohol. No overdosage of solriamfetol was reported. The subject went to bed. The following day he vomited twice, then voluntarily went to the hospital, where he was admitted with a diagnoses of depression and suicide attempt. The study drug was withdrawn. Depression was resolved by Day 213, and the subject was discharged from the hospital. He returned for an early termination visit on Day 217. The subject's C-SSRS responses were negative for any suicidal ideation or suicidal behavior through the reporting cut-off date of April 21, 2017. The investigator assessed the incident as not related to the study drug.

*Reviewer's Comment:* No previous history of depression was reported in the clinical study report. The suicide attempt reportedly was temporally related to a stressful event. The subject had tolerated the 150 mg dose of solriamfetol during Study 14-002, and the 300 mg dose of solriamfetol from Day 7 through Day 189 of Study 14-005. It is reasonable to conclude that the suicide attempt was related to the stressful event and not to the study drug.

**Subject (b) (6) Study 14-005: Anaphylactic Reaction**

The subject was a 28-year-old White female with a diagnosis of narcolepsy. The subject received placebo during the parent Study 14-002. She was titrated to a solriamfetol dose of 300 mg/day during Study 14-005, but experienced fatigue which continued despite a decrease in dose to 150 mg/day. On Day 40, study drug was withdrawn due to lack of efficacy, and the fatigue resolved. The subject returned for an early termination visit on Day 54. On Day 66, the subject began treatment with modafinil for narcolepsy. She began having generalized itching shortly after taking the first dose of modafinil, and went to an urgent care facility. While being evaluated at the urgent care facility, the subject had an anaphylactic reaction, with the sensation of throat swelling, intra-oral twitching, and mild edema of the posterior oropharynx. Symptoms improved with intramuscular epinephrine and intramuscular methylprednisolone. The investigator assessed the incident as not related to the study drug.

*Reviewer's Comment:* Agree with this assessment. The study drug had been discontinued twenty-six days prior to the anaphylactic reaction.

**Subject (b) (6) Study 14-005: Worsening Migraine**

The subject was a 28-year-old White female with a diagnosis of narcolepsy and history of migraines since 2012. The subject had received solriamfetol 75 mg/day during parent Study 14-002. On entering Study 14-005, she was started on solriamfetol 75 mg/day. The dose was titrated to 300 mg/day by Day 8. On Day 180, the subject met with a neurologist, who began making some adjustments in her medications for migraine. On Day 192, the subject had a severe migraine, with nausea upon standing, blurred vision, and pain. She went to the emergency department, and was treated with prochlorperazine, diphenhydramine, ketorolac tromethamine, and intravenous sodium chloride. The migraine resolved on the same day. The subject was not admitted to the hospital. No adjustment was made in the dose of study drug. The investigator assessed the incident as unrelated to the study drug.

*Reviewer's Comment:* Agree with the investigator's assessment. The subject had tolerated the study drug during the parent study. The severe migraine was temporally related to a series of changes in her medications for migraine control.

**Subject** (b) (6) **Study 14-005: Worsening of Cluster Headaches**

The subject was a 50-year-old White male with a diagnosis of narcolepsy and a previous history of cluster headaches. The subject received placebo during parent Study 14-002. During Study 14-005 he began treatment with solriamfetol 75 mg/day, which was titrated to a dose of 150 mg/day on Day 15. The subject had several episodes of cluster headaches, beginning on Day 9, after a four-year remission from cluster headaches. Study drug was interrupted on Day 24, and was not restarted. On Day 35, the subject was hospitalized for severe cluster headache. The investigator assessed the incident as not related to the study drug. The cluster headaches resolved on Day 37, and the subject was discharged from the hospital. He was rehospitalized on Day 79 after a return of cluster headache. Neurology was consulted, and a plan was developed to adjust the patient's headache medications. Cluster headache resolved on Day 82, and the subject was discharged from the hospital. He returned for an early termination visit on Day 98.

*Reviewer's Comment:* While the investigator assessed the two hospitalizations as unrelated to the study drug, it is not clear whether the study drug had any role in the return of cluster headaches after a four-year remission.

**SAEs: OSA, Placebo-Controlled Trial**

Among subjects with OSA participating in the placebo-controlled trial, Study 14-003, two subjects receiving placebo (1.69%) and three subjects receiving solriamfetol (0.85%) experienced serious adverse events. Serious adverse events in the placebo group were back pain, goiter, road traffic accident, and sciatica. Serious adverse events in subjects treated with solriamfetol are described below.

**Subject** (b) (6) **Study 14-003: Coronary Artery Disease**

The subject was a 57-year-old White male diagnosed with obstructive sleep apnea. Past medical history included hypertension, hypercholesterolemia, and gastroesophageal reflux disease. He was randomized to receive solriamfetol 300 mg/day. He began treatment at a dose of 150 mg/day on Day 1, and was titrated to his final dose of 300 mg/day on Day 4. At the time of his Week 1 visit on Day 7, the subject reported dyspnea, cough, and sore throat that had started four days prior to randomization (Day -4). The subject was referred to his primary care physician. On Day 15, the subject developed chest discomfort, which worsened to chest pain with exertion. Study drug was withdrawn on Day 15. The subject had a cardiac consultation on Day 17, and was hospitalized for cardiac catheterization. The catheterization revealed significant disease in the early distal left anterior descending coronary artery, which was treated with a drug-eluting stent. There was no evidence of acute myocardial infarction. The subject reported on Day 18 that the dyspnea had resolved. He was discharged from the hospital on Day 18, and was withdrawn from the study on Day 41. He had no further adverse events over the course of the study, and did not resume study drug after it was withdrawn on Day 15. The event was considered by the investigator to be unrelated to study drug.

*Reviewer's Comment:* Agree with investigator's assessment, as the subject's cardiovascular symptoms began before the first dose of study drug.

**Subject** (b) (6) **Study 14-003: Bile Duct Obstruction**

The subject was a 66-year-old Black female with a diagnosis of obstructive sleep apnea, receiving solriamfetol 37.5 mg/day. She had a past medical history of cholecystectomy in 2015. On Day 61, the subject had a TEAE of pruritic papular rash, which the investigator felt was related to the study drug. Study drug was interrupted on Day 63. Treatment was initiated with topical white soft paraffin, and the rash resolved. Study drug was resumed on Day 68, and the rash did not worsen. Beginning on Day 81, the subject had a TEAE of chromaturia. The following day she experienced vomiting, chills, and back pain. She reported to the study site on Day 83 for her overnight Week 12 PSG/MWT assessments, and received her final dose of study drug on Day 84. After her morning meal at the clinic, she developed epigastric pain and nausea. She was taken to the emergency room, where an abdominal ultrasound showed dilatation of the common bile duct. She had markedly elevated liver enzyme values for alanine aminotransferase (ALT) 9.8 x upper limit of normal (ULN), aspartate aminotransferase (AST) 4.8 x ULN, and total bilirubin 2.7 x ULN. She was admitted to the hospital. Abdominal CT scan on Day 85 revealed intrahepatic biliary duct dilatation status post cholecystectomy, prominent pancreatic duct without pancreatitis, a 2.5 cm mass in the right kidney, and no evidence of bowel obstruction. Her symptoms were felt to be the result of a retained common bile duct stone. On Day 86, endoscopic retrograde cholangio-pancreatography with stent placement was performed. The following day, the subject's liver function test values began to decrease. The subject was discharged from the hospital on Day 87. Chromaturia resolved on Day 88, and the bile duct obstruction resolved on Day 98. The PI assessed the incident as not related to the study drug.

*Reviewer's Comment:* The PI's assessment appears reasonable, as residual common bile duct stone is a known sequela of cholecystectomy.

**Subject** (b) (6) **Study 14-003: Streptococcal Endocarditis**

The subject was a 62-year-old White male with a diagnosis of obstructive sleep apnea, receiving solriamfetol 37.5 mg/day. He had a previous history of aortic valve sclerosis and replacement in 2012. On Day 24, the subject reported fever, chills, anorexia, and fatigue. He was diagnosed with moderate streptococcal endocarditis. Cultures showed *Streptococcus gordonii* sensitive to penicillin. He was initially treated on an outpatient basis, but on Day 30 he experienced syncope and collapse. He was admitted to the hospital. Results from a transesophageal electrocardiogram showed two small lesions in the bioprosthetic aortic valve. Study drug was withdrawn on Day 30. The subject began treatment with gentamicin and benzylpenicillin IV. On Day 38, the subject was deemed improved enough to be discharged from the hospital. He continued to receive IV antibiotics at home until Day 75. He returned for an early termination

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visit on Day 77. The PI assessed the incident as not related to the study drug.

*Reviewer's Comment:* This assessment appears reasonable. The clinical development program has not demonstrated a pattern of increased susceptibility to infections in subjects treated with solriamfetol.

**Subject [REDACTED] (b) (6) Study 14-003: Hyperglycemia**

The subject was a 57-year-old White male with a diagnosis of obstructive sleep apnea, receiving solriamfetol 150 mg/day. He had a previous history of diabetes mellitus diagnosed in 1995. On Day 26, the subject experienced severe hyperglycemia (lab values not included in study report). Study drug was interrupted the same day. The subject went to the emergency room on Day 28 with complaints of weakness and polyuria. He noted that he had not taken his metformin and liraglutide for several days prior to the onset of symptoms, and was not compliant with his diabetic diet. His glucose level was noted to be elevated (lab values not included in the study report). He was admitted to the hospital and started on insulin via IV. On Day 30, the subject's glucose was 139. He was discharged from the hospital the same day. The PI assessed the incident as not related to the study drug. The study drug was stopped and the patient was discontinued from the study because of the adverse event and because the subject had not been compliant with his concomitant medications, the study drug, and the study visits. He returned for an early termination visit on Day 87.

*Reviewer's Comment:* The PI's conclusion that the subject's hyperglycemia was related to his non-compliance with diabetes management appears reasonable.

**SAEs: OSA, Randomized-Withdrawal Trial**

One SAE occurred during the randomized-withdrawal trial in subjects with OSA.

**Subject [REDACTED] (b) (6) Study 14-004: Bronchitis**

The subject was a 71-year-old White female with a diagnosis of obstructive sleep apnea. She was hospitalized for bronchitis during the screening period. She began treatment with solriamfetol after resolution of the bronchitis, and completed the study.

*Reviewer's Comment:* This SAE was not related to the study drug. It occurred before the first dose of study drug.

**SAEs: OSA, Long-Term Trial**

Among subjects with OSA participating in the long-term, open-label solriamfetol trial, Study 14-005, 14 experienced SAEs. One subject with OSA, Subject [REDACTED] (b) (6) died during Study 14-005. This incident is described in Section 8.4.1, Deaths. The remaining SAEs occurring in patients

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with OSA during the long-term trial are described below.

**Subject** (b) (6) **Study 14-005: Stillbirth**

The subject was a 21-year-old Black female with a diagnosis of obstructive sleep apnea. She had received solriamfetol 150 mg/day during parent Study 14-003. On entering Study 14-005, she was started on solriamfetol 75 mg/day, and was titrated to 150 mg/day by Day 18. The subject became aware that she was pregnant after the Day 98 visit, but she did not inform the study site. All urine pregnancy tests done by the clinical site up to that point had been negative. The subject's last dose of study drug was on Day 193. On Day 199, she withdrew consent, saying that scheduling the study visits had become too difficult. On Day 257, the subject reported that she had delivered a full-term stillbirth. The subject declined to release obstetrical records. The investigator was able to retrieve records from the subject's emergency room visit on Day 257. However, the subject stated that several details in the emergency room record were incorrect. The emergency room records indicated that the emergency room visit was for a head injury following a fall, and that a urine pregnancy test was negative. The investigator initially assessed the stillbirth as related to the study drug, because of the temporal relationship between the drug and the stillbirth. A retrospective review by a consulting obstetrician concluded that the event of stillbirth was doubtful.

*Reviewer's Comment:* The discrepancies between the patient's report of the incident and data in the emergency room record makes it difficult to determine whether the SAE of stillbirth actually occurred.

**Subject** (b) (6) **Study 14-005: Atrial Fibrillation**

The subject was a 54-year-old White male with a diagnosis of obstructive sleep apnea. He received placebo during parent Study 14-003. On entering Study 14-005, he was started on solriamfetol 75 mg/day. The dose was titrated to 300 mg/day by Day 7. On Day 74, the subject went to a doctor with symptoms of restlessness and dizziness. The doctor noted abnormalities in the vital signs and ECG (results not provided). The subject was referred to the hospital, was admitted, and was diagnosed with atrial fibrillation. Study drug was discontinued on the day of admission. The subject was started on a beta blocker. The atrial fibrillation resolved on Day 75. The subject was discharged from the hospital on Day 76. The subject was discharged from the study, and returned for an early termination visit on Day 78. ECG was normal at the early termination visit. The investigator assessed the SAE as related to the study drug.

*Reviewer's Comment:* The resolution of ECG changes after discontinuation of the study drug supports the hypothesis that the SAE was related to the study drug.

**Subject** (b) (6) **Study 14-005: Chest Discomfort**

The subject was a 59-year-old White male with a diagnosis of obstructive sleep apnea. He had received solriamfetol 150 mg/day during parent Study 14-004. On entering Study 14-005, he

was started on solriamfetol 75 mg/day. The dose was titrated to 300 mg/day by Day 8. On Day 27, the subject experienced severe chest discomfort and dizziness. On Day 28, he was taken to the hospital. Nuclear stress test, laboratory testing, and head CT scan did not reveal any abnormality. The subject was discharged from the hospital on Day 29. The subject experienced recurrence of chest discomfort and dizziness, and presented to a different hospital on Day 32. Laboratory tests, ECG, head CT scan, magnetic resonance imaging and angiography of the brain, chest x-ray, and transthoracic echocardiogram were all unremarkable. Treatment with study drug was interrupted on Day 34. The chest discomfort improved, but the dizziness continued. On Day 48, the subject was started on metoprolol 12.5 mg daily. Chest discomfort resolved on Day 76. Dizziness improved, but did not resolve. Treatment with solriamfetol was reintroduced and titrated to a daily dose of 300 mg/day with no recurrence of chest discomfort and no change in dizziness. The subject continued in the study through (b) (6) (Day 287). The investigator assessed the chest discomfort and dizziness as unrelated to the study drug.

*Reviewer's Comment:* It is not clear that this SAE is unrelated to the study drug. While the subject was able to tolerate a medication rechallenge, the rechallenge was initiated after the subject was started on a beta blocker. The subject had also experienced chest pain during parent Study 14-004. During that study, the chest pain improved after the dose of solriamfetol was reduced from 300 mg to 150 mg. It is possible that the chest pain was related to the 300 mg dose of solriamfetol, and that the addition of a beta blocker allowed the patient to tolerate this higher dose.

**Subject (b) (6) Study 14-005: Cerebrovascular Accident**

The subject was a 68-year-old Black female with a diagnosis of obstructive sleep apnea. She had received solriamfetol 300 mg/day during parent Study 14-003. On entering Study 14-005, she was started on solriamfetol 75 mg/day. The dose was titrated to 150 mg/day by Day 8. On Day 119, at the end of a long car trip during which she was a passenger, she experienced difficulty speaking and confusion. In the emergency room, she had expressive aphasia and dizziness. Blood pressure was 185/83 mm Hg. Study drug was withdrawn. The subject was admitted to the intensive care unit. Magnetic resonance imaging of the brain revealed acute ischemia in the left posterior middle cerebral artery distribution. Blood pressure improved with treatment. The subject was discharged on Day 123. She continued to have slurred speech. The subject returned for an early termination visit on Day 198, and a safety follow-up visit on Day 290. The investigator assessed the incident as related to the study drug.

*Reviewer's Comment:* It is difficult to ascertain definitively whether the cerebrovascular accident was related to the study drug. In light of the significant neurological changes experienced by the subject, discontinuing the study drug seems prudent.

**Subject (b) (6) Study 14-005: Pulmonary Embolism**

The subject was a 44-year-old White female diagnosed with obstructive sleep apnea. She received solriamfetol 300 mg/day during parent Study 14-004. On entering Study 14-005, she was started on solriamfetol 75 mg/day. The dose was titrated to 300 mg/day by Day 7. On Day 23, the subject had a fall on slippery pavement, resulting in clavicle and ankle fractures. On Day 31, a CT scan revealed a severe pulmonary embolism, and angiography revealed deep vein thrombosis. The subject was hospitalized on the same day, and study drug was withdrawn. The pulmonary embolism and deep vein thrombosis were not resolved but had improved by Day 34, and the subject was discharged from the hospital. The investigator assessed the pulmonary embolism as not related to the study drug, but instead to the deep vein thrombosis, which was related to the fall.

*Reviewer's Comment:* The fall could have been related to the study drug if it made the subject dizzy. The subject had a prior history of vertigo prior to entering the parent study. She did experience motion sickness during Study 14-005, beginning on Day 7. This was treated with cyclizine hydrochloride 50 mg q day, but was considered by the investigator to be unrelated to the study drug. More detailed review of the subject's medical record would be needed to assess whether she had experienced any worsening of vertigo at the time of the fall on Day 23.

**Subject (b) (6) Study 14-005: Fall with Head Trauma**

The subject was a 33-year-old White female diagnosed with obstructive sleep apnea. The subject had received placebo during parent Study 14-003. During Study 14-005 she was started on solriamfetol 75 mg/day, and was titrated to a dose of 300 mg/day. The dose was decreased to 150 mg/day due to hand tremors. On Day 111, the subject became intoxicated from alcohol at home and fell backwards onto a tile floor. She presented to the emergency room with pain and bleeding from the right external ear canal and decreased hearing on the right. CT scan of the head revealed right parietal and temporal skull fractures. The subject's blood alcohol level was 319 mg/dL (reference range for toxicity: 150-350 mg/dL). The subject was admitted to the hospital for observation, was given antibiotics and pain medication, and was discharged the same day with a three-day supply of antibiotics and pain medication. Study drug was interrupted from Day 112 to Day 114, and resumed on Day 115. However, the subject was withdrawn from the study on Day 140 due to the adverse events of alcohol intoxication and head trauma. The investigator assessed the events as not related to the study drug.

*Reviewer's Comment:* Agree with the investigator's assessment, as the fall and head trauma occurred in the context of acute alcohol intoxication.

**Subject (b) (6) Study 14-005: Increased Blood Pressure, Vertigo**

The subject was a 59-year-old White male diagnosed with obstructive sleep apnea. The subject had received solriamfetol 75 mg/day during parent Study 14-003. During Study 14-005, the solriamfetol dose was titrated to 150 mg/day. On Day 84, the subject experienced nausea and

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severe headache. He had run out of his blood pressure medication, lisinopril, four days prior to this. He went to the emergency room, and systolic blood pressure was in the 180-200 mm Hg range. He was kept in the emergency room for observation. He received hydralazine for elevated blood pressure, ondansetron for nausea, and hydromorphone for headache. All three problems resolved by the following day, Day 85. The subject was not admitted to the hospital. The study drug was withdrawn on Day 93 due to the nausea, headache, and episode of increased blood pressure. He was hospitalized on Day 98 due to vertigo and increased blood pressure. His blood pressure medications were adjusted, and he was discharged from the hospital on Day 100. The investigator assessed the adverse events as not related to the study drug.

*Reviewer's Comment:* Agree with the investigator's assessment. The blood pressure elevation began after the subject ran out of lisinopril, improved with treatment, and recurred after the subject was withdrawn from the study drug.

**Subject** (b) (6) **Study 14-005: Chest Pain**

The subject was a 45-year-old White male diagnosed with obstructive sleep apnea. The subject had received solriamfetol 37.5 mg/day during parent Study 14-003. During Study 14-005, his dose was titrated up to 150 mg/day by Day 5. The subject self-titrated his dose to 300 mg/day on Day 14. On Day 14, the subject experienced jitteriness, dizziness, and hypervigilance. The dose of study drug was reduced back to 150 mg/day, and all three symptoms resolved by Day 15. On Day 22, the subject reported mild chest pain, and stated that the chest pain had started on Day 18. The subject was admitted to the hospital for evaluation. No cardiac cause for the chest pain was identified. The subject was prescribed glyceryl trinitrate for chest pain. The cause of the chest pain was reported as unknown. The investigator assessed the chest pain as unrelated to the study drug. Treatment with study drug was withdrawn on Day 23. The chest pain resolved by Day 24, and the subject was discharged from the hospital on Day 24. The subject returned for an early termination visit on Day 33.

*Reviewer's Comment:* The cause of the subject's chest pain remains unclear. While the chest pain resolved after the study drug was withdrawn, the cardiology evaluation did not reveal a cause for the chest pain, and the subject had tolerated the study drug in the parent study. It is possible that the chest pain was related to the higher dose of study drug used for this subject in Study 14-005.

**Subject** (b) (6) **Study 14-005: Acute Cholecystitis, Duodenal Ulcer Hemorrhage**

The subject was a 56-year-old Asian male diagnosed with obstructive sleep apnea. He received placebo during parent Study 14-003. During Study 14-005, he was started on solriamfetol 75 mg/day, and was titrated to a dose of 300 mg/day by Day 19. On Day 128, the subject went to the emergency room with epigastric pain and nausea. Treatment with study drug was discontinued. Abdominal ultrasound revealed multiple gallstones in the right upper quadrant.

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He was admitted to the hospital and underwent laparoscopic cholecystectomy and lysis of adhesions. He was in the intensive care unit overnight due to episodes of low blood pressure following surgery. Cardiac enzymes were negative. The subject's blood pressure gradually improved, and he was discharged from the hospital on Day 133. The subject was rehospitalized on Day 174 with complaints of black tarry stools, cough, dizziness, lightheadedness, and chills. He had no abdominal pain. On Day 175, an esophagogastroduodenoscopy demonstrated a duodenal bulb ulcer with active bleeding. The bleeding was treated with bipolar cautery. The subject improved, and was discharged from the hospital on Day 178. He returned to the study site for an early termination visit on Day 212. The investigator assessed the acute cholecystitis and duodenal ulcer hemorrhage as unrelated to the study drug.

*Reviewer's Comment:* It is unclear whether there was any relationship between the study drug and the two SAEs experienced by the subject. However, the safety database does not suggest a pattern of new cases of either acute cholecystitis or duodenal ulcer in patients treated with solriamfetol.

**Subject** (b) (6) **Study 14-005: Angina Pectoris**

The subject was a 69-year-old White male with a diagnosis of obstructive sleep apnea. He received placebo during parent Study 14-003. During Study 14-005 he began treatment with solriamfetol 75 mg/day. The dose was titrated to 300 mg/day on Day 8. On Day 45, the subject experienced severe angina pectoris, shortness of breath, nausea, diaphoresis, fatigue, back pain, headache, and left upper arm pain. He received glyceryl trinitrate in the emergency room, which alleviated the symptoms. He was admitted to the hospital for observation. On Day 46, study drug was interrupted due to angina pectoris. Cardiac workup including ECG, troponin I, creatine phosphokinase, chest x-ray, chest CT angiography, and myocardial nuclear stress test revealed only coronary artery calcifications and slight elevation of creatine phosphokinase to 204 IU/L (reference range not given). The subject was diagnosed with atypical chest pain. He was started on acetylsalicylic acid and metoprolol. He was discharged from the hospital on Day 46. Study drug was resumed on Day 48. The subject experienced colitis on Day 48, and study drug again was interrupted. The subject was started on antibiotics, and the event resolved on Day 51. Study drug was resumed. However, the subject withdrew his consent to continue the study on Day 59. He returned for an early termination visit on Day 88. At that visit, his creatine phosphokinase had returned to the normal range. The incident of angina pectoris was assessed by the investigator as not related to the study drug.

*Reviewer's Comment:* The subject had a previous history of chest pain, beginning in 1996. However, it is not clear that the study drug was unrelated to this incident of angina pectoris. The administration of glyceryl trinitrate and interruption of study drug occurred very close in time, making it difficult to assess which intervention resulted in resolution of the chest pain.

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**Subject** (b) (6) **Study 14-005: Malignant Melanoma**

The subject was a 76-year-old White male diagnosed with obstructive sleep apnea. The subject had a history of previous surgery for malignant melanoma removal in 2010. The subject had received solriamfetol 150 mg/day during parent Study 14-003. On entry into Study 14-005, the subject was started on solriamfetol 75 mg/day, with titration of the dose to 150 mg/day on Day 4. On Day 130, the subject was notified that a skin biopsy revealed malignant melanoma of his mid-upper back. The subject was seen by a dermatologist and scheduled for an oncology consultation. No additional results or findings were provided for this incident. As of Day 176, (b) (6) the subject was continuing in the study. The investigator assessed the incident as unrelated to the study drug.

*Reviewer's Comment:* Agree with the investigator's assessment. The safety database reveals no pattern of a relationship between treatment with solriamfetol and onset of malignant melanoma, and the subject had a previous history of malignant melanoma.

**Subject** (b) (6) **, Study 14-005: Non-Cardiac Chest Pain**

The subject was a 59-year-old Black female with a diagnosis of obstructive sleep apnea. The subject had received solriamfetol 75 mg/day during parent Study 14-004. She remained on the 75 mg dose during Study 14-005. On Day 183, the subject experienced pain in her chest, left shoulder, and back. The pain did not resolve after she took a dose of methocarbamol. She went to the emergency room. ECG, chest x-ray, and laboratory tests did not reveal any significant abnormality. She was admitted to the hospital for observation. Echocardiogram, nuclear exercise stress test, and myocardial perfusion imaging were normal. On Day 185, the pain resolved, and the subject was discharged from the hospital. As of Day 302, (b) (6) the subject was continuing in the study. The investigator assessed the chest pain as not related to the study drug, but related to left shoulder arthritis radiating to her chest.

*Reviewer's Comment:* The subject had a history of shoulder pain since 2000. The negative cardiac workup and the subject's ability to tolerate the study drug for four months after discharge from the hospital support the assessment that the incident was not related to the study drug.

**Subject** (b) (6) **, Study 14-005: Acute Bronchitis**

The subject was a 61-year-old White female with a diagnosis of obstructive sleep apnea. She received solriamfetol 75 mg/day during parent Study 14-004. During Study 14-005, her dose was titrated to 150 mg/day by Day 10. On Day 23, the subject went to the emergency room with cough, wheezing, and yellow sputum. She was diagnosed with acute bronchitis and admitted to the hospital. She was treated with antibiotics and bronchodilators. Study drug was interrupted from Day 27 to Day 29. The subject improved, and was discharged from the hospital on Day 29. Study drug was resumed after discharge. The subject had a second episode

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of bronchitis on Day 47. She was not hospitalized, but was started on salbutamol and fluticasone inhalers. She completed the stable dose period of the study, and was randomized to receive placebo during the double-blind randomized withdrawal period from Day 184 to Day 204. The subject did not have any further adverse events during the randomized withdrawal period. The investigator assessed the adverse event of acute bronchitis as not related to the study drug.

*Reviewer's Comment:* Agree with the investigator's assessment. The subject had a previous history of asthma, which increases the risk of bronchitis.

**Subject (b) (6) Study 14-005: Hematuria**

The subject was a 62-year-old White male diagnosed with obstructive sleep apnea. He had been taking warfarin since February 2016 for pulmonary embolism. The subject had received solriamfetol 300 mg/day during parent Study 14-004. On entering Study 14-005, the subject began solriamfetol 75 mg/day and was titrated to 300 mg/day by Day 9. On Day 184, the subject presented to the emergency room reporting that he had started urinating blood the previous day. Prothrombin time was 78.1 seconds (normal range 9.4-13.4 seconds), and INR was 7.3 (normal range 1.1 or below). The subject was diagnosed with warfarin-induced coagulopathy, and was hospitalized. Study drug was interrupted. The subject received a transfusion of fresh frozen plasma, and the warfarin dose was reduced. On Day 187, prothrombin time was 16.5 seconds, and INR was 1.5. The subject was discharged on Day 189. The hematuria continued, but was considered stable. Study drug was reintroduced on Day 191, with no worsening of the hematuria. The investigator assessed the incident as not related to the study drug.

*Reviewer's Comment:* Agree with the investigator's assessment. The hematuria improved with adjustment of the subject's warfarin dose, and did not worsen when the study drug was resumed.

**Serious Adverse Events in Other Studies**

**Subject (b) (6) Study (b) (4) MDD-201: Myocardial Infarction**

(b) (4) MDD-201 was a six-week, randomized, double-blind, parallel-group, active- and placebo-controlled study to assess the safety and efficacy of solriamfetol in the treatment of major depressive disorder. Subjects were randomized 1:1:1:1 to receive solriamfetol titrated to a target dose of 200 mg/day or 400 mg/day, placebo, or a fixed dose (20 mg/day) of paroxetine. The primary efficacy endpoint was change from baseline at Week 6 in the MADRS total score. Neither the 200-mg nor the 400-mg dose of solriamfetol was statistically significantly superior to placebo on the primary endpoint. This SAE was selected for review as part of the assessment of cardiovascular risk for patients taking solriamfetol.

The subject was a 46-year-old White male with a previous history of smoking, moderate hyperlipidemia, insomnia, and mild obesity, with BMI 26.4 kg/m<sup>2</sup>. On Day -8 the subject had a heart rate of 67 bpm by ECG and an RSR' pattern in lead V1, which was interpreted as abnormal but not clinically significant. Blood pressure was 112/80 mmHg supine and 116/84 mmHg standing. Pulse showed orthostatic changes with rate of 62 bpm supine and 88 bpm standing. The subject was randomly assigned to receive solriamfetol 100 mg twice daily. The subject reported palpitations on Day 1 and intermittently for the next 17 days. The investigator evaluated the palpitations as probably related to study medication but considered them mild in severity and took no action. The subject did not take his study medication from Days 20 to 27 (reason unknown). He restarted study medication at the scheduled visit on Day 28. Vital signs on Day 28 prior to restarting study medication showed blood pressure of 136/90 mmHg supine and 139/97 mmHg standing. Pulse showed a widening postural change, with rate of 66 bpm supine and 103 bpm standing. The subject took both doses of solriamfetol on Day 28 and the morning dose on Day 29. On Day 29, after an episode of increased physical activity, the subject experienced acute shortness of breath, diaphoresis, severe stabbing left chest and arm pain, a heavy feeling in his chest, and a fluctuating level of consciousness. He was hospitalized, diagnosed with acute myocardial infarction, and underwent angioplasty, with stent placement in the right coronary artery. The Investigator initially assessed the myocardial infarction as unlikely to be related to study drug. However, the Sponsor reclassified the event as possibly related to study drug.

*Reviewer's Comment:* It may not be possible to definitively ascertain whether the subject's myocardial infarction was related to study drug. It is notable that the subject began experiencing palpitations on the first day of exposure to study drug. We have no information on whether the subject's blood pressure was elevated on Day 20, the first day that he did not take the study medication. It is possible that his blood pressure on Day 20 was significantly higher than the blood pressure of 139/97 mmHg that was recorded seven days after he stopped taking the study drug. While the myocardial infarction occurred following an episode of increased physical activity, the subject's blood pressure was already significantly elevated compared to baseline on the day prior to this physical activity. At this time, a causal relationship between the study drug and the myocardial infarction cannot be ruled out.

#### **8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects**

##### **Narcolepsy: Dropouts, Placebo-Controlled Trials**

In the 12-week placebo-controlled studies in narcolepsy, a higher proportion of subjects treated with solriamfetol (5.5%, 12/220) compared with placebo (2.3%, 3/108) had at least one TEAE leading to withdrawal from study drug. Across treatment groups a dose-related increase in withdrawals due to TEAEs was observed, with 1.7%, 5.9%, and 6.1% withdrawals in the 75 mg,

150 mg, and 300 mg solriamfetol dose groups, respectively. The SOC with the highest proportion of subjects discontinuing in the narcolepsy population was Psychiatric Disorders (2.3%). The TEAEs in this SOC that resulted in study withdrawal were affect lability, anxiety, bruxism, conversion disorder, depressive symptom, initial insomnia, and insomnia.

### **Narcolepsy: Dropouts, Long-Term Trial**

During the long-term trial, 8.8% of subjects with narcolepsy discontinued from the study due to a TEAE. TEAEs leading to withdrawal occurred most frequently in the SOCs of psychiatric disorders (12 subjects, 5.3%) and nervous system disorders (three subjects, 1.3%). TEAEs that led to withdrawal in more than one subject with narcolepsy were anxiety (5 subjects, 2.2%), depression (three subjects, 1.3%), and insomnia (two subjects, 0.9%). Cluster headache, headache, and migraine each led to withdrawal of a single subject with narcolepsy.

### **OSA: Dropouts, Placebo-Controlled Trials**

In the 12-week placebo-controlled trials, withdrawals due to TEAEs occurred in 7.1% (25/353) of subjects with OSA treated with solriamfetol and 3.4% (4/118) of subjects treated with placebo. Across treatment groups, 5.2%, 3.3%, 4.3%, and 12.7% withdrawals occurred in the 37.5 mg, 75 mg, 150 mg, and 300 mg solriamfetol dose groups, respectively. While there was not a consistent dose-related increase in withdrawals, the percentage of withdrawals in the 300 mg dose group was higher than in any of the lower dose groups. The SOC with the highest proportion of subjects discontinuing in the OSA population was Psychiatric Disorders (2.8%). TEAEs in this SOC that resulted in study withdrawal were anxiety, agitation, restlessness, tic, claustrophobia, hypervigilance, insomnia, nervousness, panic attack, tachyphrenia, depressed mood, and suicidal ideation.

### **OSA: Dropouts, Randomized-Withdrawal Trial**

Of the 174 subjects in the safety population for this study, there were six withdrawals due to TEAEs. The adverse events leading to withdrawals were nausea, vomiting, depersonalization, derealization, insomnia, headache, anxiety, nervousness, increased heart rate, palpitations, visual flashes, and dizziness. Headache and palpitations occurred in two subjects, while each of the other TEAEs occurred in one subject.

### **OSA: Dropouts, Long-Term Trial**

During the long-term trial, 7.3% of subjects with OSA discontinued from the study due to a TEAE. TEAEs leading to withdrawal occurred most frequently in the SOCs of nervous system disorders (10 subjects, 2.4%), psychiatric disorders (7 subjects, 1.7%), and gastrointestinal disorders (6 subjects, 1.5%). The most frequently reported TEAEs leading to withdrawal among

OSA patients were dry mouth, nausea, dizziness, irritability, and headache, each reported in three subjects with OSA (0.7%).

#### 8.4.4. Significant Adverse Events: Cardiovascular System

Table 57 summarizes serious cardiovascular adverse events that occurred in the course of the solriamfetol development program. These events have been discussed earlier in this document. They are presented here to facilitate comparisons. There were no serious cardiovascular adverse events among subjects treated with placebo in the development program.

**Table 57: Serious Cardiovascular Adverse Events, Solriamfetol Development Program**

Subject ID	Study	Indication	Solriamfetol Dose	Event	Relation of Event to Study Drug		Location in This Document
					Investigator Assessment	Reviewer Assessment	
(b) (6)	MDD-201	MDD	100 mg bid	myocardial infarction	possibly related	possibly related	page 162
(b) (6)	14-005	OSA	150 mg/day	cerebro-vascular accident	possibly related	possibly related	page 157
(b) (6)	14-005	OSA	300 mg/day	atrial fibrillation	possibly related	possibly related	page 156
(b) (6)	14-005	OSA	300 mg/day	angina pectoris	not related	possibly related	page 160
(b) (6)	14-005	OSA	300 mg/day	sepsis, myocardial infarction, respiratory failure	not related	not related	page 149
(b) (6)	14-003	OSA	300 mg/day	coronary artery disease	not related	not related	page 153

Source: reviewer-generated table.

There are some commonalities among the subjects represented in these events. All except one was diagnosed with obstructive sleep apnea. All were receiving treatment with solriamfetol in the higher dose range (150 mg/day to 300 mg/day). However, the number of incidents is small compared to the size of the overall safety database (approximately 1600 unique subjects). Two of the events (for Subjects (b) (6)) do not appear to have any relationship to exposure to solriamfetol. A causal relationship to study drug cannot be definitively established for the other four events.

As described later in Section 8.4.7 (Vital Signs), analysis of blood pressure and pulse measurements in the 12-week placebo-controlled trials of solriamfetol indicate dose-related increases in blood pressure and pulse. It has been established in other large clinical studies that sustained increases in blood pressure and heart rate can increase the risk of cardiovascular adverse events. [REDACTED] (b) (4)

[REDACTED] This reviewer does not believe that the six events that occurred in the development program provide evidence for a causal relationship between exposure to solriamfetol and the incidence of cardiovascular adverse events.

#### 8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

##### **Narcolepsy: TEAEs, Study ADX-N05-202**

The most common TEAEs in the solriamfetol-treated group in Study ADX-N05-202 were insomnia, headache, nausea, decreased appetite, anxiety, and diarrhea. In the study design, each subject in the drug-treated group received the 150 mg/day dose of solriamfetol for four weeks, then the 300 mg/day dose of solriamfetol for eight weeks. A TEAE that occurred in one subject during both treatment phases is recorded once for each of the two solriamfetol doses. Table 58 and Table 59 show the TEAEs occurring in more than 2% of the solriamfetol-treated group and in a higher percentage of solriamfetol-treated subjects than placebo-treated subjects. Because of the small size of the study population, TEAEs that occurred in only one subject in the solriamfetol-treated group achieved a frequency of 2.3%. These TEAEs were omitted from the tables. Table 58 is sorted in decreasing frequency of occurrence of the TEAE in the combined solriamfetol treatment group. Table 59 is organized by System Organ Class.

**Table 58: TEAEs in Study ADX-N05-202, Safety Population, with Frequency ≥ 2% and Frequency Higher in Combined Solriamfetol Group than in Placebo Group, Ordered by Frequency in Combined Solriamfetol Treatment Group**

System Organ Class	Preferred Term	Treatment					
		150 mg (n)	300 mg (n)	All SLFTOL (n)	All SLFTOL (%)	PBO (n)	PBO (%)
Nervous system disorders	Insomnia	5	6	11	25.0%	4	8.2%
Nervous system disorders	Headache	6	4	10	22.7%	5	10.2%
Gastrointestinal disorders	Nausea, vomiting	1	6	7	15.9%	3	6.1%
Metabolism and nutrition disorders	Decreased appetite	4	2	6	13.6%	0	0.0%
Psychiatric disorders	Anxiety	4	2	6	13.6%	0	0.0%
Gastrointestinal disorders	Diarrhoea	2	3	5	11.4%	3	6.1%
Cardiac disorders	Palpitations	3	1	4	9.1%	1	2.0%
General disorders and administration site conditions	Irritability, agitation	2	2	4	9.1%	1	2.0%
Infections and infestations	Nasopharyngitis	2	1	3	6.8%	1	2.0%
Nervous system disorders	Dizziness	1	2	3	6.8%	1	2.0%
Psychiatric disorders	Bruxism	3	0	3	6.8%	0	0.0%
Psychiatric disorders	Irritability, agitation	3	0	3	6.8%	0	0.0%
Ear and labyrinth disorders	Cerumen impaction	0	2	2	4.5%	0	0.0%
Gastrointestinal disorders	Abdominal pain	1	1	2	4.5%	2	4.1%
Gastrointestinal disorders	Constipation	1	1	2	4.5%	0	0.0%
Gastrointestinal disorders	Frequent bowel movements	2	0	2	4.5%	0	0.0%
General disorders and administration site conditions	Chest pain	1	1	2	4.5%	0	0.0%
Musculoskeletal and connective tissue disorders	Arthralgia	2	0	2	4.5%	1	2.0%
Respiratory, thoracic and mediastinal disorders	Bronchospasm, asthma	2	0	2	4.5%	0	0.0%
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	1	1	2	4.5%	0	0.0%

Source: reviewer-generated table.

**Table 59: TEAEs in Study ADX-N05-202, Safety Population, with Frequency ≥ 2% and Frequency Higher in Combined Solriamfetol Treatment Group than in Placebo, Ordered by System Organ Class**

System Organ Class	Preferred Term	Treatment					
		150 mg (n)	300 mg (n)	All SLFTOL (n)	All SLFTOL (%)	PBO (n)	PBO (%)
Cardiac disorders	Palpitations	3	1	4	9.1%	1	2.0%
Ear and labyrinth disorders	Cerumen impaction	0	2	2	4.5%	0	0.0%
Gastrointestinal disorders	Nausea, vomiting	1	6	7	15.9%	3	6.1%
	Diarrhoea	2	3	5	11.4%	3	6.1%
	Abdominal pain	1	1	2	4.5%	2	4.1%
	Constipation	1	1	2	4.5%	0	0.0%
	Frequent bowel movements	2	0	2	4.5%	0	0.0%
General disorders and administration site conditions	Irritability, agitation	2	2	4	9.1%	1	2.0%
	Chest pain	1	1	2	4.5%	0	0.0%
Infections and infestations	Nasopharyngitis	2	1	3	6.8%	1	2.0%
Metabolism and nutrition disorders	Decreased appetite	4	2	6	13.6%	0	0.0%
Musculoskeletal and connective tissue disorders	Arthralgia	2	0	2	4.5%	1	2.0%
Nervous system disorders	Insomnia	5	6	11	25.0%	4	8.2%
	Headache	6	4	10	22.7%	5	10.2%
	Dizziness	1	2	3	6.8%	1	2.0%
Psychiatric disorders	Anxiety	4	2	6	13.6%	0	0.0%
	Bruxism	3	0	3	6.8%	0	0.0%
	Irritability, agitation	3	0	3	6.8%	0	0.0%
Respiratory, thoracic and mediastinal disorders	Bronchospasm, asthma	2	0	2	4.5%	0	0.0%
	Oropharyngeal pain	1	1	2	4.5%	0	0.0%

Source: reviewer-generated table.

### Narcolepsy: TEAEs, Study 14-002

The most common TEAEs in the solriamfetol-treated group in Study 14-002 were headache, nausea, decreased appetite, nasopharyngitis, dry mouth, anxiety, and diarrhea. Table 60 and Table 61 show the TEAEs occurring in more than 2% of the combined solriamfetol-treated group and in a higher percentage of solriamfetol-treated subjects than placebo-treated subjects. Table 60 is sorted in decreasing frequency of occurrence of the TEAE in the combined solriamfetol treatment group. Table 61 is organized by System Organ Class.

**Table 60: TEAEs in Study 14-002, Safety Population, with Frequency ≥ 2% and Frequency Higher in Combined Solriamfetol Group than in Placebo Group, Ordered by Frequency in Combined Solriamfetol Treatment Group**

System Organ Class	Preferred Term	Treatment						
		75 mg (n)	150 mg (n)	300 mg (n)	All SLFTOL (n)	All SLFTOL (%)	PBO (n)	PBO (%)
Nervous system disorders	Headache	6	14	18	38	21.5%	3	5.1%
Gastrointestinal disorders	Nausea, vomiting	3	7	10	20	11.3%	1	1.7%
Metabolism and nutrition disorders	Decreased appetite	5	5	9	19	10.7%	1	1.7%
Infections and infestations	Nasopharyngitis	5	8	3	16	9.0%	3	5.1%
Gastrointestinal disorders	Dry mouth, thirst	3	4	6	13	7.3%	2	3.4%
Psychiatric disorders	Anxiety	1	3	5	9	5.1%	1	1.7%
Gastrointestinal disorders	Diarrhoea	2	3	3	8	4.5%	1	1.7%
General disorders and administration site conditions	Asthenia, Fatigue	0	3	4	7	4.0%	0	0.0%
Psychiatric disorders	Insomnia	2	1	4	7	4.0%	0	0.0%
Gastrointestinal disorders	Dyspepsia	1	2	3	6	3.4%	0	0.0%
Gastrointestinal disorders	Abdominal pain	3	1	1	5	2.8%	1	1.7%
Infections and infestations	Sinusitis	2	1	2	5	2.8%	0	0.0%
Infections and infestations	Upper respiratory tract infection	1	4	0	5	2.8%	1	1.7%
Investigations	Weight decreased	1	1	3	5	2.8%	0	0.0%
Skin and subcutaneous tissue disorders	Acne	2	2	1	5	2.8%	0	0.0%
Gastrointestinal disorders	Constipation	3	1	0	4	2.3%	1	1.7%
General disorders and administration site conditions	Pyrexia	0	2	2	4	2.3%	0	0.0%
Investigations	Heart rate increased	0	0	4	4	2.3%	0	0.0%

Source: reviewer-generated table.

**Table 61: TEAEs in Study 14-002, Safety Population, with Frequency ≥ 2% and Frequency Higher in Combined solriamfetol Treatment Group than in Placebo Group, Ordered by System Organ Class**

System Organ Class	Preferred Term	Treatment						
		75 mg (n)	150 mg (n)	300 mg (n)	All SLFTOL (n)	All SLFTOL (%)	PBO (n)	PBO (%)
Gastrointestinal disorders	Nausea, vomiting	3	7	10	20	11.3%	1	1.7%
	Dry mouth, thirst	3	4	6	13	7.3%	2	3.4%
	Diarrhoea	2	3	3	8	4.5%	1	1.7%
	Dyspepsia	1	2	3	6	3.4%	0	0.0%
	Abdominal pain	3	1	1	5	2.8%	1	1.7%
	Constipation	3	1	0	4	2.3%	1	1.7%
General disorders and administration site conditions	Asthenia, Fatigue	0	3	4	7	4.0%	0	0.0%
	Pyrexia	0	2	2	4	2.3%	0	0.0%
Infections and infestations	Nasopharyngitis	5	8	3	16	9.0%	3	5.1%
	Sinusitis	2	1	2	5	2.8%	0	0.0%
	Upper respiratory tract infection	1	4	0	5	2.8%	1	1.7%
Investigations	Weight decreased	1	1	3	5	2.8%	0	0.0%
	Heart rate increased	0	0	4	4	2.3%	0	0.0%
Metabolism and nutrition disorders	Decreased appetite	5	5	9	19	10.7%	1	1.7%
Nervous system disorders	Headache	6	14	18	38	21.5%	3	5.1%
Psychiatric disorders	Anxiety	1	3	5	9	5.1%	1	1.7%
	Insomnia	2	1	4	7	4.0%	0	0.0%
Skin and subcutaneous tissue disorders	Acne	2	2	1	5	2.8%	0	0.0%

Source: reviewer-generated table.

### Narcolepsy: TEAEs, Study 14-005

Of the 638 subjects in the safety population for the open-label long-term study, 226 were diagnosed with narcolepsy. Among those subjects, the most frequent TEAEs were nausea, headache, anxiety, nasopharyngitis, insomnia, decreased appetite, and dry mouth. Table 62 and Table 63 show the TEAEs occurring in more than 2% of subjects participating in the study. Table 62 is sorted in decreasing frequency of occurrence of the TEAE in all subjects. Table 63 is organized by System Organ Class.

**Table 62: TEAEs in Subjects with Narcolepsy in Study 14-005, Safety Population, with Frequency ≥ 2%, Ordered by Frequency**

System Organ Class	Preferred Term	Treatment				
		75 mg (n)	150 mg (n)	300 mg (n)	All SLFTOL (n)	All SLFTOL (%)
Gastrointestinal disorders	Nausea, vomiting	2	13	13	28	12.4%
Nervous system disorders	Headache	5	6	17	28	12.4%
Psychiatric disorders	Anxiety, nervousness	4	13	4	21	9.3%
Infections and infestations	Nasopharyngitis	2	7	9	18	8.0%
Psychiatric disorders	Insomnia	0	10	8	18	8.0%
Metabolism and nutrition disorders	Decreased appetite	2	8	7	17	7.5%
Gastrointestinal disorders	Dry mouth, thirst	1	6	7	14	6.2%
Infections and infestations	Sinusitis	0	3	9	12	5.3%
Gastrointestinal disorders	Abdominal pain	2	2	6	10	4.4%
Infections and infestations	Upper respiratory tract infection	0	2	8	10	4.4%
Cardiac disorders	Palpitations	1	3	5	9	4.0%
Nervous system disorders	Tremor	0	3	4	7	3.1%
Psychiatric disorders	Depression	1	4	2	7	3.1%
Gastrointestinal disorders	Diarrhoea	1	2	3	6	2.7%
Infections and infestations	Influenza	0	3	3	6	2.7%
Musculoskeletal and connective tissue disorders	Back pain	0	2	4	6	2.7%
Psychiatric disorders	Irritability, agitation	1	3	2	6	2.7%
General disorders and administration site conditions	Asthenia, fatigue	0	2	3	5	2.2%
Infections and infestations	Gastroenteritis viral	0	0	5	5	2.2%
Musculoskeletal and connective tissue disorders	Arthralgia, arthritis	0	3	2	5	2.2%
Musculoskeletal and connective tissue disorders	Muscle spasms	0	1	4	5	2.2%
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	0	1	4	5	2.2%
Musculoskeletal and connective tissue disorders	Pain in extremity	0	2	3	5	2.2%
Nervous system disorders	Fall, dizziness	1	2	2	5	2.2%
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1	2	2	5	2.2%
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	0	2	3	5	2.2%

Source: reviewer-generated table.

**Table 63: TEAEs in Subjects with Narcolepsy in Study 14-005, Safety Population, with Frequency ≥ 2%, Ordered by System Organ Class**

System Organ Class	Preferred Term	Treatment				
		75 mg (n)	150 mg (n)	300 mg (n)	All solriamfetol (n)	All solriamfetol (%)
Cardiac disorders	Palpitations	1	3	5	9	4.0%
Gastrointestinal disorders	Nausea, vomiting	2	13	13	28	12.4%
	Dry mouth, thirst	1	6	7	14	6.2%
	Abdominal pain	2	2	6	10	4.4%
	Diarrhoea	1	2	3	6	2.7%
General disorders and administration site conditions	Asthenia, fatigue	0	2	3	5	2.2%
Infections and infestations	Nasopharyngitis	2	7	9	18	8.0%
	Sinusitis	0	3	9	12	5.3%
	Upper respiratory tract infection	0	2	8	10	4.4%
	Influenza	0	3	3	6	2.7%
	Gastroenteritis viral	0	0	5	5	2.2%
Metabolism and nutrition disorders	Decreased appetite	2	8	7	17	7.5%
Musculoskeletal and connective tissue disorders	Back pain	0	2	4	6	2.7%
	Arthralgia, arthritis	0	3	2	5	2.2%
	Muscle spasms	0	1	4	5	2.2%
	Musculoskeletal pain	0	1	4	5	2.2%
	Pain in extremity	0	2	3	5	2.2%
Nervous system disorders	Headache	5	6	17	28	12.4%
	Tremor	0	3	4	7	3.1%
	Fall, dizziness	1	2	2	5	2.2%
Psychiatric disorders	Anxiety, nervousness	4	13	4	21	9.3%
	Insomnia	0	10	8	18	8.0%
	Depression	1	4	2	7	3.1%
	Irritability, agitation	1	3	2	6	2.7%
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1	2	2	5	2.2%
	Oropharyngeal pain	0	2	3	5	2.2%

Source: reviewer-generated table.

**OSA: TEAEs, Study 14-003**

The most common TEAEs in the solriamfetol-treated group in Study 14-003 were headache, nausea, decreased appetite, anxiety, diarrhea, dry mouth, and insomnia. Table 64 and Table 65 show the TEAEs occurring in more than 2% of the combined solriamfetol-treated group and in a

higher percentage of solriamfetol-treated subjects than placebo-treated subjects. Table 64 is sorted in decreasing frequency of occurrence of the TEAE in the combined solriamfetol treatment group. Table 65 is organized by System Organ Class.

**Table 64: TEAEs in Study 14-003, Safety Population, with Frequency ≥ 2% and Frequency Higher in Combined Solriamfetol Group than in Placebo Group, Ordered by Frequency in Combined Solriamfetol Treatment Group**

System Organ Class	Preferred Term	Treatment							
		37.5 mg (n)	75 mg (n)	150 mg (n)	300 mg (n)	All SLFTOL (n)	All SLFTOL (%)	PBO (n)	PBO (%)
Nervous system disorders	Headache	4	5	10	19	38	10.7%	10	8.4%
Gastrointestinal disorders	Nausea, vomiting	4	3	12	12	31	8.7%	7	5.9%
Metabolism and nutrition disorders	Decreased appetite	1	3	9	14	27	7.6%	1	0.8%
Psychiatric disorders	Anxiety, nervousness	1	2	6	17	26	7.3%	1	0.8%
Gastrointestinal disorders	Diarrhoea	1	3	5	8	17	4.8%	1	0.8%
Gastrointestinal disorders	Dry mouth	1	1	5	9	16	4.5%	2	1.7%
Psychiatric disorders	Insomnia	1	0	3	12	16	4.5%	3	2.5%
General disorders and administration site conditions	Feeling jittery	3	3	1	7	14	3.9%	0	0.0%
Gastrointestinal disorders	Abdominal pain	0	0	7	5	12	3.4%	2	1.7%
Nervous system disorders	Fall, dizziness	2	1	3	5	11	3.1%	1	0.8%
Psychiatric disorders	Irritability, agitation	3	0	5	3	11	3.1%	1	0.8%
General disorders and administration site conditions	Chest discomfort	2	0	3	4	9	2.5%	0	0.0%
Infections and infestations	Urinary tract infection	1	2	4	2	9	2.5%	0	0.0%
Cardiac disorders	Palpitations	1	1	5	1	8	2.3%	0	0.0%
Musculoskeletal and connective tissue disorders	Back pain	2	0	3	3	8	2.3%	2	1.7%

Source: reviewer-generated table.

**Table 65: TEAEs in Study 14-003, Safety Population, with Frequency ≥ 2% and Frequency Higher in Combined Solriamfetol Treatment Group than in Placebo Group, Ordered by System Organ Class**

System Organ Class	Preferred Term	Treatment							
		37.5 mg (n)	75 mg (n)	150 mg (n)	300 mg (n)	All SLFTOL (n)	All SLFTOL (%)	PBO (n)	PBO (%)
Cardiac disorders	Palpitations	1	1	5	1	8	2.3%	0	0.0%
Gastrointestinal disorders	Nausea, vomiting	4	3	12	12	31	8.7%	7	5.9%
	Diarrhoea	1	3	5	8	17	4.8%	1	0.8%
	Dry mouth	1	1	5	9	16	4.5%	2	1.7%
	Abdominal pain	0	0	7	5	12	3.4%	2	1.7%
General disorders and administration site conditions	Feeling jittery	3	3	1	7	14	3.9%	0	0.0%
	Chest discomfort	2	0	3	4	9	2.5%	0	0.0%
Infections and infestations	Urinary tract infection	1	2	4	2	9	2.5%	0	0.0%
Metabolism and nutrition disorders	Decreased appetite	1	3	9	14	27	7.6%	1	0.8%
Musculoskeletal and connective tissue disorders	Back pain	2	0	3	3	8	2.3%	2	1.7%
Nervous system disorders	Headache	4	5	10	19	38	10.7%	10	8.4%
	Fall, dizziness	2	1	3	5	11	3.1%	1	0.8%
Psychiatric disorders	Anxiety, Nervousness	1	2	6	17	26	7.3%	1	0.8%
	Insomnia	1	0	3	12	16	4.5%	3	2.5%
	Irritability, agitation	3	0	5	3	11	3.1%	1	0.8%

Source: reviewer-generated table.

### OSA: TEAEs, Study 14-004

In Study 14-004, a randomized-withdrawal study, all subjects were exposed to solriamfetol, including those who were randomized to placebo during the withdrawal phase. The most common TEAEs among all subjects participating in the study were insomnia, dry mouth, influenza, nasopharyngitis, and headache. Table 66 and Table 67 show the TEAEs occurring in more than 2% of subjects participating in the study. Table 66 is sorted in decreasing frequency of occurrence of the TEAE in all subjects. Table 67 is organized by System Organ Class.

**Table 66: TEAEs in Study 14-004, Safety Population, with Frequency ≥ 2%, Order by Frequency**

System Organ Class	Preferred Term	Treatment				
		75 mg (n)	150 mg (n)	300 mg (n)	All solriamfetol (n)	All solriamfetol (%)
Psychiatric disorders	Insomnia	3	2	3	8	4.6%
Gastrointestinal disorders	Dry mouth	2	1	3	6	3.4%
Infections and infestations	Influenza	3	0	3	6	3.4%
Infections and infestations	Nasopharyngitis	0	2	2	4	2.3%
Nervous system disorders	Headache	2	0	2	4	2.3%

Source: reviewer-generated table.

**Table 67: TEAEs in Study 14-004, Safety Population, with Frequency ≥ 2%, Ordered by System Organ Class**

System Organ Class	Preferred Term	Treatment				
		75 mg (n)	150 mg (n)	300 mg (n)	All solriamfetol (n)	All solriamfetol (%)
Gastrointestinal disorders	Dry mouth	2	1	3	6	3.4%
Infections and infestations	Influenza	3	0	3	6	3.4%
	Nasopharyngitis	0	2	2	4	2.3%
Nervous system disorders	Headache	2	0	2	4	2.3%
Psychiatric disorders	Insomnia	3	2	3	8	4.6%

Source: reviewer-generated table.

### OSA: TEAEs, Study 14-005

Of the 638 subjects in the safety population for the open-label long-term study, 412 were diagnosed with OSA. Among those subjects, the most frequent TEAEs insomnia, headache, nasopharyngitis, dry mouth, nausea, feeling jittery, and anxiety. Table 68 and Table 69 show the TEAEs occurring in more than 2% of subjects participating in the study. Table 68 is sorted in decreasing frequency of occurrence of the TEAE in all subjects. Table 69 is organized by System Organ Class.

**Table 68: TEAEs in Subjects with OSA in Study 14-005, Safety Population, with Frequency ≥ 2%, Ordered by Frequency**

System Organ Class	Preferred Term	Treatment				
		75 mg (n)	150 mg (n)	300 mg (n)	All SLFTOL (n)	All SLFTOL (%)
Psychiatric disorders	Insomnia	13	21	13	47	11.4%
Nervous system disorders	Headache	12	12	14	38	9.2%
Infections and infestations	Nasopharyngitis	2	10	20	32	7.8%
Gastrointestinal disorders	Dry mouth, thirst	8	8	14	30	7.3%
Gastrointestinal disorders	Nausea, vomiting	3	18	8	29	7.0%
General disorders and administration site conditions	Feeling jittery	5	14	6	25	6.1%
Psychiatric disorders	Anxiety, nervousness	1	14	5	20	4.9%
Infections and infestations	Upper respiratory tract infection	0	6	13	19	4.6%
Nervous system disorders	Fall, dizziness	5	7	7	19	4.6%
Infections and infestations	Sinusitis	2	4	12	18	4.4%
Psychiatric disorders	Irritability, agitation	2	5	8	15	3.6%
Metabolism and nutrition disorders	Decreased appetite	2	4	8	14	3.4%
Infections and infestations	Influenza	3	3	7	13	3.2%
Musculoskeletal and connective tissue disorders	Arthralgia, arthritis	1	4	7	12	2.9%
Musculoskeletal and connective tissue disorders	Back pain	1	3	7	11	2.7%
Gastrointestinal disorders	Diarrhoea	1	4	5	10	2.4%
Infections and infestations	Bronchitis	1	5	4	10	2.4%
Investigations	Blood pressure increased	2	4	4	10	2.4%
Respiratory, thoracic and mediastinal disorders	Cough	0	2	8	10	2.4%

Source: reviewer-generated table.

**Table 69: TEAEs in Subjects with OSA in Study 14-005, Safety Population, with Frequency ≥ 2%, Ordered by System Organ Class**

System Organ Class	Preferred Term	Treatment				
		75 mg (n)	150 mg (n)	300 mg (n)	All SLFTOL (n)	All SLFTOL (%)
Gastrointestinal disorders	Dry mouth, thirst	8	8	14	30	7.3%
	Nausea, vomiting	3	18	8	29	7.0%
	Diarrhoea	1	4	5	10	2.4%
General disorders and administration site conditions	Feeling jittery	5	14	6	25	6.1%
Infections and infestations	Nasopharyngitis	2	10	20	32	7.8%
	Upper respiratory tract infection	0	6	13	19	4.6%
	Sinusitis	2	4	12	18	4.4%
	Influenza	3	3	7	13	3.2%
	Bronchitis	1	5	4	10	2.4%
Investigations	Blood pressure increased	2	4	4	10	2.4%
Metabolism and nutrition disorders	Decreased appetite	2	4	8	14	3.4%
Musculoskeletal and connective tissue disorders	Arthralgia, arthritis	1	4	7	12	2.9%
	Back pain	1	3	7	11	2.7%
Nervous system disorders	Headache	12	12	14	38	9.2%
	Fall, dizziness	5	7	7	19	4.6%
Psychiatric disorders	Insomnia	13	21	13	47	11.4%
	Anxiety, nervousness	1	14	5	20	4.9%
	Irritability, agitation	2	5	8	15	3.6%
Respiratory, thoracic and mediastinal disorders	Cough	0	2	8	10	2.4%

Source: reviewer-generated table.

**Summary: Most Common TEAEs for Each of the Registration Studies**

Table 70 presents the most common adverse events occurring in each of the five registration studies, in decreasing order of frequency. The final row of the table is a composite ranked list of TEAEs across all five studies.

**Table 70: Most Common TEAEs Across Registration Studies**

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

Source: reviewer-generated table.

#### 8.4.6. Laboratory Findings

##### **Narcolepsy: Labs, Study ADX-N05-202**

Over the course of the study, there was no pattern of change suggestive of a drug-treatment effect in any clinical laboratory parameter. There were five TEAEs related to clinical laboratory findings. Three occurred in subjects randomized to placebo, and two occurred in subjects randomized to solriamfetol. Of the two solriamfetol-treated subjects, one had a TEAE of decreased vitamin D level, which resolved after giving oral vitamin D once daily for ten days. The other subject reportedly had a slight elevation of blood glucose (actual value unknown) found by her regular physician. However, blood glucose levels checked at the study site at screening, Week 4, and Week 12 were normal.

##### **Narcolepsy: Labs, Study 14-002**

No clinically meaningful changes were noted over the course of the study in mean changes in hematology, chemistry, or urinalysis parameter values. An increase in the percentage of subjects with low neutrophil count compared to baseline was noted in both the solriamfetol group (1.1% at baseline, 6.5% at Week 12) and the placebo group (1.7% at baseline, 6.0% at Week 12). There were no TEAEs related to abnormal hematological parameter values. Two subjects were terminated early due to positive urine drug screens. No other clinically significant changes in urinalysis parameter values were reported.

At baseline, 18.6% of subjects in the placebo group and 18.9% of subjects in the combined solriamfetol group had high blood glucose levels. At Week 12, the percentage of subjects with high glucose levels did not change significantly in the combined solriamfetol group (21.9%) or the placebo group (19.2%). However, a substantial increase in the percentage of subjects with

elevated blood glucose was seen in the 75 mg solriamfetol group (11.9% at baseline, 19.6% at Week 12) but not in the 150 mg or 300 mg solriamfetol groups. The percentage of subjects with elevated AST compared to baseline at Week 12 decreased for the placebo, solriamfetol 75 mg, and solriamfetol 300 mg groups, but increased in the solriamfetol 150 mg group.

The percentage of subjects with elevated levels of ALT at baseline decreased in the 75 mg, and 300 mg solriamfetol groups (11.9% and 18.6%, respectively, at baseline compared with 6.4% and 7.1%, respectively, at Week 12) and increased in the placebo and 150 mg solriamfetol groups (15.3% and 6.8%, respectively, at baseline compared with 17.3% and 10.0%, respectively, at Week 12). The percentage of subjects with elevated AST at Week 12 decreased compared with baseline for the 300 mg solriamfetol, 75 mg solriamfetol, and placebo groups but increased slightly in the 150 mg solriamfetol group. The percentage of subjects with elevated alkaline phosphatase levels at baseline decreased in the placebo group at Week 12. In the combined solriamfetol group, there was an overall decrease in the percentage of subjects with elevated alkaline phosphatase levels at Week 12 compared with baseline. Across the individual solriamfetol groups, a similar decrease was seen in the 75 mg (5.1% at baseline and 4.3% at Week 12) and 150 mg (8.5% at baseline and 2.0% at Week 12) solriamfetol groups, with a slight increase seen in the 300 mg solriamfetol group.

Subject (b) (6) in the 75 mg solriamfetol group had TEAEs of increased ALT (1.9 x ULN) and increased AST (1.3 x ULN) that resolved during the study. Subject (b) (6) in the 75 mg solriamfetol group had baseline elevations of AST (1.4 x ULN) and ALT (2 x ULN) prior to randomization. Both elevations resolved by Day 54. On Day 82, the last day of study drug dosing, the subject experienced an elevation of conjugated bilirubin (1.2 x ULN), while total bilirubin, AST, ALT, and alkaline phosphatase were within normal ranges on the same day.

*Reviewer's Comment:* The reported mean changes in liver enzymes over time, and the TEAEs of elevated liver enzymes in individual subjects, do not reflect a clear pattern of a relationship between solriamfetol treatment and changes in liver enzyme values.

#### **Narcolepsy: Labs, Study 14-005**

Two subjects with narcolepsy experienced TEAEs related to abnormal hematology results:

- Subject (b) (6) (300 mg), lymphocyte count increased and neutrophil count decreased, Day 104 – Day 108;
- Subject (b) (6) (150 mg), lymphocyte count decreased, Day 14 – Day 56.

All elevations were mild in relationship to baseline values.

One subject with narcolepsy experienced a TEAE related to elevated creatine kinase. This occurred one month after stopping study drug, and was assessed as not related to study drug.

Four subjects with narcolepsy experienced TEAEs related to elevated liver enzymes: two with

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elevated ALT, one with elevated AST, and one with elevated alkaline phosphatase. All four subjects were receiving solriamfetol 300 mg/day.

One subject with narcolepsy experienced a TEAE of increased blood glucose. This subject had a previous history of Type II diabetes. Two subjects experienced TEAEs of increased blood cholesterol.

*Reviewer's Comment:* Overall, review of clinical labs did not reveal a pattern of changes in lab values for subjects with narcolepsy treated with solriamfetol.

### **OSA: Labs, Study 14-003**

No clinically significant differences in mean changes from baseline to Week 12 in hematology parameter values were noted between the solriamfetol groups and the placebo group. One subject in the 150 mg solriamfetol group had a TEAE of leukocytosis on Day 81. This resolved without any action taken.

The percentage of subjects with high ALT or AST values at Week 12 compared to baseline were comparable among treatment groups. Elevations in ALT or AST to greater than 3 x ULN were reported for two subjects, one in the placebo group and one in the 300 mg solriamfetol group. The largest changes in ALT (9.58 x ULN) and AST (3.62 x ULN) were for a subject in the 37.5 mg solriamfetol group who had an SAE of common bile duct obstruction requiring surgery. The event was assessed as not related to study drug.

One subjects in the 37.5 mg solriamfetol group had a creatine kinase (CK) elevation of 3.13 x ULN, while two subjects in the placebo group had CK elevations of 4.88 x ULN and 3.98 x ULN. One other subject in the 37.5 mg group and one subject in the 300 mg group each had CK elevations of less than 2 x ULN.

*Reviewer's Comment:* The high values noted for ALT, AST, and CK in a small number of subjects do not reflect a pattern of differences between patients treated with study drug and those treated with placebo.

Two subjects (0.7%) in the 300 mg solriamfetol group had decreases in creatinine clearance (CrCl) values compared to baseline. For Subject (b) (6), CrCl decreased from 68 to 59 mL/min, while serum creatinine increased minimally from 0.82 to 0.84 µmol/L. For Subject (b) (6) CrCl decreased from 66 to 58 mL/min, while serum creatinine did not change from the baseline level of 1.4 µmol/L.

One subject in the 150 mg solriamfetol group had an SAE of hyperglycemia requiring hospitalization and initiation of insulin. The subject had a previous history of diabetes and poor

compliance with diabetes treatment.

*Reviewer's Comment:* Overall, no clinically significant patterns or differences in mean changes from baseline to Week 12 in serum chemistry or urinalysis values were noted between the solriamfetol groups and the placebo group.

#### **OSA: Labs, Study 14-004**

Four subjects experienced TEAEs related to labs:

- Subject (b) (6) (placebo), elevated blood glucose;
- Subject (b) (6) (300 mg), creatine kinase increased from 60 U/L to 604 U/L on Day 42, but decreased to 107 U/L (reference range 32 - 294 U/L) on Day 57;
- Subject (b) (6) (75 mg), hypercholesterolemia with level of 6.8 Mmol/L on Day 6 (reference range 0 – 5.2 Mmol/L), discontinued from the study after not meeting MWT criteria;
- Subject (b) (6) (75 mg), blood triglycerides increased from 1.92 Mmol/L at baseline to 2.6 Mmol/L on Day 1, discontinued from the study after not meeting MWT criteria.

*Reviewer's Comment:* While there were some individual elevations in serum chemistries, no clinically significant patterns or differences in mean changes from baseline to Week 12 in serum chemistry, hematology, or urinalysis values were noted between the solriamfetol groups and the placebo group.

#### **OSA: Labs, Study 14-005**

Two subjects with OSA experienced TEAEs related to abnormal hematology results:

- Subject (b) (6) (300 mg), monocyte count increased, Day 116 – ongoing;
- Subject (b) (6) (300 mg), eosinophil count increased, Day 291 – ongoing.

Both elevations were mild in relationship to baseline values.

Four subjects with OSA experienced TEAEs related to elevated creatine kinase. These events were either associated with exertional activity, were not significant changes from baseline, or resolved with continued drug dosing.

Four subjects with OSA experienced TEAEs related to elevated liver enzymes. All subjects were receiving solriamfetol 300 mg/day. One subject had increases in ALT and AST that correlated with increases in CK, suggesting that the source of the ALT and AST elevations were muscle rather than liver. For the other subjects, values either were not significantly increased above the upper limit of normal, showed minimal change from baseline, or showed a return to baseline with continued dosing of solriamfetol.

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One subject with OSA experienced a TEAE related to increased serum creatinine. The subject's creatinine was also elevated at baseline.

Two subjects with OSA experienced TEAEs of increased blood glucose. Both had a previous history of Type II diabetes.

*Reviewer's Comment:* Overall, review of clinical labs did not reveal a pattern of changes in lab values for subjects with OSA treated with solriamfetol.

#### 8.4.7. Vital Signs

##### **Narcolepsy: Vital Signs, Study ADX-N05-202**

*Blood Pressure:* Calculated mean baseline values for blood pressure were 114/73 for the solriamfetol treatment group and 110/70 for the placebo group. Compared to placebo, a 2 mmHg mean increase in systolic blood pressure (SBP) occurred at 1-2 hours after dosing and inconsistently at 4-6 hours, but not at later time points (8, 9-10, 14, and 24 hours after dosing). A 1-3 mmHg mean increase in diastolic blood pressure (DBP) occurred at 4 to 8 hours after dosing, but not at later time points (9-10, 14, and 24 hours after dosing). Blood pressure changes from baseline observed at Week 4 (end of the solriamfetol 150 mg/day treatment phase) were similar to those observed at Week 12 (end of the solriamfetol 300 mg/day treatment phase). The highest individual SBP measured at any time point was 165 mmHg for the placebo group and 170 mmHg for the solriamfetol treatment group. The highest individual DBP measured at any time point was 97 mmHg for the placebo group and 100 mmHg for the solriamfetol group.

*Heart Rate:* Calculated mean baseline values for heart rate were 68 bpm for the solriamfetol treatment group and 66 bpm for the placebo group. At both Week 4 and Week 12, subjects treated with solriamfetol demonstrated a 1 to 2.5 bpm mean increase in heart rate compared to placebo at 1 to 8 hours after dosing and inconsistently at 9 and 14 hours, but not at 24 hours after dosing. Heart rate changes from baseline observed at Week 4 (end of the 150 mg/day phase) were similar to those observed at Week 12 (end of the 300 mg/day phase). Six subjects treated with solriamfetol had an increase in heart rate from 30 to 44 bpm, compared with none of the placebo subjects. The highest individual maximum heart rate was 96 bpm in the placebo group and 114 bpm in the solriamfetol group.

*Respiratory Rate:* Not routinely assessed in this study protocol.

*Body Temperature:* No clinically meaningful changes in body temperature were noted during the study.

*Body Weight:* Weights in the placebo group increased by a mean of 1.51 kg. Weights in the solriamfetol group decreased by a mean of 0.28 kg.

**Narcolepsy: Vital Signs, Study 14-002**

*Blood Pressure:* On MWT days across all post-baseline visits, mean changes from baseline in SBP and DBP were minimal for the placebo and 75 mg solriamfetol groups and showed small increases for the 150 mg and 300 mg solriamfetol groups. Mean changes from baseline in SBP and DBP for the 150 mg and 300 mg solriamfetol groups were seen by Week 1 and persisted at Week 12. At Week 12, mean increases from baseline in SBP for the 150 mg and 300 mg solriamfetol groups were 1.20 mmHg and 2.04 mm Hg, respectively, compared with 0.62 mmHg in the placebo group. Mean changes in DBP were 1.43 mmHg and 2.13 mmHg, respectively, compared with -0.58 mmHg in the placebo group.

Time-matched comparisons for SBP and DBP showed no clear separation from baseline at Week 12 for the placebo group and an increase from baseline for each of the solriamfetol groups. The increases were associated with dosing, with minimal changes observed at trough/pre-dose times and maximum changes observed at the expected  $t_{max}$  of 1-4 hours post-dose. Table 71 shows the mean changes in SBP and DBP from baseline to Week 12 at trough and peak levels. The magnitude of the effect was dose-dependent, with the largest mean changes observed at the 150 mg (4.9 mmHg) and 300 mg (5.0 mmHg) solriamfetol doses. Compared to the overall mean changes in SBP and DBP from baseline to Week 12, the mean changes at peak blood levels may give a more realistic assessment of the magnitude of blood pressure change that might occur on a typical day for a patient taking solriamfetol on a daily basis.

**Table 71: Study 14-002, Systolic and Diastolic Blood Pressure on MWT Days, Mean Changes from Baseline to Week 12 at Trough and Peak, Safety Population**

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

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

The duration of the effect was also dose-dependent, with the 300 mg solriamfetol group showing the longest duration. At Week 12, the peak (two hours post-dose) mean increases from baseline for SBP and DBP were 4.94 mmHg and 4.24 mmHg, respectively, for the 150 mg solriamfetol group; 5.02 mmHg and 4.03 mmHg, respectively, for the 300 mg solriamfetol group; and -0.1 mmHg and -1.8 mmHg, respectively, for the placebo group. At the lower doses of solriamfetol, the duration of the effect on SBP and DBP was approximately four hours, while at the 300 mg dose the effect was six to eight hours. There were no apparent effects of solriamfetol on blood pressure when measured at trough/pre-dose.

*Heart Rate:* Mean changes in HR at Week 12 were 2.5 bpm and 4.3 bpm for the 150 mg and 300 mg solriamfetol groups, compared with 0.5 bpm in the placebo group. Table 72 shows the mean changes in heart rate from baseline to Week 12 at trough and peak levels. At Week 12, the peak (four hours post-dose) mean change in heart rate from baseline was 4.3 bpm and 5.9 bpm for the 150 mg and 300 mg groups, respectively, compared with -0.1 bpm for the placebo group.

**Table 72: Study 14-002, Heart Rate on MWT Days, Mean Changes from Baseline to Week 12 at Trough and Peak, Safety Population**

Vital Sign Time Point	Parameter	Placebo (N = 59)	Solriamfetol 75 mg (N = 59)	Solriamfetol 150 mg (N = 59)	Solriamfetol 300 mg (N = 59)
HR (bpm)					
Trough (pre-dose)	n	49	48	48	43
	Mean (SD)	0.0 (8.8)	-1.2 (8.6)	0.6 (9.6)	1.2 (9.6)
Peak (4 hrs post-dose)	n	49	47	47	42
	Mean (SD)	-0.1 (9.3)	-0.9 (9.4)	4.3 (7.7)	5.9 (9.6)

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

At the 150 mg and 300 mg solriamfetol doses, the duration of effect on heart rate appeared longer than 10 hours. There were no apparent effects of solriamfetol on heart rate when measured at trough/pre-dose.

*Respiratory Rate:* There were no clinically meaningful difference between treatment groups in mean and median changes in respiratory rate. Most subjects had no change from baseline in respiratory rate.

*Body Temperature:* There were no clinically meaningful difference between treatment groups in mean and median changes in body temperature.

*Body Weight:* At Week 12, mean percentage changes in weight were +3.1% for placebo, -0.5% for 75 mg solriamfetol, +2.0% for 150 mg solriamfetol, and +2.1% for 300 mg solriamfetol. A higher percentage of subjects in the placebo group (30.8%) had a mean increase in weight of ≥

5% from baseline to Week 12, compared with 4.1% for 75 mg solriamfetol, 4.0% for 150 mg solriamfetol, and 7.0% for 300 mg solriamfetol.

**OSA: Vital Signs, Study 14-003**

*Blood Pressure:* For the solriamfetol groups, changes from baseline in SBP compared to placebo were generally dose-dependent, with minimal effects in the 37.5 mg and 75 mg dose groups and larger effects in the 150 mg and 300 mg dose groups. From Week 1 to Week 12, differences in the mean SBP between solriamfetol and placebo ranged from 0.3 to 3.1 mmHg for the 150 mg group, and from 1.1 to 4.1 mmHg for the 300 mg group. The effects of 150 mg and 300 mg solriamfetol on SBP were observed at Week 1, and remained consistent across the study.

Table 73 shows the mean changes in SBP and DBP from baseline to Week 12 at trough and peak levels. The peak effects of the 150 mg and 300 mg groups occurred between 1 and 4 hours post-dose. The duration and magnitude of effect was dose-dependent. At 150 mg, the duration of effect on blood pressure appeared more transient, lasting around six hours, with a difference in magnitude of 1.8 mmHg and 0.7 mmHg for SBP and DBP, respectively, in comparison to placebo at two hours post-dose. At 300 mg, the duration of effect lasted about ten hours, with a difference in magnitude of 3.4 mmHg and 1.6 mmHg for SBP and DBP, respectively, in comparison to placebo at two hours post-dose. BP assessments taken prior to the morning dose of solriamfetol showed no apparent effect of solriamfetol on BP at trough.

**Table 73: Study 14-003, Systolic and Diastolic Blood Pressure on MWT Days, Mean Changes from Baseline to Week 12 at Trough and Peak, Safety Population**

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

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

*Heart Rate:* For the solriamfetol groups, mean changes from baseline in HR were generally dose-dependent, with minimal effects in the 37.5 mg and 75 mg dose groups and larger effects

in the 150 mg and 300 mg dose groups. Differences in mean HR between solriamfetol and placebo ranged from 2.0 to 2.9 bpm for the 150 mg group, and from 1.6 to 4.6 bpm for the 300 mg group. The effects of 150 mg and 300 mg solriamfetol on HR were observed at Week 1 and were generally consistent across the study.

Table 74 shows the mean changes in heart rate from baseline to Week 12 at trough and peak levels. The peak effect of solriamfetol on HR occurred between 1 and 4 hours post-dose, and its magnitude was dose-dependent with minimal effects at 37.5 mg and 75 mg doses. At 150 mg and 300 mg, the duration of the effect on HR was longer than ten hours. The maximum increases in HR compared to placebo, at four hours post-dose, were 2.7 bpm for the 150 mg dose and 4.2 bpm for the 300 mg dose. HR assessments taken prior to the morning dose of solriamfetol showed no apparent effect of solriamfetol on HR at trough.

**Table 74: Study 14-003, Heart Rate on MWT Days, Mean Changes from Baseline to Week 12 at Trough and Peak, Safety Population**

Vital Sign Time Point	Parameter	Placebo (N = 119)	Solriamfetol 37.5 mg (N = 58)	Solriamfetol 75 mg (N = 62)	Solriamfetol 150 mg (N = 117)	Solriamfetol 300 mg (N = 118)
HR (bpm)	n	99	49	53	103	91
Trough Change (pre-dose)	Mean (SD)	0.6 (7.3)	1.2 (8.2)	1.0 (9.0)	1.6 (8.1)	0.6 (9.4)
Peak Change (4 hr post-dose)	Mean (SD)	0.2 (8.2)	0.4 (10.0)	1.0 (8.2)	2.9 (7.8)	4.5 (7.2)

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

**Body Weight:** Mean and median weight were generally reduced from baseline to a greater extent for solriamfetol treatment groups (with the exception of the 75 mg group) than for the placebo group. The mean change from baseline was -0.05 kg at Week 12 for the placebo group. The mean changes from baseline for the solriamfetol groups were -0.16 kg for the 37.5 mg group, 0.14 kg for the 75 mg group, -1.05 kg for the 150 mg group, and -2.46 kg for the 300 mg group.

**OSA: Vital Signs, Study 14-004**

**Blood Pressure:** Blood pressure was measured at seven timepoints across MWT days at baseline (Day -1), Week 4, and Week 6, including at the time of the expected plasma concentration “trough” (i.e., predose at Week 4 and Week 6 or the matching time at baseline) and at “peak” (2 hours postdose). Mean changes in BP from baseline to Week 6 showed a slight reduction for the Placebo group and a small increase in the solriamfetol group. There were no clear dose-related changes in BP at the 75- and 150-mg doses (sample size was small at the 75-mg dose).

At Week 6 mean changes (SD) from baseline in SBP and DBP for the Placebo group were -1.5 (7.64) mmHg and -0.5 (4.33) mmHg, respectively, compared to increases of 1.6 (8.74) mmHg and 0.8 (5.33) mmHg for the solriamfetol group (Table 43). At the 300-mg dose, mean increases from baseline for SBP and DBP were 2.6 (11.03) mmHg and 1.6 (5.88) mmHg, respectively.

*Heart Rate:* Heart rate was measured at each Clinic Visit (Baseline, Weeks 2, 4, and 6), independent of the time drug was taken on that day. No clinically significant changes in vital signs measured at study visits were observed for the solriamfetol group in any phase of the study. There were no apparent dose-dependent changes. In general, a similar percentage of solriamfetol subjects had values of heart rate >100 bpm between baseline and post-baseline visits in the Titration and Stable Dose phase as well as between Weeks 4 and 6 in the Double-Blind Withdrawal phase. The percentages of subjects who had a categorical increase or decrease from baseline heart rate were generally similar for the solriamfetol groups across visits. No consistent patterns were observed across the solriamfetol dose groups or between the placebo and solriamfetol groups across all assessments.

*Respiratory Rate:* Mean and median changes in respiratory rate were minimal across all study phases and showed no clinically meaningful differences between treatment groups.

*Body Temperature:* Mean and median changes in temperature were minimal across all study phases and showed no clinically meaningful differences between treatment groups.

*Body Weight:* From baseline to the end of Week 4 (after open-label treatment) three (1.7%) subjects had a weight decrease of >5%: two subjects (1.2%) at Week 2 in the Titration Phase (one each at 150 mg and 300 mg) and one (0.7%) at Week 4 in the Stable Dose phase (150 mg). In the Double-Blind Withdrawal Phase, three subjects (4.8%) on placebo and five subjects (8.2%) on solriamfetol (two subjects at 150 mg, three at 300 mg) reported a weight decrease of >5%. No subjects experienced weight increase in the Titration or Stable-Dose phases. Two subjects (3.2%) in the Placebo group experienced a weight increase from baseline >5% during the Double-Blind Withdrawal Phase.

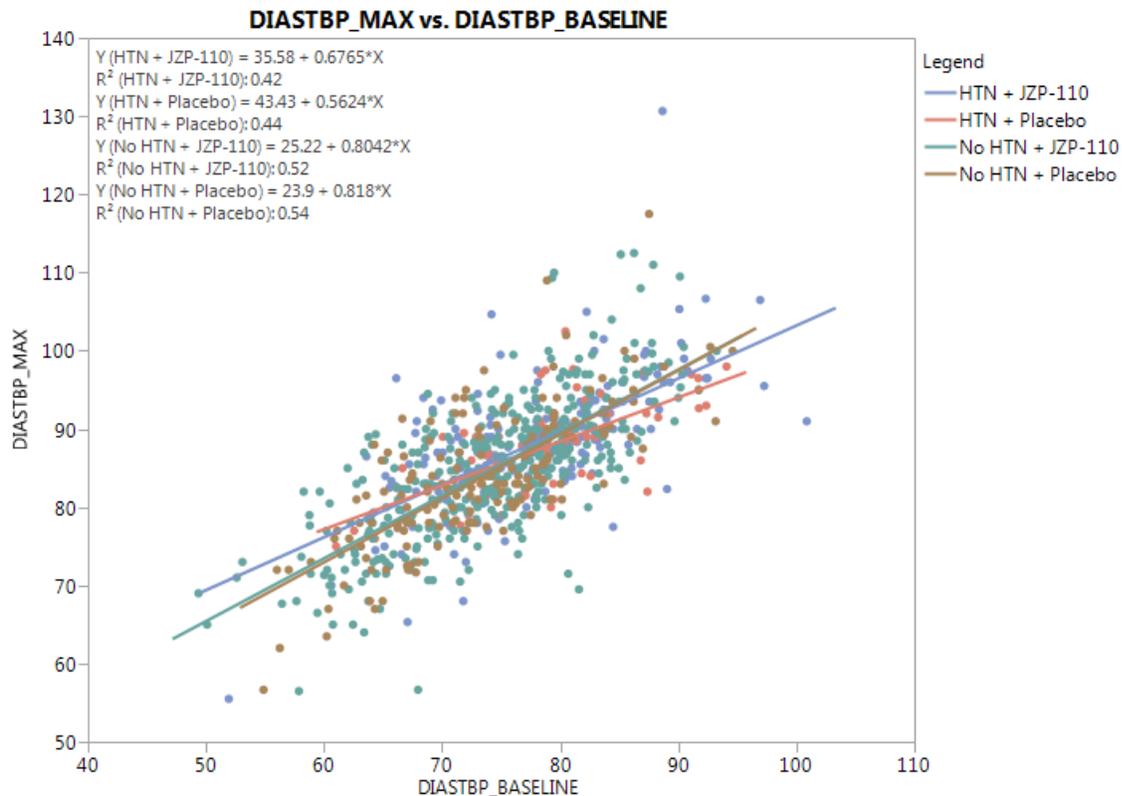
### **Comparison of Changes in Vital Signs in Subjects With and Without Pre-existing Hypertension**

To examine whether the effects of solriamfetol on heart rate and blood pressure differ between subjects with and without pre-existing hypertension, this reviewer performed an analysis of the vital signs data in the dataset comprised of subjects participating in the three 12-week placebo-controlled trials. For each of the 799 subjects, the mean of the baseline heart rate, systolic blood pressure, and diastolic blood pressure values, and to retrieve the maximum heart rate, systolic blood pressure, and diastolic blood pressure over the course of the subject's participation in the 12-week study were calculated. Also for each subject, the concomitant medications data was searched to identify and flag subjects who were taking medications for

hypertension. Relevant subjects were those for whom the Indication field in the concomitant medications dataset included any variant of the term “hypertension,” including “antihypertensive,” “elevated blood pressure,” “high blood pressure,” “increased blood pressure,” “HTN,” “borderline hypertension,” misspelled variants, and similar terms. This analysis did not include retrieval of minimum heart rate, systolic blood pressure, or diastolic blood pressure values.

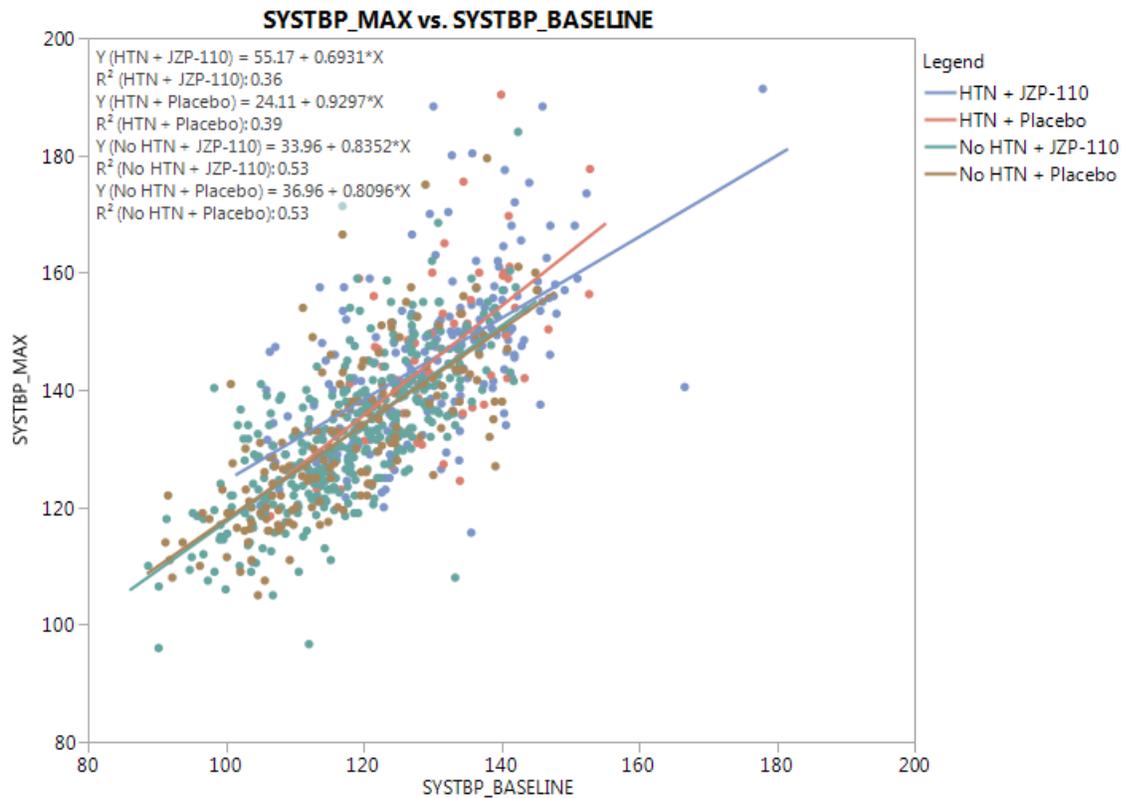
Figures 1, 2, and 3 depict the relationships between baseline and maximum diastolic blood pressure, baseline and maximum systolic blood pressure, and baseline and maximum heart rate for the safety population from the three 12-week placebo-controlled trials. For each figure, subjects are stratified by the presence of pre-existing hypertension (HTN vs no HTN) and by treatment (solriamfetol vs placebo).

Figure 1 shows that, for subjects with no pre-existing hypertension, the relationship between baseline diastolic blood pressure and maximum diastolic blood pressure is very similar for subjects treated with solriamfetol (slope = 0.80) and subjects treated with placebo (slope = 0.82). Subjects with pre-existing hypertension who started the study with an elevated diastolic blood pressure and who were treated with solriamfetol tended to have higher maximum diastolic blood pressures than hypertensive subjects with elevated baseline diastolic blood pressure who were treated with placebo. This finding supports the Applicant’s proposed label warning that pre-existing hypertension should be treated prior to initiating therapy with solriamfetol.



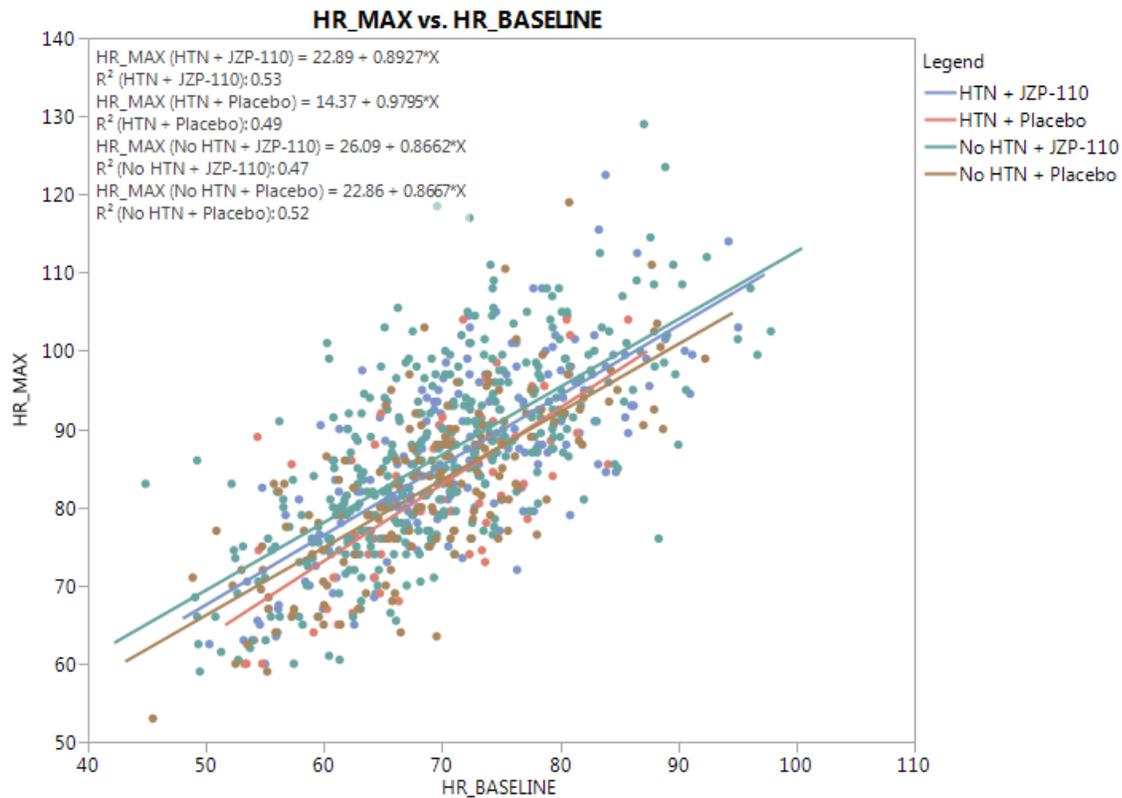
**Figure 1: Relationship of Baseline Diastolic Blood Pressure to Maximum Diastolic Blood Pressure for Subjects in the 12-Week Placebo-Controlled Trials, Stratified by Presence of Pre-Existing Hypertension and by Treatment**

Figure 2 shows that, for subjects with no pre-existing hypertension, the relationship between baseline systolic blood pressure and maximum systolic blood pressure is very similar for subjects treated with solriamfetol (slope = 0.81) and subjects treated with placebo (slope = 0.84). Subjects with pre-existing hypertension who started the study with an elevated systolic blood pressure and who were treated with placebo appeared to have higher maximum systolic blood pressures than hypertensive subjects with elevated baseline systolic blood pressure who were treated with solriamfetol. However, it may be difficult to draw clear conclusions about subjects with pre-existing hypertension from this figure because of the higher amount of variability among subjects with hypertension ( $R^2 = 0.36$  for the solriamfetol group,  $R^2 = 0.39$  for the placebo group) compared to the subjects without hypertension ( $R^2 = 0.53$  for the solriamfetol group;  $R^2 = 0.53$  for the placebo group).



**Figure 2: Relationship of Baseline Systolic Blood Pressure to Maximum Systolic Blood Pressure for Subjects in the 12-Week Placebo-Controlled Trials, Stratified by Presence of Pre-Existing Hypertension and by Treatment**

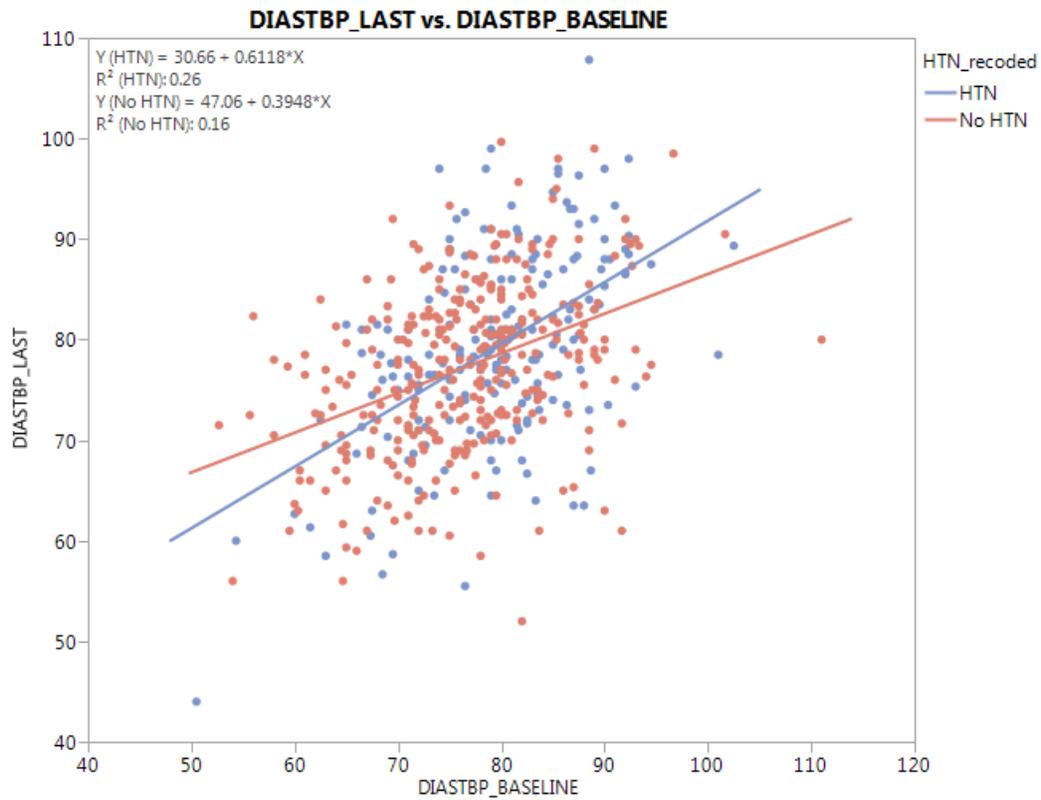
Figure 3 shows that, for subjects with no pre-existing hypertension, the relationship between baseline heart rate and maximum heart rate is very similar for subjects treated with solriamfetol (slope = 0.87) and subjects treated with placebo (slope = 0.87). Subjects with pre-existing hypertension who were treated with solriamfetol tended to have higher elevations in pulse rate than subjects with pre-existing hypertension who were treated with placebo. This finding supports the Applicant's proposed label warning that pre-existing hypertension should be treated prior to initiating therapy with solriamfetol.



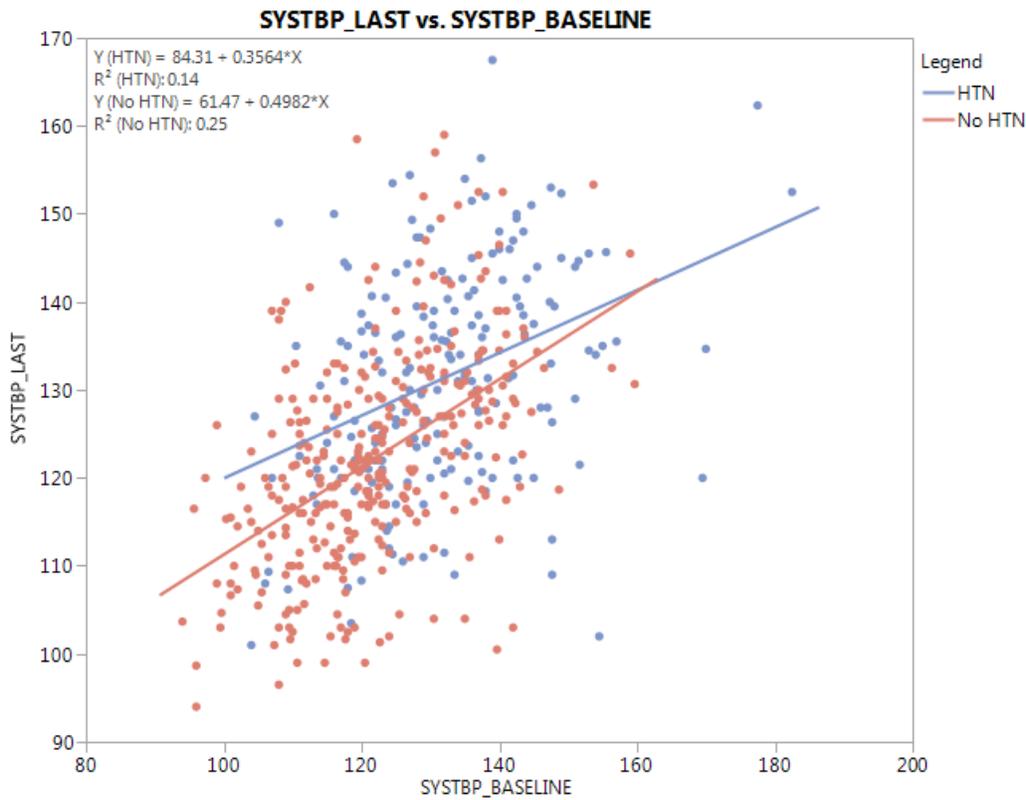
**Figure 3: Relationship of Baseline Heart Rate to Maximum Heart Rate for Subjects in the 12-Week Placebo-Controlled Trials, Stratified by Presence of Pre-Existing Hypertension and by Treatment**

While it is difficult to offer firm conclusions from this analysis because of the high amount of variability among subjects, Figure 1 and Figure 3 both support the Applicant's proposed label warning that pre-existing hypertension should be treated prior to initiating therapy with solriamfetol.

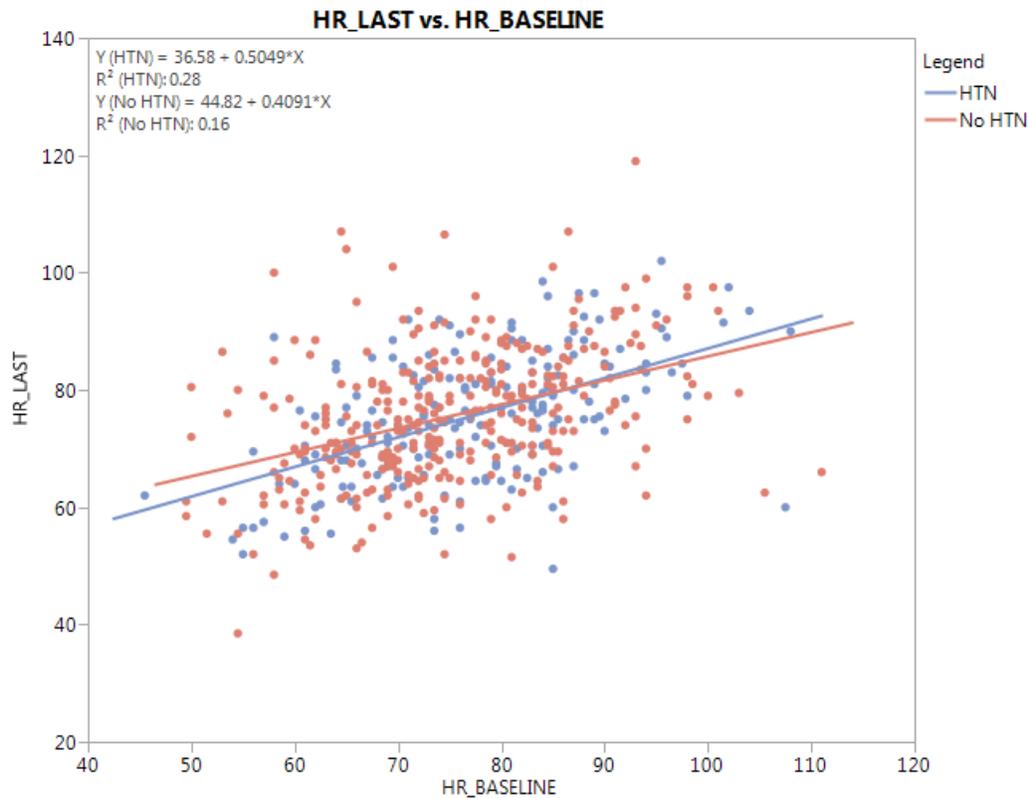
Figures 4, 5, and 6 depict the relationships between baseline and last diastolic blood pressure, baseline and last systolic blood pressure, and baseline and last heart rate for the safety population from the long-term, open-label trial. For each figure, subjects are stratified by the presence of pre-existing hypertension (HTN vs no HTN). These figures do not reveal clear relationships between baseline vital signs and vital signs at the end of the study. All three figures show a high amount of variability among subjects, with no figure showing an R<sup>2</sup> value higher than 0.28.



**Figure 4: Relationship of Baseline Diastolic Blood Pressure to Last Diastolic Blood Pressure for Subjects in the Open-Label Long-Term, Stratified by Presence of Pre-Existing Hypertension**



**Figure 5: Relationship of Baseline Systolic Blood Pressure to Last Systolic Blood Pressure for Subjects in the Open-Label Long-Term, Stratified by Presence of Pre-Existing Hypertension**



**Figure 6: Relationship of Baseline Heart Rate to Last Heart Rate for Subjects in the Open-Label Long-Term, Stratified by Presence of Pre-Existing Hypertension**

In Figure 5, there is a slight clustering of subjects without hypertension to the lower left of the figure, suggesting that subjects with no pre-existing hypertension and lower systolic blood pressures at baseline tended to experience less elevation of systolic blood pressure over the course of the study than subjects with pre-existing hypertension. This observation adds some support for the Applicant's proposed label warning that pre-existing hypertension should be treated prior to initiating therapy with solriamfetol.

#### **Assessment of Cardiovascular Risk Related to Increases in Blood Pressure and Heart Rate**

DPP consulted the Division of Cardioresenal Products (DCRP) to discuss the level of increased risk of cardiovascular adverse events posed by the magnitude and duration of increase in blood pressure and heart rate that were observed in the solriamfetol clinical trials. DCRP confirmed a dose-dependent increase in systolic blood pressure, diastolic blood pressure, and heart rate compared to placebo when measured at the time of estimated peak of solriamfetol blood levels. The increases were noted for vital sign cuff measurements taken at  $C_{max}$  during Weeks 1, 4, and 12 for both patients with narcolepsy and patients with OSA. DCRP review of ambulatory blood pressure data in Studies 14-002 and 14-003 confirms means elevations in systolic blood

pressure and diastolic blood pressure over 24 hours of up to 3 mmHg, and mean elevations in heart rate over 24 hours of up to 5 beats per minute.

Epidemiological studies have shown that increases in blood pressure increase the risk of major adverse cardiovascular events (MACE) in both patients with no previous vascular disease and in patients at high cardiovascular risk. The risk of MACE is increased if both blood pressure and heart rate are increased simultaneously. It is expected that many patients for whom solriamfetol may be considered are likely to have pre-existing cardiovascular risk factors that predispose them to MACE events. This is particularly true for patients with OSA, a population with high rates of hypertension, hyperlipidemia, diabetes, and obesity. Obesity is also a common co-morbidity in patients with narcolepsy.

DPP has concluded that the product labeling for solriamfetol should include (b) (4) description of the blood pressure and heart rate changes in the Warnings and Precautions section of the labeling. Details of the proposed labeling will be presented in Section 10.1, Prescription Drug Labeling.

#### 8.4.8. Electrocardiograms (ECGs)

##### **Narcolepsy: ECGs, Study ADX-N05-202**

The calculated baseline heart rates were 67.5 bpm for the solriamfetol group and 66.9 bpm for the placebo group. At Week 4 the change from baseline in the two-hour post-dose heart rate was + 3.4 bpm in the solriamfetol group, compared with + 0.3 bpm in the placebo group. Thus, the placebo-corrected increase in heart rate associated with solriamfetol treatment at the two-hour post-dose time point was 3.1 bpm. However, the change from baseline in the placebo-corrected nine-hour post-dose heart rate was a decrease of 1.0 bpm. At Week 12, the placebo-corrected change in the two-hour post-dose heart rate was an increase of 5.0 bpm, while the change in the nine-hour post-dose heart rate was an increase of 3.0 bpm.

*Reviewer's Comment:* These results suggest that increases in heart rate compared to placebo are transient. The increase is most prominent close to the time of dosing, and is less prominent by nine hours after dosing.

A maximum on-therapy increase of more than 30 bpm occurred in one subject receiving solriamfetol. The subject's calculated baseline heart rate was 53 bpm. Four Week 12 ECGs, collected during the same 32-minute period, revealed ECG-derived heart rates of 84 (an increase of 31 bpm), 65, 65, and 64 bpm.

Decreases in heart rate of greater than 15 bpm occurred in four subjects (9%) in the solriamfetol group and six subjects (12%) in the placebo group.

### **Narcolepsy: ECGs, Study 14-002**

Compared with placebo, a higher mean increase in heart rate was observed in the 150 mg and 300 mg solriamfetol groups, with mean increases ranging from 4.9 to 5.9 bpm for 150 mg, 5.5 to 8.4 bpm for 300 mg, and -0.4 to 1.6 bpm for placebo. In the 75 mg solriamfetol group, differences compared with placebo were smaller, ranging from -0.7 bpm to 1.5 bpm. Consistent with the HR increase in the 150 mg and 300 mg solriamfetol groups, there was a decrease in RR intervals in these two higher solriamfetol dose groups.

### **OSA: ECGs, Study 14-003**

Compared to placebo, a higher mean increase from baseline in heart rate was seen across all post-baseline study visits for solriamfetol dose groups. The increase was dose-dependent. The mean increases ranged from 3.2 to 6.0 bpm in the solriamfetol 300 mg group and from -0.5 to 2.1 bpm in the placebo group. Mean changes in QRS and QTcF were small and similar between solriamfetol dose groups and placebo.

### **OSA: ECGs, Study 14-004**

Mean values for ECG interval parameters (PR, QRS, QTcF) showed only minor changes from baseline across all dose levels in each phase of the study. At Weeks 2 and 4, subjects in the solriamfetol group had a mean increase in heart rate of 3-4 bpm and a corresponding mean reduction in RR interval. The change resolved in placebo subjects at Week 6 but remained unchanged for subjects receiving active treatment.

## **8.4.9. QT**

A thorough QT study was completed. The study did not reveal any clinically significant QT or QTcF prolongation, including at 900 mg, which is three times the therapeutic dose.

### **Narcolepsy: QT, Study ADX-N05-202**

The solriamfetol and placebo treatment groups had similar calculated baseline values for PR, QRS, QTcB, and QTcF. Mean placebo-corrected QT values (but not QTcB or QTcF) decreased by 5-9 msec at the two-hour post-dose time at Weeks 4 and 12. There were no subjects on active treatment with baseline or on-therapy QTcF values that exceeded 450 msec for males or 470 msec for females. Two subjects in the placebo group exceeded these values. No subject in either treatment group experienced a maximum on-therapy increase of QTcF of greater than 60 msec. There were six subjects in each treatment group who experienced a maximum on-therapy increase of QTcF from baseline of greater than 30 msec but less than 60 msec.

### **Narcolepsy: QT, Study 14-002**

Changes in QTcF interval from baseline to Weeks 1, 4, 8, and 12 were low. No subjects had a QTcF of > 500 msec. One subject in the placebo group had a QTcF of > 480 msec. Six subjects had QTcF change from baseline of 30-60 msec: one subject in the 75 mg solriamfetol group, three subjects in the 150 mg solriamfetol group, and two subjects in the 300 mg solriamfetol group. At safety follow-up, two subjects had QTcF change from baseline of 30-60 msec: one subject in the 150 mg solriamfetol group and one subject in the 300 mg solriamfetol group.

### **Narcolepsy: QT, Study 14-005**

One subject ( [REDACTED] <sup>(b) (6)</sup> ), whose parent study (14-002) baseline QTcF value was 461 msec and whose final QTcF value in the parent study was 486 msec, had a QTcF value of 510 msec at the Week 2 study visit. The subject was receiving solriamfetol 300 mg/day. For this subject, QTcF prolongation was reported as a TEAE and resulted in withdrawal from the study, as the subject met the study stopping criterion of a QTcF value > 500 msec.

No subject diagnosed with narcolepsy had a post-treatment change in QTcF > 60 msec compared with baseline in the parent study.

### **OSA: QT, 14-003**

Changes from baseline in QTcF interval in the range of 30 to 60 msec were observed for subjects in both the placebo and solriamfetol dose groups; 4/119 in the placebo group, 9/58 in the 37.5 mg group, 5/62 in the 75 mg group, 2/117 in the 150 mg group, and 4/118 in the 300 mg group. One subject in the 300 mg group had a post-baseline QTcF > 480 msec at Week 8 of 496 msec, which was a change from baseline of > 60 msec.

### **OSA: QT, Study 14-004**

No subject experienced a clinically significant change in any QT interval (QT, QTcF, QTcB). No subject had a QTcF value > 480 msec at any assessment, and none had a QTcF change from baseline > 60 msec. A change from baseline QTcF of 30-60 msec was observed in two subjects (2%) in the solriamfetol group at Week 2, one subject each at 150 mg and 300 mg, and in one subject (1.6%) in the placebo group at Week 6.

### **OSA: QT, Study 14-005**

One subject ( [REDACTED] <sup>(b) (6)</sup> ), whose parent study (14-003) baseline QTcF value was 448 msec and whose final QTcF value in the parent study was 447 msec, had a QTcF value > 480 msec during

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the open-label treatment phase of Study 14-005. The subject was receiving solriamfetol 75 mg/day. The subject discontinued the study due to an AE of insomnia, and had a QTcF value of 481 msec at the early termination visit on Day 22.

No subject diagnosed with OSA had a post-treatment change in QTcF > 60 msec compared with baseline in the parent study.

#### 8.4.10. Immunogenicity

No immunogenicity data was submitted with this application.

### 8.5. Analysis of Submission-Specific Safety Issues

#### 8.5.1. Columbia-Suicide Severity Rating Scale

##### **Narcolepsy: C-SSRS, Study ADX-N05-202**

Baseline administration of the C-SSRS identified several subjects with findings suggestive of pre-existing suicide risk or prior suicide attempt. Administration of the C-SSRS at Weeks 1, 2, 4, 6, 8, 12, and 13 (follow-up visit) did not reveal a new onset of suicidal ideation or suicidal behavior in any subject.

##### **Narcolepsy: C-SSRS, Study 14-002**

At baseline, no subjects in any treatment group reported suicidal ideation, suicidal behavior, or self-injurious behavior with suicidal intent. C-SSRS scores were zero at baseline for all subjects. Changes from baseline in C-SSRS scores were observed for three subjects, one in the 75 mg solriamfetol group and two in the 300 mg solriamfetol group, with a maximum C-SSRS score of one (“wish to be dead”) in each case, indicating passive suicidal ideation. One subject in the 300 mg solriamfetol group terminated early due to depressive symptoms, and the other terminated early due to a papular rash. The subject in the 75 mg solriamfetol group completed the study.

##### **Narcolepsy: C-SSRS, Study 14-005**

At the time of data cut-off for the interim report, one subject diagnosed with narcolepsy had a TEAE of suicide attempt by intentional medication overdose in conjunction with alcohol consumption. This event, which was serious and resulted in withdrawal from the study, is discussed in Section 8.4.2 ([Subject \(b\) \(6\), Study 14-005: Suicide Attempt](#)). There were no other reports of suicidal ideation or behavior post-baseline in patients with narcolepsy, in either the

open-label phase or randomized withdrawal period, as assessed by the C-SSRS.

**OSA: C-SSRS, 14-003**

At baseline, no subjects reported suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent. For all subjects, C-SSRS scores for each of these categories at baseline were zero. During active treatment, shifts from baseline C-SSRS were observed for two subjects in the placebo group and one subject in the solriamfetol group. No subject exhibited suicidal behavior over the course of the study. The highest C-SSRS score on suicidal ideation for the two placebo subjects was 3 (active suicidal ideation without plan and without intent to act). The highest C-SSRS score on suicidal ideation for the solriamfetol 300 mg subject was 1 (passive suicidal ideation / wish to be dead). Both placebo subjects were withdrawn from the study due to depression and suicidal ideation. The subject in the solriamfetol 300 mg group remained in the study.

**OSA: C-SSRS, Study 14-004**

At screening, seven subjects had C-SSRS scores suggestive of prior suicidal risk, while 167 subjects had no prior findings of suicidal risk. There were no new positive responses for any subject who completed the C-SSRS assessments during the study. No TEAEs related to suicidal ideation or behavior were reported in the study. One subject experienced an AE of depression without suicidal ideation or behavior.

**OSA: C-SSRS, Study 14-005**

At the time of data cut-off for the interim report, there were no reports of suicidal ideation or behavior post-baseline for patients with OSA, in either the open-label phase or randomized withdrawal period, as assessed by the C-SSRS.

## **8.6. Safety Analyses by Demographic Subgroups**

### **8.7. Specific Safety Studies/Clinical Trials**

### **8.8. Additional Safety Explorations**

#### **8.8.1. Human Carcinogenicity or Tumor Development**

No human carcinogenicity data was submitted with this application. The Applicant submitted reports of two animal carcinogenicity studies, one in rats and one in mice. The studies were intended to assess the carcinogenic potential of solriamfetol in rats and mice when administered orally by gavage at low, medium, and high dose levels for about 104 weeks.

The rat study showed no statistically significant increase or decrease in mortality between drug-treated groups and the control group. Pairwise comparisons showed statistically significant increases in the low dose groups compared to controls for the incidence of islet cell carcinoma of the pancreas in male rats, and statistically significant increases in the low dose groups compared to controls for the incidence of fibroadenoma of the mammary gland in female rats. However, no tumor type demonstrated a statistically significant dose response relationship in tumor incidence with increased solriamfetol dose in rats of either sex.

The mouse study showed no statistically significant increase in mortality across the control group and the low, medium, and high drug-treated groups in either sex of mice. Pairwise comparisons in male mice showed a statistically significant increased mortality in medium dose groups compared to the control group. The pairwise comparisons in female mice showed no statistically significant increase or decrease in mortality between each of the drug-treated groups and the control group. No tumor types demonstrated a statistically significant dose response relationship in tumor incidence with increased solriamfetol dose in mice of either sex. Pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidence in the drug-treated groups compared to controls in either male or female mice.

### 8.8.2. Human Reproduction and Pregnancy

The Division of Pediatric and Maternal Health (DPMH) conducted a review of data regarding the use of solriamfetol during pregnancy. At this time, the available data are very limited and are insufficient to make an assessment of drug associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are no data available on the presence of solriamfetol or its metabolites in human milk, the effects on the breastfed infant, or the effect of solriamfetol on milk production. Nonclinical studies indicate that solriamfetol is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

DPMH recommends a pregnancy exposure registry to monitor outcomes in women exposed to solriamfetol during pregnancy. DPMH recommends text in the product labeling to encourage healthcare providers to register pregnant patients, and to inform healthcare providers that pregnant women may enroll themselves in the registry. DPMH also recommends text instructing clinicians to consider the developmental and health benefits of breastfeeding along with the mother's clinical need for solriamfetol and any potential adverse effects on the breastfed child from solriamfetol or from the underlying maternal condition, and to monitor

breastfed infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain. Postmarketing requirements are described in Section 12, Postmarketing Requirements and Commitments.

### **8.8.3. Pediatrics and Assessment of Effects on Growth**

No pediatric patients were enrolled in studies conducted in association with this NDA. For the narcolepsy indication, this application is exempt from the Pediatric Research Equity Act (PREA) requirement for pediatric studies because the Applicant has been granted an orphan drug designation for use of an (b) (4) phenylalanine derivative for treatment of narcolepsy. For the OSA indication, the Applicant will apply for a waiver of the PREA requirement for pediatric studies, on the following basis: [1] the primary treatment of OSA in pediatric patients is surgical management, and professional treatment guidelines do not recommend pharmaceutical therapy; [2] the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; [3] the product is not likely to be used in a substantial number of pediatric patients; and [4] pediatric studies would be impossible or highly impractical to conduct.

### **8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

The Applicant has recommended a Schedule IV listing for solriamfetol. The Applicant has conducted a human abuse potential (HAP) study comparing solriamfetol to phentermine, which is a Schedule IV drug. The study found that Liking at the Moment, Overall Next Day Drug Liking, and Willingness to Take the Drug Again for solriamfetol were comparable to placebo, and were lower for solriamfetol than for phentermine. The Applicant conducted a search of adverse events across all studies using queries “drug abuse and dependence” and “drug misuse,” and found no signal of drug misuse, abuse, or dependence. The most frequent adverse events related to solriamfetol, i.e. insomnia, dizziness, irritability, fatigue, agitation, nausea, and diarrhea, are not likely to contribute to continued intentional misuse. The adverse event of euphoric mood, which might promote abuse, was observed only at very low frequency. Tolerance and withdrawal were not observed in the long-term open-label study. Solriamfetol is not a biochemical precursor to any controlled substance. Modafinil and armodafinil, both of which are also prescribed for excessive daytime sleepiness, are Schedule IV drugs, so a Schedule IV designation for solriamfetol would place it in the same class as two related drugs.

## **8.9. Safety in the Postmarket Setting**

### **8.9.1. Safety Concerns Identified Through Postmarket Experience**

No postmarket experience to date, as solriamfetol is not yet marketed in the United States or any foreign country.

### **8.9.2. Expectations on Safety in the Postmarket Setting**

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The Division recommends postmarketing studies to assess the safety of solriamfetol in pregnancy and lactation. See Section 12, Postmarketing Requirements and Commitments.

### 8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues have been raised by other disciplines.

### 8.10. Integrated Assessment of Safety

This safety review has not identified any safety issues that would preclude the approval of this NDA application.

## 9. Advisory Committee Meeting and Other External Consultations

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Arguments against presenting this NME to an Advisory Committee include the following:

1. Solriamfetol is not a first-in-class drug. The stimulants modafinil and armodafinil have also been approved for excessive daytime sleepiness in narcolepsy and OSA.
2. An Advisory Committee was held for modafinil. The panel approved the use of a stimulant to treat the same target population as that for solriamfetol.
3. The substance abuse potential for solriamfetol appears to be lower than that of phentermine.
4. The adverse event profile for solriamfetol is similar to that of modafinil and armodafinil.
5. The absence of CYP450 metabolism for solriamfetol suggests possible safer use with patients taking other medications, compared with modafinil and armodafinil.

The evaluation of the safety data did not reveal safety concerns requiring additional consultation. This application was not presented to an Advisory Committee.

## 10. Labeling Recommendations

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### 10.1. Prescription Drug Labeling

DPP recommends the following (b) (4) :

(b) (4)

(b) (4)



The following text is recommended for the Warnings and Precautions section of the product labeling:

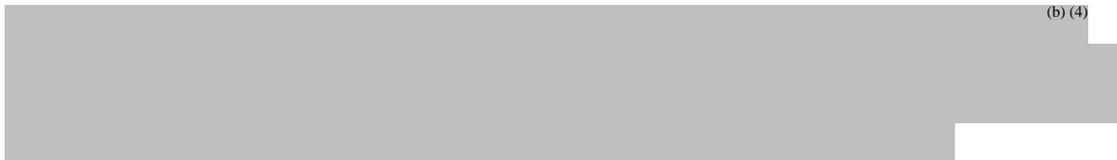
### **Blood Pressure and Heart Rate Increases**

Systolic blood pressure, diastolic blood pressure, and heart rate were all elevated in a dose-related fashion after taking SUNOSI in both patients with narcolepsy and patients with OSA. (b) (4)



Chronic elevations in heart rate and blood pressure over long periods of time have been associated with increased risks of major adverse cardiac events (MACE), including heart attack, stroke, heart failure, and death. The magnitude of the absolute increased risk in MACE is dependent on the baseline risk of MACE in the population being treated. Many of the narcolepsy and OSA subjects in controlled clinical trials demonstrated multiple risk factors for MACE at baseline, including hypertension, diabetes, hyperlipidemia, and high body mass index (BMI).

(b) (4)



Patients with moderate or severe renal impairment could be at a higher risk of increases in blood pressure and heart rate because of the prolonged half-life of SUNOSI.

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Assess blood pressure and heart rate before initiating treatment with SUNOSI. Pre-existing hypertension should be controlled before initiating treatment with SUNOSI. Periodically reassess the need for continued treatment. Monitor for and treat new-onset hypertension or exacerbations of pre-existing hypertension. Exercise caution when treating patients with pre-existing hypertension or cardiovascular or cerebrovascular conditions that might be compromised by increases in blood pressure.

If a patient experiences a sustained increase in blood pressure or heart rate that cannot be managed with dose reduction of SUNOSI or other appropriate medical intervention, consider discontinuation of SUNOSI. Concomitant use of SUNOSI with drugs that increase blood pressure and heart rate has not been evaluated, and such combinations should be used with caution.

In the Dosage and Administration section, the product labeling will recommend a lower starting dose for patients with OSA than for patients with narcolepsy:

- Starting dose for patients with narcolepsy: 75 mg once daily.
- Starting dose for patients with OSA: 37.5 mg once daily.

At the time of completion of this review, the Agency and the Applicant had not yet reached an agreement on the final content and wording of the product label.

#### **End of Review Cycle**

As of the original PDUFA goal date of 12/20/2018, the Agency and the Applicant were unable to reach agreement on the product labeling. The Applicant did not agree (b) (4)

After discussion with the Agency to determine a path forward, the Applicant submitted a Major Amendment on 12/19/2018 proposing (b) (4)

The Applicant bases this proposal on clinical study data (b) (4)

(b) (4) the Applicant believes that the low incidence of serious adverse cardiovascular events and the efficacy data originally submitted with the application support the approval of 150 mg/day as the maximum recommended dosage

The Agency accepted the Major Amendment. The new goal date is 3/20/2019.

## 10.2. Nonprescription Drug Labeling

Not relevant for this application.

## 11. Risk Evaluation and Mitigation Strategies (REMS)

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A REMS has not been implemented or proposed for solriamfetol.

## 12. Postmarketing Requirements and Commitments

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The Division has proposed the following three postmarketing requirements (PMRs) related to safety assessment in pregnancy and lactation:

### PMR 3475-1

- Subject: Pregnancy (1 of 2)
- Description: “A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to solriamfetol during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.”
  - Draft Protocol Submission: March 20, 2019
  - Final Protocol Submission: June 20, 2019
  - Study/Trial Completion: June 20, 2029
  - Final Report Submission: June 20, 2030

### PMR 3475-2

- Subject: Pregnancy (2 of 2)
- Description: “An additional pregnancy study that uses a different design from the Pregnancy Registry (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to solriamfetol during pregnancy compared to an unexposed control population.”
  - Draft Protocol Submission: March 20, 2019
  - Final Protocol Submission: June 20, 2019

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- Study/Trial Completion: June 20, 2024
- Final Report Submission: June 20, 2025

**PMR 3475-3**

- Subject: Lactation
- Description: “Perform a lactation study (milk only) in lactating women who have received therapeutic doses of solriamfetol using a validated assay to assess concentrations of solriamfetol in breast milk and the effects on the breastfed infant.”
  - Draft Protocol Submission: March 20, 2019
  - Final Protocol Submission: June 20, 2019
  - Study/Trial Completion: June 20, 2020
  - Final Report Submission: June 20, 2021

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

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### 13. Appendices

#### 13.1. References

No literature review was conducted for this NDA review.

#### 13.2. Financial Disclosure

**Covered Clinical Study (Name and/or Number): ADX-N05-202, 14-002, 14-003, 14-004, 14-005**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>732</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):  Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u>  Significant payments of other sorts: <u>2</u>  Proprietary interest in the product tested held by investigator: <u>0</u>  Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason: N/A	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

*Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators.<sup>1</sup> Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:*

- *If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)*
- *If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)*

*Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.*

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[1] (b) (6) was an investigator for Studies 14-002, 14-003, and 14-005. (b) (6) received speaking and consulting fees from the Sponsor from (b) (6), totaling \$170,639.16. The Sponsor states that these activities were related to the product (b) (6), which is a different product from solriamfetol. The Sponsor also states that (b) (6) did not receive any direct personal payment for participation in the trials, and that the Sponsor's Clinical Operations Lead discussed with (b) (6) the fundamentals of a blinded study and the importance of maintaining the integrity of the study data.

The financial arrangements disclosed for (b) (6) do not appear to adversely affect the approvability of the application.

[2] (b) (6) was an investigator for Studies 14-002, 14-003, and 14-005. (b) (6) was paid annual royalty fees (b) (6) totaling \$10,000. (b) (6) The Sponsor states that the amount of the royalty payments does not vary depending on the outcome of the study, is not associated with any equity interest in Jazz Pharmaceuticals, and is not tied to the success or sales of any Jazz Pharmaceutical products. The Reviewer notes that (b) (6) for any of the studies submitted as part of the NDA application, though (b) (6) for Study 14-004.

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The financial arrangements disclosed for (b) (6) do not appear to adversely affect the approvability of the application.

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APPEARS THIS WAY ON ORIGINAL

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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DAVID H MILLIS  
12/20/2018 01:18:07 PM

JAVIER A MUNIZ  
01/02/2019 04:08:47 PM



# Center for Drug Evaluation and Research

## Division of Cardiovascular and Renal Products

DCRP Consult NDA 211230

**DATES:** Date of Document: 12/20/2017  
Date of Consult: 10/24/2018  
Date of Assignment: 10/31/2018  
Desired Completion Date: 11/8/2018  
Date of Completion: 11/6/2018

**FROM:** Preston M. Dunnmon, M.D., M.B.A., Medical Officer  
Division of Cardiovascular and Renal Products, HFD-110

**THROUGH:** Karen Hicks, M.D., Medical Team Leader  
Division of Cardiovascular and Renal Products, HFD-110

Norman Stockbridge, M.D., Ph.D., Division Director  
Division of Cardiovascular and Renal Products, HFD-110

**TO:** Sarah Seung, Regulatory Program Manager  
Division of Psychiatry Products (DPP), HFD-120

David Millis, MD, M.B.A., Ph.D., Medical Officer  
Division of Neurology Products (DPP), HFD-120

**DRUG NAME:** Solriamfetol (JSP-110)

**DOSE/FORMULATION:** Tablet

**PRODUCT CLASS:** Selective dopamine and norepinephrine reuptake inhibitor (DNRI)

**APPLICANT:** Jazz Pharmaceuticals Ireland Limited

**INDICATION:** To improve wakefulness and reduce excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA)

**BACKGROUND:**

*“Jazz submitted NDA 211230 for solriamfetol (JSP-110), a phenylalanine derivative selective dopamine and norepinephrine reuptake inhibitor, to improve wakefulness and reduce excessive sleepiness in adult patients with narcolepsy (Original 1) and improve*

DCRP Consult NDA 211230

wakefulness and reduce excessive sleepiness in adult patients with obstructive sleep apnea (OSA) (Original 2). Solriamfetol was developed under IND 107203 (for narcolepsy) and IND 122590 (for OSA). The NDA is an NME.

Data from the three 12-week placebo-controlled trials suggest minimal changes in mean systolic blood pressure, mean diastolic pressure, and mean heart rate from baseline to the end of treatment. However, comparison of blood pressure readings timed at expected peak and trough blood levels indicates potentially significant blood pressure changes over the course of a day, i.e. around 5 mmHg increase from trough to peak, sustained over several hours, with the magnitude and duration of increase appearing dose-dependent. (b) (4)

(b) (4) DPP requests advice from DCRP on summarizing the blood pressure changes for labeling such that clinicians are fully informed about the level of risk that might be seen in clinical practice.”

**CONSULT QUESTION:** The review Division, (b) (4)

(b) (4) DPP requests advice from DCRP on summarizing the blood pressure changes for labeling such that clinicians are fully informed about the level of risk that might be seen in clinical practice.”

**DOCUMENTS FROM WHICH BP WAS REVIEWED:**

- ISS

**ISS DATA POOLING STRUCTURE**

**Table 2: Study Grouping and Pooling for the JZP-110 Integrated Summary of Safety**

Study Grouping/Pooling		Studies
1	All 12-Week Placebo-Controlled Narcolepsy and OSA Studies (Integrated)	12-Week Placebo-Controlled Narcolepsy Studies (Integrated): ADX-N05 202, 14-002
		12-Week Placebo-Controlled OSA Study: 14-003
2	All Narcolepsy and OSA Studies (Integrated)	All Narcolepsy Studies (integrated): ADX-N05 201, ADX-N05 202, 14-002, 14-005
		All OSA Studies (Integrated): 14-003, 14-004, 14-005
3	MDD Studies (Integrated)	All MDD Studies (Integrated): SKUP-9801, R228060-USA-10, R228060-MDD-201
4	Healthy Volunteer Studies (Integrated)	All HV Studies (Integrated): YUKIC 9603-01, R228060-P01-101, YUKIC 9702-01, R228060-NED-1, 15-002, 15-009

**BLOOD PRESSURE DATA:**

*In the ISS, vital signs, including blood pressure and heart/pulse rate, were summarized and presented for the 12-week placebo-controlled narcolepsy and OSA studies (Pool 1). Vital signs were assessed in 3 ways in the narcolepsy and OSA studies: regular vital sign measurements (at baseline, Weeks 1, 4, 8, and 12); multiple vital sign measurements on maintenance of wakefulness (MWT) days relative to dosing at baseline, Weeks 1, 4, and 12 (pre-dose and 1, 2, 4, 6, 8, and 10 hours post-dose); and 24-hour ambulatory blood pressure monitoring (ABPM) at baseline and Week 8. Results for ABPM are included in the individual clinical study reports (CSRs).*

Blood pressure data were reviewed separately for a 6-week randomized withdrawal study (14-004) in patients with OSA and for the TQT study (15-002).

Integrated Pool 1 Data (from sponsor ISS) – central tendencies, changes from baseline by indication, by dose, and by time

**Table 181: Regular Vital Signs at Each Clinic Visit: Summary of Mean Change (SD) from Baseline in Blood Pressure and Heart Rate (By Indication-Safety Population)**

Parameter Mean (SD) Across Time Points	JZP-110 (Narcolepsy)				Placebo N = 118	JZP-110 (OSA)			
	Placebo N = 108	75 mg N = 59	150 mg N = 102	300 mg N = 99		37.5 mg N = 58	75 mg N = 61	150 mg N = 116	300 mg N = 118
<b>SBP (mmHg)</b>									
Week 1, n	104	58	97	58	113	56	56	114	115
	1.178 (10.662)	-1.707 (10.109)	1.878 (10.957)	-1.865 (8.798)	-3.487 (10.880)	-0.762 (13.067)	-3.455 (11.513)	-1.836 (11.244)	-0.988 (11.947)
Week 4, n	98	52	91	55	109	52	54	110	102
	0.883 (10.943)	-2.385 (10.125)	-0.359 (11.918)	-1.473 (10.129)	-1.428 (10.831)	-1.359 (11.414)	-1.312 (13.081)	-1.286 (10.475)	-0.462 (12.181)
Week 8, n	91	49	51	83	104	49	53	108	97
	0.925 (11.704)	-1.330 (10.871)	-0.029 (11.350)	2.667 (11.086)	-3.742 (12.391)	0.847 (11.599)	-1.613 (14.087)	-0.739 (11.415)	0.369 (12.469)
Week 12, n	89	49	50	79	100	49	53	106	94
	2.296 (9.498)	-1.878 (10.023)	0.953 (10.922)	0.899 (11.323)	-1.920 (11.938)	1.163 (10.194)	-0.896 (12.249)	0.099 (11.566)	-0.285 (15.135)
<b>DBP (mmHg)</b>									
Week 1, n	104	97	97	58	113	56	56	114	115
	1.673 (7.388)	-1.592 (7.308)	1.905 (9.316)	0.851 (8.191)	-1.363 (7.792)	0.673 (7.954)	-0.961 (8.413)	-0.284 (7.208)	0.326 (7.600)
Week 4, n	98	52	91	55	109	52	54	110	102
	1.583 (8.447)	-2.631 (6.714)	-0.130 (8.377)	-0.585 (8.422)	-0.190 (7.641)	0.369 (7.340)	-0.543 (8.180)	-0.238 (6.623)	-0.209 (6.885)
Week 8, n	91	49	51	83	104	49	53	108	97
	2.020 (8.552)	-0.786 (6.935)	2.275 (9.323)	2.520 (8.676)	-0.223 (9.184)	0.755 (8.492)	-0.016 (9.266)	-0.052 (8.317)	0.302 (8.053)
Week 12, n	89	49	50	79	100	49	53	106	94
	2.522 (7.918)	-1.721 (6.836)	1.770 (7.648)	0.977 (8.245)	0.678 (8.419)	1.190 (6.054)	-0.450 (8.280)	0.182 (8.576)	-0.254 (8.073)
<b>Heart Rate (bpm)</b>									
Week 1, n	104	58	97	58	113	56	56	114	115
	1.99 (9.548)	-0.66 (8.095)	4.11 (10.691)	3.48 (11.128)	-3.08 (10.066)	-1.28 (10.685)	-0.68 (9.862)	-0.64 (10.146)	-0.37 (9.251)
Week 4, n	98	52	91	55	109	52	54	110	102
	1.90 (8.513)	-0.37 (7.830)	4.06 (10.782)	1.95 (12.375)	-0.98 (10.101)	2.82 (11.303)	0.65 (10.635)	1.78 (10.314)	0.49 (9.261)
Week 8, n	91	49	51	83	104	49	53	108	97
	1.05 (10.378)	-2.70 (10.915)	2.30 (12.740)	4.40 (13.135)	-3.06 (10.084)	-4.71 (11.408)	-4.61 (10.678)	-1.06 (11.231)	-0.30 (9.980)
Week 12, n	89	49	50	79	100	49	53	106	94
	2.12 (9.842)	-1.83 (9.620)	4.04 (9.787)	4.20 (11.657)	-1.43 (9.895)	0.81 (11.171)	1.16 (10.559)	1.36 (10.942)	3.05 (9.623)

- *Sponsor assessment:* In summary, baseline values for BP and HR were within normal range for both indications but generally higher in the OSA population compared to the narcolepsy population (data for absolute values not shown). For narcolepsy, no clinically meaningful trends were observed for mean changes in BP for JZP-110 over time (relative to placebo, changes were small and not dose-related); for OSA, mean increases in SBP for JZP-110 relative to placebo were observed. For both indications, dose-related increases in HR for JZP-110 relative

to placebo were observed; the magnitude of change across the study was generally similar between the two populations.

- *Reviewer’s assessment:* For all measurements, the differences with placebo are smaller than the standard deviation of the measurements. Some of these changes are driven by negative changes from baseline in the placebo groups. However, the sponsor’s overall observations appear to be correct. For the OSA group, there appears to be both a time and a dose-related element in the elevation of heart rate (maximal single delta HR increase of 4 bpm).

**Table 183: Vital Signs on MWT Day: Summary of Mean Change (SD) from Baseline in Blood Pressure and Heart Rate (By Indication-Safety Population)**

Parameter Mean (SD) Across Time Points	Placebo N = 108	JZP-110 (Narcolepsy)			Placebo N = 118	JZP-110 (OSA)				
		75 mg N = 59	150 mg N = 102	300 mg N = 99		37.5 mg N = 58	75 mg N = 61	150 mg N = 116	300 mg N = 118	
<b>SBP (mmHg)</b>										
Week 1, n	23	25	22	24	35	17	17	38	35	
	-0.725 (5.715)	-0.527 (6.936)	0.854 (6.546)	-0.430 (7.346)	-0.262 (6.005)	2.532 (7.623)	1.838 (5.140)	0.123 (4.666)	2.086 (7.020)	
Week 4, n	96	51	89	53	105	51	53	107	99	
	0.912 (7.713)	-0.428 (6.738)	0.705 (7.587)	2.570 (7.733)	0.253 (6.796)	1.243 (8.959)	1.653 (6.696)	1.020 (7.782)	1.782 (8.462)	
Week 12, n	88	48	47	79	97	49	52	102	91	
	1.892 (8.183)	0.719 (7.254)	1.750 (7.786)	2.493 (7.817)	0.091 (7.892)	2.032 (8.300)	0.661 (9.010)	0.914 (7.597)	2.940 (10.515)	
<b>DBP (mmHg)</b>										
Week 1, n	23	25	22	24	35	17	17	38	35	
	-0.055 (4.707)	0.060 (4.607)	2.095 (5.424)	1.194 (4.153)	-0.718 (4.779)	0.264 (4.852)	1.477 (4.565)	-0.126 (4.051)	0.823 (4.400)	
Week 4, n	96	51	89	53	105	51	53	107	99	
	-0.148 (4.791)	0.192 (4.529)	1.303 (5.922)	1.681 (5.577)	0.224 (4.446)	0.730 (5.560)	1.088 (5.092)	0.730 (5.097)	1.080 (5.246)	
Week 12, n	88	48	47	79	97	49	52	102	91	
	0.255 (5.316)	1.231 (4.823)	2.089 (5.085)	2.263 (5.363)	0.042 (4.881)	0.691 (5.020)	0.190 (6.758)	0.721 (5.655)	1.792 (5.910)	
<b>Heart Rate (bpm)</b>										
Week 1, n	23	25	22	24	35	17	17	38	35	
	0.02 (6.366)	0.34 (3.180)	1.74 (5.748)	3.44 (7.199)	-1.34 (4.877)	0.78 (5.125)	0.18 (6.045)	1.84 (6.898)	1.97 (6.669)	
Week 4, n	96	51	89	53	105	51	53	107	99	
	0.34 (5.804)	0.12 (6.450)	1.86 (6.366)	4.32 (7.406)	0.39 (5.783)	0.85 (5.604)	1.74 (5.208)	1.68 (6.963)	2.72 (6.339)	
Week 12, n	88	48	47	79	97	49	52	102	91	
	1.15 (6.306)	0.90 (6.847)	2.73 (5.249)	3.67 (7.459)	0.12 (5.271)	0.61 (7.294)	0.81 (5.333)	2.33 (6.511)	3.28 (5.614)	

- *Sponsor assessment:* Baseline values for BP were generally higher in the OSA population compared to the narcolepsy population (baseline HR was similar between the populations) (data for absolute values not shown). The largest mean increases in SBP, DBP, and HR for both populations were observed for 300 mg JZP-110 relative to placebo and indicate a dose-dependent effect. The magnitude of the increase over time was generally similar for both populations.
- *Reviewer assessment:* In a single delta analysis (change from baseline, not placebo corrected) for both indications, in the setting of the “stress” of MWT testing, there were dose and time related elevations of SBP (maximum 3 mmHg), DBP (maximum 2 mm Hg), and HR (maximum 4 BPM).

**Integrated Pool 1 Data (from sponsor ISS) – central tendencies, changes from baseline by indication, by dose, and by time at trough and peak**

**Table 185: Vital Signs on MWT Days: Summary of Mean Changes from Baseline to Post-Baseline Visits at Trough and Peak (By Indication-Safety Population)**

Vital Sign Time Point Change	Parameter	Placebo N = 108	JZP-110 (Narcolepsy)				Vital Sign Time Point Change	Placebo N = 118	JZP-110 (OSA)			
			75 mg N = 59	150 mg N = 102	300 mg N = 99	37.5 mg N = 58			75 mg N = 61	150 mg N = 116	300 mg N = 118	
<b>SBP (mmHg)</b>												
<b>Week 1</b>												
Trough (Pre-dose)	n	22	25	22	23	Trough (Pre-dose)	34	18	17	38	35	
	Mean (SD)	-3.068 (13.929)	-0.133 (7.697)	-3.038 (9.179)	-3.594 (7.917)		-1.598 (9.060)	-0.778 (10.886)	-0.657 (8.596)	0.158 (12.240)	-1.814 (10.066)	
Peak (2 hours post-dose)	n	23	25	22	23	Peak (4 hours post-dose)	35	17	17	38	35	
	Mean (SD)	-1.601 (9.930)	2.180 (8.597)	2.811 (7.689)	3.232 (12.870)		0.729 (7.874)	2.147 (10.859)	3.706 (6.893)	-0.886 (8.336)	4.524 (9.958)	
<b>Week 4</b>												
Trough (Pre-dose)	n	96	51	89	53	Trough (Pre-dose)	105	51	52	107	98	
	Mean (SD)	-1.976 (10.854)	-2.075 (8.983)	-2.399 (10.159)	1.075 (11.384)		-1.378 (11.913)	0.324 (15.651)	0.074 (12.030)	-1.171 (9.933)	-0.636 (11.487)	
Peak (2 hours post-dose)	n	51	51	49	53	Peak (4 hours post-dose)	105	51	53	106	99	
	Mean (SD)	-0.291 (10.624)	3.092 (10.489)	1.636 (11.070)	6.767 (12.816)		0.067 (10.193)	1.820 (12.204)	2.956 (9.918)	1.987 (9.994)	1.939 (9.456)	
<b>Week 12</b>												
Trough (Pre-dose)	n	87	48	46	79	Trough (Pre-dose)	97	49	52	102	91	
	Mean (SD)	0.360 (11.199)	-2.101 (7.726)	-1.822 (11.172)	-0.369 (9.539)		-1.758 (11.816)	0.224 (13.369)	0.006 (11.411)	-0.407 (11.166)	-0.015 (11.696)	
Peak (2 hours post-dose)	n	50	48	47	43	Peak (4 hours post-dose)	97	49	52	101	91	
	Mean (SD)	-0.110 (10.245)	1.500 (10.628)	5.057 (11.361)	5.016 (9.242)		0.132 (12.398)	1.986 (11.485)	2.580 (12.587)	2.322 (11.249)	2.875 (13.331)	
<b>DBP (mmHg)</b>												
<b>Week 1</b>												
Trough (Pre-dose)	n	22	25	22	23	Trough (Pre-dose)	34	18	17	38	35	
	Mean (SD)	-2.394 (9.081)	-0.507 (5.667)	-3.288 (8.318)	-1.739 (7.346)		-0.044 (6.419)	-0.704 (6.790)	-0.206 (9.525)	-1.075 (7.414)	-0.905 (6.328)	
Peak (2 hours post-dose)	n	23	25	22	23	Peak (4 hours post-dose)	35	17	17	38	35	
	Mean (SD)	-2.478 (8.787)	0.053 (7.842)	2.735 (7.134)	2.268 (6.326)		0.405 (8.029)	0.010 (5.984)	3.196 (8.055)	0.276 (7.004)	2.590 (9.026)	
<b>Week 4</b>												
Trough (Pre-dose)	n	96	51	89	53	Trough (Pre-dose)	105	51	52	107	98	
	Mean (SD)	-0.392 (7.100)	-1.337 (5.973)	-0.886 (7.803)	1.009 (8.856)		0.219 (7.324)	0.425 (9.827)	-1.272 (6.745)	-1.417 (6.633)	0.367 (8.589)	
Peak (2 hours post-dose)	n	51	51	49	53	Peak (4 hours post-dose)	105	51	53	106	99	
	Mean (SD)	-1.245 (6.801)	1.709 (7.754)	3.061 (8.163)	4.223 (9.774)		0.351 (7.715)	-0.003 (7.071)	2.525 (7.905)	1.769 (7.366)	1.120 (7.398)	
<b>Week 12</b>												
Trough (Pre-dose)	n	87	48	46	79	Trough (Pre-dose)	97	49	52	102	91	
	Mean (SD)	0.554 (7.862)	-0.569 (5.902)	-1.351 (10.132)	0.930 (6.817)		-0.227 (8.328)	0.347 (7.305)	-2.083 (7.960)	-0.657 (7.133)	-0.374 (8.175)	
Peak (2 hours post-dose)	n	50	48	47	43	Peak (4 hours post-dose)	97	49	52	101	91	
	Mean (SD)	-1.750 (8.437)	1.247 (5.659)	4.152 (7.612)	4.035 (6.816)		0.072 (7.556)	1.092 (7.202)	1.112 (8.308)	1.238 (8.116)	2.073 (8.773)	
<b>HR (bpm)</b>												
<b>Week 1</b>												
Trough (Pre-dose)	n	22	25	22	23	Trough (Pre-dose)	33	18	17	38	35	
	Mean (SD)	0.80 (6.912)	1.04 (6.702)	-0.07 (10.015)	-0.30 (8.272)		-0.76 (6.466)	-0.97 (8.450)	-1.00 (6.576)	-0.33 (8.426)	-0.11 (6.206)	
Peak (4 hours post-dose)	n	23	25	22	24	Peak (2 hours post-dose)	35	17	17	38	35	
	Mean (SD)	-0.72 (9.621)	-0.86 (7.215)	3.27 (8.899)	6.00 (8.108)		-1.19 (9.100)	1.35 (8.122)	1.76 (8.541)	2.20 (9.275)	4.06 (7.044)	
<b>Week 4</b>												
Trough (Pre-dose)	n	96	51	89	53	Trough (Pre-dose)	105	51	52	107	98	
	Mean (SD)	0.80 (6.244)	-1.22 (8.087)	0.85 (8.875)	-0.61 (8.785)		-0.26 (7.299)	0.28 (7.546)	1.34 (8.291)	-0.21 (8.146)	0.93 (9.522)	
Peak (2 hours post-dose)	n	51	51	49	53	Peak (2 hours post-dose)	105	51	53	107	98	
	Mean (SD)	0.69 (7.482)	1.54 (8.683)	4.95 (8.898)	6.15 (9.913)		0.77 (8.081)	0.82 (6.525)	1.56 (6.247)	2.23 (8.906)	3.70 (7.741)	
<b>Week 12</b>												
Trough (Pre-dose)	n	87	48	46	79	Trough (Pre-dose)	97	49	52	102	91	
	Mean (SD)	-0.02 (7.897)	-1.15 (8.622)	0.50 (9.676)	1.30 (9.416)		0.75 (7.344)	1.19 (8.240)	1.14 (9.039)	1.55 (8.124)	0.62 (9.379)	
Peak (2 hours post-dose)	n	50	48	47	43	Peak (4 hours post-dose)	97	49	51	101	91	
	Mean (SD)	1.01 (9.934)	1.69 (7.469)	5.09 (9.428)	5.56 (10.299)		0.20 (8.289)	0.43 (9.957)	1.06 (8.230)	2.90 (7.859)	4.48 (7.192)	

*Reviewer's assessment: Prominent Cmax effect on SBP, DBP, and HR*

Integrated Pool 1 Data (from sponsor ISS) – Categorical Changes from Baseline at Any Post-Baseline Visit in Mean Blood Pressure and Heart Rate (Regular Vital Signs) for the Overall Population

**Table 189: Categorical Changes from Baseline to Any Post-baseline Visit in Mean Blood Pressure and Heart Rate (Regular Vital Signs) (Overall-Safety Population)**

Parameter Visit Category	Placebo N=226 n (%)	37.5 mg N=58 n (%)	75 mg N=120 n (%)	150 mg N=218 n (%)	300 mg N=217 n (%)
<b>Systolic Blood Pressure (mmHg)</b>					
n	223	57	120	217	214
Increase from Baseline ≥ 5	136 (60.99)	36 (63.16)	58 (48.33)	126 (58.06)	125 (58.41)
Increase from Baseline ≥ 10	91 (40.81)	25 (43.86)	39 (32.50)	87 (40.09)	87 (40.65)
Increase from Baseline ≥ 20	37 (16.59)	7 (12.28)	9 (7.50)	20 (9.22)	33 (15.42)
Increase from Baseline ≥ 30	9 (4.04)	3 (5.26)	1 (0.83)	4 (1.84)	12 (5.61)
Decrease from Baseline ≥ 5	141 (63.23)	39 (68.42)	79 (65.83)	125 (57.60)	128 (59.81)
Decrease from Baseline ≥ 10	87 (39.01)	27 (47.37)	49 (40.83)	81 (37.33)	83 (38.79)
Decrease from Baseline ≥ 20	33 (14.80)	7 (12.28)	15 (12.50)	29 (13.36)	27 (12.62)
Decrease from Baseline ≥ 30	6 (2.69)	1 (1.75)	2 (1.67)	6 (2.76)	4 (1.87)
Low (<90)	3 (1.35)	0	0	0	2 (0.93)
High (≥140)	55 (24.66)	25 (43.86)	25 (20.83)	46 (21.20)	57 (26.64)
<b>Diastolic Blood Pressure (mmHg)</b>					
n	223	57	120	217	214
Increase from Baseline ≥ 5	127 (56.95)	34 (59.65)	46 (38.33)	121 (55.76)	124 (57.94)
Increase from Baseline ≥ 10	73 (32.74)	19 (33.33)	24 (20.00)	66 (30.41)	65 (30.37)
Increase from Baseline ≥ 20	9 (4.04)	3 (5.26)	3 (2.50)	11 (5.07)	9 (4.21)
Increase from Baseline ≥ 30	2 (0.90)	1 (1.75)	0	1 (0.46)	0
Decrease from Baseline ≥ 5	116 (52.02)	27 (47.37)	67 (55.83)	102 (47.00)	99 (46.26)
Decrease from Baseline ≥ 10	59 (26.46)	11 (19.30)	32 (26.67)	53 (24.42)	50 (23.36)
Decrease from Baseline ≥ 20	8 (3.59)	2 (3.51)	3 (2.50)	14 (6.45)	7 (3.27)
Decrease from Baseline ≥ 30	0	0	1 (0.83)	1 (0.46)	0
Low (<60)	17 (7.62)	2 (3.51)	9 (7.50)	15 (6.91)	14 (6.54)
High (≥90)	36 (16.14)	14 (24.56)	18 (15.00)	37 (17.05)	42 (19.63)
<b>Heart Rate (bpm)</b>					
n	223	57	120	217	214
Increase from Baseline ≥ 5	127 (56.95)	31 (54.39)	69 (57.50)	149 (68.66)	149 (69.63)
Increase from Baseline ≥ 10	85 (38.12)	23 (40.35)	45 (37.50)	97 (44.70)	105 (49.07)
Increase from Baseline ≥ 15	53 (23.77)	11 (19.30)	17 (14.17)	51 (23.50)	61 (28.50)
Increase from Baseline ≥ 30	3 (1.35)	1 (1.75)	0	6 (2.76)	8 (3.74)
Decrease from Baseline ≥ 5	129 (57.85)	36 (63.16)	70 (58.33)	108 (49.77)	106 (49.53)
Decrease from Baseline ≥ 10	79 (35.43)	25 (43.86)	44 (36.67)	60 (27.65)	60 (28.04)
Decrease from Baseline ≥ 15	37 (16.59)	10 (17.54)	23 (19.17)	26 (11.98)	34 (15.89)
Decrease from Baseline ≥ 30	3 (1.35)	0	1 (0.83)	5 (2.30)	1 (0.47)
Low (<60)	53 (23.77)	12 (21.05)	23 (19.17)	35 (16.13)	34 (15.89)
High (>100)	10 (4.48)	5 (8.77)	3 (2.50)	16 (7.37)	15 (7.01)

*Reviewer’s assessment: There is a tendency for more frequent blood pressures above 140/90 in the 300 mg arm compared to placebo, and a convincing increase in all categories of heart rate elevation for the 300 mg dose compared to placebo.*

**Table 191: Categorical Changes from Baseline to Week 12 (MWT Vital Signs) (Overall-Safety Population)**

Parameter Visit Category	Placebo N=226 n (%)	37.5 mg N=58 n (%)	75 mg N=120 n (%)	150 mg N=218 n (%)	300 mg N=217 n (%)
<b>Systolic Blood Pressure (mmHg)</b>					
Week 12					
n	190	49	102	155	173
Increase from Baseline $\geq 5$	57 (30.00)	18 (36.73)	26 (25.49)	45 (29.03)	64 (36.99)
Increase from Baseline $\geq 10$	22 (11.58)	6 (12.24)	13 (12.75)	16 (10.32)	35 (20.23)
Increase from Baseline $\geq 20$	0	1 (2.04)	1 (0.98)	1 (0.65)	6 (3.47)
Increase from Baseline $\geq 30$	0	0	0	0	1 (0.58)
Decrease from Baseline $\geq 5$	40 (21.05)	9 (18.37)	24 (23.53)	24 (15.48)	35 (20.23)
Decrease from Baseline $\geq 10$	16 (8.42)	5 (10.20)	8 (7.84)	10 (6.45)	13 (7.51)
Decrease from Baseline $\geq 20$	0	0	1 (0.98)	1 (0.65)	1 (0.58)
Decrease from Baseline $\geq 30$	0	0	0	1 (0.65)	0
Normal ( $\geq 90$ to $<140$ )	176 (92.63)	41 (83.67)	92 (90.20)	138 (89.03)	158 (91.33)
Low ( $<90$ )	0	0	0	0	0
High ( $\geq 140$ )	14 (7.37)	8 (16.33)	10 (9.80)	17 (10.97)	15 (8.67)
<b>Diastolic Blood Pressure (mmHg)</b>					
Week 12					
n	190	49	102	155	173
Increase from Baseline $\geq 5$	31 (16.32)	9 (18.37)	18 (17.65)	37 (23.8)	58 (33.53)
Increase from Baseline $\geq 10$	5 (2.63)	0	5 (4.90)	7 (4.52)	15 (8.67)
Increase from Baseline $\geq 20$	0	0	0	1 (0.65)	0
Increase from Baseline $\geq 30$	0	0	0	0	0
Decrease from Baseline $\geq 5$	30 (15.79)	6 (12.24)	14 (13.73)	14 (9.03)	19 (10.98)
Decrease from Baseline $\geq 10$	4 (2.11)	2 (4.08)	4 (3.92)	2 (1.29)	2 (1.16)
Decrease from Baseline $\geq 20$	0	0	0	0	0
Decrease from Baseline $\geq 30$	0	0	0	0	0
Normal ( $\geq 60$ to $<90$ )	179 (94.21)	44 (89.80)	94 (92.16)	142 (91.61)	165 (95.38)
Low ( $<60$ )	4 (2.11)	2 (4.08)	5 (4.90)	7 (4.52)	2 (1.16)
High ( $\geq 90$ )	7 (3.68)	3 (6.12)	3 (2.94)	6 (3.87)	6 (3.47)
<b>Heart Rate (bpm)</b>					
Week 12					
N	190	49	102	155	173
Increase from Baseline $\geq 5$	35 (18.42)	12 (24.49)	25 (24.51)	51 (32.90)	73 (42.20)
Increase from Baseline $\geq 10$	8 (4.21)	4 (8.16)	7 (6.86)	15 (9.68)	18 (10.40)
Increase from Baseline $\geq 15$	4 (2.11)	1 (2.04)	0	2 (1.29)	7 (4.05)
Increase from Baseline $\geq 30$	0	0	0	0	0
Decrease from Baseline $\geq 5$	23 (12.11)	10 (20.41)	15 (14.71)	12 (7.74)	16 (9.25)
Decrease from Baseline $\geq 10$	7 (3.68)	4 (8.16)	3 (2.94)	6 (3.87)	6 (3.47)
Decrease from Baseline $\geq 15$	2 (1.05)	2 (4.08)	2 (1.96)	1 (0.65)	1 (0.58)
Decrease from Baseline $\geq 30$	0	0	0	0	0

*Reviewer's assessment: In the setting of "stress" induced by MWT testing, prominent upward categorical shifts in SBP, DBP, and HR were observed.*

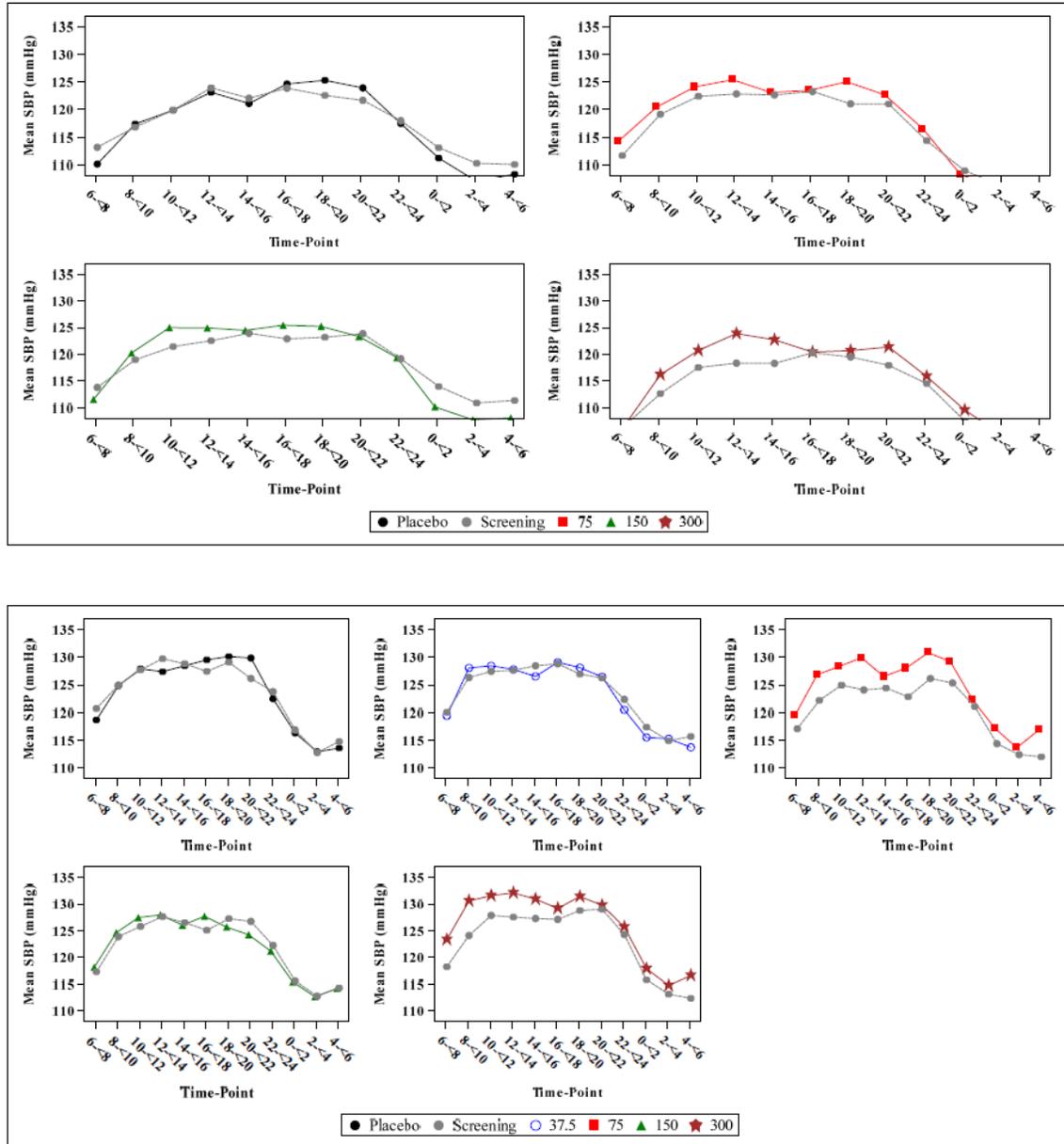
Ambulatory Blood Pressure Monitoring (ABPM, 12-Week Placebo-Controlled Studies 14-002 and 14-003)

*Ambulatory blood pressure monitoring (ABPM) was assessed in individual studies 14-002 and 14-003 and the data were not summarized as part of the 12-week placebo-controlled studies in narcolepsy and OSA (Pool 1). The following section briefly summarizes the ABPM data for individual studies 14-002 and 14-003 (for further information, see the individual CSRs for Study 14-002 and 14-003).*

*For ABPM, blood pressure 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 the study drug in the morning after waking up, but the precise time of dosing was not recorded. Mean SBP, DBP, and HR are expressed as observed values presented in 2-hour intervals at Week 8 and compared to the corresponding 2-hour interval at baseline (see Figures 8-10 below). Time-matched mean changes from baseline to Week 8 are also summarized overall (24 hours) and by daytime (7 AM to 10 PM) and night time (10 PM to 7 AM) time periods (see Table 186 below).*

**Figure 8: Vital Signs for ABPM (Systolic Blood Pressure): Line Plot of Observed Value Matched by Time Point at Week 8 in Individual 12-Week Placebo-Controlled Studies 14-002 and 14-003**

a) Systolic Blood Pressure at Baseline and Week 8 for Study 14-002 Narcolepsy (top) and Study 14-003 OSA (bottom)

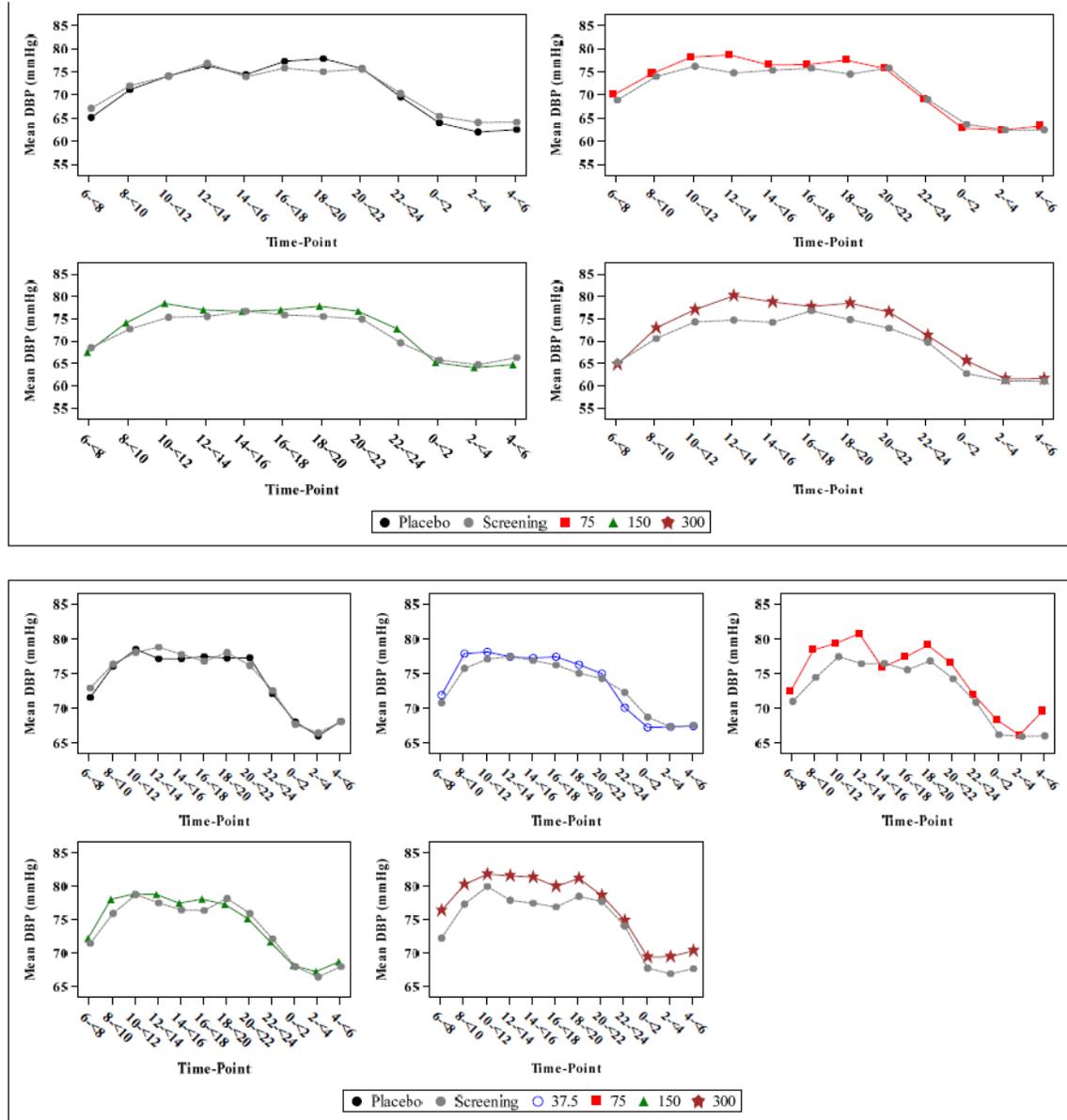


SBP = systolic blood pressure ABPM = ambulatory blood pressure monitoring.

Source: CSR 14-002/Table 14.3.3.3.3; CSR 14-003/Table 14.3.3.3.3

**Figure 9: Vital Signs for ABPM (Diastolic Blood Pressure): Line Plot of Observed Value Matched by Time Point at Week 8 by Individual 12-Week Placebo-Controlled Studies 14-002 and 14-003**

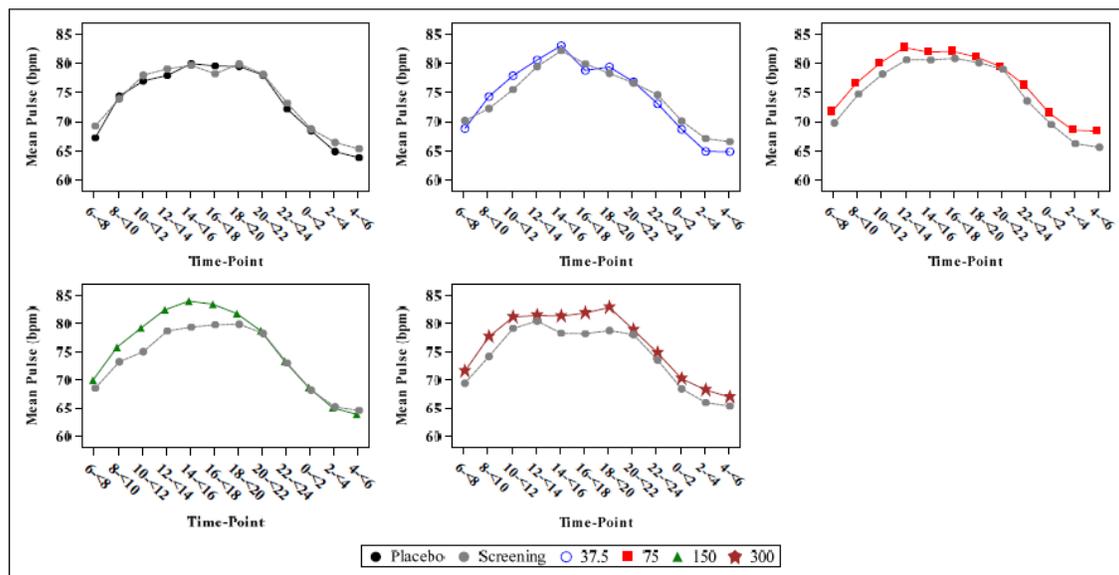
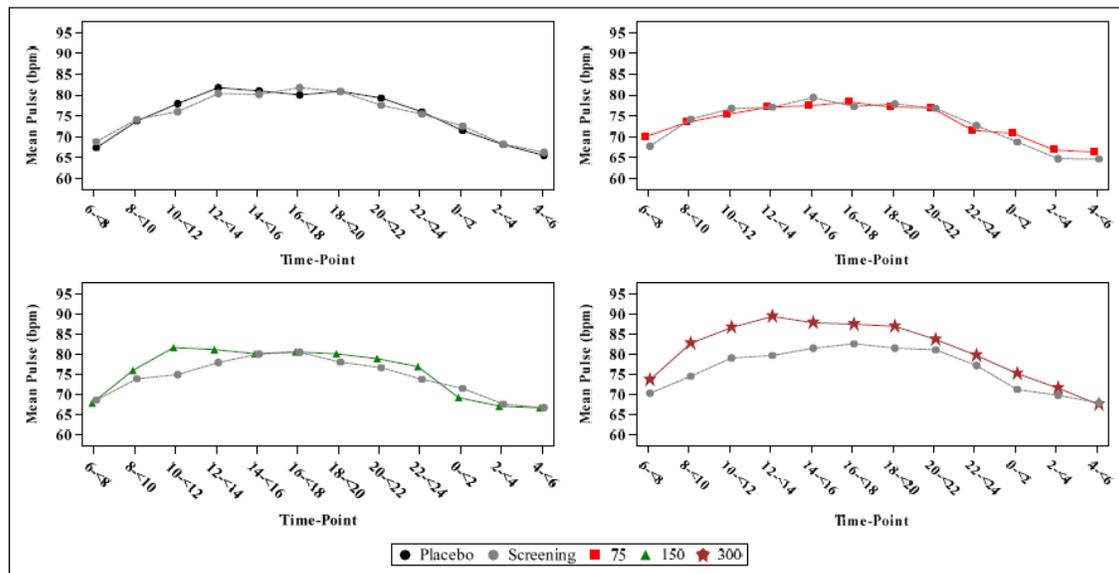
**b) Diastolic Blood Pressure at Baseline and Week 8 for 14-002 Narcolepsy (top) and 14-003 OSA (bottom)**



DBP = diastolic blood pressure ABPM = ambulatory blood pressure monitoring.  
 Source: CSR 14-002/Table 14.3.3.3.3; CSR 14-003/Table 14.3.3.3.3

**Figure 10: Vital Signs for ABPM (Heart Rate): Line Plot of Observed Value Matched by Time Point at Week 8 by Individual 12-Week Placebo-Controlled Studies 14-002 and 14-003 (Continued)**

**a) Heart Rate at Baseline and Week 8 for 14-002 Narcolepsy (top) and 14-003 OSA (bottom)**



BPM = beats per minute ABPM = ambulatory blood pressure monitoring.  
 Source: CSR 14-002/Table 14.3.3.3.3; CSR 14-003/Table 14.3.3.3.3

**Table 186: Vital Signs on ABPM: Summary of Mean Change Screening to Week 8 by Individual 12-Week Placebo-Controlled Studies 14-002 and 14-003**

Vital Sign Time Period	Parameter	Study 14-002 Narcolepsy				Study 14-003 OSA				
		Placebo N = 59	75 mg JZP-110 N = 59	150 mg JZP-110 N = 59	300 mg JZP-110 N = 59	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
<b>SBP (mmHg)</b>	N	50	46	46	41	94	43	51	102	87
<b>Overall</b>	Mean (SD)	-0.3 (9.28)	1.8 (6.53)	-0.5 (5.51)	2.4 (5.97)	-0.8 (7.97)	0.7 (10.19)	2.2 (9.82)	-0.5 (8.64)	2.9 (13.41)
<b>Daytime</b>	Mean (SD)	0.8 (9.88)	1.8 (7.16)	0.7 (5.90)	2.7 (8.09)	-0.2 (8.68)	1.6 (9.03)	2.7 (10.54)	-0.3 (9.74)	3.1 (13.80)
<b>Nighttime</b>	Mean (SD)	-1.1 (9.62)	1.5 (8.55)	-2.2 (7.90)	1.4 (7.41)	-2.1 (10.83)	0.3 (12.58)	2.0 (10.32)	0.0 (10.52)	1.8 (14.33)
<b>DBP (mmHg)</b>	N	50	46	46	41	94	43	51	102	87
<b>Overall</b>	Mean (SD)	-0.1 (7.23)	1.4 (5.13)	0.4 (4.46)	3.0 (4.97)	-0.1 (5.57)	0.8 (6.09)	0.7 (6.55)	-0.2 (5.10)	2.5 (8.66)
<b>Daytime</b>	Mean (SD)	0.8 (7.44)	1.8 (6.05)	0.6 (4.69)	3.4 (5.81)	-0.1 (6.15)	1.1 (6.12)	1.2 (7.16)	0.2 (5.55)	2.6 (8.49)
<b>Nighttime</b>	Mean (SD)	-0.5 (6.46)	0.5 (6.30)	0.0 (5.50)	1.8 (6.10)	-0.2 (6.93)	0.1 (8.35)	1.4 (7.22)	-0.1 (7.50)	1.8 (10.44)
<b>HR (bpm)</b>	N	50	46	46	41	94	43	51	102	87
<b>Overall</b>	Mean (SD)	-0.6 (7.00)	1.0 (7.95)	0.7 (7.12)	5.3 (7.55)	-0.5 (6.51)	0.7 (5.57)	0.4 (7.70)	1.5 (6.53)	1.9 (5.56)
<b>Daytime</b>	Mean (SD)	-0.1 (7.62)	0.2 (8.49)	1.3 (7.64)	6.4 (8.27)	-0.2 (6.73)	1.8 (6.74)	-0.1 (8.79)	2.6 (6.84)	2.3 (6.57)
<b>Nighttime</b>	Mean (SD)	-0.1 (7.25)	0.9 (7.30) <sup>b</sup>	-0.4 (8.00)	2.8 (8.29)	-1.0 (8.03)	-1.4 (5.96)	1.8 (6.47)	-0.1 (7.08)	0.8 (6.32)

*Reviewer’s assessments: ABPM figures as rendered by the sponsor with 2-hour averages on the x-axis smooths out Cmax effects. The table above confirms maximum 3 mmHg 24-hour elevations in SBP and DBP with a maximum 5 bpm 24-hour increase in heart rate.*

*To put this into context, in the SCOUT trial which used cuff measurements, sibutramine (on average from the lead-in period to the final visit) elevated SBP by 1.2 mmHg, DBP by 1.4 mmHg, and HR by 3.7 BPM (NEJM 363;10:905-17).*

## EXECUTIVE SUMMARY:

Solriamfetol (JSP-110) elevates 24-hour systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) by ambulatory blood pressure monitoring (ABPM) by a larger magnitude than did sibutramine by cuff measurements in the SCOUT trial. Specifically, Ambulatory Blood Pressure Monitoring (ABPM) of patients with obstructive sleep apnea (OSA) and narcolepsy who received solriamfetol demonstrates maximum 3 mmHg 24-hour elevations in both SBP and DBP with a maximum 5 bpm 24-hour increase in heart rate in these two patient groups.

The SCOUT Trial studied 10,744 patients at high cardiovascular risk and demonstrated an increased risk of nonfatal myocardial infarction (NFMI) and nonfatal stroke in the sibutramine treatment group compared to placebo, leading to sibutramine’s withdrawal from the US market. Although the mean blood pressure decreased in both treatment groups, there were greater reductions in SBP and DBP in the placebo group compared to sibutramine (mean difference, 1.2/1.4 mm Hg). An earlier meta-analysis in one million adults with no previous vascular disease from 61 prospective observational studies of blood pressure and mortality also demonstrated a direct relationship between “usual blood pressure” throughout middle and old age and vascular (and overall) mortality “without any evidence of a threshold down to at least 115/75 mm Hg” (The Lancet

2002:360:1903–13). Hence, blood pressure increases major adverse cardiovascular events (MACE) in patients with no previous vascular disease and in patients at high cardiovascular risk.

DCARP notes that the population evaluated in the studies referenced above is not low risk. These subjects generally have a number of cardiovascular risk factors and are at increased risk of MACE events.

DCARP thinks DPP should consider what cardiovascular risk assessment profile would be acceptable with this drug product in this patient population and proceed accordingly (e.g., warning for patients at elevated risk, box warning). Only DPP can determine whether the clinical benefit of chronic solriamfetol therapy outweighs the expected long-term risk of increased MACE.

### **RESPONSE TO DPP’S QUESTIONS:**

1. The review Division, (b) (4)  
 *DPP requests advice from DCRP on summarizing the blood pressure changes for labeling such that clinicians are fully informed about the level of risk that might be seen in clinical practice.”*

**DCARP Response: As summarized in Dr. Unger’s email dated Tuesday, November 20, 2018:**

**“For cuff measurements, the blood pressure changes should be expressed relative to placebo, i.e., a placebo-subtracted difference or double-delta (a placebo comparison is necessary for cuff BP). For ABPM, no placebo group is needed, and so a placebo group is not relevant.**

**“Ideally, the text could say something like this:**

**‘Blood pressure was assessed in the 12-week efficacy trials using cuff blood pressure measurements and ambulatory blood pressure monitoring. Mean increases in blood pressure (systolic/diastolic) were A/B, C/D, E/F, and G/H mm Hg for the 37.5-, 75-, 150-, and 300-mg doses of tradename, respectively.’”**

**DCARP also recommends including the mean increases in heart rate by dose for the drug product.**

**SUPPORTIVE INFORMATION:**

**From:** Unger, Ellis

**Sent:** Tuesday, November 20, 2018 4:50 PM

**To:** Hicks, Karen <Karen.Hicks@fda.hhs.gov>; Seung, Sarah <Sarah.Seung@fda.hhs.gov>; Mathis, Mitchell <Mitchell.Mathis@fda.hhs.gov>; Farchione, Tiffany <Tiffany.Farchione@fda.hhs.gov>; Millis, David <David.Millis@fda.hhs.gov>; Muniz, Javier <Javier.Muniz@fda.hhs.gov>; Dunnmon, Preston <Preston.Dunnmon@fda.hhs.gov>; Bhattaram, Atul <Atul.Bhattaram@fda.hhs.gov>

**Cc:** Temple, Robert <Robert.Temple@fda.hhs.gov>

**Subject:** RE: NDA 211230: Solriamfetol - Labeling Meeting

Thanks, Karen. That's a definite "yes!"

**From:** Hicks, Karen

**Sent:** Tuesday, November 20, 2018 4:45 PM

**To:** Unger, Ellis <[Ellis.Unger@fda.hhs.gov](mailto:Ellis.Unger@fda.hhs.gov)>; Seung, Sarah <[Sarah.Seung@fda.hhs.gov](mailto:Sarah.Seung@fda.hhs.gov)>; Mathis, Mitchell <[Mitchell.Mathis@fda.hhs.gov](mailto:Mitchell.Mathis@fda.hhs.gov)>; Farchione, Tiffany <[Tiffany.Farchione@fda.hhs.gov](mailto:Tiffany.Farchione@fda.hhs.gov)>; Millis, David <[David.Millis@fda.hhs.gov](mailto:David.Millis@fda.hhs.gov)>; Muniz, Javier <[Javier.Muniz@fda.hhs.gov](mailto:Javier.Muniz@fda.hhs.gov)>; Dunnmon, Preston <[Preston.Dunnmon@fda.hhs.gov](mailto:Preston.Dunnmon@fda.hhs.gov)>; Bhattaram, Atul <[Atul.Bhattaram@fda.hhs.gov](mailto:Atul.Bhattaram@fda.hhs.gov)>

**Cc:** Temple, Robert <[Robert.Temple@fda.hhs.gov](mailto:Robert.Temple@fda.hhs.gov)>

**Subject:** RE: NDA 211230: Solriamfetol - Labeling Meeting

Hi Ellis:

Thanks for summarizing our discussion.

I would suggest including in the label the mean increases in heart rate for this drug product as well.

Thanks,

Karen

**From:** Unger, Ellis  
**Sent:** Tuesday, November 20, 2018 4:11 PM  
**To:** Seung, Sarah <[Sarah.Seung@fda.hhs.gov](mailto:Sarah.Seung@fda.hhs.gov)>; Mathis, Mitchell <[Mitchell.Mathis@fda.hhs.gov](mailto:Mitchell.Mathis@fda.hhs.gov)>; Farchione, Tiffany <[Tiffany.Farchione@fda.hhs.gov](mailto:Tiffany.Farchione@fda.hhs.gov)>; Millis, David <[David.Millis@fda.hhs.gov](mailto:David.Millis@fda.hhs.gov)>; Muniz, Javier <[Javier.Muniz@fda.hhs.gov](mailto:Javier.Muniz@fda.hhs.gov)>; Dunnmon, Preston <[Preston.Dunnmon@fda.hhs.gov](mailto:Preston.Dunnmon@fda.hhs.gov)>; Hicks, Karen <[Karen.Hicks@fda.hhs.gov](mailto:Karen.Hicks@fda.hhs.gov)>; Bhattaram, Atul <[Atul.Bhattaram@fda.hhs.gov](mailto:Atul.Bhattaram@fda.hhs.gov)>  
**Cc:** Temple, Robert <[Robert.Temple@fda.hhs.gov](mailto:Robert.Temple@fda.hhs.gov)>  
**Subject:** RE: NDA 211230: Solriamfetol - Labeling Meeting

All,

I had a hallway discussion with Drs. Temple and Hicks about expressing the BP effects of the drug.

For cuff measurements, the BP changes should be expressed relative to placebo, i.e., a placebo-subtracted difference or double-delta (a placebo comparison is necessary for cuff BP). For ABPM, no placebo group is needed, and so a placebo group is not relevant.

Ideally, the text could say something like this:

“Blood pressure was assessed in the 12-week efficacy trials using cuff blood pressure measurements and ambulatory blood pressure monitoring. Mean increases in blood pressure (systolic/diastolic) were A/B, C/D, E/F, and G/H mmHg for the 37.5-, 75-, 150-, and 300-mg doses of tradename, respectively.”

We'll need to decide whether to present the data separately, or together, for the two indications.

Ellis

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

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/s/  
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PRESTON M DUNNMON  
11/28/2018

KAREN A HICKS  
11/28/2018

NORMAN L STOCKBRIDGE  
11/28/2018