CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211230Orig1s000
211230Orig2s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	211, 230
Link to EDR	\\Cdsesub1\evsprod\NDA211230\0001
Submission Date	12/20/2017
Submission Type	Standard
Brand Name	SUNOSI
Generic Name	Solriamfetol
Dosage Form and Strength	75, 150 (b) (4) IR tablet
Route of Administration	PO
Proposed Indication	Treatment of excessive daytime sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA)
Applicant	Jazz Pharmaceuticals
Associated INDs	107,203; 122,590
OCP Review Team	Huixia Zhang, Atul Bhattaram, Kevin Krudys, Hao Zhu
OCP Final Signatory	Mehul Mehta Division Director Division of Clinical Pharmacology I

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1. Executive Summary

Jazz Pharmaceuticals is seeking approval of solriamfetol (JZP-110 ([R]-2-amino-3-phenylpropylcarbamate hydrochloride) for the treatment of excessive daytime sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA). Solriamfetol is a phenylalanine derivative that inhibits dopamine and norepinephrine reuptake. It was granted orphan drug designation in 2012 and BCS class I designation in 2016.

The clinical development program for solriamfetol included 7 Phase 1 clinical pharmacology trials (i.e.,mass balance, single- and multiple-ascending dose, food effect, renal impairment, and QT studies), 4 Phase 2 trials (3 in patients with major depressive disorder and one dosing finding study in treating excessive daytime sleepiness) and 5 Phase 3 efficacy/safety trials (4 completed and 1 ongoing): 1) The efficacy and safety of JZP-110 as a treatment for narcolepsy was evaluated in 3 studies: 2 randomized, double-blind, placebo-controlled, 12-week studies (Study ADX-N05 202 and Study 14-002) and the ongoing Study 14-005 (which also included subjects with OSA); 2) The efficacy and safety of JZP-110 in OSA was evaluated in 3 studies: 1 randomized, double-blind, placebo-controlled, 12-week study (Study 14-003), 1 randomized withdrawal, double-blind, placebo-controlled 6-week study (Study 14-004) and the ongoing Study 14-005 (which also includes subjects with narcolepsy). In addition, exposure-response analyses were performed to evaluate relationships between JZP-110 exposure and clinical efficacy and safety endpoints in subjects with narcolepsy and OSA.

Two key review issues are identified for this application: (1) the appropriateness of the dosing instruction in general patients; and (2) recommendations in specific patient populations (i.e., renal impairment).

The Sponsor evaluated the benefit-risk of three dose levels (75, 150 and 300 mg) in the registration studies (Study 14-002 in patients with narcolepsy and Study 14-003 in patients with OSA). These doses have been shown to be efficacious with 75 mg being the lowest dose for treatment initiation. Among the various safety events in clinical studies, increases in diastolic blood pressure (DBP), systolic blood pressure (DBP) and heart rate (HR) along with insomnia were observed and analysis suggested that they are related to the solriamfetol concentration-time profile. These findings were considered in determining the adequacy of the lower doses and proposed slower titration schedule . . Due to the prolonged half-life of solriamfetol in patients with moderate and severe renal impairment, a higher risk for insomnia and sustained increase in DBP, SBP and HR is

likely, despite the proposed dose adjustments. Appropriate language conveying this risk is being proposed in the label.

In this review, the term of Sunosi is used interchangeably with solriamfetol and JZP-110.

1.1. Recommendations

Review Issue	Recommendations and Comments
Supportive evidence of effectiveness	Substantial evidence of effectiveness was demonstrated by the registration trials. Significant dose/exposure-response relationship indicated that between a daily dose of 75 mg to 300 mg, higher dose/exposure is associated with higher reduction in day time sleepiness.
General dosing instructions	Overall, the proposed dosing concept in the general patient population is acceptable. However, OCP recommends an initial dose of 75 mg for all populations with a titration interval of 7 days (rationale is provided in Section 2.2.1) - The initial dose of solriamfetol is 75 mg once daily, taken upon awakening. Based on efficacy and tolerability, solriamfetol may be increased by doubling the dose at intervals of 7 days. The maximum recommended dose is (b) (4) mg per day. - Solriamfetol can be administered with or without food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Dosage adjustment is recommended in subgroups of patients based on relevant PK studies, the established exposure-response relationships, and the understanding of the mechanism of drug elimination. Different from the sponsor's proposal, OCP recommends a consistent interval for dose titration (7 days) according to the following: - Mild renal impairment (eGFR:60-89 mL/min/1.73m2): No dosage adjustment recommended. - Moderate renal impairment (eGFR:30-59 mL/min/1.73m2): Initiate dosing at 75 mg once daily. Based on efficacy and tolerability, dose may be increased at intervals of 7 days to a maximum of 150 mg once daily. - Severe renal impairment (eGFR:15-29 mL/min/1.73m2): Initiate dosing at 37.5 mg once daily. Based on efficacy and tolerability the dose can be increased at intervals of 7 days, to a maximum of 75 mg. - End Stage Renal Disease (ESRD, eGFR: < 15mL/min/1.73m2): JZP-110 is not recommended for use in patients with ESRD.
Labeling	Pending satisfactory agreement with the Sponsor

Bridge between the to-be-marketed and clinical trial formulations	JZP-110 has been granted BCS class I designation (highly soluble, highly permeable, and rapidly dissolving). The to-be-marketed formulation (film-coated tablet) is expected to show similar effectiveness and safety profile as compared to the clinical trial formulation (over-encapsulated film-coated tablet). Refer to CMC/Biopharm review for details.
Other (specify)	NA

1.2. Post-Marketing Requirements and Commitments
None.

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2. Summary of Clinical Pharmacology Assessment

2.1 Pharmacology and Clinical Pharmacokinetics

Solriamfetol is a derivative of the amino acid phenylalanine. The mechanism(s) by which solriamfetol exerts its wake-promoting effects in humans are presumed to be through its activity as a selective dopamine and norepinephrine reuptake inhibitor (DNRI). Following oral administration, solriamfetol is minimally metabolized, and is mainly excreted unchanged in the urine. The following is a summary of the clinical pharmacokinetic features of solriamfetol:

Absorption: Solriamfetol is readily absorbed after oral administration, with peak plasma concentrations occurring at a median T_{max} of 2 hours (range 1.25 to 3.0 hours) under fasted conditions. Solriamfetol has an oral bioavailability of greater than 90% with negligible first pass metabolism, based on the percentage of dose excreted unchanged in the urine.

Distribution: Solriamfetol has an apparent volume of distribution of approximately 199 L. Plasma protein binding ranged from 13.3% to 19.4% over solriamfetol concentration range of 0.059 to 10.1 mcg/mL in human plasma. The mean blood-to-plasma concentration ratio ranged from 1.16 to 1.29.

Elimination: Solriamfetol exhibits first-order elimination after oral administration. The apparent mean elimination half-life is about 7.1 hours. The apparent oral clearance of solriamfetol is approximately 19.5 L/h, and renal clearance is about 18.2 L/h.

- Metabolism: Solriamfetol does not undergo CYP-mediated phase 1 metabolism in humans; 1% or less of dose was recovered in urine as the minor inactive metabolite N-acetyl solriamfetol.

- Excretion: In a human mass-balance study, approximately 95% of the dose was recovered in urine as unchanged solriamfetol. Renal clearance represented the majority of apparent total clearance and exceeded creatinine clearance by approximately 3-fold, indicating that active renal secretion of the parent drug is the major elimination pathway.

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

OCP recommends that SUNOSI should be taken once daily upon awakening.

- Starting dose: 75 mg.
- Based on efficacy and tolerability, SUNOSI may be increased by doubling the dose at an interval of 7 days.
- Maximum dose is (b) (4) mg.

The main difference betweem OCP's recommendations and Sponsor's proposal is that we recommend (1) 75mg as the initial dose for all the general population and (2) a titration interval of 7 days because of the following reasons:

1) The sponsor initially proposed that (b) (4) ;

2) The main reason for recommending a starting dose of 75 mg and a slow titration of SUNOSI (i.e., recommended titration interval increases from at least 3 days to 7 days) is to avoid unnecessarily dose escalation and to minimize the risks for cardiac adverse events associated with increased blood pressure. As shown in the clinical trials, SUNOSI increases blood pressure in a dose/exposure-dependent manner. Per FDA guidance (Assessment of Pressor Effects of Drugs Guidance for Industry), even a small increase in blood pressure following a chronic treatment may lead to increased risks for severe cardiac events (e.g., stroke). Therefore, we recommend that all patients should start with 75 mg and patients only receive higher doses (i.e., 150 mg (b) (4)) when there is inadequate clinical response. In addition, we recommend that dose may be increased at an interval of 7 days, not 3 days, to ensure sufficient treatment duration for reaching anticipated clinical response for a given dose. Based on the trial design, the earliest time point in which the clinical response was observed was 7 days. It is prudent that patients take a higher risk for cardiac events only when sufficient evidence (i.e., inadequate response with sufficient treatment duration at a selected dose) exists to support the need for dose escalation.

3) As shown in clinical trials, some patients may obtain sufficient treatment effect at 75mg. In the open-label study 14-005, about 10% of subjects have been on a stable dose of 75 mg; the 75mg dose has reached statistical significane on the co-primary endpoints in patients with OSA (study 14-003), and has reached statitiscal significance on the co-primary endpoint of ESS, but not MWT in patients with narcolepsy (Study14-002).

4) Our recommendation of a 7-day interval for dose escalation will be applied to all patients irrespective to the renal function The same dosing interval of 7-days may also decrease the potential medication error.

2.2.2 Therapeutic Individualization

The proposed dosing regimen allows for initiation of therapy at a lower dose (b) (4) and allows for dose escalation based on the need of a patient.

Renal Impairment: In a study of patients with different levels of renal impairment, the AUC_{inf} and $t_{½}$ values of a single dose of 75 mg solriamfetol increased with more severe

levels of renal impairment. Based on the geometric mean ratios, AUC_{inf} was higher by approximately 1.5-, 2.3-, and 4.4-fold, and $t_{½}$ increased approximately 1.2-, 1.9-, and 3.9-fold in patients with mild (eGFR 60-89 mL/min/1.73 m^2), moderate (eGFR 30–59 mL/min/1.73 m^2), or severe (eGFR<30 mL/min/1.73 m^2) renal impairment, respectively, compared with patients with normal (eGFR ≥90 mL/min/1.73 m^2) renal function. In patients with ESRD hemodialysis, JZP-110 AUC_t was nearly 6.2-fold higher than in subjects with normal renal function. Dosage adjustment is recommended for patients with moderate or severe renal impairment. Because of the prolonged half-life of solriamfetol in patients with moderate and severe renal impairment, a higher risk for insomnia and sustained increase in DBP, SBP and HR is likely even with the proposed dose adjustments. Soriamfetol is not recommended for patients with ESRD. In addition, OCP recommends a titration interval of 7 days for mild, moderate and severe renal impaired patients for the same reasons listed under Section 2.2.1.

Food effect: Ingestion of solriamfetol with a high-fat meal resulted in minimal change in C_{max} and AUC_{inf}; however, a delay of approximately 1 hour was observed in T_{max}. The results show that solriamfetol can be taken without regard to food.

2.3 Outstanding Issues

NA

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts be included in the final package insert:

- The recommended dose range for solriamfetol is 75 mg to (b) (4) once daily. Solriamfetol should be initiated at 75 mg once daily. A titration interval of 7 days is recommended if an increase in dose is clinically warranted.
- For patients with renal dysfunction, dosage adjustment is recommended:
  - Mild renal impairment (eGFR:60-89 mL/min/1.73m^2): No dosage adjustment recommended.
  - Moderate renal impairment (eGFR:30-59 mL/min/1.73m^2): Initiate dosing at 75 mg once daily. Based on efficacy and tolerability, dose may be increased at intervals of 7 days to a maximum of 150 mg once daily.
  - Severe renal impairment (eGFR:15-29 mL/min/1.73m^2): Initiate dosing at 37.5 mg once daily. Based on efficacy and tolerability the dose can be increased at intervals of 7 days, to a maximum of 75 mg.
  - End Stage Renal Disease (ESRD, eGFR: < 15mL/min/1.73m^2): JZP-110 is not recommended for use in patients with ESRD.
- JZP-110 can be taken with or without food.
- In general, no dose adjustment is necessary in patients based on race, age or gender.
- No significant QTc prolongation effect of JZP-110 at the doses of 900 mg was detected in a thorough QT study.

3. Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

Sunosi contains solriamfetol, a derivative of the amino acid phenylalanine. It is indicated for the treatment of excessive daytime sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA). Currently, Provigil and Nuvigil have been approved for the same indications. Solriamfetol has received orphan drug and BCS class I designations.

3.2 General Pharmacology and Pharmacokinetic Characteristics

<table>
<tr><td colspan="3">Pharmacology</td></tr>
<tr><td>Mechanism of Action</td><td colspan="2">The mechanism of action of solriamfetol for the treatment of excessive daytime sleepiness is unknown. It is believed to function as a selective dopamine and norepinephrine reuptake inhibitor (DNRI).</td></tr>
<tr><td>Active Moieties</td><td colspan="2">Solriamfetol</td></tr>
<tr><td>QT Prolongation</td><td colspan="2">The effect of solriamfetol on the QT/QTcF interval was investigated in healthy subjects. At a dose 3 times the maximum approved recommended dosage, solriamfetol does not prolong the QTcF interval to any clinically relevant extent.</td></tr>
<tr><td colspan="3">General Information</td></tr>
<tr><td>Bioanalysis</td><td colspan="2">Solriamfetol concentration was measured using HPLC-UV or LC-/MS/MS methods in clinical trials. A summary of the respective method deployed in each study was included in the individual study</td></tr>
<tr><td>Drug exposure at steady state following the therapeutic dosing regimen</td><td colspan="2">No designated PK study was conducted following the proposed dosing regimen at the recommended therapeutic doses. The predicted steady state exposure based on PopPK analysis is shown below.
<table>
<tr><th rowspan="2">Parameter (units)</th><th rowspan="2">Statistics</th><th colspan="4">Dose (mg) – JZP-110</th></tr>
<tr><th>37.5 (n=49)</th><th>75 (n=103)</th><th>150 (n=157)</th><th>300 (n=137)</th></tr>
<tr><td rowspan="3">AUC_{tau} (ng•hr/mL)</td><td>Mean (CV%)</td><td>1940 (37.7%)</td><td>4300 (34.4%)</td><td>8430 (32.8%)</td><td>19100 (41.9%)</td></tr>
<tr><td>Median [Min, Max]</td><td>1680 [1140, 4610]</td><td>4120 [2230, 10600]</td><td>7920 [2980, 17100]</td><td>17200 [4620, 63700]</td></tr>
<tr><td>[95% PI]</td><td>[1210, 4080]</td><td>[2380, 7990]</td><td>[4500, 15500]</td><td>[9880, 38300]</td></tr>
</table></td></tr>
<tr><td rowspan="2">Maximum tolerated dose or exposure</td><td>Single Dose</td><td>Not Available</td></tr>
<tr><td>Multiple Dose</td><td>Not Available</td></tr>
<tr><td>Dose Proportionality</td><td colspan="2">Solriamfetol exposure is dose-proportional over the dose range of 42 to 1008 mg.</td></tr>
<tr><td>Accumulation</td><td colspan="2">Accumulation factor: ~1.1</td></tr>
<tr><td colspan="3">Absorption</td></tr>
<tr><td colspan="3">- Bioavailability: ≥ 90% based on amount of the dose excreted unchanged in the urine
- T_{max}: median Tmax of 2 hours (range 1.25 to 3.0 hours)
- Food effect (high-fat): ingestion of solriamfetol with a high-fat meal did not result in a clinically significant change in C_{max} and AUC_{inf}; however, a delay of approximately 1 hour was observed in T_{max}.</td></tr>
<tr><td colspan="3">Distribution</td></tr>
</table>

- Volume of distribution: ~199 L. - Plasma protein binding: 13.3% to 19.4% - Blood to Plasma ratio: 1.16 to 1.29
Elimination: - Clearance: the apparent clearance is ~20 L/h and renal clearance is approximately 18 L/h - Mean terminal elimination $T_{1/2}$: ~7 hours. - Primary elimination pathway: renal excretion. Mass balance study showed that approximately 95% of the dose was recovered in urine as unchanged solriamfetol. - Metabolism: minimal metabolism - Transporters: does not appear to be a substrate or inhibitor for P-gp, BCRP, OATP1B1, OATP1B3, OAT1, or OAT3. JZP-110 is not an inhibitor of OCT1, MATE2-K, OCTN1, or OCTN2, and was a weak inhibitor of OCT2 (IC_{50} of 146 µM) and MATE1 (IC_{50} of 211 µM), which is not expected to cause significant drug interactions at clinically relevant concentrations. - Inhibitor/Inducer to CYP enzymes: solriamfetol is unlikely to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, CYP3A4/5, and UGT enzymes, or induce CYP1A2, CYP2B6, CYP3A4/5, and UGT enzymes at clinically relevant concentrations.

3.3 Clinical Pharmacology Review Questions

3.3.1. Does the available clinical pharmacology information provide supportive evidence of effectiveness?

The evidence of effectiveness of JZP-110 in reducing excessive daytime sleepiness and improving wakefulness throughout the day is primarily supported by a dose-related increase in patients' ability to stay awake, as measured by increase in mean sleep latency on the maintenance of wakefulness test (MWT) score (Figure 1), and patient-reported excessive sleepiness as measured by the reduction in Epworth Sleepiness Scale (ESS) score (Figure 2), relative to baseline as compared to the placebo group from Phase 3 trials. The results from an internal risk-benefit analysis using Phase 3 data (Figure 3) were consistent with the observed dose-response relationship and thus provided additional supportive evidence.

Figure 1: MWT: Change from Baseline by Study Visit (Week) in Patients with Narcolepsy or OSA

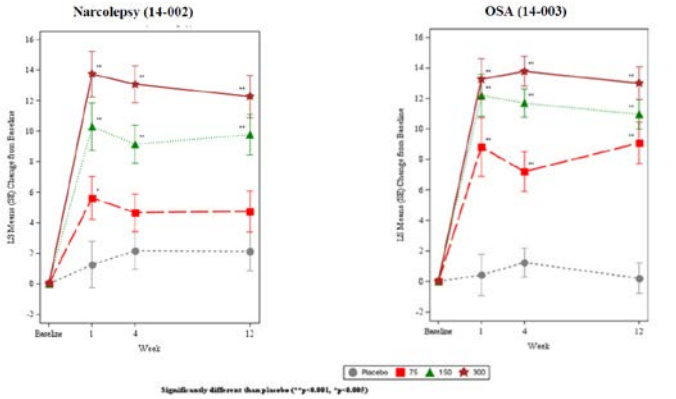
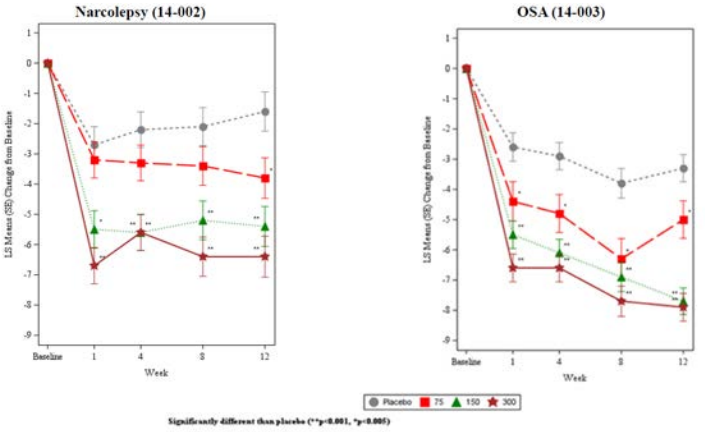


Figure 2: ESS: Change from Baseline by Study Visit (Week) in Patients with Narcolepsy or OSA



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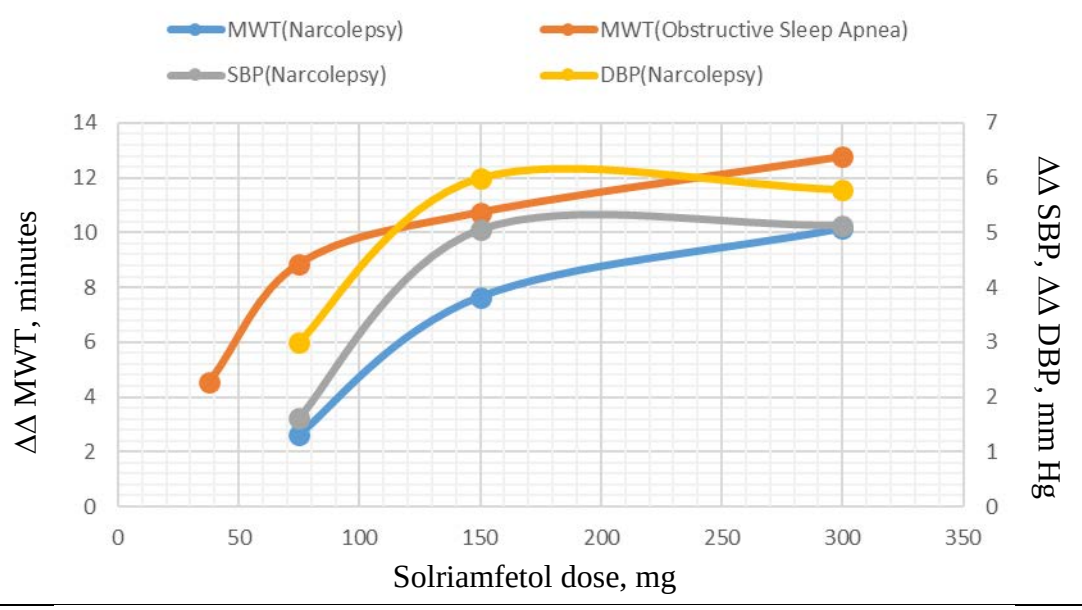
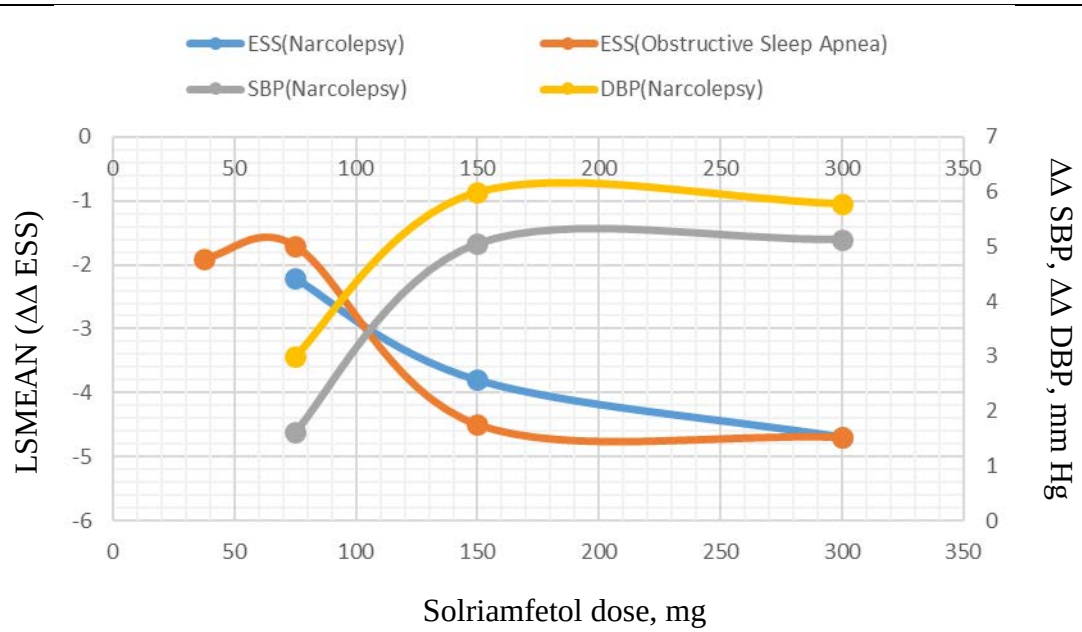
3.3.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Though the proposed dosing concept is appropriate for the general population with narcolepsy or obstructive sleep apnea (OSA), for reasons listed in Section 2.2.1, the following modification is proposed by OCP: the initial dose of solriamfetol is (b) (4) mg once daily, taken upon awakening. Based on efficacy and tolerability, solriamfetol may be increased by doubling the dose at intervals of (b) (4) days. The maximum recommended dose is (b) (4) mg per day.

Figure 3 shows the dose-response relationship for treatment benefit (ΔΔMWT and ΔΔESS) in Studies 14-002 (patients with narcolepsy) and 14-003 (patients with OSA) and risk (ΔΔSBP at 2h post-dose, ΔΔDBP at 2h post-dose) in Study 14-002. Study 14-002 was chosen to show the risk for increase in SBP and DBP since fewer patients were on anti-hypertensives relative to Study 14-003. It should be noted that only Study 14-003 included the 37.5 mg dose. Figure 3 suggests that modest additional benefit is observed at 300 mg dose compared to 150 mg dose. Greater sustained increases in blood presssure (ΔΔDBP, ΔΔSBP, mm Hg) during the day are observed at 300 mg (Figure 6 in Appendix). Also, higher proportion of patients in 300 mg dose experienced insomnia compared to lower doses (5-9% at 300 mg dose versus 2-3% at 37.5-150 mg dose). The applicant's dosing guidelines take into account these aspects (b) (4) .

Figure 3. Dose response relationship for benefit (ΔΔMWT, ΔΔESS) in Study 14-002 and Study 14-003 and risk (ΔΔSBP, ΔΔDBP (2h post-dose) in Study 14-002.





Source: Reviewer's analysis. Data from Table 13 on Page 95 in cs-14-002.pdf, Table 14 on Page 88 in cs-14-003.pdf, Table 15 on page 89 in cs-14-003.pdf., Table 57 on page 189 in cs-14-002.pdf

3.3.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic factors?

Yes.

<u>Renal Impairment</u>

An alternative dosing regimen is required for patients with moderate or severe renal impairment. The proposed alternative dosing regimen is:

- Renal impairment: Dose range is (b) (4) mg in patients with moderate renal impairment and (b) (4) mg in patients with severe renal impairment. Not recommended for use in patients with end stage renal disease (ESRD).

Table 1 shows a detailed version of the recommended dosing regimen in patients with nmild, moderate and severe renal impairment.

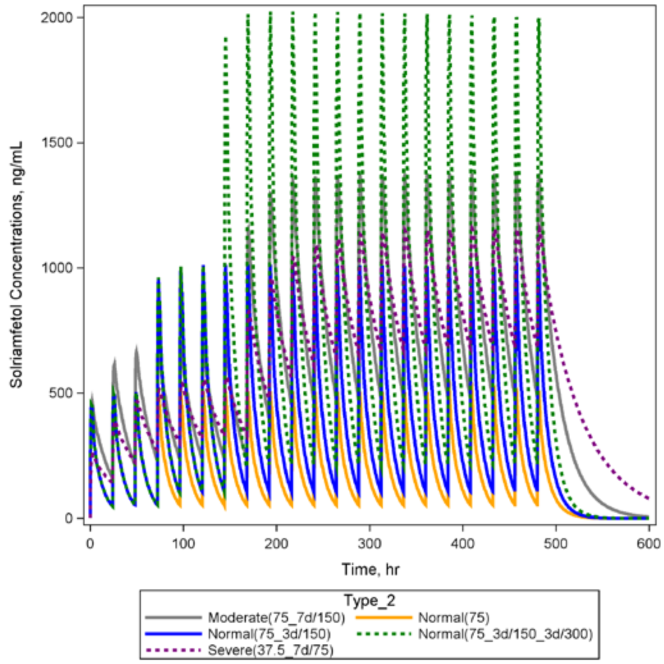
Table 1. Proposed dose/dosing regimen of solriamfetol in mild, moderate or severe renal impairment.

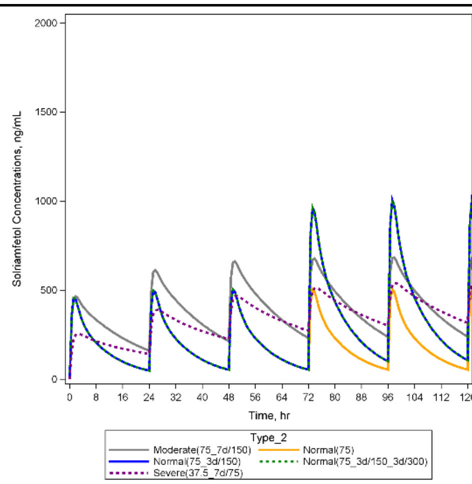
- Mild renal impairment (eGFR:60-89 mL/min/1.73m2): No dosage adjustment recommended.
- Moderate renal impairment (eGFR:30-59 mL/min/1.73m2): Initiate dosing at (b) (4) once daily. Based on efficacy and tolerability, dose may be increased at intervals of 7 days to a maximum of (b) (4) once daily.
- Severe renal impairment (eGFR:15-29 mL/min/1.73m2): Initiate dosing at 37.5 mg once daily. (b) (4)

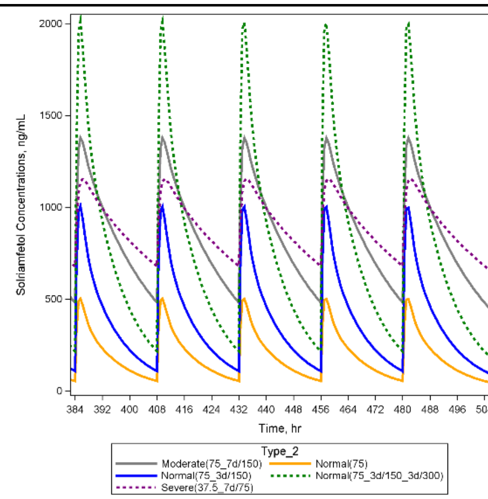
Simulations were conducted to evaluate FDA's alternate titration schedule for all patients. During the initial 7 days of treatment, the peak concentrations of solriamfetol in patients with moderate and severe renal impairment will be in the range of those observed in patients with mild or normal renal function at 75 mg dose level. At steady-state this dosing regimen in patients with moderate and severe renal impairment will result in solriamfetol peak concentrations that will be in the range of those observed at 150-300 mg dose group in patients with normal renal function (Figure 4). At steady-state, solriamfetol concentrations after 150 mg dose in patients with normal renal function are being used the reference group since at this dose MWT changes were significantly different from placebo (Figure 2). The findings indicate that the proposed dosing regimen in patients with moderate and severe renal impairment would be efficacious.

Figure 4. Simulated solriamfetol concentrations in patients with normal/mild, moderate or severe renal impairment (b) (4) Shown in the graph are the solriamfetol concentrations (b) (4).
A dosing regimen of 75_7d/150 refers to administration of 75 mg for 7 days followed by 150 mg every day. A dosing regimen of 75 refers to 75 mg every day. A dosing regimen of 75_3d/150 refers to administration of 75 mg for 3 days followed by 150 mg

every day. A dosing regimen of 75_3d/150_3d/300 refers to administration of 75 mg for 3 days followed by 150 mg for 3 days and subsequently 300 mg every day. A dosing regimen of 37.5_7d/75 refers to 37.5 mg for 7 days followed by 75 mg every day.





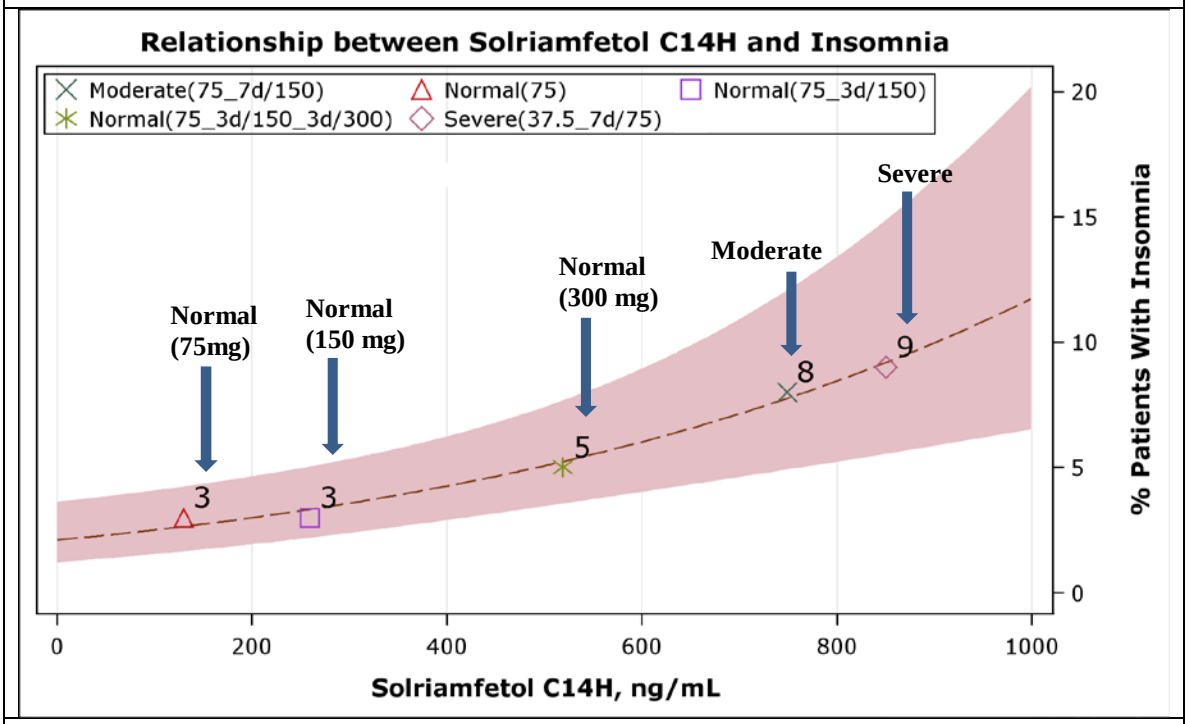


Source: Reviewer's analysis

(b) (4) dosing regimen in patients with moderate or severe renal impairment would result in peak solriamfetol concentrations between 150 and 300 mg doses and be efficaious, there would be an increased risk for insomnia and DBP, SBP, and HR elevation due to the prolonged half-life of solriamfetol. To assess the increased risk of insomnia, predicted steady-state concentrations at 14h were used. To assess the increased risk for DBP and SBP elevation, predicted steady-state concentrations at pre-dose and 2h post-dose were used. These predicted concentrations were obtained based on the reviewer's analysis of solriamfetol concentration data from Study 15-001.

Figure 5 shows that a higher percentage of patients with moderate and severe renal impairment (b) (4), would experience insomnia compared to patients with normal renal function or mild renal impairment. The higher risk for insomnia in moderate and severe renal impairment should be communicated in the label.

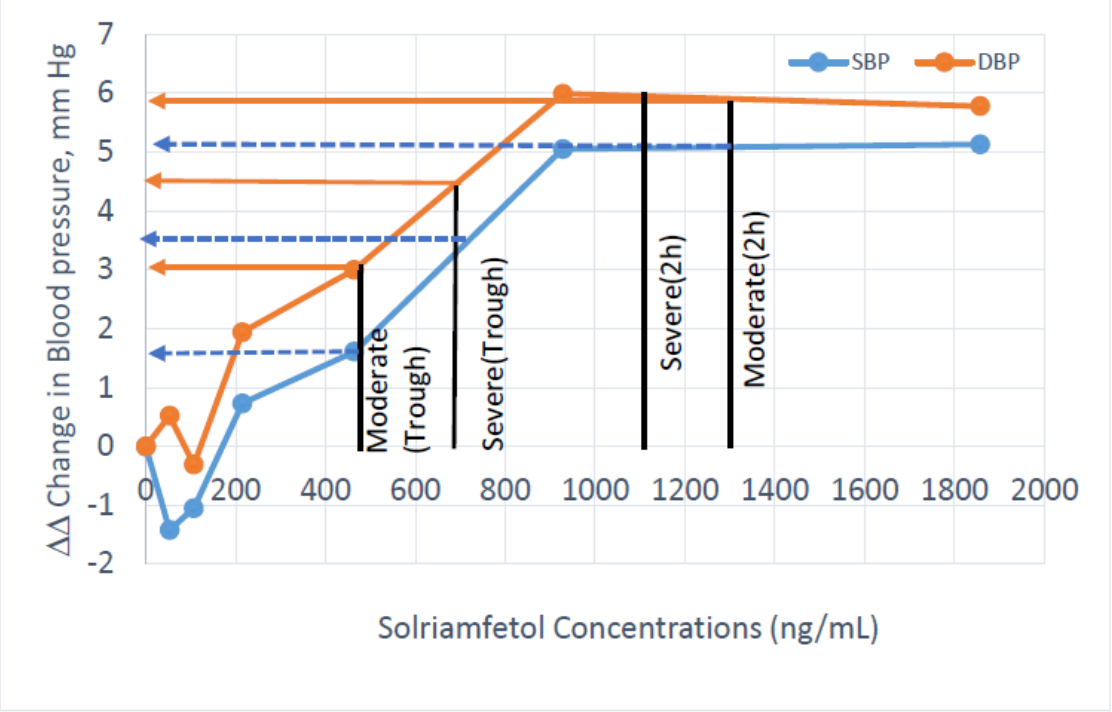
Figure 5. Relationship between steady-state solriamfetol concentrations at 14h post-dose (C14H) and % of patients with insomnia. A dosing regimen of 75_7d/150 refers to administration of 75 mg for 7 days followed by 150 mg every day. A dosing regimen of 75 refers to 75 mg every day. A dosing regimen of 75_3d/150 refers to administration of 75 mg for 3 days followed by 150 mg every day. A dosing regimen of 75_3d/150_3d/300 refers to administration of 75 mg for 3 days followed by 150 mg for 3 days and subsequently 300 mg every day. A dosing regimen of 37.5_7d/75 refers to 37.5 mg for 7 days followed by 75 mg every day.



Source: Reviewer's analysis

Figure 6 shows the relationship between predicted pre-dose and 2h post-dose solriamfetol concentrations and ΔΔSBP and ΔΔDBP. Information on ΔΔSBP and ΔΔDBP from patients with normal/mild renal impairment from study 14-002 are shown as orange or blue filled-circles. ΔΔSBP and ΔΔDBP at the corresponding concentrations in moderate or severe renal impairment are shown in Figure 6. The table in Figure 6 shows the predicted ΔΔSBP and ΔΔDBP changes. The projected changes suggest that, while ΔΔSBP and ΔΔDBP return to baseline at the time of next-day dose in patients with normal renal function, these changes would likely remain sustained in patients with moderate or severe renal impairment. This aspect should be conveyed accordingly in the label.

Figure 6. Relationship between solriamfetol concentrations and ΔΔSBP, ΔΔDBP changes. Filled circles (blue, orange) represent the observed data from study 14-002. Vertical black lines represent the simulated solriamfetol concentrations at trough (pre-dose) and 2h post-dose.



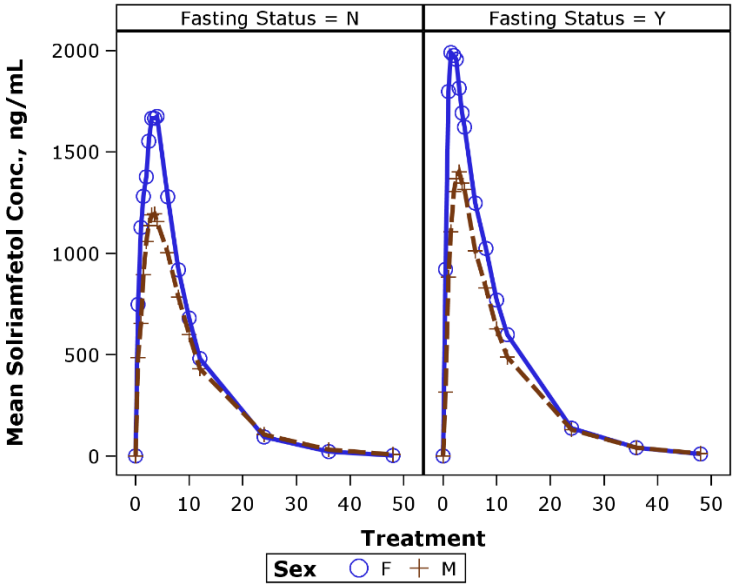
Category	Dose	ΔΔ SBP, mm Hg		ΔΔ DBP, mm Hg	
		2h	Pre-dose	2h	Pre-dose
Normal	75	1.6	-1.4	3.0	0.5
	150	5.0	-1.0	5.9	-0.3
	300	5.1	0.7	5.8	1.9
Moderate	75/150	~5.1	~1.6	~5.8	~3.0
Severe	37.5/75	~5.1	~3.5	~5.8	~4.5

Source: Reviewer's analysis

Race, Gender, Age

No dosage adjustment is necessary based on age, race or gender. Population PK analysis indicated that gender and race do not have clinically relevant effects on the pharmacokinetics of solriamfetol. In addition, analysis using clinical data showed that though Cmax was higher in females than males after solriamfetol administration, either under fasting (~53% higher) or fed (~40% higher) conditions, C14hr levels were comparable (Figure 7). The differences are not considered clinically significant for dose adjustment. Dose adjustments were not done in the clinical studies that enrolled patients between 65 and above.

Figure 7: Plasma concentration time profiles in males and females after administration of 300mg solriamfetol under fasting or fed conditions (Trial 15-009)



3.3.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No.

Effect of Food

Solriamfetol exposure (C_{max} and AUC_{inf}) was lowered by ≤6% and median Tmax was delayed by 1 hour in healthy subjects following administration of solriamfetol with a high-fat, high-calorie meal. These changes are not considered clinically significant. Therefore, solriamfetol may be administered without regard to meals.

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4. Appendices

4.1 Clinical PK and/or PD Assessments

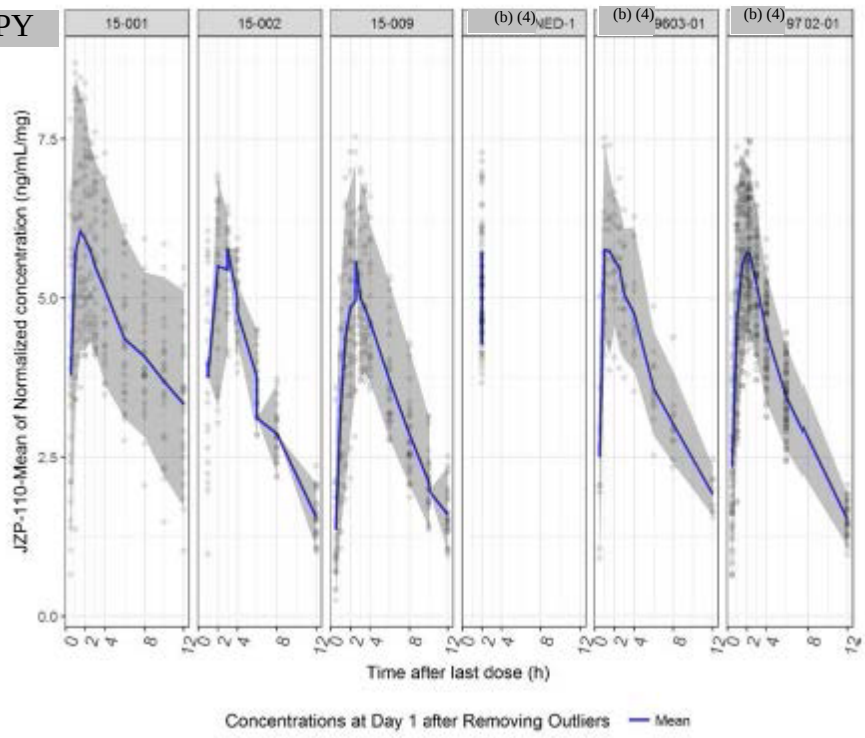
Review of individual study reports will be finalized in DARRTS separately.

4.2 Population PK and/or PD Analyses

Population PK analyses were performed to support dosing recommendations of JZP-110 in patients with narcolepsy, OSA.

Concentration-time profiles of JZP-110 following oral administration of the first dose on Day 1 in healthy subjects are presented in Figure 8.

Figure 8. Mean (95% CI) and individual normalized concentrations following oral administration of JZP-110 in healthy subjects.



Source: Figure 2 on page 36 in jazp-pcs-100-pop-pk.pdf

The population PK model was developed based on data collected in 791 Phase 1 and Phase 3 subjects treated with JZP-110. A 1-compartment model with first-order absorption rate constant (Ka) with lag time (Tlag) was used to characterize the PK of JZP-110. JZP-110 exposure was dose proportional, and the accumulation ratio based on once daily dosing was 1.06. The population estimates of CL/F and V/F for JZP-110 were 19.49 L/h and 198.72 L, respectively, and would be for a male narcolepsy/OSA patient who is 92.5 kg, has a CRCL of 116.5 mL/min, and is taking a dose of 150 mg. Based on the population PK model, the half-life of JZP-110 was 7.07 h.

The summary of baseline characteristics in the population PK dataset are shown in Table 2.

Table 2. Summary of baseline characteristics in the PK population

Baseline Characteristics	Phase 1 (n=278)	Phase 3 (n=513)	Overall (n=791)
Gender			
Male	169 (60.8%)	268 (52.2%)	437 (55.2%)
Female	109 (39.2%)	245 (47.8%)	354 (44.8%)
Age Group			
Non-Elderly (18-64 years)	265 (95.3%)	452 (88.1%)	717 (90.6%)
Elderly (≥65 years)	13 (4.7%)	61 (11.9%)	74 (9.4%)
Renal Impairment			
Normal	166 (59.7%)	170 (33.1%)	336 (42.5%)
Mild	91 (32.7%)	317 (61.8%)	408 (51.6%)
Moderate	8 (2.9%)	24 (4.7%)	32 (4.0%)
Severe	4 (1.4%)	0 (0.0%)	4 (0.5%)
ESRD	9 (3.2%)	0 (0.0%)	9 (1.1%)
Missing	0 (0.0%)	2 (0.4%)	2 (0.3%)
Race			
White	188 (67.6%)	402 (78.4%)	590 (74.6%)
Black	68 (24.5%)	81 (15.8%)	149 (18.8%)
Asian	1 (0.4%)	19 (3.7%)	20 (2.5%)
Native Hawaiian Or Other Pacific Islander	1 (0.4%)	2 (0.4%)	3 (0.4%)
Multiple	0 (0.0%)	7 (1.4%)	7 (0.9%)
American Indian or Alaska native	0 (0.0%)	2 (0.4%)	2 (0.3%)
Hispanic	16 (5.8%)	0 (0.0%)	16 (2.0%)
Oriental	3 (1.1%)	0 (0.0%)	3 (0.4%)
Other	1 (0.4%)	0 (0.0%)	1 (0.1%)
Ethnic Group			
Hispanic or Latino	66 (23.7%)	39 (7.6%)	105 (13.3%)
Non-Hispanic or Latino	57 (20.5%)	474 (92.4%)	531 (67.1%)
Missing	155 (55.8%)	0 (0.0%)	155 (19.6%)
Disease Status			
Healthy Subjects*	278 (100.0%)	0 (0.0%)	278 (35.1%)
Subjects with Narcolepsy	0 (0.0%)	171 (33.3%)	171 (21.6%)
Subjects with OSA	0 (0.0%)	342 (66.7%)	342 (43.2%)

eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; n: number of subjects; OSA: obstructive sleep apnea. Normal renal function: eGFR ≥90 mL/min/1.73m^2; Mild renal impairment: eGFR ≥60 and <90 mL/min/1.73m^2; Moderate renal impairment: eGFR ≥30 and <60 mL/min/1.73m^2; Severe renal impairment: eGFR ≥15 and <30 mL/min/1.73m^2 and not on hemodialysis; End-stage renal disease: eGFR <15 mL/min/1.73 m^2 and not on hemodialysis or patients on hemodialysis.
* Study 15-001 included subjects with normal and impaired renal functions, and subjects with end-stage renal disease.

Baseline Characteristics	Phase 1 (n=278)	Phase 3 (n=513)	Overall (n=791)
Age (years)			
Mean (CV%)	36.9 (35.3%)	47.9 (29.3%)	44.0 (33.3%)
Median [Min, Max]	36.0 [18.0, 80.0]	49.0 [18.0, 75.0]	44.0 [18.0, 80.0]
Weight (kg)			
Mean (CV%)	74.1 (17.0%)	92.9 (22.3%)	86.3 (23.6%)
Median [Min, Max]	72.8 [46.6, 110]	92.6 [45.4, 153]	84.4 [45.4, 153]
BMI (kg/m^2)			
Mean (CV%)	25.0 (12.1%)	31.5 (19.2%)	29.2 (20.7%)
Median [Min, Max]	24.7 [18.3, 35.0]	31.5 [18.0, 45.4]	28.2 [18.0, 45.4]
BSA (m^2)			
Mean (CV%)	1.87 (11.0%)	2.04 (12.3%)	1.98 (12.6%)
Median [Min, Max]	1.85 [1.42, 2.44]	2.05 [1.40, 2.77]	1.97 [1.40, 2.77]
AST (U/L)			
Mean (CV%)	20.2 (30.8%)	25.8 (33.4%)	23.8 (34.8%)
Median [Min, Max]	19.0 [8.00, 58.0]	24.0 [13.0, 99.0]	22.0 [8.00, 99.0]
ALT (U/L)			
Mean (CV%)	22.4 (47.7%)	29.2 (53.2%)	26.8 (53.7%)
Median [Min, Max]	20.0 [5.00, 58.0]	26.0 [7.00, 109]	23.0 [5.00, 109]
Missing	3 (1.1%)	0 (0.0%)	3 (0.4%)
ALB (g/L)			
Mean (CV%)	43.2 (8.59%)	43.8 (5.87%)	43.6 (6.70%)
Median [Min, Max]	44.0 [33.00,52.0]	44.0 [37.00,52.00]	44.0 [33.00,52.0]
Missing	93 (33.5%)	0 (0.0%)	93 (11.7%)
CRCL (mL/min)			
Mean (CV%)	113 (31.3%)	122 (27.6%)	119 (29.1%)
Median [Min, Max]	116 [6.00, 206]	116 [58.5, 252]	116 [6.00, 252]
Missing	0 (0.0%)	2 (0.4%)	2 (0.3%)
eGFR (mL/min/1.73 m^2)			
Mean (CV%)	93.5 (28.7%)	83.5 (20.6%)	87.0 (24.8%)
Median [Min, Max]	94.1 [4.00, 175]	81.8 [39.6, 159]	86.5 [4.00, 175]
Missing	0 (0.0%)	2 (0.4%)	2 (0.3%)

ALB: albumin; ALT: alanine aminotransaminase; AST: asparagine aminotransaminase; BMI: body mass index; BSA: body surface area; CRCL: creatinine clearance; CV: coefficient of variation; eGFR: estimated glomerular filtration rate; Max: maximum; Min: minimum; n: number of subjects.

Source: Tables 2 and 3 on page 34 and 35 in jazp-pcs-100-pop-pk.pdf

The population PK analyses, simulations and sensitivity analyses were performed using Phoenix™ NLME (Version 7.0). Dataset construction, figure generation, and tables of descriptive statistics were performed using R (3.3 or later). PK/PD and exposure-response analyses were performed using Phoenix™ NLME (Version 7.0) and R (3.3 or later).

The analyses show that:

- Consistent with renal excretion of unchanged drug being the primary route of elimination, CRCL and ESRD were the most important covariates describing the variability of CL/F of JZP-110.
- The additional statistically significant covariates describing variability of CL/F (body weight, dose, gender, and healthy vs narcolepsy/OSA), V/F (body weight and gender) and Ka (fed conditions, formulation, and dose) did not have a clinically relevant impact (larger than 2-fold increase or decrease) on exposure parameters of JZP-110 (AUCtau and Cmax).
- Covariates such as age, race, and markers of liver function were not identified as statistically significant covariates describing variability in CL/F, V/F and Ka.
- All PK parameters were similar between OSA and narcolepsy patients.
- The dose-normalized concentrations determined using the HPLC method appeared to be lower than those determined using LC-MS/MS. The PK model was therefore optimized accordingly to adequately characterize samples assayed with both methods (HPLC and LC-MS/MS). The conversion factor was estimated from the population PK analysis.

Reviewer's Comments: The reviewer was able to derive similar parameter estimates as reported by the applicant. However, it is not clear why dose-normalized concentrations determined using HPLC method were lower than those determined using LC-MS/MS. Lack of samples for re-analysis makes it difficult to understand the potential reasons for this difference other than the analytical method. The various goodness-of-fit plots provided by the applicant shows that the model describes the data reasonably well.

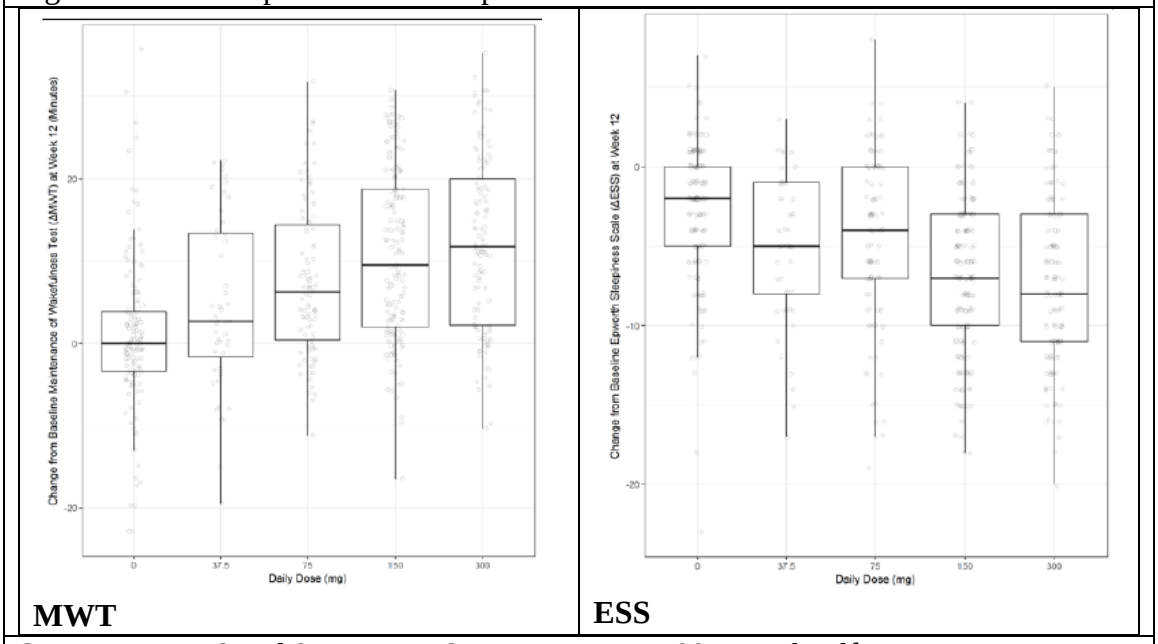
The 2-fold increase or decrease criteria, set by the applicant, for a clinically relevant change in AUCtau and Cmax for a covariate effect is wide. For example, if a covariate increases Cmax by 2-fold then patients treated with 150 mg dose would have plasma solriamfetol concentrations equivalent to 300 mg which has shown to be associated with greater safety aspects such as insomnia and increases in SBP, DBP and HR.

The analysis showed that age, gender and race did not significantly impact the pharmacokinetics of solriamfetol. These findings are reasonable since solriamfetol is eliminated via renal pathway and the studies enrolled patients with normal or mild renal impairment (age related changes). Influence of gender on solriamfetol pharmacokinetics was also looked at using data from Study 15-009 (Figure 7). The findings do not suggest the need for dose adjustment by gender.

4.3 Exposure-Response Analyses

Exposure-response analyses of efficacy and safety endpoints were performed to support dosing recommendations of JZP-110 in patients with narcolepsy/OSA. The final population PK model was used to derive exposure parameters (i.e., AUCtau, Cmax, and Cmin) in Phase 3 studies and exposure-response analyses of primary endpoints (ΔMWT and ΔESS at Week 12) and secondary endpoints (PGIc and CGIc) were performed. The relationship between dose and ΔMWT and ΔESS at Week 12 in studies 14-002 and 14-003.

Figure 9. Dose-response relationship at week 12.



MWT **ESS**

Source: Figure 8 and 9 on page 56-57 in jazp-pcs-100-pop-pk.pdf

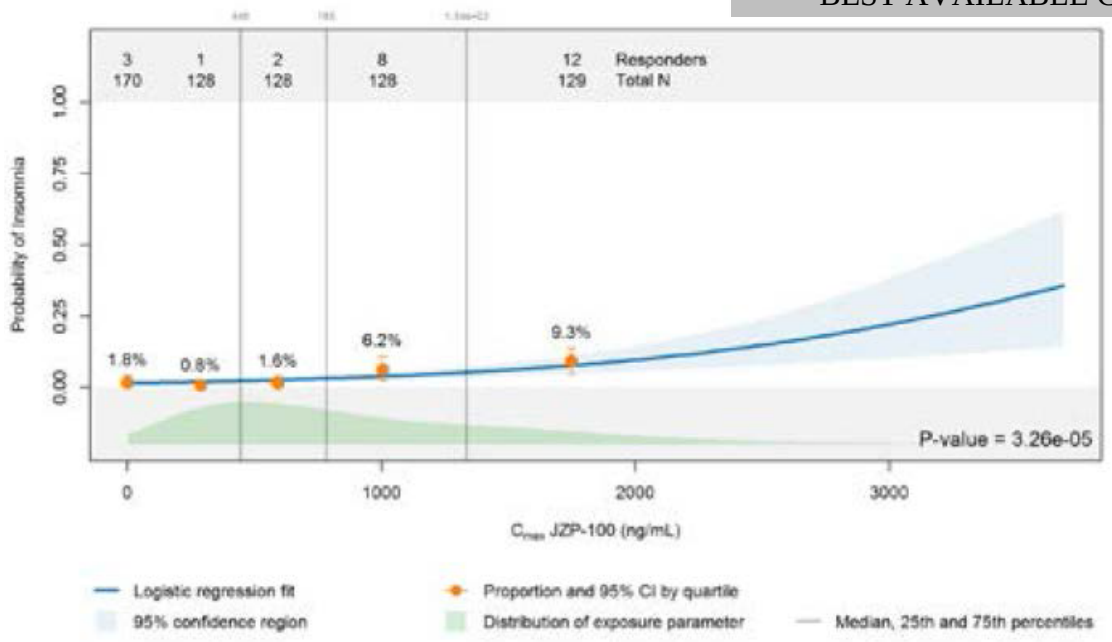
The analysis showed that

- Placebo effect (E0) on ΔMWT at Week 12 was +0.796 minutes for OSA and narcolepsy subjects.
- The placebo-subtracted drug effect (Emax) of JZP-110 on ΔMWT at Week 12 was +13.3 minutes for OSA and narcolepsy subjects.
    - E0 and Emax parameters were similar between OSA and narcolepsy subjects.
    - The overall effect of JZP-110 was +14.1 minutes (i.e., + 0.796 + 13.2).
    - The AUC50 was 3174 ng.h/mL and the AUC80 was 12696 ng.h/mL.

The relationship between concentration metrics (Cmax, Ctrough and C14h) and risk for insomnia and blood pressure changes were explored. Of all exposure metrics, Cmax resulted in the best goodness of fit for the probability of insomnia.

Figure 10 shows the relationship between Cmax and probability of insomnia. Higher probabilities of insomnia (6.2% and 9.3%, respectively) are expected for 150 and 300 mg doses with 50% and 99% of Cmax values in combined 3rd and 4th quartiles, respectively.

Figure 10. (Top) Exposure-Safety (Bottom) Dose-Safety Relationship – Effect on Probability of Insomnia.



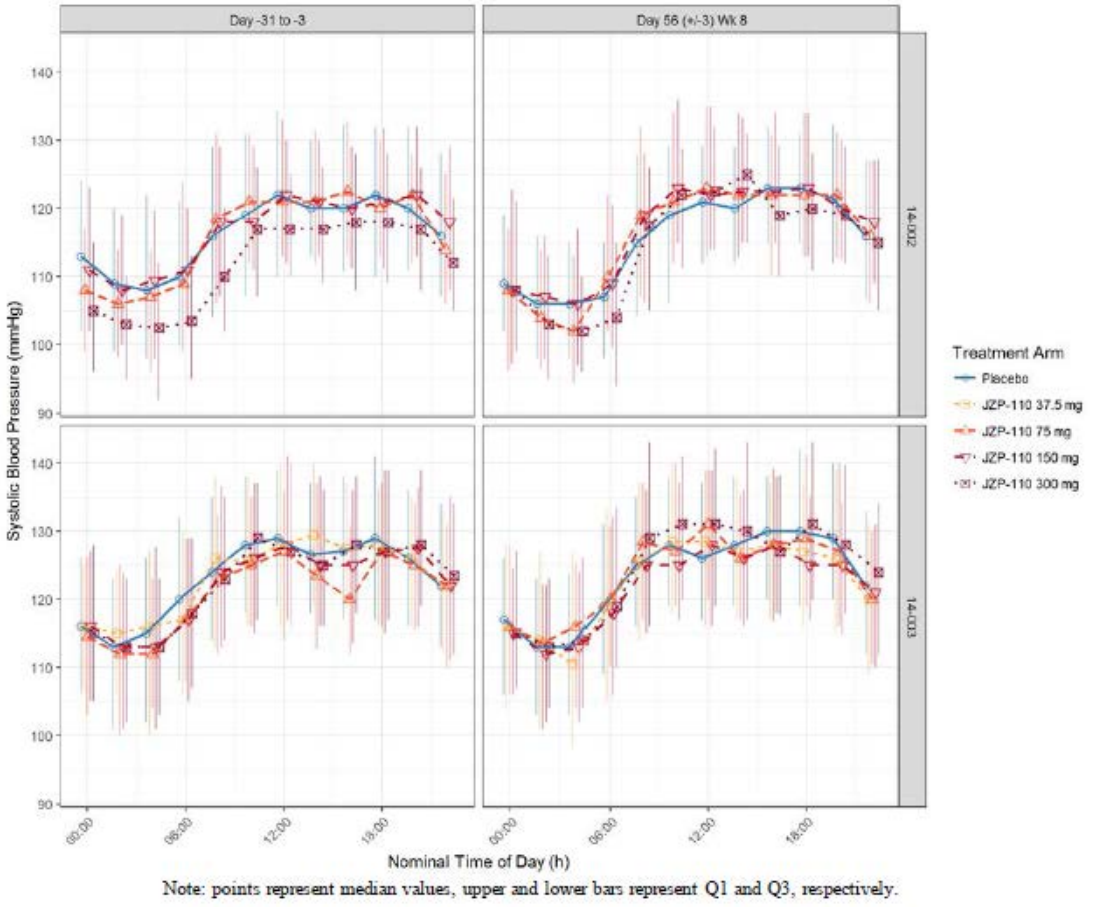
	Probability of Insomnia	95% Confidence Interval
Dose Level		
Placebo	1.8	0.0, 4.1
37.5 mg	1.8	0.0, 5.4
75 mg	1.7	0.0, 4.3
150 mg	2.3	0.6, 4.7
300 mg	9.4	5.3, 14.0
Steady State C_{max} (ng/mL)		
Placebo	1.8	0.0, 4.1
1st Quartile: ≥116 to <445	0.8	0.0, 2.3
2nd Quartile: ≥445 to <785	1.6	0.0, 3.9
3rd Quartile: ≥785 to <1340	6.2	2.3, 10.9
4th Quartile: ≥1340 to ≤3690	9.3	4.7, 14

C_{max}: maximum concentration at steady state

Source: Figure 26 and Table 27 on pages 81-82 in jazp-pcs-100-pop-pk.pdf

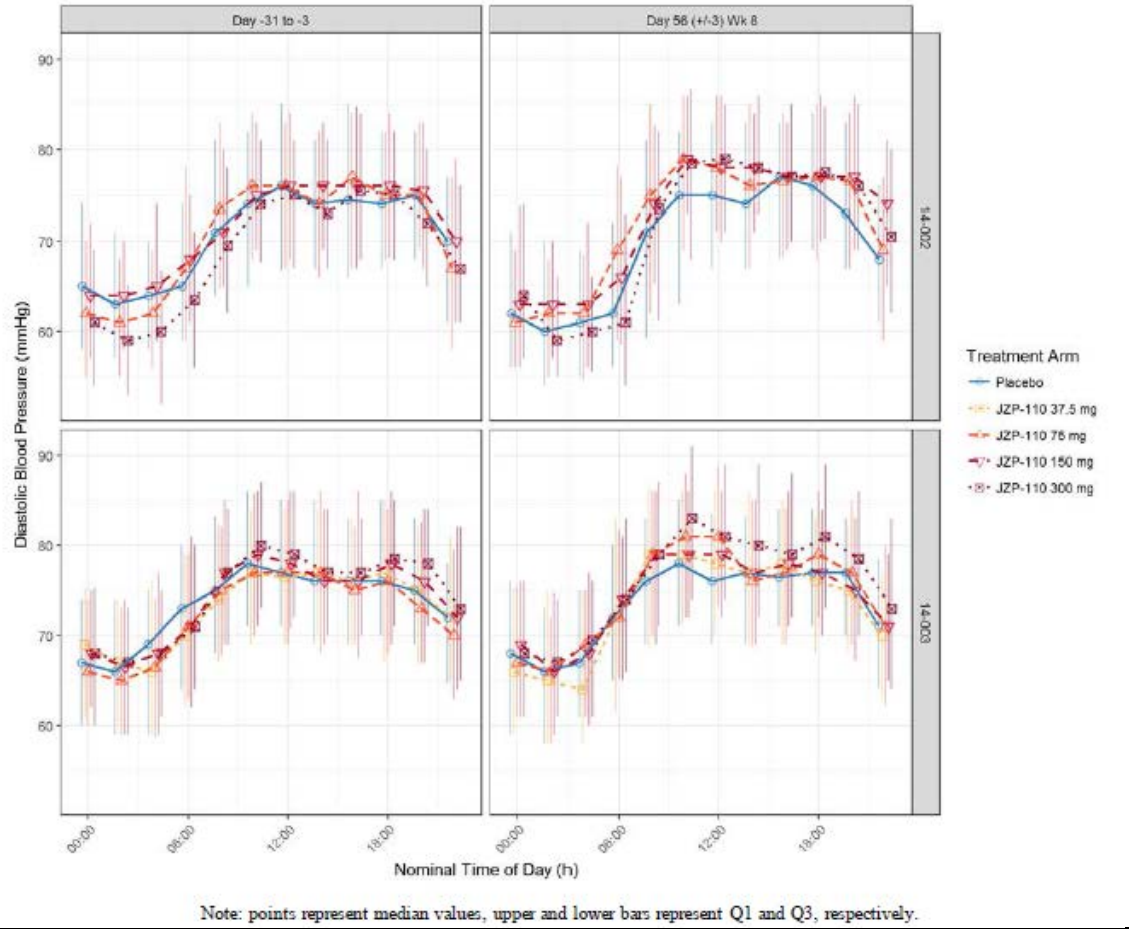
The relationship between solriamfetol concentrations and changes in hemodynamic endpoints were explored during MWT visit at week 12 and at the ABPM Visit (week 8) in studies 14-002 and 14-003.

Figure 11. Time profiles of systolic blood pressure – ABPM Visit in studies 14-002 and 14-003



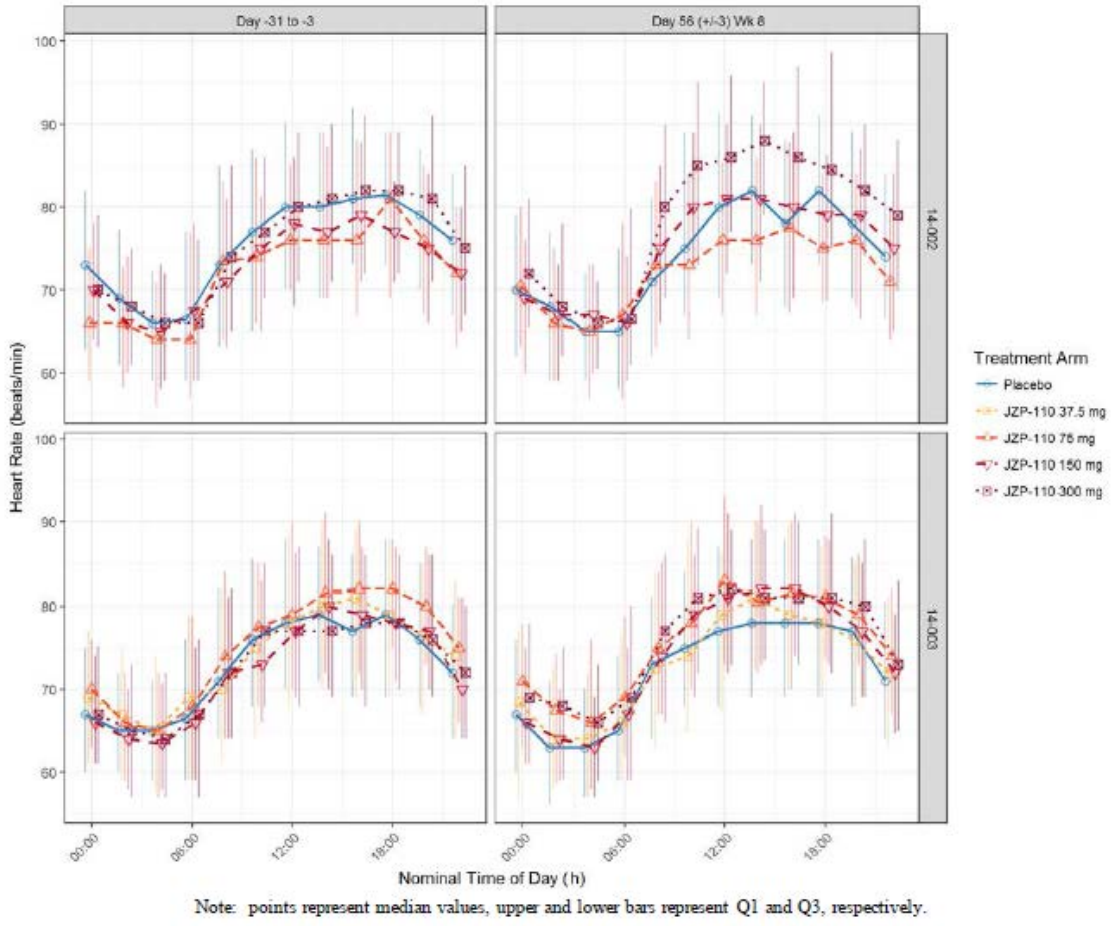
Source: Figure 18 on page 69 in jazp-pcs-100-pop-pk.pdf

Figure 1. Time profiles of diastolic blood pressure – ABPM Visit in studies 14-002 and 14-003.



Source: Figure 19 on page 70 in jazp-pcs-100-pop-pk.pdf

Figure 2. Time profiles of heart rate – ABPM Visit in studies 14-002 and 140-003.



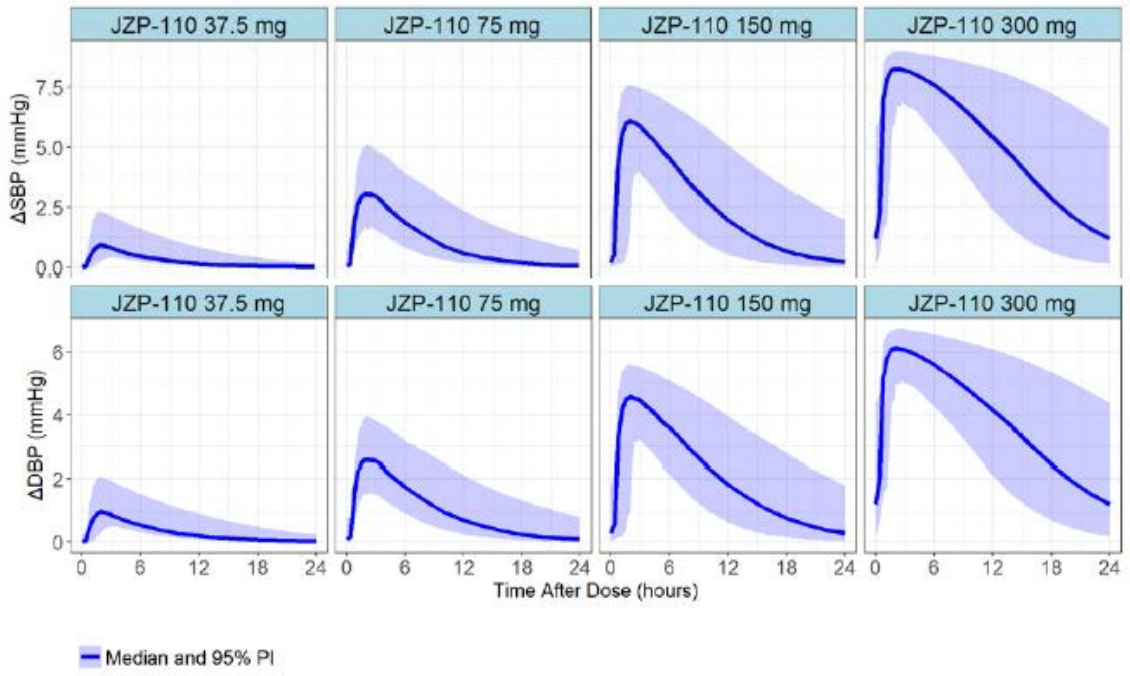
Source: Figure 21 on page 73 in jazp-pcs-100-pop-pk.pdf

The analysis suggested that

- The maximum predicted placebo-subtracted drug effects on SBP and DBP (Emax) were 9.38 (95% CI: 5.89– 12.9) and 7.17 (95% CI: 4.22 – 10.1) mm Hg, respectively.
- The estimated EC50 of JZP-110 for SBP and DBP were 561 and 546 ng/mL (i.e., 0.561 and 0.546 μg/mL), respectively.
- Median Cmax values of JZP-110 following administration of the 150 and 300 mg doses were 785 and 1580 ng/mL, respectively, hence these results suggest that the typical Cmax at the 150 mg dose level was slightly above the EC50 for SBP and DBP, while that observed at the 300 mg dose levels was approximately 3-fold higher than the estimated EC50.

Simulations were performed using the above PK/PD models to predict the effect of JZP-110 on SBP and DBP over time in each treatment group. The overall effect of JZP-110 on change from baseline in SBP (ΔSBP) and DBP (ΔDBP) are presented in Figure 14.

Figure 3. Simulated concentration-effect relationship of JZP-110 – ΔSBP and ΔDBP at ABPM Visit



Source: Figure 20 on page 72 in jazp-pcs-100-pop-pk.pdf

Simulations suggest that

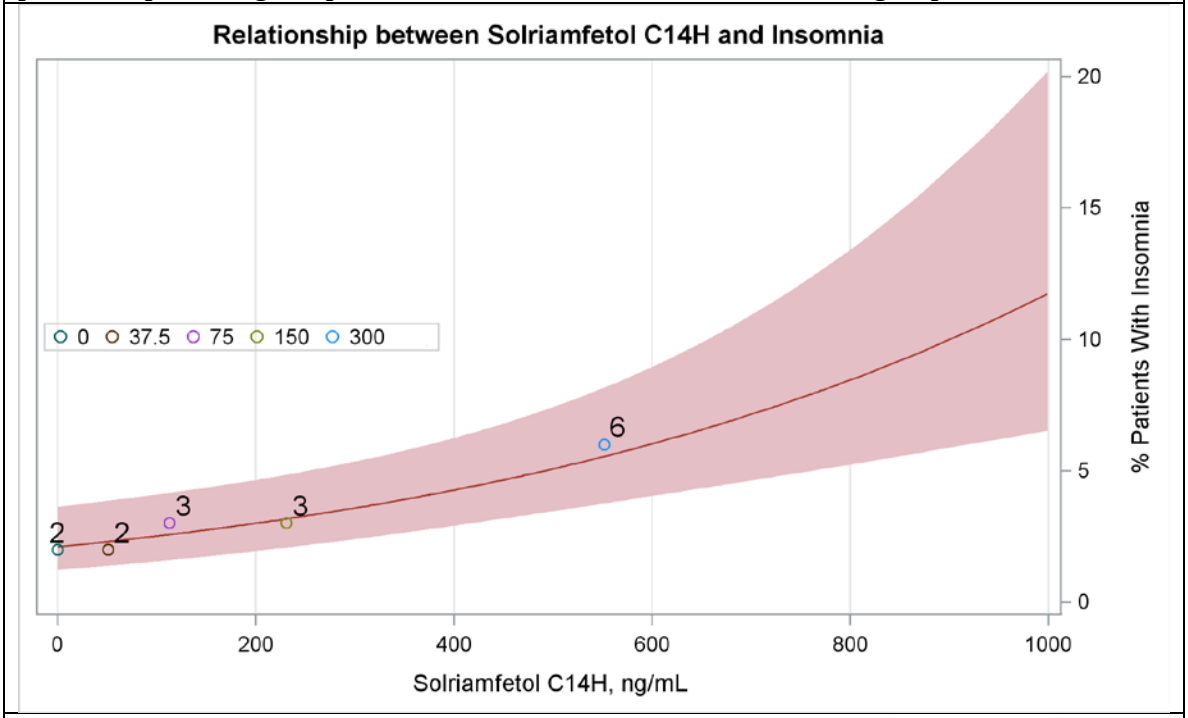
- Maximum mean effects (95% PI) on ΔSBP for the 37.5, 75, 150 and 300 mg dose levels were 1.02 (0.231– 2.28), 3.23 (1.59 – 5.11), 5.88 (1.67 – 7.59), and 8.11 (6.28 – 8.98) mm Hg, respectively.
- Maximum mean effects (95% PI) on ΔDBP for the 37.5, 75, 150 and 300 mg dose levels were 1.04 (0.304– 2.05), 2.69 (1.53 – 3.93), 4.44 (1.55 – 5.60), and 6.01 (4.70 – 6.72) mm Hg, respectively.
- Maximum mean effects (95% PI) on ΔHR for the 37.5, 75, 150 and 300 mg dose levels were 1.01 (0.285 –2.00), 2.64 (1.49 – 3.87), 4.37 (1.51 – 5.48), and 5.86 (4.62 – 6.52) beats/min, respectively.

Reviewer's Comments:
The reviewer analyzed the relationship between solriamfetol concentrations and risk for insomnia and increases in DBP, SBP and HR. This analysis was conducted to understand the risk for these events in patients with moderate or severe renal impairment.

E-R analysis for insomnia
Instead of using solriamfetol Cmax in the E-R analysis for insomnia, the reviewer used predicted steady-state plasma concentrations at 14h post-dose (C14H) as they are relatively closer to the event occurrence (next-day morning). The analysis was conducted using the database, which included information on C14H and safety events, provided by

the applicant. The applicant used this database for E-R analysis. Figure 15 shows the relationship between C14H and the proportion of patients with insomnia in studies 14-002 and 14-003 derived using logistic regression analysis.

Figure 4. Relationship between the predicted steady-state solriamfetol concentrations at 14h post-dose (C14H) and % of patients with insomnia. Shown in symbols are the predicted percentage of patients with insomnia in the various dose groups.



Source: Reviewer's analysis

The observed proportion, from studies 14-002 and 14-003, and the predicted proportion of patients with insomnia are shown in Table 3. The model reasonably predicts the overall dose-response shape indicating that C14H is a reasonable concentration metric for E-R analysis, although there are differences in observed proportions between the studies.

Table 3. Observed and predicted proportion of patients with insomnia

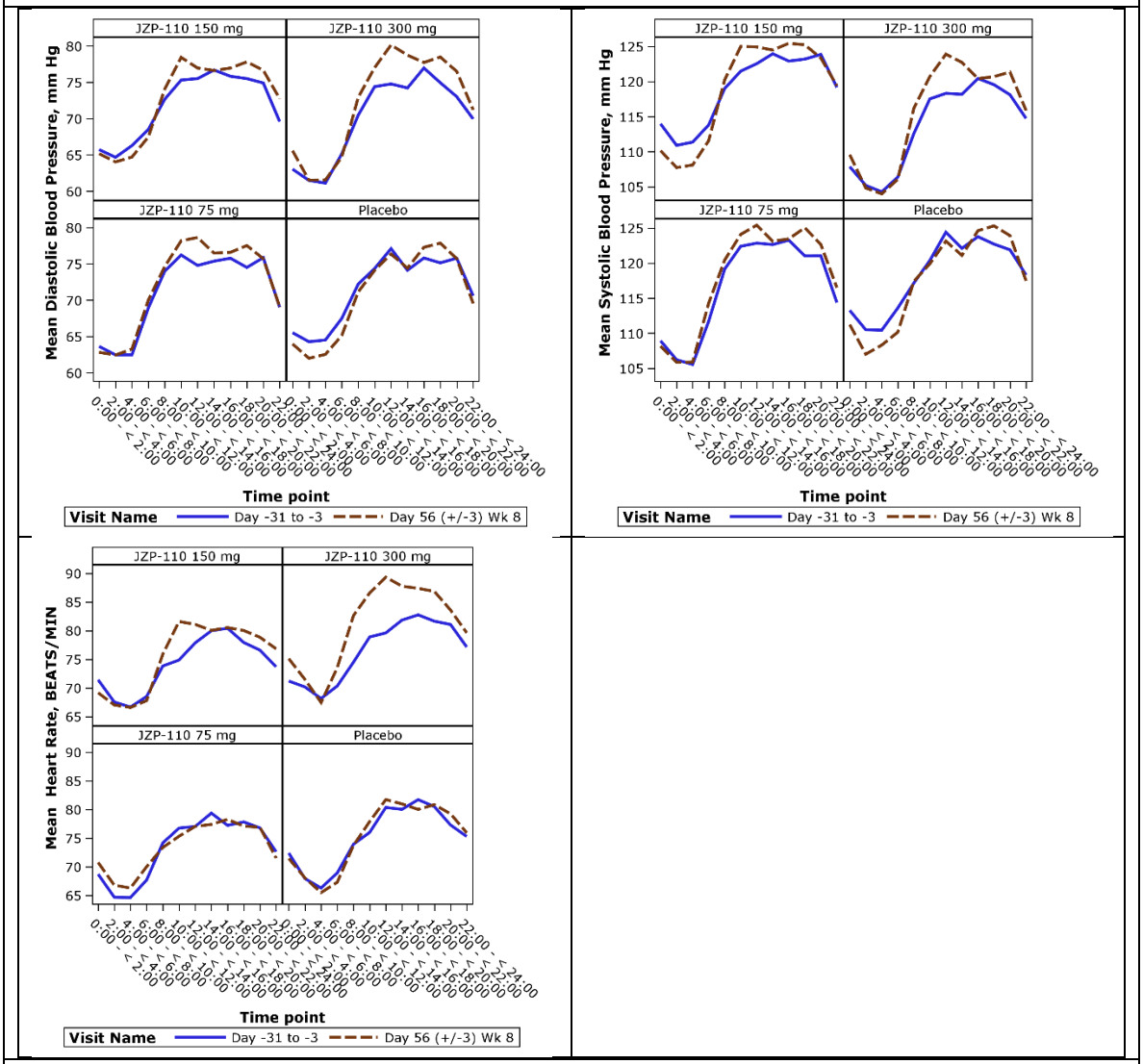
Treatment group	Observed proportion of patients with insomnia		Predicted proportion of patients with insomnia
	Study 14-002	Study 14-003	
Placebo	0	1.7	2
37.5 mg		1.7	2
75 mg	3.4	0	3
150 mg	0	2.6	3
300 mg	5.1	9.3	6

Source: Reviewer's analysis

E-R analysis for DBP, SBP and HR changes

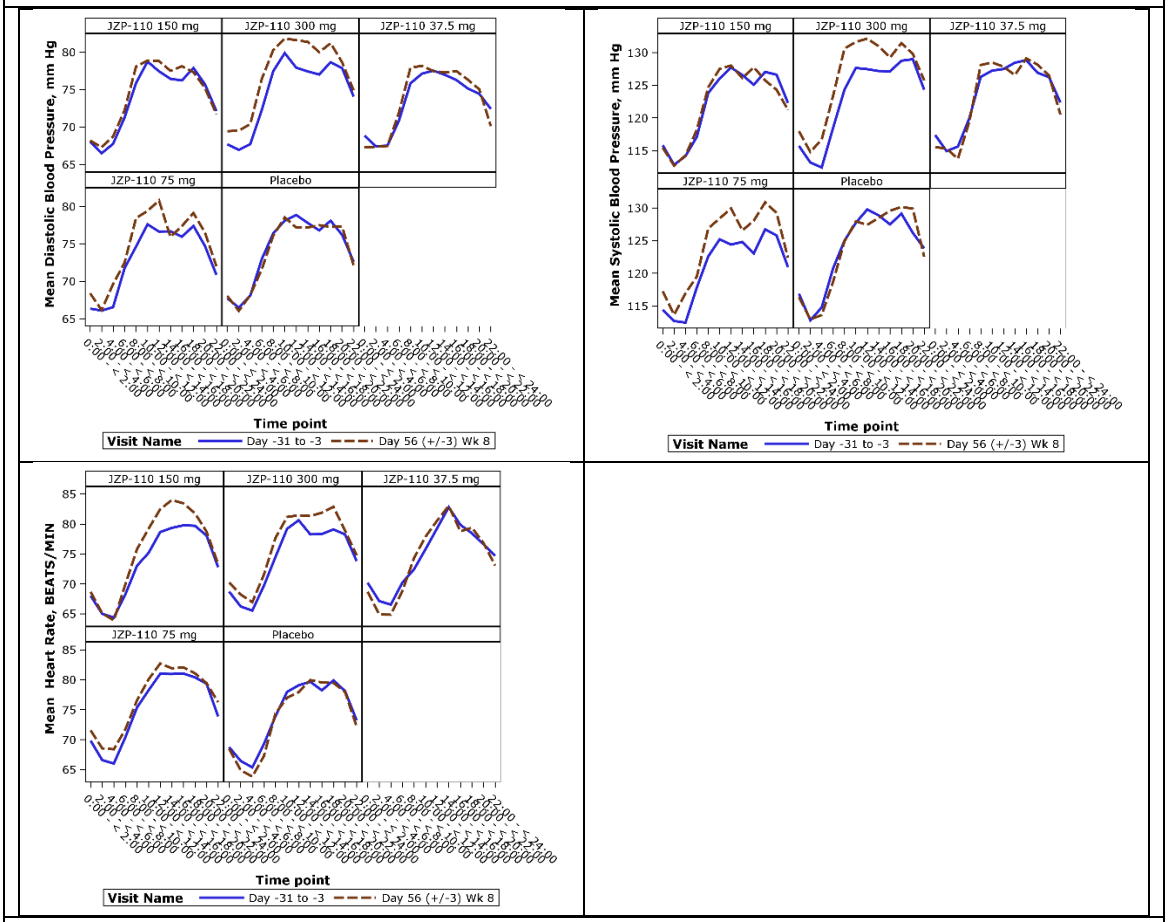
Figure 16 and Figure 17 shows the changes in DBP, SBP and HR on ABPM visit (Week 8) in study 14-002. The effects on DBP, SBP and HR are prolonged for a longer time in the 300 mg dose group.

Figure 5. Mean DBP, SBP and HR at ABPM visit in study 14-002.



Source: Reviewer's analysis

Figure 6. Mean DBP, SBP and HR at ABPM visit in study 14-003.



Source: Reviewer's analysis

Table 4 shows the DBP, SBP and HR changes at pre-dose and 2h post-dose in studies 14-002 and 14-003.

Table 4. SBP, DBP and HR changes on MWT Days: Summary of mean changes from baseline to week 12 at trough and peak in study 14-002.

Vital Sign Time Point Change	Parameter	Placebo N = 59	75 mg JZP-110 N = 59	150 mg JZP-110 N = 59	300 mg JZP-110 N = 59
SBP (mmHg)					
Trough (Pre-dose)	n	49	48	48	43
	Mean (SD)	-0.68 (11.603)	-2.10 (7.726)	-1.73 (11.128)	0.05 (10.810)
Peak (2 hours post-dose)	n	50	48	49	43
	Mean (SD)	-0.11 (10.245)	1.50 (10.628)	4.94 (11.245)	5.02 (9.242)
DBP (mmHg)					
Trough (Pre-dose)	n	49	48	48	43
	Mean (SD)	-1.09 (6.793)	-0.57 (5.902)	-1.40 (9.917)	0.85 (8.135)
Peak (2 hours post-dose)	n	50	48	49	43
	Mean (SD)	-1.75 (8.437)	1.25 (5.659)	4.24 (7.721)	4.03 (6.816)
HR (bpm)					
Trough (Pre-dose)	n	49	48	48	43
	Mean (SD)	0.03 (8.823)	-1.15 (8.622)	0.57 (9.548)	1.16 (9.583)
Peak (4 hours post-dose)	n	49	47	47	42
	Mean (SD)	-0.14 (9.345)	-0.88 (9.413)	4.27 (7.720)	5.86 (9.613)

Note: The MWT Day average was calculated across timepoint within each MWT day. Time points on baseline visit were based on lights on time, while time points on post-baseline visits were based on dosing time, which occurred 1 hour after lights on.
BPM = beats per minute; DBP = diastolic blood pressure; HR = heart rate; MWT = Maintenance of Wakefulness Test; SD = standard deviation; SBP = systolic blood pressure.

Source: Table 57 on page 198 in csr-14-002.pdf

Table 5. SBP, DBP and HR changes on MWT Days: Summary of mean changes from baseline to week 12 at trough and peak in study 14-003.

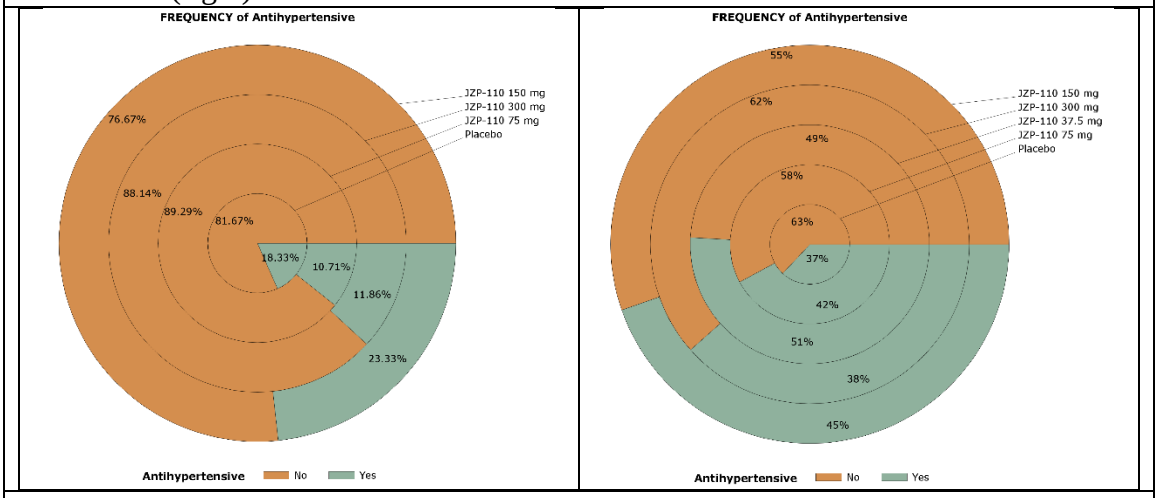
Vital Sign Time Point Change	Parameter	Placebo N = 119	37.5 mg JZP-110 N = 58	75 mg JZP-110 N = 62	150 mg JZP-110 N = 117	300 mg JZP-110 N = 118
SBP (mmHg)	n	99	49	53	103	91
Trough Change (pre-dose)	Mean (SD)	-1.63 (11.731)	0.22 (13.369)	-0.03 (11.305)	-0.35 (11.124)	-0.01 (11.696)
Peak Change (2 h post-dose)	Mean (SD)	0.61 (10.266)	1.90 (11.563)	1.09 (10.166)	2.44 (10.277)	3.97 (13.710)
DBP (mmHg)	n	99	49	53	103	91
Trough Change (pre-dose)	Mean (SD)	-0.12 (8.300)	0.35 (7.305)	-2.14 (7.893)	-0.69 (7.105)	-0.37 (8.175)
Peak Change (2 h post-dose)	Mean (SD)	0.45 (6.827)	0.13 (6.135)	0.97 (9.163)	1.10 (7.333)	2.06 (8.252)
HR (bpm)	n	99	49	53	103	91
Trough Change (pre-dose)	Mean (SD)	0.62 (7.334)	1.19 (8.240)	0.96 (9.049)	1.59 (8.091)	0.62 (9.379)
Peak Change (4 h post-dose)	Mean (SD)	0.24 (8.222)	0.43 (9.957)	1.00 (8.160)	2.89 (7.821)	4.48 (7.192)

Note: The MWT Day average was calculated across time point within each MWT day. Time points on baseline visit were based on lights on time, while time points on post-baseline visits were based on dosing time, which occurred 1 hour after lights on.
DBP = diastolic blood pressure; h = hour; HR = heart rate; MWT=Maintenance of Wakefulness Test; N = number of subjects within each treatment group; n = number of subjects with non-missing values at the specific visit; SBP = systolic blood pressure; SD = standard deviation

Source: Table 55 on page 189 in csr-14-003.pdf

Table 4 and Table 5 show the DBP, SBP and HR changes in studies 14-002 and 14-003 with greater changes in study 14-002. To understand this further, the reviewer looked at the background use of antihypertensives in the two studies. Figure 18 shows that a greater percentage of patients with OSA, in study 14-003, took antihypertensives than patients with narcolepsy in study 14-002. This could be a potential reason for lower SBP, DBP changes in study 14-003 compared to study 14-002.

Figure 7. Frequency of antihypertensive use at baseline and during study 14-002 (left) and 14-003 (right).



Source: Reviewer's analysis

The reviewer generated a graph showing the relationship between solriamfetol concentrations and changes in SBP and DBP from Study 14-002 since fewer patients were on background antihypertensives. The findings are shown in Figure 6. The findings from both Figure 5 and Figure 6 were utilized for quantifying risk in patients with moderate or severe renal impairment. Insomnia and DBP/SBP changes were considered for benefit-risk assessment in these patients since these events are likely associated with the concentration-time profile. Dose-response for HR also suggests that prolonged solriamfetol concentrations would lead to increases in HR in patients with moderate or severe renal impairment. Overall, the findings suggest that patients with moderate or severe renal impairment are at a higher risk for insomnia and increases in DBP, SBP and HR due to the prolonged half-life of solriamfetol.

Based on these analysis, the reviewer recommends that the following language be added to Section 5.2 (Blood Pressure and Heart Rate Increases) of the label.

"Patients with moderate or severe renal impairment could be be at a higher risk of increases in blood pressure and heart rate due to the prolonged half-life of solriamfetol."

In Section 5.3 (Psychiatric Symptoms) of the label, the reviewer recommends that the following language be added.

"Patients with moderate or severe renal impairment could be be at a higher risk of insomnia due to the prolonged half-life of solriamfetol."

4.4 Summary of Bioanalytical Method Validation

Refer to the summary of bioanalytical method performance included in the individual study review.

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

/s/

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