CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211230Orig1s000
211230Orig2s000

NON-CLINICAL REVIEW(S)

Tertiary Pharmacology/Toxicology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO
NDA: 211230
Submission date: 12/20/2017
Drug: solriamfetol
Applicant: Jazz Pharmaceuticals
Indication: reduce excessive daytime sleepiness in adult patients with narcolepsy or obstructive sleep apnea
Reviewing Division: Division of Psychiatry Products

Discussion:
The pharmacology/toxicology reviewer and supervisor recommended that solriamfetol could be approved from the pharmacology/toxicology perspective for the indication listed above.

Solriamfetol inhibits reuptake of dopamine and norepinephrine. Therefore, an established pharmacologic class of “Dopamine and Norepinephrine Reuptake Inhibitor” is appropriate.

Two-year carcinogenicity studies were conducted in rats and mice. The executive carcinogenicity assessment committee concluded that these studies were adequate and that there were no drug-related neoplasms in either study.

Developmental and reproductive toxicity studies did not reveal adverse developmental outcomes in the absence of maternal toxicity.

Conclusions:
The pharmacology/toxicology reviewer and supervisor conducted a thorough evaluation of the nonclinical information submitted in support of this NDA. I agree that this NDA may be approved for the above indication.

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/

PAUL C BROWN
12/19/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH;

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 211230
Supporting document/s:	SDN 1 and SDN 4
Applicant's letter date:	12/18/2017
CDER stamp date:	12/20/2017
Product:	Solriamfetol
Indication:	reduce excessive daytime sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA)
Applicant:	Jazz Pharmaceuticals Ireland Limited (Jazz)
Review Division:	DPP
Reviewer:	Jia Yao, PhD
Supervisor/Team Leader:	Aisar Atrakchi, PhD
Division Director:	Mitchell Mathis, MD
Project Manager:	Sarah Seung, PharmD

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1 Executive Summary

1.1 Introduction

Solriamfetol is a new molecular entity under development by Jazz Pharmaceuticals, LLC for the treatment of excessive daytime sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA). The mechanism(s) of action of solriamfetol is unclear. However, its efficacy could be mediated through its activity as a dopamine and norepinephrine reuptake inhibitor. Solriamfetol is not approved outside of the U.S.

1.2 Brief Discussion of Nonclinical Findings

A complete nonclinical package was submitted under NDA 211230 to allow for an adequate nonclinical safety assessment and to support market approval of solriamfetol from a nonclinical perspective.

Solriamfetol has relatively low binding affinity for the dopamine transporter (DAT) and norepinephrine transporter (NET, Ki= 14,200 nM and 3700 nM, respectively) and inhibits the reuptake of dopamine and norepinephrine with relatively low potency (IC_{50}= 2900 nM and 4400 nM for dopamine and norepinephrine, respectively). At therapeutically relevant levels (≤ 10 µM), solriamfetol had minimal serotonergic activities and does not stimulate the release of dopamine, norepinephrine, or serotonin. In *in vivo* rodent models, solriamfetol treatment increased active wakefulness and reduced the time in light, deep, and rapid eye movement (REM) sleep with a subsequent rebound increase in deep sleep time. The effects of solriamfetol on sleep-wake architecture were similar to those of amphetamine treatment and were not orexin-dependent. The safety pharmacology of solriamfetol was evaluated in the cardiovascular, respiratory, and CNS systems. No severe adverse effects were identified at the clinically relevant doses. At high doses (> 50 times the C_{max} at the maximum recommended human dose (MRHD) of 300 mg), IV infusion of solriamfetol led to significantly decreased cardiac output (↓ > 95%) and premature death in the dog.

In mice, rats, and dogs, the oral bioavailability of solriamfetol was moderate to high (72% to 100%, compared to ~95% in humans); and the plasma protein binding was low in all species tested (~ 8% to 13%, compared to ~ 16.1% in humans). After oral administration, solriamfetol was extensively distributed into pigmented and non-pigmented tissues, including the brain. In the latter, radioactivity remained relatively high throughout a 6-hour sampling period, whereas the plasma level declined rapidly after reaching C_{max}. In pregnant rats, after oral administration, solriamfetol was present in non-reproductive and reproductive tissues as well as the fetus; and the exposure in these tissues generally paralleled those in the blood. The *in vivo* metabolism profiles of solriamfetol are similar between dogs and humans, for which limited hepatic metabolism is observed and the majority of the 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, most likely due to its stimulant-like pharmacology. The severity of CNS clinical signs increased dose dependently from hyperactivity at lower doses to tremor, convulsion, and even self-injury (in rats) at higher doses. Solriamfetol also caused dose-dependent decreases in body weight gain with correlative decreases in food consumption, particularly during the first few weeks after treatment initiation. In both rats and dogs, the target organ of the drug is the lung with elevated macrophages and phospholipidosis-like inclusion bodies (without functional adversity in the lung). In addition, adipose tissue atrophy was observed, which was likely associated with decreases in body weight and food consumption. Additional target organs observed only in the rat included the adrenal gland, kidney, and liver. These drug effects were reversible or at least partially reversible with treatment cessation.

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, based on AUC. However, it should be noted that many of the dose limiting toxicities in animal studies were due to the pharmacology-related CNS signs and/or body weight decreases, which are clinically monitorable and were reversible upon treatment cessation. Therefore, I conclude that these small safety margins do not impose unacceptable risks for the proposed indication and therefore do not preclude the approval of solriamfetol.

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.

Nonclinical data describing the adverse developmental, reproductive, and fertility effects of solriamfetol are incorporated into the drug label. Solriamfetol did not affect fertility or sperm parameters when administered orally to male rats for 8 weeks at doses approximately 1- and 3.5- times the MRHD, based on mg/m^2 body surface area. However, at approximately 11 times the MRHD based on mg/m^2 body surface area, sperm count and sperm concentration were decreased (↓~10%) without affecting fertility. Solriamfetol did not affect fertility when administered orally to female rats for 2 weeks premating, during mating, and through gestation day 7 at approximately 0.5-, 2-, and 9.5- times the MRHD, based on mg/m^2 body surface area.

In embryo-fetal developmental studies, oral administration of solriamfetol during organogenesis caused maternal and fetal toxicities in rats and rabbits at doses ≥ 2- and 2.5- times- and was *teratogenic* at doses 9.5- and ≥ 2.5- times, respectively, the MRHD based on mg/m^2 body surface area.

In the rat study, solriamfetol, at 2- and 9.5- times the MRHD based on mg/m^2 body surface area, caused maternal toxicity that included hyperactivity, significant decreases in body weight, weight gain, and food consumption. Fetal toxicity at these maternally toxic doses included increased incidence of early resorption and post-implantation loss,

and decreased fetal weight. Solriamfetol was teratogenic at 9.5 times the MRHD, it increased the incidence of fetal malformations that included severe sternebrae mal-alignment, hindlimb rotation, bent limb bones, and situs inversus. This dose was also maternally toxic. The no-adverse-effect level for malformation is 2 times and for maternal and embryofetal toxicity is approximately 0.5 times the MRHD based on mg/m^2 body surface area.

In the rabbit study, solriamfetol, at 5 times the MRHD based on mg/m^2 body surface area, caused maternal toxicity of body weight loss and decreased food consumption. Solriamfetol was teratogenic at ≥ 2.5 times the MRHD, it caused fetal skeletal malformation (slight-to-moderate sternebrae mal-alignment) and decreased fetal weight. The no-adverse-effect level for malformation and fetal toxicity is approximately 1 time and for maternal toxicity is approximately 2.5 times the MRHD based on mg/m^2 body surface area.

In the pre- and post-natal developmental toxicity study in the rat, at 3.5- and 11- times the MRHD based on mg/m^2 body surface area, solriamfetol caused maternal toxicities of decreased body weight gain, food consumption, and hyperpnea. At these maternally toxic doses, fetal toxicities included increased incidence of stillbirth, postnatal pup mortality, and decreased pup weight. Developmental toxicities in the offspring pups included decreased body weight, weight gain, and delayed sexual maturation. Mating and fertility of offspring pups were decreased at maternal doses 11 times the MRHD, without affecting learning and memory. The NOAEL of maternal and developmental toxicity in the rat was approximately 1 time the MRHD based on mg/m^2 body surface area. Solriamfetol was excreted in the milk of lactating rats at concentrations 3 to 4 times higher than the plasma.

Based on the overall assessment of the nonclinical results in rodent and nonrodent animals, there are no specific or additional monitoring recommended 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.

1.3 Recommendations

1.3.1 Approvability

From a pharmacology/toxicology perspective, the nonclinical studies submitted under this NDA 211230 support the approval of solriamfetol for the treatment of excessive daytime sleepiness in adult patients with narcolepsy or obstructive sleep apnea.

1.3.2 Additional Non-Clinical Recommendations

None

1.3.3 Labeling

Sections of the labeling supported by nonclinical data are under negotiation with the Applicant at the time of completion of this review.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): 178429-65-7

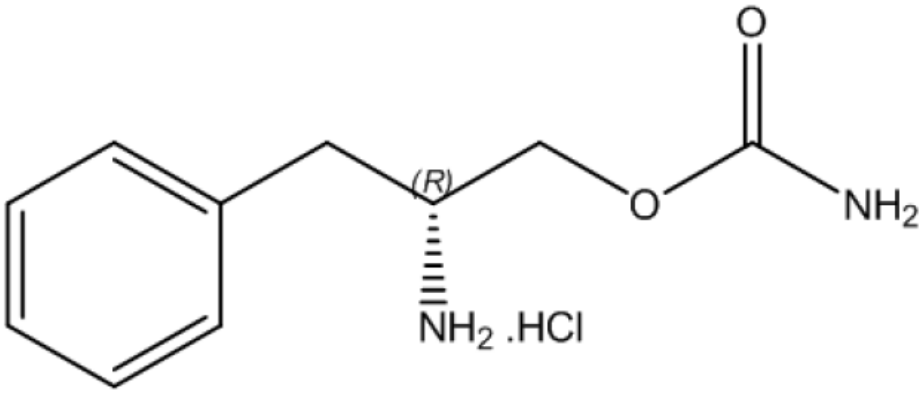
Generic Name: Solriamfetol

Code Name: JZP-110 (previously YKP10A, ADX-N05, [redacted])

Chemical Name: (R)-2-amino-3-phenylpropylcarbamate hydrochloride

Molecular Formula/Molecular Weight: $C_{10}H_{15}N_2O_2Cl$/194.23(free base); 230.69 (Hydrochloride (HCl) salt)

Structure or Biochemical Description



Pharmacologic Class: Dopamine and Norepinephrine Reuptake Inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

INDs [redacted], 107203, 122590,

2.3 Drug Formulation

Solriamfetol drug product is a film-coated immediate-release tablet. [redacted] commercial tablet strengths are 75, 150, [redacted] mg solriamfetol free base. Each tablet strength is differentiated by size, weight, shade of yellow film-coat [redacted] and debossing on one side to indicate the strength. The 75-mg tablet has a score line on the side opposite to the debossed text. See Chemistry review for details.

2.4 Comments on Novel Excipients

There are no novel excipients in the drug product. All excipients used in the formulation are compendial except for [redacted] for which there is no compendial specification; however, all the components of these [redacted] are compendial and therefore are considered to be acceptable.

2.5 Comments on Impurities/Degradants of Concern

The Applicant conducted *in silico* assessment of solriamfetol and 7 drug substance-related impurities. An independent QSAR for bacterial gene mutation assay was

conducted by the FDA computational toxicology group and the findings are consistent with the Applicant's conclusion that these compounds are considered to be non-mutagenic and therefore are controlled as regular impurities. In addition, the quality (CMC) reviewers for the drug substance and drug product have confirmed that there are no concerns regarding these impurities or degradation products that would require additional nonclinical safety testing.

2.6 Proposed Clinical Population and Dosing Regimen

Treatment of excessive daytime sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA). Drug to be administered daily as a single oral tablet.

2.7 Regulatory Background

Solriamfetol is a new molecular entity (NME) under NDA 211230 with a 12-month review clock. A series of nonclinical information requests were sent during the NDA review and the Applicant provided adequate responses.

3 Studies Submitted

3.1 Studies Reviewed

All nonclinical studies submitted under this NDA

3.2 Studies Not Reviewed

Dependence and drug abuse studies under Module 4.2.3.7.6 are not reviewed.

3.3 Previous Reviews Referenced

Dr. Aisar Atrakchi's reviews (filed in DARRTs), for the Carcinogenicity special protocol assessment (SPA) and the corresponding ECAC meeting minutes (b) (4).

Overall comments on dose conversion between hydrochloride salt and free base equivalent form in nonclinical studies: During the review of this NDA, I identified inconsistency regarding the dose conversion between the hydrochloride salt and the free base equivalent form of the drug in some Legacy nonclinical study reports. An information request was sent to the Applicant for clarification. In response (SDN-10, NDA 211230, 05/21/2018), the Applicant clarified that "all drug lots/batches used in the nonclinical studies were solriamfetol hydrochloride salt." and "when the form of the test article dose was not explicitly stated in the original report, it was assumed to be the HCl salt to provide a worst-case estimate of the free-base equivalent." The Applicant also submitted a summary table of the dose conversion for pivotal nonclinical studies, which included safety pharmacology, repeat dose general toxicology, genotoxicity, and reproductive and development toxicity studies. For consistency, I also applied the same dose conversion factor (1.19) to other non-pivotal Legacy general toxicology studies, such as single dose and shorter-duration repeat dose studies. The dose conversion ***does not*** apply to the mouse and rat carcinogenicity studies, the male rate fertility study, and the pre- and post-natal rat development toxicology study. The Applicant has specified that these studies were conducted using the free base equivalent doses.

In this review, unless stated otherwise, all drug doses are presented as free base equivalent. The salt-to-free base equivalent conversion led to slightly different values of the doses relative to the original study reports with a factor of 1.19. Given the small magnitude, I conclude that the changes do not significantly affect the safety assessment of the drug.

In this review, unless stated otherwise, all figures and tables are excerpted or re-formatted based on study reports submitted by the Applicant.

4 Pharmacology

4.1 Primary and Secondary Pharmacology

Overall comments: A large number of pharmacology studies were submitted, some of which were conducted to investigate the antidepressant mechanism of action. None of these studies provided a definitive mechanism for the current indication of solriamfetol. Some of the studies showed inconsistent findings, possibly due to difference in assay sensitivity with the methods/models and the low specificity of pharmacological agonists/antagonists used. The exact mechanisms of action for solriamfetol are unclear. The results from the majority of pharmacology studies suggest that solriamfetol penetrates into the brain and the CNS effects of solriamfetol are likely mediated by the 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. Solriamfetol, at therapeutically relevant levels, showed negligible serotonergic activity, and had minimal effects at stimulating the release of dopamine, norepinephrine, or serotonin.

The Applicant claims that solriamfetol is a non-amphetamine wake-promotor and the mechanisms of action are different from amphetamine. I do not agree, because 1) the proposed norepinephrine and dopamine reuptake inhibition is a known mechanism shared by amphetamine[1]; and 2) when compared to different selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOs), or amphetamine (stimulants), the neurobehavioral effects of solriamfetol, albeit some differences, were mostly similar to those of amphetamine or dexamphetamine.

Main findings from these primary and secondary pharmacology studies are reviewed and summarized below.

***In vitro* and *Ex vivo* Pharmacodynamic Studies**

In *in vitro* binding assays, solriamfetol showed low binding affinity for DAT (Ki= 14,200 nM) and NET (Ki=3700 nM) when compared to cocaine and other psychostimulant drugs. At clinically relevant concentrations (≤ 10 μM), solriamfetol had no appreciable affinity for serotonin transporter (SERT) (Table 1, Study Nos. (b) (4) Y1-DA-5007-03-B,

[1] Adderall Label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/011522s040lbl.pdf

NO1DA-7-8071, (b) (4) 96-2389, (b) (4) 8470, (b) (4) 5318, and (b) (4) 100032012). In autoradiography studies in rodent brains, solriamfetol showed no significant occupancy at SERT, NET, or DAT (Study No. (b) (4) 0893).

In studies that evaluate monoamine kinetics, solriamfetol, at therapeutically relevant concentrations (≤10 μM), primarily affected the reuptake of dopamine and norepinephrine, but not serotonin; and did not stimulate the release of dopamine, norepinephrine, or serotonin (Table 2).

In cells expressing human DAT, NET, or SERT, compared to cocaine, solriamfetol exhibited low potency at blocking the reuptake of [^{3}H] dopamine or [^{3}H] norepinephrine, with no appreciable effect at blocking the reuptake of [^{3}H] serotonin (Study No. (b) (4) Y1-DA-5007-03-B). In rat brain synaptosomes, solriamfetol showed low affinity for DAT, and inhibited the reuptake of dopamine and norepinephrine with low potency; solriamfetol had no affinity for SERT and had no effect on serotonin reuptake (Study No. (b) (4) 5318). In an *in vitro* assay of monoamine release, unlike methamphetamine or p-chloroamphetamine, solriamfetol at concentrations up to 100 μM did not stimulate the release of dopamine, norepinephrine, or serotonin (Study No. (b) (4) Y1-DA-5007-03-A). However, in rat brain synaptosomes, solriamfetol at 30 μM induced the release of dopamine and serotonin with low potency, but not norepinephrine (Study No. (b) (4) 5318). In cells expressing human vesicular monoamine transporter 2 (VMAT2), solriamfetol showed minimal binding affinity for VMAT 2 (Ki > 250 μM for displacement of [^{3}H]dihydrotetrabenazine) and low potency at blocking the uptake of [^{3}H]serotonin by VMAT 2 (IC_{50} = 6.3 μM). In isolated pig coronary artery rings, solriamfetol, similar to bupropion, induced constriction of coronary artery, suggesting possible adrenergic activity of solriamfetol (Study No. (b) (4) 0336).

Table 1: Relatively Low Binding Affinity of solriamfetol at Monoamine Transporters (DAT, NET, and SERT)

Study	Cell/Tissue Type	Radioligand	Test/Reference Ligand	Binding Affinity (K_i or IC_{50}) (nM)		
				DAT	NET	SERT
(b) (4) Y1-DA-5007-03-B [a]	HEK293 cells	[^{125}I]RTI-55	**JZP-110**	**14,200±3,500**	**3700±1,000**	**81,500±2,900**
			Cocaine	236±58	505±67	361±55
(b) (4) 5318	Rat brain synaptosomes (striatum for DAT and SERT)	[^{3}H]Mazindol for DAT; [^{3}H]Citalopram for SERT	**JZP-110**	**~10,000**	–	**>10,000**
			GBR-12909	5	–	–
			Bupropion	450	–	–
			Fluoxetine	-	–	1.3
(b) (4) 8470	Rat brain synaptosomes (striatum)	[^{3}H]Cocaine	**JZP-110**	**4,100** [b]	–	–
			Cocaine	30 [b]	–	–
			Mazindol	3 [b]	–	–
			Amphetamine	1,500 [b]	–	–
(b) (4) 8470	Rat brain synaptosomes (striatum)	[^{3}H]Win35438	**JZP-110**	**2,600** [b]	–	–
			Cocaine	160 [b]	–	–
			Mazindol	22 [b]	–	–
			Amphetamine	14,800 [b]	–	–
(b) (4) 96-2389	Guinea pig striatal membrane	[^{3}H]Win35438	**JZP-110**	**3,410**	–	–
			GBR-12909	6.76	–	–

DAT = dopamine transporter; hDAT=human dopamine transporter; HEK=human embryonic kidney; hNET=human norepinephrine transporter; hSERT=human serotonin transporter; IC_{50} = half-maximal inhibitory concentration; K_i = binding affinity; NET=norepinephrine transporter; SERT=serotonin transporter; -=not determined.
[a] For Study Y1 DA 5007-03-B, hDAT, hNET, and hSERT were used.
[b] Binding affinity calculated as IC_{50} rather than K_i.

Table 2: Low Potency of solriamfetol at Blocking Dopamine, Norepinephrine, and Serotonin Reuptake

Monoamine Reuptake Inhibition Studies

Study	Cell/Tissue Type	Radioligand	Test/Reference Ligand	Binding Affinity (IC_{50}) (nM)		
				DAT	NET	SERT
(b) (4) Y1-DA-5007-03-B [a]	HEK293 cells	[^{3}H]dopamine, [^{3}H]norepinephrine, or [^{3}H]5-HT	JZP-110	2,900±920	4,400±1100	>100,000
			Cocaine	385±54	194±29	355±39
(b) (4) 5318	Rat brain synaptosomes (striatum for DAT hypothalamus for NET)	[^{3}H]dopamine or [^{3}H]norepinephrine	JZP-110	21,000	6,500	–
			GBR-12909	8	–	–
			Bupropion	1700	–	–
			Desipramine	–	4.2	–

DAT = dopamine transporter; hDAT=human dopamine transporter; HEK=human embryonic kidney; hNET=human norepinephrine transporter; hSERT=human serotonin transporter; IC_{50} = half-maximal inhibitory concentration; NET=norepinephrine transporter; SERT=serotonin transporter.
[a] For Study Y1 DA 5007-03-B, hDAT, hNET, and hSERT were used.

In vivo Pharmacodynamic Studies

Data from the majority of *in vivo* pharmacology studies demonstrated the dopaminergic and adrenergic activity of solriamfetol. These studies are reviewed and summarized below:

Dopaminergic Activity of Solriamfetol

In rats and mice, solriamfetol reversed behavioral deficits induced by monoamine-depleting agents (Study No. (b) (4) 1783). Solriamfetol, at 30 mg/kg SC[2], increased striatal dopamine levels and prefrontal cortical norepinephrine levels, but not serotonin levels. A lower dose of 10 mg/kg was ineffective (Study No. (b) (4) 8880). In male SD rats, solriamfetol dose-dependently antagonized haloperidol-induced catalepsy, suggesting the dopaminergic activity of solriamfetol (Study No. (b) (4) -1833). In a study that investigated the effects on the synthesis and metabolism of different monoamines in various regions of the rat brain, solriamfetol showed similar dopaminergic effects to cocaine in the striatum, hypothalamus, nucleus accumbens, and hippocampus, whereas in frontal cortex and brain stem, solriamfetol induced serotonergic effects similar to amphetamine (Study No. (b) (4)). In force swimming tests in male mice, solriamfetol at 15 mg/kg IP or 30 mg/kg PO, increased activities associated with dopaminergic transmission, which were partially abolished by dopamine D1 and D2 receptor antagonists (Study Nos. (b) (4) 2003a and (b) (4) 96-5).

Adrenergic Activity of Solriamfetol

In mice, solriamfetol, at 15, 20, and 30 mg/kg IP, antagonized the hypoactive effects of clonidine, a *presynaptic* α_2 receptor agonist, on motor activity (Study No. (b) (4) 96-4), suggesting adrenergic activity of solriamfetol. However, solriamfetol, unlike imipramine (a norepinephrine reuptake inhibitor), did not protect mice against oxotremorine-induced tremors (Study No. (b) (4) 95-8). In a head-twitching test in mice, solriamfetol, at 30 or 60 mg/kg PO, decreased the serotonin-mediated head-twitch responses whereas fluoxetine, an SSRI, increased the head-twitch response, suggesting possible α_{2A} agonist but not a serotonergic pharmacology of solriamfetol (Study No (b) (4) 96-3). Solriamfetol, at 30 mg/kg PO, antagonized the apomorphine-induced hypothermia, an effect similar to several norepinephrine reuptake inhibitors but not serotonergic-reuptake inhibitors (Study No. (b) (4) 95-6). However, solriamfetol, at a higher dose of 60 or 100 mg/kg IP, induced hypothermia in mice (↓ ~ 2 ^{o}C in rectal temperature), an effect similar to bupropion (Study Nos. (b) (4) 96-5 and (b) (4) 95-12).

Comparison between Amphetamine and Solriamfetol

In DAT knockout mice, solriamfetol, *similar to amphetamine*, dose dependently reduced locomotor, rearing, and stereotypy activities, indicating that the CNS effects of solriamfetol are not solely mediated by DAT (Study No. (b) (4) 3946). In wild-type mice, some differences of CNS effects between solriamfetol and amphetamines were observed in that solriamfetol did not increase spontaneous activities (Study No. (b) (4) 3946). This difference could be due to the relatively low potency of solriamfetol in mice instead of different mechanisms of action because solriamfetol was shown to increase local motor activities in multiple studies in rats and dogs. In a rat open field test to compare the behavioral effects of dexamphetamine, modafinil, and solriamfetol, solriamfetol showed a profile similar to dexamphetamine (Study No. (b) (4) 2802).

[2] Route of administration: SC, subcutaneous; IP, intraperitoneal; PO, oral; IV, intravenous.

Wakefulness Promoting Effects of solriamfetol

The efficacy of solriamfetol to promote wakefulness was investigated in a few rodent studies. In male rats, solriamfetol, at 30 mg/kg IP, significantly increased active wakefulness and reduced the time spent in light sleep, deep sleep, and REM sleep during the first 3 to 4 hours after treatment, followed by a rebound increase in deep sleep time between 4 to 10 hours after treatment. The psychostimulant effects of solriamfetol were similar to those of amphetamine administered at lower doses (1 mg/kg IP) (Study No. (b) (4) 1485). In both wild-type and orexin-deficient narcoleptic mice, solriamfetol dose dependently suppressed non-REM and REM sleep and induced continuous wakefulness, indicating that the wakefulness promoting effects of solriamfetol are not directly dependent on orexin (Study No. SU-001).

In other pharmacology studies, oral administration of solriamfetol, suppressed submissive behavior in male rats (Study No. SH-02-02-02-1082). Solriamfetol also dose-dependently potentiated the yohimibine-induced toxicity (Study No. (b) (4) 95-15). These studies were primarily conducted to investigate the effects of solriamfetol as a potential antidepressant. The relevance of these studies to the current indication of solriamfetol appears limited.

4.2 Secondary Pharmacology

Overall comments: No dedicated secondary pharmacology studies of solriamfetol were submitted. Many of the secondary pharmacology data were included as part of the primary pharmacology studies. Relevant findings are reviewed and summarized below:

In *in vitro* binding studies, solriamfetol showed weak affinity for 5-HT_{1A} receptor (IC_{50}= 1-3 μM) but did not induce functional response at the 5-HT_{1A} receptor. Solriamfetol had no affinity for 5-HT_{2A}, 5-HT_{2c}, D_1, D_2, or D_3 receptors (IC_{50} > 10 μM, Study Nos. (b) (4) 7-8072 and (b) (4) 8470). Solriamfetol is a weak antagonist at the adrenergic α_{2A} and α_{2B} receptors (53.2% inhibition at 10 μM), and has no affinity or functional activity at the histamine H_1, H_2, H_3, $orexin_2$ receptors, or 89 G-protein coupled receptors (GPCRs) (Study Nos. (b) (4) 870 and 871 and DD06604, (b) (4) 6605, and (b) (4) 16253887-22457057). In a kinase screening assay against more than 100 kinases, solriamfetol had no enzyme inhibition or activation activity at most kinases tested, except for a weak inhibition against SGK (serum- and glucocorticoid-regulated protein kinase) and FGFR3 (fibroblast growth factor receptor-3) and activation of Tie-2(endothelial-specific receptor tyrosine kinase). The biological relevance of this weak inhibition or activation is unclear. In autoradiography studies in rodent brains, solriamfetol showed no significant occupancy at dopamine D_2, adrenergic α_{2A} or α_{2C} receptors (Study No. (b) (4) 0893).

4.3 Safety Pharmacology

Comments on the non-GLP status of safety pharmacology studies:

In general, GLP compliance is required for safety pharmacology studies per ICHS7A guidance. For studies that are not feasible to conduct in compliance with GLP, ICHS7A guidance stipulates that “data quality and integrity should be ensured in the absence of formal adherence to principles of GLP.” Most of the safety pharmacology studies in this NDA application were conducted prior to issuance of ICHS7A and therefore were not performed with full GLP compliance. The Applicant stated that they “undertook a careful

evaluation of the pharmacodynamic properties of solriamfetol prior to initiating and continuing during clinical development" and that the non-GLP status of the safety pharmacology studies did not "impact the overall integrity or interpretation of the study results and conclusions". After evaluating all the study reports, I did not identify any significant issues that may have compromised the quality of the study or the interpretation of the data; and therefore consider these safety pharmacology studies to be acceptable

Overall summary of safety pharmacology studies:
The safety pharmacology of solriamfetol was evaluated in the cardiovascular, respiratory, and CNS systems. No adverse effects were identified at the clinically relevant doses. In one anesthetized dog, an IV infusion of 100 mg/kg solriamfetol caused significant decrease in cardiac output (↓up to 95%) and premature death. This dose of 100 mg/kg IV is high (> 50-fold the C_{max} at MRHD) and unlikely to occur in clinical settings; therefore, the clinical relevance of the death at such high dose appears limited. Other drug-related effects included slight increases in heart rate and blood pressure, increases in the locomotor activity, slight and transient increases in respiratory rate. These effects are expected based on the pharmacology of solriamfetol and are not considered to be adverse.

Cardiovascular and Respiratory

Effects of solriamfetol on hERG channel current (Study No. (b) (4) CPF-924, *non-GLP*)
The impact of solriamfetol on hERG channel current was evaluated in a hERG-HEK 293 cell model. Compared to vehicle controls (culture buffer), solriamfetol did not induce significant inhibition of the hERG channel. Solriamfetol at concentrations of 0.1, 1, and 10 μM only induced 5%, 13%, and 19% inhibition of the hERG current, whereas the positive control astemizole induced 93% inhibition of hERG current at 10 nM.

Effects of solriamfetol on cardiovascular and respiratory function in the telemetered dog (Study No. (b) (4) Tox-6188, GLP)
In telemetered male beagle dogs under conscious condition, compared to vehicle controls (water), a single oral administration of solriamfetol at 4, 13, and 42 mg/kg induced dose-dependent increases in locomotor activity and clinical signs of vomiting (4 and 13 mg/kg) and restlessness and headshaking (42 mg/kg). Solriamfetol at 4 mg/kg had no significant effects on cardiovascular- (blood pressure, heart rate, and ECG) or respiratory- parameters over a 12-hour period. At 13 and 42 mg/kg, solriamfetol dose dependently increased blood pressure, respiratory rate and decreased tidal volume. Heart rate was also slightly increased at 13 and 42 mg/kg, likely due to increased locomotor activity. These neurobehavioral, cardiovascular, and respiratory effects are expected based on the pharmacology of solriamfetol. The no observed effect level (NOEL) for solriamfetol in this study is 4 mg/kg, PO; the corresponding plasma level of solriamfetol at 70 minutes post-dose is 1132 ng/mL.

Effects of solriamfetol on cardio-hemodynamic, electrophysiological, and behavioral parameters in conscious dogs (Study No. (b) (4) CPF-536, non-GLP).
In conscious male beagle dogs, compared to vehicle controls (water), oral administration of solriamfetol at 4 mg/kg had no significant effects on heart rate, blood

pressure, cardiac contractility and relaxation, cardiac output, stroke volume, systemic vascular resistance, the duration of QRS-, QT-interval, and QT-dispersion, or ECG morphology. No changes in behavioral parameters were observed either. A slight increase in the duration of the PQ-interval (↑12% relative to 210 min baseline compared to ↓6% relative to the baseline in controls) and a slight decrease in the QTc Bazett-interval (↓4-8% relative to baseline compared to no change in controls) were observed. Given the small magnitude, I consider these changes to be non-adverse. The plasma level of solriamfetol was 2138 ng/mL at 60 minutes after treatment.

Effects of solriamfetol on cardio-hemodynamic and electrophysiological parameters in anesthetized guinea pigs (Study No. (b) (4) CPF-533, non-GLP).
In anesthetized male guinea pigs, compared to vehicle controls (saline), sequential IV administration of solriamfetol at doses of 0.13 to 4 mg/kg (total dose of 8.3 mg/kg) at 15-minute dose intervals, had no significant effects on heart rate, mean arterial blood pressure, or the duration of PQ-, QRS-, QT-, and QTc Bazett-interval. The plasma level of solriamfetol at 5 minutes after the last IV injection was 5001 ng/mL.

Effects of solriamfetol on cardiac and circulatory functions in open-chest anesthetized dogs (Study No. (b) (4) -247-YU-001-95, non-GLP).
In anesthetized male beagle dogs, compared to vehicle controls (saline), IV infusion of solriamfetol at 3 and 8 mg/kg over 15 minutes had no significant effects on cardiac and circulatory functions. At 29 mg/kg, IV infusion of solriamfetol over 15 minutes slightly decreased cardiac output (↓~ 2 to 10%) and increased blood pressure (↑~ 5 to 20%), which returned to baseline value by 60 minutes after treatment. However, at 84 mg/kg, IV infusion of solriamfetol over 15 minutes caused significant decreases in all cardiac and circulatory parameters (↓up to 95% in cardiac output) and caused premature death at 98 minutes after treatment. Therefore, 84 mg/kg exceeded MTD. In study (b) (4) CPF-533, an IV dose of 4 mg/kg produced a plasma level of 5001 ng/mL, which is approximately 2.7-fold over the C_{max} of 1880 ng/mL at the maximal recommended human dose (MRHD) of 300 mg. At 84 mg/kg dose, the plasma level is expected to be over 50-fold over the C_{max} at MRHD. Based on the knowledge of potential intrinsic/extrinsic factors that may affect the pharmacokinetics of solriamfetol, a 50-fold level of the C_{max} at MRHD is unlikely to occur. Therefore, I conclude that the clinical relevance of the premature deaths in the dog at 84 mg/kg IV is limited.

Effects of solriamfetol on cardiovascular functions in anesthetized rats (Study No. (b) (4) 95-14, non-GLP).
In anesthetized male Wistar rats, compared to vehicle controls (saline), IV administration of solriamfetol at 8, 25, and 84 mg/kg, dose-dependently decreased systolic blood pressure and heart rate within 10 minutes post-dose, but had no significant effect on electrocardiogram parameters. IV administration of solriamfetol at doses up to 8 mg/kg slightly antagonized the pressor effect of tyramine.

A few *ex vivo* cardiovascular safety pharmacology studies of solriamfetol were conducted. In isolated spontaneous beating right atrium of the guinea pig, solriamfetol at concentrations up to 10 μM did not affect the rate or the force of contraction (Study No. (b) (4) 5899, non-GLP). In isolated rabbit Purkinje fibers, solriamfetol at

concentrations up to 10 μM did not induce abnormal action potentials or any other abnormal electrophysiological parameters (Study No. (b) (4) CPF-922, non-GLP).

CNS

Effects of solriamfetol on motor function, general activity, and alertness

In male SD rats, a single oral administration of 25 or 50 mg/kg solriamfetol slightly increased motor activity relative to the saline controls (Study No. (b) (4) 95-9, non-GLP). In male CD-1 mice, compared to vehicle controls (saline), a single oral administration of solriamfetol at 25, 50, or 84 mg/kg slightly increased motor activity; in comparison, imipramine at 30 mg/kg PO reduced motor activity in mice. At higher doses of 672 to 1512 mg/kg PO, solriamfetol caused a dose-dependent decrease in rotarod performance in male CD-1 mice. The median neurotoxic dose for solriamfetol (TD_{50}, 50% of the mice fails the rotarod test) was 1360 mg/kg. Imipramine, a tricyclic antidepressant, also dose-dependently decreased rotarod performance with a TD_{50} of 97 mg/kg, PO (Study No. (b) (4) 95-16, non-GLP). In a spontaneous motor activity test in male Long-Evans rats, compared to vehicle controls (0.5% w/v methylcellulose), solriamfetol at 29 mg/kg PO induced a moderate increase in horizontal activity but did not induce anxiogenic effects (Study No. (b) (4) 15756, non-GLP).

In male CF-1 (Carworth Farms colony) mice, compared to vehicle controls (water), solriamfetol, at 84 mg/kg PO given prior to a nonhypnotic dose of ethanol, did not induce anesthesia (Study No. 1868). In male CD-1 mice, compared to vehicle controls (saline), solriamfetol, at 25 and 84 mg/kg PO reduced the mean sleeping time induced by hexobarbital, whereas imipramine at 84 mg/kg PO increased the sleeping time (Study No. (b) (4) 95-7).

Effects of solriamfetol on seizure potential and neurotoxicity

In male CF-1 mice, compared to vehicle controls (saline), pretreatment of solriamfetol at the doses of 42, 63, and 84 mg/kg PO protected 2/8, 2/8, and 6/8 mice, respectively, from the maximal electroshock (MES) induced convulsions. The ED_{50} value of solriamfetol is 68.6 mg/kg PO (Study No. (b) (4) 95-13, non-GLP). In male CF-1 mice, compared to vehicle controls (saline), solriamfetol, at the supratherapeutic doses of 168 to 840 mg/kg IP, induced dose-dependent CNS effects, progressing from ataxia to prostration to loss of righting reflex, to eventually respiratory distress and death at very high doses; however, no convulsion was observed. Bupropion, as a comparative compound, induced ataxia, prostration and fore- and hind-limb extension at 84 mg/kg, clonic seizures, spasms, and loss of righting reflex at 168 mg/kg, and clonic seizures, dyspnea, and death at 252 mg/kg. These data suggest that solriamfetol has low potential to induce convulsions at therapeutically relevant levels (Study No. (b) (4) 7316, non-GLP). In male CD-1 mice, compared to vehicle controls (water), solriamfetol at doses of 25 or 84 mg/kg PO did not induce any observable CNS effects on general behavior; solriamfetol at 84 mg/kg PO partially reversed the sedative effects induced by 4-biphenylacetic acid (BFA, 400 mg/kg IP). In mice treated with pro-convulsant pentylenetetrazol (PTZ, 52 mg/kg SC), solriamfetol, at 25 mg/kg PO, did not potentiate the pro-convulsant effects of pentylenetetrazol (Study No. (b) (4) 8742, non-GLP).

Effects of solriamfetol on cognitive performance

In a water maze study to determine the effects of solriamfetol on learning and memory in mice, solriamfetol, at the doses of 2.5, 8.4, and 42 mg/kg/day SC for four consecutive days, did not have any significant effects on memory storage or retention in male C57/BL6 mice (Study No. (b) (4) 6751, non-GLP). In a visual discrimination study in male Long-Evans rats, compared to vehicle controls (saline), a single treatment of solriamfetol at the doses of 2.5 and 25 mg/kg IP, significantly improved performance; similar performance enhancement effects were also observed with d-amphetamine treatment at 1.0 mg/kg IP (2.5 to 25 times more potent than solriamfetol). However, solriamfetol, at 8.4 mg/kg IP, did not have any effects; therefore, there was no clear dose relationship of solriamfetol effects on visual discrimination (Study No. (b) (4) 4015, non-GLP). In a five-choice serial reaction time (5-CSRT) task to assess attention performance and impulsive/compulsive behaviors in male Long-Evans rats, compared to vehicle controls (saline), solriamfetol, at doses of 2.5, 8.4, and 25 mg/kg/day IP for over two weeks, did not affect attention performance but induced a dose-dependent increase in impulsive behaviors. At 25 mg/kg IP, solriamfetol significantly increased the impulsive and compulsive behaviors to a level comparable to d-amphetamine at 1.0 mg/kg IP (Study No. (b) (4) 2397, non-GLP).

Effects of solriamfetol on food intake

In male Wistar rats, compared to vehicle controls (saline), IP administration of solriamfetol (dose not provided in the study report) slightly reduced the amount of sweetened milk intake (5.4 mL in solriamfetol treated rats compared to 6 mL in vehicle controls). In comparison, amphetamine at 0.5 mg/kg IP significantly reduced the milk intake (3.8 mL in amphetamine treated rats). Solriamfetol did not potentiate the effects of amphetamine on milk intake (4.2 mL in the solriamfetol + amphetamine group, Study No. (b) (4) 95-10, non-GLP). In male C57BL/6n mice, compared to vehicle controls (saline), solriamfetol, at 50 and 100 mg/kg SC, significantly decreased food intake irrespective of the time of the day (in both the dark and light phases) or nutrition status (food deprived or non-deprived), which correlated with decreases in body weights (Study No. (b) (4) 7006, non-GLP). In male and female Wistar rats, a 7-day dietary treatment of solriamfetol at 294 mg/kg/day induced significant decreases in food consumption (4.4 g per day in solriamfetol treated rats compared to 18 g per day in controls) and body weight (50 g body weight loss in solriamfetol treated rats compared to 26 g body weight gain in controls); the decreases in body weight and food consumption recovered during the treatment-free period. Solriamfetol also induced mild stimulation. These effects solriamfetol were similar to amphetamine at 15 mg/kg/day (Study No. 95-4a, non-GLP).

Effects of solriamfetol on behavioral despair (forced swimming tests of solriamfetol in rats and mice

In a forced swimming test in male Wistar rats (Study No. 96-05, non-GLP), a single oral dose of solriamfetol at 4, 15, and 29 mg/kg dose-dependently decreased immobility time with an ED_{50} value of 6.4 mg/kg PO, which corresponded to a plasma level of 0. 553 µg/mL solriamfetol at 1 hour post-dose. In male CD-1 mice (Study No. (b) (4) 95-1, non-GLP), compared to vehicle controls (saline), a single dose of solriamfetol at 8.4, 12.6, and 25 mg/kg PO dose-dependently decreased in the immobility time with an ED_{50} value of 14 mg/kg PO. Greater potency to reduce immobility time was observed when

solriamfetol was administered multiple times at 2.5, 4.2, and 6.7 mg/kg PO (twice a day for 3 days with an additional dose on Day 4), with an ED_{50} value of 4.6 mg/kg. Similar effects of solriamfetol to reduce immobility duration were observed in a separate forced swimming study, with an ED_{50} value of 11.4 mg/kg PO in CD-1 male mice and 6.2 mg/kg PO in male Wistar rats (Study No. (b) (4) 95-2, non-GLP).

It should be noted that the immobility reduction effects of solriamfetol were chiral-specific since the enantiomer had no effects on the duration of immobility in a forced swimming test in male CD-1 mice (Study No. (b) (4) 96-6, non-GLP). Neither solriamfetol nor its enantiomer showed anti-cholinergic effects at doses up to 100 mg/kg PO or neurotoxic effects at doses up to 800 mg/kg PO (Study No. (b) (4) 96-6, non-GLP).

4.4 Other pharmacology studies

In a few rodent models of depression, solriamfetol exhibited anti-depressant activity via a mechanism similar to bupropion (Study Nos. (b) (4) 5550, (b) (4) 95-3, (b) (4) 95-4, (b) (4) 95-5, (b) (4) 96-1, non-GLP). Solriamfetol did not exhibit anxiolytic properties in a shock avoidance test in rats (Study No. (b) (4) 96-2). These studies have limited relevance to the current indication of solriamfetol.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Absorption

Solriamfetol is highly water soluble with a pKa value of 8.5 $\pm$ 0.1; therefore, solriamfetol is expected to be positively charged (a cation base) over the physiological range. In *in vitro* trans-epithelial assays in Caco2 and MDCK cells (Study No. (b) (4) FK5029, non-GLP), solriamfetol exhibited high permeability with an apparent permeability coefficient (P_{app}) value of 39 $X10^{-6}$ and 18 $X10^{-6}$ cm/s in Caco2 and MDCK cells, respectively, similar to theophylline, a high permeability reference compound. The absorptive transport (apical to basolateral) of solriamfetol increased with increasing pH; therefore, changes in H^+-gradient may affect the trans-epithelial transport of solriamfetol. Solriamfetol at concentrations of 5 to 100 µM did not affect the P-gp mediated taxol transport (Study No. (b) (4) FK5029, non-GLP).

The pharmacokinetic profiles of solriamfetol after a single oral or IV dose were investigated in mice, rats, and dogs (Study Nos. (b) (4) 95-06, (b) (4) 96-02, and (b) (4) 96-03, non-GLP). Orally administered solriamfetol exhibited moderate to high oral bioavailability in rats (71.2%) and high bioavailability in mice (101%) and dogs (86.5%) with short T_{max} (0.25 to 1.33 hours) and relatively short half-life ($T_{1/2}$, 0.95 to 4.1 hours). The systemic clearance of solriamfetol was low in dogs and high in mice and rats. The apparent volume of distribution of solriamfetol in animals exceeded total blood volume, indicating extensive tissue distribution beyond the vascular compartment (Table 3). Similar PK parameters of solriamfetol were observed in mass balance studies in rats with no significant sex difference between males and females (Study Nos. 0830XY01-001, non-GLP and 0830XY01-002, GLP).

Table 3: Mean PK Parameters of solriamfetol after a Single Dose in Mice, Rats, and Dogs

Species (sex, n)	Dose (mg/kg)/ Route	C_{max} (µg/mL)	t_{max} (h)	$AUC_{0\text{-}inf}$ (µg•h/mL)	CL [a] (L/h/kg)	V [a] (L/kg)	$t_{1/2}$ (h)	F (%)
Mouse (M, 4)	29 / IV	–	–	8.04	4.36	5.98	0.95	–
Mouse (M, 4)	29 / PO	7.68	0.25	8.14	–	–	0.96	101
Rat (M, 4)	29 / IV	–	–	8.83	3.99	9.35	1.63	–
Rat (M, 4)	29 / PO	4.50	0.25	6.29	–	–	1.94	71.2
Dog (M, 4)	29 / IV	–	–	99.7	0.352	2.08	4.10	–
Dog (M, 4)	29 / PO	11.4	1.33	86.6	–	–	3.80	86.5

[a] CL and V as reported in study reports, which estimated values based on doses calculated using the JZP-110 HCl salt weight.

$AUC_{0\text{-}inf}$=area under the concentration-time curve from time 0 to infinity; CL=systemic clearance; C_{max}=maximum observed plasma concentration; F%=percent bioavailability; M=male; PO=by mouth; $t_{1/2}$=half-life; t_{max}=time of maximum concentration; V=apparent volume of distribution.

The pharmacokinetic profiles of solriamfetol were also evaluated in a preliminary juvenile rat study (PND 28, Study No. (b) (4) 20082733, non-GLP). PK parameters were in general, similar to those in adult rats. No significant difference was observed between males and females. After a single oral dose at 35, 80, and 200 mg/kg, solriamfetol was quickly absorbed with the peak level observed at 0.5 hours post-dose for all groups. The half-life ($T_{1/2}$) ranged from 1.41 to 4.38 hours. C_{max} increased less than dose proportionally whereas the $AUC_{(0\text{-}t)}$ increased slightly greater than dose proportionally.

Distribution

The plasma protein binding of solriamfetol was low in all species tested, with values of ~13% in mouse, rat, and human plasma; and ~ 8% in rabbit and dog plasma. In human plasma, the protein binding of solriamfetol was concentration independent (Study No. (b) (4) 0833XY01-001, non-GLP).

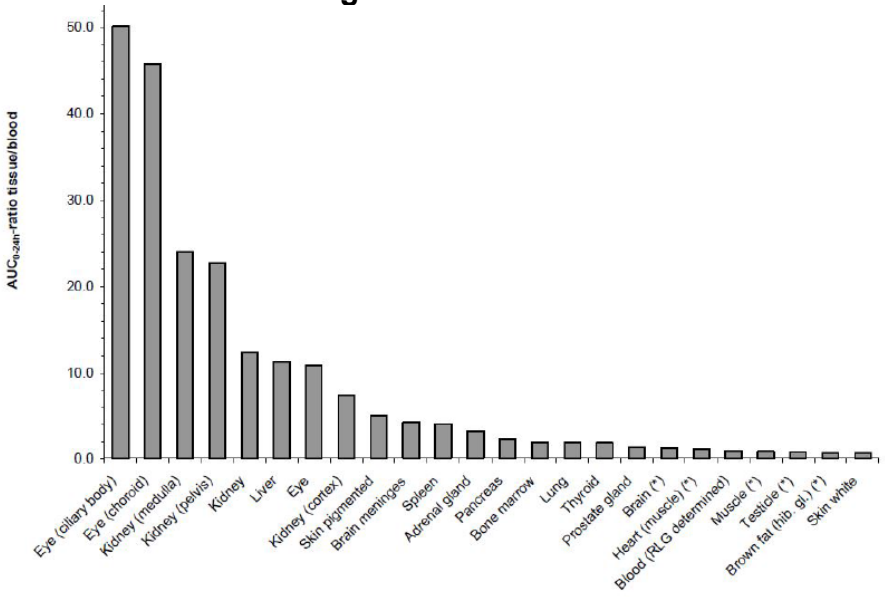
In mass balance studies in Wistar rats (Study Nos. 0830XY01-001 non-GLP and 0830XY01-002, GLP), following both oral and IV administration of ^{14}C-solriamfetol at 35mg/kg, radioactivity was rapidly distributed to the systemic tissues with a T_{max} of 1 hour in most tissues, except cecum and large intestine where the highest concentration was observed at 8 hours post-dose. Measurable levels of radioactivity were observed in most tissues up to 8 hours post-dose, whereas the radioactivity was mostly below the limit of quantitation by 24 hours post-dose. At 72 hours post-dose, the majority of radioactive concentration (~ 84%) was excreted in the urine and a minor fraction (~ 14%) was excreted via feces. Males and females had similar mass balance profiles.

In pigmented male Long-Evans rats (Study No. (b) (4) FK4423, non-GLP), following an oral dose of 100 mg/kg ^{14}C-solriamfetol, tissue distribution was rapid with a T_{max} of 5 hours in the blood, pigmented, and non-pigmented tissues. In general, the highest radioactivity was observed in pigmented tissues, such as the viz, choroid, and ciliary body of the eyes (46 to 50 times the blood level). In non-pigmented tissues, highest radioactivity was observed in the liver and kidney (11 to 12 times the blood level, Figure

1). Radioactive levels in non-pigmented tissues declined at a rate similar to the blood and were mostly below quantification limit by 96 hours post-dose, whereas in pigmented tissues, the radioactive concentration declined at a slower rate with a low but quantifiable level in the choroid and ciliary body of the eye at 14 days post-dose.

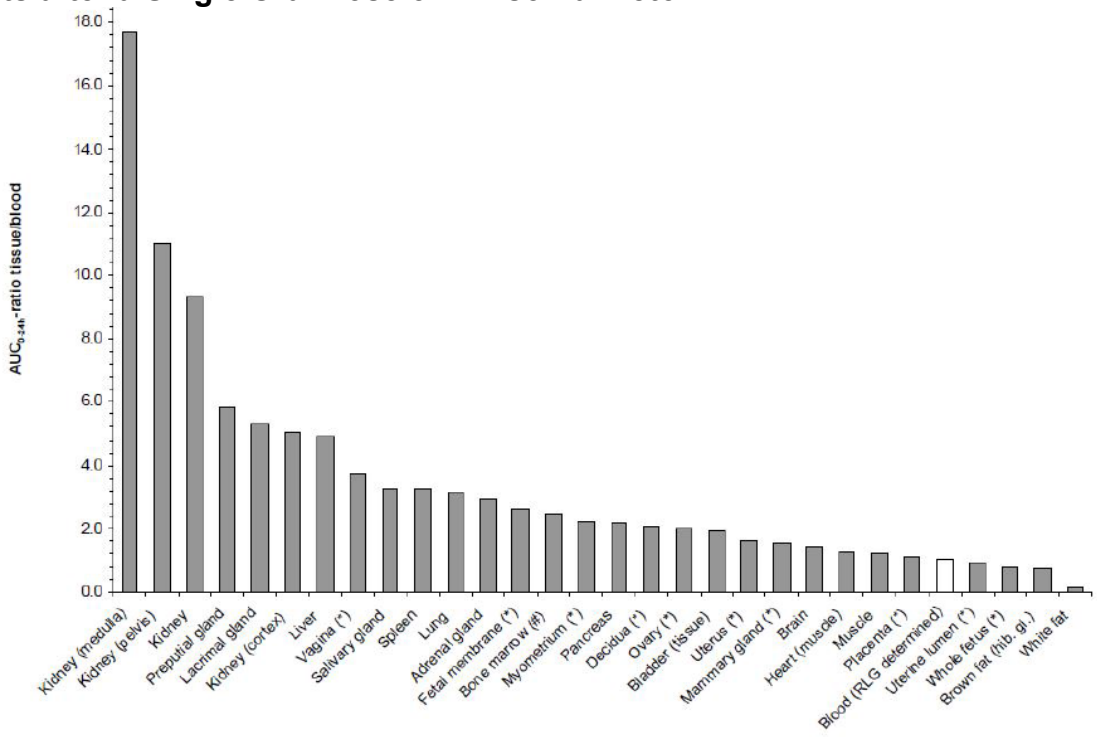
In pregnant SD rats (Study No. (b) (4) FK4424, non-GLP), after an oral dose of 100 mg/kg ^{14}C-solriamfetol, rapid distribution was also observed in both reproductive and non-reproductive tissues and the fetus with a T_{max} of 3 hours post-dose. The total radioactivity in reproductive tissues, non-reproductive tissues, and the fetus paralleled those in the blood and declined rapidly. The 24-hour post-dose level represented only 9% of the 3-hour level. The relative radioactive concentrations in reproductive tissues, non-reproductive tissues, and the fetus are listed in Figure 2. These data indicated a trans-placenta distribution of solriamfetol; however, there was no retention of solriamfetol in the reproductive organs or the fetus in pregnant rats.

Figure 1: Tissue-to-blood AUC_{0-24} Ratios of Total Radioactivity in Male Pigmented Long-Evans Rats after a Single Oral Dose of ^{14}C-solriamfetol



^{14}C-JZP-110 Dose=100 mg /kg.
* Tissue-to-blood ratios based on AUC_{0-5} values.

Figure 2: Tissue-to-Blood AUC_{0-24} Ratios of Total Radioactivity in Pregnant SD Rats after a Single Oral Dose of ^{14}C-solriamfetol



* Typical procreative tissues.
# Tissue-to-blood ratios based on AUC_{0-8} values.
Analytical Method: radioluminography and liquid scintillation counting.
Dose: 100 mg/kg.

The brain distribution of solriamfetol was evaluated in the cortical and striatal brain regions of freely moving, conscious male SD rats (Study No. (b) (4) FK4713, non-GLP). After a single subcutaneous dose of solriamfetol at 10 and 30 mg/kg, solriamfetol was measurable in plasma and the pre-frontal cortex and striatal regions of the brain. The plasma C_{max} of solriamfetol was observed earlier and was 2 to 3 times higher than the C_{max} in the extracellular fluid collected from the prefrontal cortex and striatal regions (Table 4). However, the brain levels of solriamfetol remained relatively constant throughout the 6-hour sampling period (C_{6h} was ≥29% of C_{max}), whereas the plasma concentration declined rapidly after reaching T_{max} (C_{8h} was < 5% of C_{max}), suggesting potentially longer exposure to solriamfetol in the brain than the plasma.

Table 4: Mean Pharmacokinetic Parameters of solriamfetol in the Plasma and Brain in Male SD Rats after a Single Subcutaneous Dose

PK Parameter	Plasma		ECF of Prefrontal Cortex		ECF of Striatum	
Dose (mg/kg)	10	30	10	30	10	30
N	8	12	11	11	11	14
t_{max} (h)	0.31	0.7	0.79	1.9	1.2	2.3
C_{max} (ng/mL)	1240	2700	578	1390	465	1030
AUC (ng•h/mL)	2110	7910	1290	4290	1120	3370

Note: Mean data from male Sprague-Dawley rats.
AUC=area under the concentration-time curve; C_{max}=maximum plasma concentration; ECF=extracellular fluid; N=number of animals/group; t_{max}=time of maximum plasma concentration.

Metabolism and Excretion

In vitro Metabolism Studies

Solriamfetol is not extensively metabolized in hepatocytes or liver preparations (microsomes or liver S9 fractions) derived from the rat, mouse, rabbit, dog, or human (Study Nos. (b) (4) DM99394, (b) (4) FK4422, and (b) (4) FK3675). Only a limited number of metabolites were identified at relatively low levels, particularly in human samples, and no unique human metabolites were identified (Table 5). Solriamfetol was not metabolized in the rat kidney subcellular fractions. The main metabolic pathways of solriamfetol in the liver included aliphatic hydroxylation (M7), aromatic hydroxylation (M5), carbamate hydrolysis (M8), glucuronidation (M1), alcohol oxidation (M4), *N*-acetylation (M11), and glutathione conjugation (M2). However, due to the lack of significant metabolism of solriamfetol in human liver microsomes, the involvement of specific CYP enzymes could not be determined using the common inhibitor experiments. Minimal or no metabolism of solriamfetol was observed in *E.coli* microsomes expressing human CYP enzymes in combination with human reductase (Study No. (b) (4) FK3675).

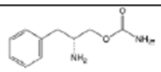
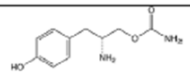
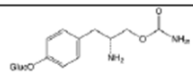
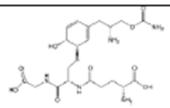
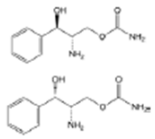
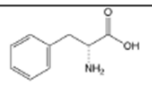
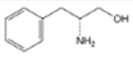
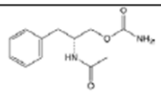
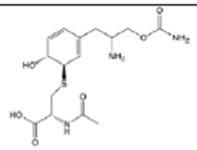
In vivo Metabolism and Excretion Studies

In male and female SD rats (Study Nos. (b) (4) FK4450 and (b) (4) FK4409, non-GLP), after a single oral dose of radiolabeled [^{14}C]-solriamfetol at 100 mg/kg, solriamfetol was metabolized relatively slowly with a limited number of metabolites formed. During the 48-hour post-dose period, the excretion of unchanged drug accounted for 41.2% and 54.1% of the dose in male and female rats, respectively. Unchanged solriamfetol was

mainly excreted via the urine in both sexes, and less than 5% of the unchanged solriamfetol was excreted in feces. The metabolic pathway of solriamfetol was comparable between male and female rats, including aromatic hydroxylation (M5), O-glucuronidation (M1), pre-mercapturic acid formation (M13 and 14) and N-acetylation (M11). The relative abundance of solriamfetol and the metabolites in the plasma, urine, and feces in rats are listed in Table 6. In male beagle dogs (Study No. (b) (4) FK4618, non-GLP), after a single oral dose of radiolabeled [^{14}C]-solriamfetol at 10mg/kg, solriamfetol was largely not metabolized and was mainly excreted as unchanged drug in the urine (70% of the dose). Only 3 minor metabolites were detected in the urine during the 48-hour post-dose period: M5 (para-hydroxy metaboliteM7 (aliphatic hydroxy metabolite), and M3 (unknown). Excretion of radioactivity in feces was low in the dog, accounting for less than 2% of the dose with no metabolites detected (Table 6).

Table 5: Structure and Species Comparison of solriamfetol Metabolite Profile in Liver Preparations

Species	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
$[M+H]^+$	387	518	-	166	211	-	211	152	-	-	237	-
Mouse	√	√			√				√	√	√	√
Rat	√	√	√	√	√		√	√			√	√
Rabbit	√	√	√		√	√	√	√	√	√	√	√
Dog				√	√		√		√	√		√
Human					√			√		√		√

Structures	Code	$[M+H]^+$ (*m/z*)	Description
	JZP-110	195	Parent
	M5	211	p-hydroxy JZP-110
	M1	387	p-hydroxy JZP-110 glucuronide
	M2	518	Preglutathione conjugate of JZP-110
	M7	211	Hydroxy JZP-110
	M4	166	Phenylalanine
	M8	152	Phenylalaninol
	M11	237	*N*-acetyl JZP-110
	M13 and M14	374	Premercapturic acid *S*-conjugate of JZP-110

These *in vivo* metabolism data indicate that after oral administration, solriamfetol undergoes limited metabolism in the dog and is mainly excreted as unchanged drug in the urine, which is similar to the metabolic profile in humans. In contrast, in the rat, hepato-metabolism of solriamfetol was observed to a greater degree (Table 6).

Table 6: In Vivo Metabolite Profile of solriamfetol in Rats and Dogs

Species	Sample	Sampling Time (h)	% Dose	% of Total Radioactivity in Sample							
				Parent	M1	M3	M5	M7	M11 [b]	M13 [b]	M14
Sprague-Dawley Rat	Plasma	1	–	83.5 (M) 94.5 (F)	17.1 (M) 8.6 (F)	ND	ND	ND	ND	ND	ND
		4	–	47.3 (M) 52.1 (F)	45.5 (M) 13.0 (F) [a]	ND	ND	ND	ND	ND	ND
		8	–	31.4 (M) 39.8 (F)	52.9 (M) 3.8 (F) [a]	ND	ND	ND	ND	ND	ND
	Urine	0-48	62.48 (M) 72.02 (F)	36.26 (M) 51.39 (F)	14.67 (M) 12.46 (F)	ND	1.71 (M) 2.36 (F)	ND	ND	0.77 (M) 0.54 (F)	2.93 (M) 3.52 (F)
	Feces	0-48	33.96 (M) 22.42 (F)	4.92 (M) 2.74 (F)	ND	ND	13.53 (M) 10.69 (F)	ND	ND	ND	ND
	Total (Urine + Feces)	0-48	96.44 (M) 94.44 (F)	41.18 (M) 54.13 (F)	14.67 (M) 12.46 (F)	ND	15.24 (M) 13.05 (F)	ND	ND	0.77 (M) 0.54 (F)	2.93 (M) 3.92 (F)
Beagle Dog	Plasma	1	–	69.7	ND	4.1	ND	ND	ND	ND	ND
		4	–	54.8	ND	5.4	1.4	ND	ND	ND	ND
		8	–	53.2	ND	3.4	ND	ND	ND	ND	ND
		24	–	51.3	ND	ND	ND	ND	ND	ND	ND
	Urine	0-48	82.43	70.08	ND	2.82	1.75	0.73	ND	ND	ND
	Feces	0-48	<2	<0.1	NR	NR	NR	NR	NR	NR	NR
Human	Plasma	0-48	–	[c]	ND	ND	ND	ND	ND	ND	ND
	Urine	0-168	96.16	95	ND	ND	ND	ND	0.21 – 0.74	ND	ND
	Feces	0-168	0.19	ND	ND	ND	ND	ND	ND	ND	ND

Note: Values in table represents mean data.
[a] Percentages for M1 in the 4- and 8-hour samples for female rats may be underestimated due to technical problems during HPLC analysis.
[b] Metabolites M11 and M13 could not be detected in rat plasma by radio-HPLC analysis, but were identified by LC-MS/MS.
[c] Unchanged drug accounted for majority of the total radioactivity in human plasma (87%).
F=female; M=male; M1=p-hydroxy JZP-110 glucuronide; M3=unknown (*m/z* 432); M5=p-hydroxy JZP-110; M7=hydroxy JZP-110; M11=*N*-acetyl JZP-110; M13/M14=premercapturic acid *S*-conjugate of JZP-110; ND=not detected; NR=not reported.
Source: (b) (4) FK4450; (b) (4) FK4618; (b) (4) P01-101.

The excretion of solriamfetol in milk was assessed in the pre- and post-natal developmental toxicity studies in the rat (Study No. (b) (4) 20078502, GLP). The study is reviewed in detail under the reproductive toxicity section. Briefly, after oral administration of solriamfetol to pregnant and lactating rats at doses of 35, 110, and 350 mg/kg, solriamfetol was quantifiable in milk samples collected on postpartum Day 15. The mean concentration of solriamfetol in the plasma and milk increased dose proportionally and the milk drug level was higher than the plasma level.

Drug-Drug Interaction

Effects of solriamfetol on Transporters

In *in vitro* cell lines (HEK293, Caco-2, or MDCKII-BCRP) that express various human transporters (namely, P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCTN1, OCTN2, MATE1 and MATE2-K), solriamfetol was evaluated for its potential as an inhibitor or substrate (Study Nos. XT168124, (b) (4) 8304273, and (b) (4) 8335453, non-GLP). Solriamfetol was not a substrate of OAT1, OAT3, OATP1B1, OATP1B3, or MATE2-K and appeared to be a low-affinity and non-selective substrate for multiple renal cation transporters such as OCT2, MATE1, OCTN1, and OCTN2.

At concentrations up to 1000 μM, solriamfetol did not significantly inhibit P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCTN1, or OCTN2. Solriamfetol showed weak inhibition of OCT2 (IC_{50}=146 μM). These data indicate that solriamfetol is unlikely to result in clinically significant drug-drug interactions with substrates for these transporters.

Effects of solriamfetol on CYP Enzymes

In human liver microsomes or primary human hepatocytes (Study Nos, TX165105, FK 4801, (b) (4) 8322976, and (b) (4) 8322977, non-GLP), solriamfetol, at concentrations up to 1000 μM, did not inhibit UGT1A, UGT2B7, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4. Solriamfetol showed weak inhibition against CYP2D6 (IC_{50}=360 μM). Similarly, in "supersomes containing individual human CYP450 enzymes" (Study No. (b) (4) 0796, non-GLP), solriamfetol at concentrations up to 40 μM, did not inhibit CYP1A2, 2C9, 2C19, 2D6, and 3A4 (IC_{50}> 40 μM). Given that the plasma C_{max} level after oral administration of solriamfetol to humans at 300 mg/day is approximately 7.6 μM (1482 ng/mL), the clinical relevance of the weak inhibition of solriamfetol against CYP2D6 appears limited.

As part of the 6-month repeat dose toxicology study in SD rats (Study No. (b) (4) Tox-5705, GLP), the impacts of chronic administration of solriamfetol on liver CYP enzyme induction were investigated (Study No. (b) (4) FK4915, GLP). After 6 months of solriamfetol oral administration at 0 (vehicle control, water), 29 (LD), 253 (MD), and 505/379 (HD) mg/kg/day, female rats had dose-dependent increases in microsomal CYP3A-depdent testosterone 6β-hydroxylase activity (↑38%, 88%, and 125% relative to controls in LD, MD, and HD, respectively) and small increase in microsomal 7 -pentoxyresorufin O-dependentylase (↑33% to 46%), 4-nitrophenol hydroxylase (↑39% to 54%), and lauric acid 11-hydroxylase (↑33% to 51%) activities in HD. In male rats, minimal drug effects on hepatic microsomal CYP enzymes were observed. Solriamfetol had minimal effects on CYP4A-dependent lauric acid 12-hydroxylase or thyroxine UDP-glucuronosyltransferase activity, suggesting that solriamfetol is unlikely to induce peroxisome proliferation or thyroid stimulation in rats. At after 3 months of recovery, no toxicologically significant changes in CYP enzyme were observed in male or female rats.

Collectively, these data indicate that solriamfetol is a weak inducer of hepatic CYP3A enzymes in female rats and may weakly induce CYP2B and possibly other CYP subfamily forms in female rats but has little-to-no effects in male rats. The hepatic induction effects of solriamfetol in rats are reversible.

5.2 Toxicokinetics

Toxicokinetic studies conducted with the general toxicology, carcinogenicity, reproductive and developmental toxicology studies are reviewed in the corresponding toxicology study section.

6 General Toxicology

6.1 Single-Dose Toxicity

Single oral and IV non-GLP dose studies were conducted in mice (CD-1), rats (Wistar) and dogs (Beagle).

Mice (8/sex/group) were orally dosed at 0 (vehicle control, saline), 504, 1260/1008 (M/F), and 1765/1680 (M/F) mg/kg; and additional groups of male mice (8/group), received IV injection of solriamfetol at 0 (vehicle control, saline), 25, 84, and 109 mg/kg. Mice were monitored over 14 days post-dose. Mortality occurred in males dosed at ≥ 1260 mg/kg PO and at 109 mg/kg IV. Drug-related clinical signs of hyperactivity, exophthalmos, tremor, prostration, dyspnea, and convulsions were observed in both sexes at all oral doses, and in males injected IV at ≥ 84 mg/kg. Gross pathology findings included surface vascularization of the stomach in females at ≥ 1008 mg/kg PO; kidney discoloration in males at all PO and IV doses; and enlarged gelatinous pancreas, small heart, and lung discoloration in males at 109 mg/kg IV. Histopathology was not done. The minimal lethal doses in mice were 1500 mg/kg PO and 130 mg/kg IV.

Rats (5/sex/group) were orally dosed solriamfetol at 0 (vehicle control, saline), 630, and 1260 mg/kg. An additional 5/sex/group were injected IV with solriamfetol at 0 (vehicle control, saline), 42, and 84 mg/kg. All animals were monitored over 13 days post-dose. The drug was well tolerated with no mortality or serious clinical signs at doses up to the highest dose of 1260mg/kg PO and 84 mg/kg IV. Only mild stimulatory behaviors were observed at all doses via both routes of administration, and gradually diminished afterwards.

Dogs (beagle, 1/sex) received sequential oral administration of solriamfetol at 59, 118, and 176 mg/kg on Days 0, 1, and 4. At 118 mg/kg, mydriasis, restlessness, panting and/or slight to marked elevation of body temperature were observed by 30 minutes post-dose and continued for over 12 hours. At 176 mg/kg, the severity of drug-related clinical signs increased. Both dogs had significant increases in the body temperature, 107.9 ^{o}C (M) and 104^{o}C (F) relative to the control and were consequently sacrificed. Minimal drug-related effects were observed at 59 mg/kg PO whereas 176 mg/kg PO exceeded the MTD.

6.2 Repeat-Dose Toxicity

6.2.1 Repeat Dose Studies in the Rat

6.2.1.1 6-month repeated dose oral toxicity study with 3-month recovery in the rat.

Study no.:	(b) (4) TOX5705
Study report location:	EDR, SDN-1, 12/20/2017
Conducting laboratory and location:	(b) (4)
Date of study initiation:	03/11/2003
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	solriamfetol, Z (b) (4) PFA051, ≥ 99.9%

Key Study Findings

- Solriamfetol caused pharmacology-related and dose-dependent increases in excitatory neurobehaviors at all doses. The severity of hyperactivity, tremors, and ataxia in MD and HD indicated adversity; HD had clonic convulsions, self-injury, and premature deaths.
- Solriamfetol caused dose-dependent decreases in body weight and body weight gain in MD and HD with correlative decreases in food consumption.
- Solriamfetol caused histopathology changes in multiple tissues/organs in MD and HD, including the adrenal gland, liver, lung, kidney, ovary, bone marrow, pancreas, thymus, adipose tissue, and skin. In the *adrenals, kidneys, liver, lungs, and skin,* the histopathology changes correlated with organ weight changes and/or gross pathology findings.
- Drug-related histopathology findings in the adrenal gland (swelling of the adrenal zona fasciculata cells) and lung (foamy macrophages and multi-focal alveolitis with the presence of fibrinous material within alveoli and bronchi) only partially reversed at the end of the recovery period.
- Females have higher drug exposure than males, with a female-to-male AUC ratio of 1.5, which may have contributed to the higher sensitivity of females to drug treatment.
- Given the limited and reversible effects in LD, 29 mg/kg/day is considered to be the NOAEL. The corresponding exposure levels after 6 months of treatment are 2277 and 2457 ng/mL for C_{max} and 6660 and 8691 h*ng/mL for $AUC_{0\text{-}24h}$ in males and females, respectively.

Methods

Doses:	0 (control), 29 (LD), 253 (MD), and 505/379 (HD) mg/kg/day
Frequency of dosing:	once daily
Route of administration:	oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	demineralized H_2O
Species/Strain:	Sprague Dawley rats (SPF Crl:CD) from (b) (4)
Number/Sex/Group:	n=20/sex/group and an extra n=10/sex for control and HD recovery groups
Age:	approximately 6 weeks old at treatment initiation
Weight:	approximately ~ 190 g for males and 160 g for females at treatment initiation
Satellite groups:	n=6/sex in the LD, MD, and HD groups for TK analysis
Unique study design:	None
Deviation from study protocol:	none that significantly impacted the interpretation of the study data

Observations and Results

Mortality: No drug-related mortality occurred in LD or MD in the main study; no mortality occurred during the recovery period.

Drug-related mortality in HD animals: During the dosing period, multiple drug-related premature deaths occurred in both sexes in the HD/505mg/kg/day group in the main study: 1/30 M and 7/30 Fs. Because of the high mortality, the HD dose was reduced to 379 mg/kg/day; however, mortality continued to occur after dose reduction in 1/29 M and 2/23 Fs. Many of the premature death animals, particularly the HDFs, exhibited clinical signs of severe excitatory behaviors, which subsequently led to injuries such as femur fraction, blood loss from oral cavity, nose bleeds, missing toes. Drug-related severe excitatory behaviors and self-mutilation in rodents have been reported with stimulants, such as amphetamine[3,4]. Given the stimulant-like excitatory pharmacology of solriamfetol as evidenced by the drug-related clinical signs, I consider the premature deaths to be drug-related.

In post-mortem necropsy, 4 HDFs (Nos. 291, 292, 301, and 306) had hepatocyte necrosis; 3 HDFs (Nos. 298, 306, and 317) had vacuolation in the cerebral cortex with perivascular edema and presence of shrunken, dark staining neurons in the

[3] Self-injurious behavior vs. nonsuicidal self-injury: the CNS stimulant pemoline as a model of self-destructive behavior. Bloom CM, Holly S, Miller Am. Crisis. 2012 Jan 1;33(2):106-12. doi: 10.1027/0227-5910/a000127.

[4] Self-mutilation and severe self-injurious behavior associated with amphetamine psychosis. Kratofil PH, Baberq HT, and Dimsdale JE. Gen Hosp Psychiatry. 1996 Mar;18(2):117-20.

hippocampus. These findings could be drug-related; however, the post-mortem or moribund condition could have confounded the evaluation.

In the TK animals, mortality occurred in 2 HDMs and 2 HDFs. These animals had similar drug-related clinical signs and the mortality is considered to be drug-related.

Incidental mortality: In the main study, incidental premature deaths occurred in 3 control males (Nos. 5 and 27, gavage error; and No. 18, lymphoid leukemia), 2 control females (Nos. 204 and 219, trauma and hemorrhages caused by blood sampling), 1 LD male (No. 42, fibrosarcoma on the thorax), and 1 HD male (No 108, gavage error). In the TK animals, incidental premature death occurred in 1 LD male.

All animals were monitored daily for mortality and clinical signs. In addition, during the first month of dosing, on Days 0, 1, 8, 15, 22, and 29 and then once monthly on Days 58, 90, 113, 142, and 171, time-related clinical observations were conducted in all main study animals at pre-dose (-1 hour), and at 0, 1, 2, 4, 6, and 24 hours post-dose.

Clinical Signs

Treatment of solriamfetol induced multiple CNS clinical signs, including agitation, excitation, and salivation at all doses; hyperactivity, tremors, and ataxia in MD and HD; and clonic convulsions in HD. In general, the incidence (number of observations and number of animals affected), severity, and duration of these clinical signs increased dose-dependently (Table 7). These clinical signs are likely due to the norepinephrine and dopamine reuptake inhibitor pharmacology of solriamfetol.

Other drug-related clinical signs included alopecia, skin irritation, tail irritation, lacrimation, wet urogenital region, chromodacryorrhea, nose bleeding and red stained nares, blood loss from the oral cavity, crusty nose (correlated with nose bleeding), piloerection, exophthalmia, and general poor condition (thin appearance, rough haircoat, hypopnea, and hypothermia, Table 7).

The clinical signs observed in LD animals were generally mild, affected a small number of animals, lasted a few hours, and are likely to be non-adverse. In comparison, in MD and HD animals, drug-induced CNS signs (hyperactivity, tremors, ataxia, and/or convulsion) occurred more frequently, lasted longer, and had greater severity, and therefore are considered adverse.

Table 7: Solriamfetol-related Clinical Signs in the 6-month Rat Repeat Dose Study

Daily Dose (mg/kg/d): [a]	0 (Control)		29		253		505/379	
Toxicity Phase (No. of Animals)	M: 30	F: 30	M:20	F: 20	M: 20	F: 20	M: 30	F: 30
Clinical Observations								
Bad condition	1	0	1	0	0	0	1	3
Hypothermia	0	0	0	0	0	0	1	0
Alopecia	5	2	4	1	10 *	8 **	27***	19 ***
Rough hair coat	0	0	3	1	1	0	3	0
Skin irritation	0	1	2	0	6 **	3	10 ***	6
Tail irritation	0	0	0	0	3	1	7 *	7 *
Piloerection	1	0	0	0	1	0	3	4
Chromodacryorrhea	5	2	0	3	5	9 **	14 *	7
Red stained external nares	0	0	0	0	0	0	2	1
Crusty nose	1	0	2	0	0	4 *	7	3
Waste of water	1	0	4	7 ***	13 ***	19 ***	27 ***	30 ***
Wet urogenital region	0	0	1	1	1	18 ***	11 ***	25 ***
Agitation	0	1	2	8 **	20 ***	20 ***	30 ***	30 ***
Spastic	0	0	0	0	0	0	2	2
Tremors	0	0	0	0	0	4 *	15 ***	19 ***
Hyperactive	1	0	0	0	14 ***	19 ***	27 ***	30 ***
Salivation	0	0	8 ***	4 *	11 ***	15 ***	26 ***	22 ***
Athetoid movements	0	0	0	0	0	0	1	2
Lacrimation	0	0	0	0	2	5 **	6 *	6 *
Convulsions, clonic	0	0	0	0	0	0	6 *	8 **
Hyperreactive to noise	0	0	0	0	0	2	4	3
Hyperreactive to touch	0	0	2	0	1	7 ***	7	5
Nose blood	0	0	2	0	1	5 **	2	4
Biting (out of normal)	0	0	0	0	0	0	0	1
Pedaling movements	0	0	0	0	0	0	0	4
Blood loss from oral cavity	0	0	0	0	0	0	0	1
Thin animal	0	0	0	0	0	0	0	5
Exophthalmia	0	0	0	0	0	1	0	4
Hypopnea	0	0	0	0	0	0	0	1

* p <.05 ** p <.01 *** p <.001; (–)=no noteworthy findings; (†)=number examined; NA=not applicable; NOAEL=no-observed-adverse-effect level.

[a] JZP-110 doses in the legacy study report were calculated and expressed based on the weight of the HCL salt.

* p <.05 ** p <.01 *** p <.001; (–)=no noteworthy findings; (†)=number examined; NA=not applicable; NOAEL=no-observed-adverse-effect level.

[a] JZP-110 doses in the legacy study report were calculated and expressed based on the weight of the HCL salt.

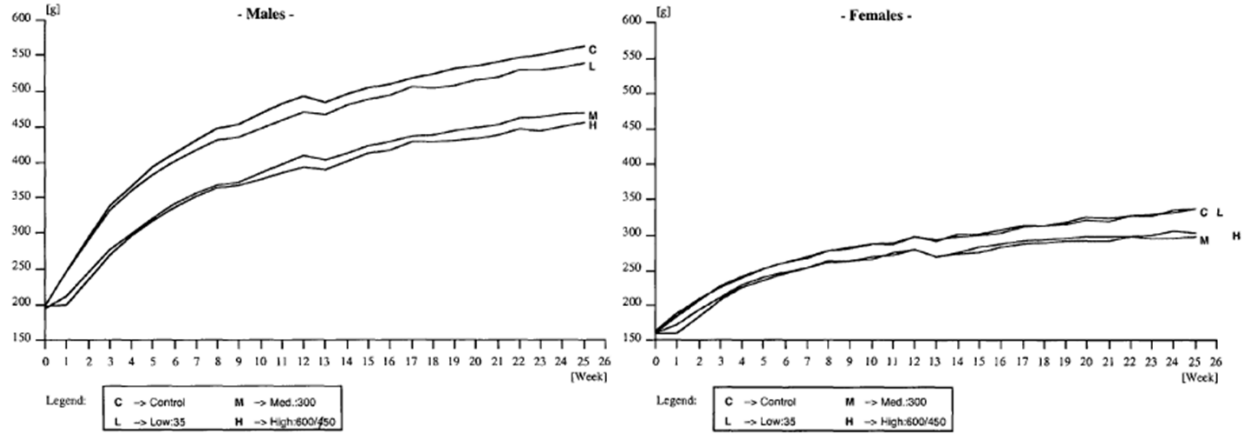
During the recovery period, most of the drug-related clinical signs were not observed. However, excitation persisted in 1/9 HDM up to the 5th day of recovery and occasional alopecia was observed in 7/9 HDMs and 4/8 HDFs up to the end of recovery period.

Body Weights

Solriamfetol caused dose-dependent decreases in body weight (Figure 3) and body weight gain (Figure 4), particularly in MD and HD. At the end of the treatment period, body weight gain was decreased up to 32% and 21% in HDMs and HDFs, respectively. The decreases in body weight and body weight gain correlated with decreases in food consumption that occurred during the early weeks of the treatment period (first 12 and 4 weeks for males and females, respectively).

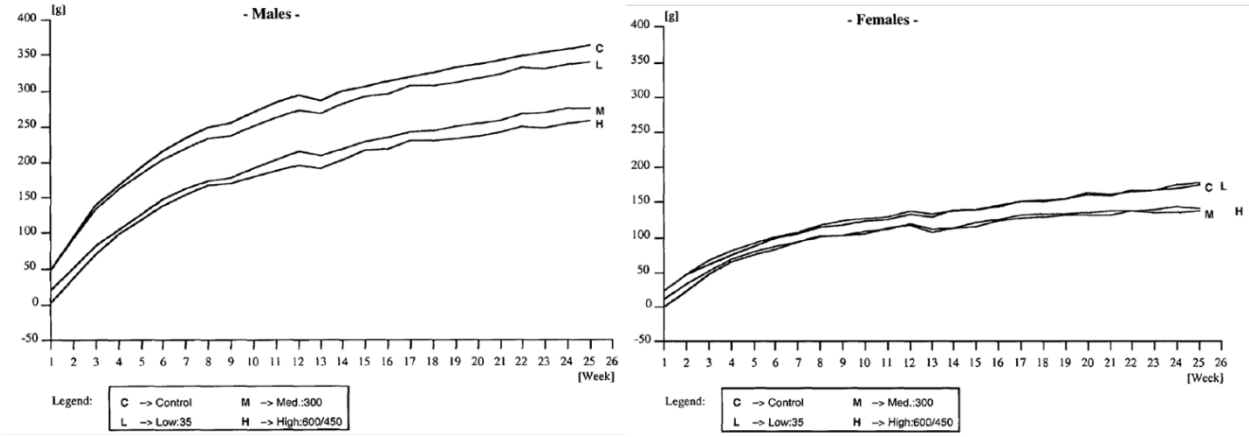
Decreases in body weight and body weight gain are likely associated with drug-induced neurobehavioral changes (hyperactivity, agitation, etc.). It should be noted that decreases in body weight and body weight gain have been reported with stimulants in rodents, such as amphetamine.

Figure 3: Solriamfetol-related Decreases in Body Weight in the 6-month Repeat Dose Rat Study



[Doses in the table are presented as the hydrochloride salt weight; the free base equivalent doses are 0, 29, 253, 505/379 mg/kg/day]

Figure 4: Solriamfetol-related Decreases in Body Weight Gain in the 6-month Repeat Dose Rat Study



[Doses in the table are presented as the hydrochloride salt weight; the free base equivalent doses are 0, 29, 253, 505/379 mg/kg/day]

During the recovery period, decreases in body weight gain partially recovered in males and almost completely recovered in females.

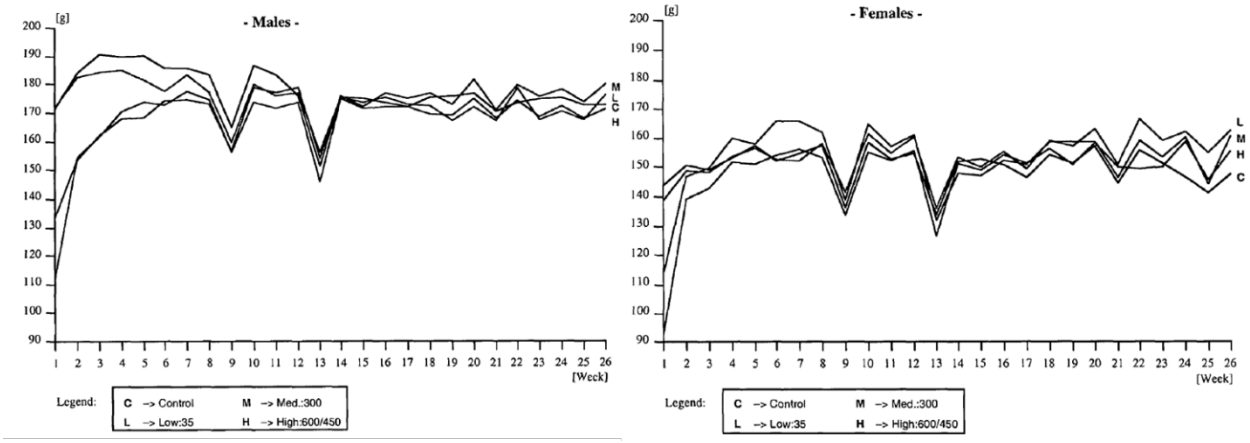
Body weights were recorded from all animals at weekly intervals.

Food Consumption

Solriamfetol induced dose-dependent decreases in food consumption during the first 12 and 4 weeks of treatment in males and females (Figure 5). Decreases in food consumption correlated with decreases in body weight and body weight gain.

No significant change in food consumption was observed during the recovery period.

Figure 5: Solriamfetol-related Decreases in Food Consumption in the 6-month Repeat Dose Rat Study



[Doses in the table are presented as the hydrochloride salt weight; the free base equivalent doses are 0, 29, 253, 505/379 mg/kg/day]

Food consumption was recorded for all main study animals at weekly intervals.

Ophthalmoscopy
There was no drug-related ophthalmic change during the dosing or recovery period

Ophthalmoscopy was performed on the last 10 animals of each sex in the control and HD groups at the beginning (Day -1) and towards the end of dosing (Day 181) and recovery (Day 272) period.

ECG
Not performed

Hematology
Most of the drug-related changes in hematology and coagulation were mild with full recovery at the end of the recovery period, therefore, these changes are not considered to be adverse. At the terminal necropsy (Week 26), compared to the controls, MD and HD had slight increases in red blood cell content (↑4% to 7%, in hemoglobin, hematocrit, and in some occasions, red blood cell numbers); slight to moderate increases in white blood cell numbers (↑13% to 120%) without relative changes in the subpopulations; and slight decreases in coagulation parameters (↓7% to 17%, Table 8). Comparable changes in the same parameters were also observed at earlier time points during the study (Weeks 9 and 13).

At the recovery necropsy, no changes in hematology and coagulation parameters were observed, indicating full recovery.

Table 8: Solriamfetol-related Changes in Hematology and Coagulation in the 6-month Rat Repeat Dose Study

Daily Dose (mg/kg/d): [a]	0 (Control)		29		253		505/379	
Toxicity Phase (No. of Animals)	**M: 30**	**F: 30**	**M:20**	**F: 20**	**M: 20**	**F: 20**	**M: 30**	**F: 30**
Hematology – Week 26								
Act part. thromb time (sec)	22.18	–	–	–	0.920 *	–	0.829 ***	–
Prothrombin time (sec)	17.07	–	–	–	0.906 *	–	0.857 ***	–
WBC (10^3/ µL)	9.4	4.6	–	–	1.160 **	1.717 ***	1.234 ***	1.826 ***
RBC (10^6/ µL)	–	8.27	–	–	–	1.044 **	–	1.074 ***
Hemoglobin (g/dL)	–	15.1	–	–	–	1.046 ***	–	1.073 ***
Hematocrit (%)	–	44.7	–	–	–	1.047 ***	–	1.069 ***
Neutrophils (10^3/ µL)	1.65	1.16	–	–	1.364 *	–	1.321 ***	1.681 ***
Lymphocytes (10^3/ µL)	7.07	3.11	–	–	1.129 *	1.868 ***	1.235 **	1.852 ***
Monocytes (10^3/ µL)	–	0.20	–	–	–	2.000 ***	–	2.200 ***
Eosinophils (10^3/ µL)	–	0.15	–	–	–	–	–	1.267 *
Basophils (10^3/ µL) [d]	–	0.00	–	–	–	0.01 ***	–	0.01 ***

[Group mean values are presented for controls; for treated groups, multiples of controls/baselines are presented. Statistical significance is based on actual data; *, p< 0.05; **, p< 0.01; ***, p< 0.001; (-) no significant changes]

An adequate battery of hematology and coagulation parameters was evaluated in blood samples collected in Weeks 9, 13, and on the days of terminal or recovery necropsy.

Clinical Chemistry

At the terminal necropsy, compared to controls, multiple changes in clinical chemistry parameters were observed at all doses, and were more profound in MD and HD (Table 9). These changes included slight to moderate increases in electrolytes (↑2% to 12% in potassium, 2% to 7% in calcium, and 9% to 64% inorganic phosphate); slight decreases in total protein (↓3% to 4%), albumin (↓2% to 6%), glucose (↓15% to 23%), and creatinine (↓9% to 12 %); slight increases in urea nitrogen (↑15% to 19%), total bilirubin (↑18% to 27%), and alkaline phosphatase (↑16% to 74%); and decreases in triglyceride levels (↓50% to 55%). Comparable changes were also observed at earlier time points in Weeks 9 and 13, particularly in Week 13. The decreases in triglycerides could be associated decreases in body weight and body weight gain. Changes in the electrolyte levels could be associated with the adrenergic and excitatory pharmacology of the drug. Other changes in clinical chemistry parameters were of small magnitude with full recovery, and therefore were not considered to be adverse.

At the recovery necropsy, compared to controls decreases in triglyceride persisted in HDMs (↓37%) and, to a smaller magnitude, in HDFs (↓10%); other changes in clinical chemistry parameters fully recovered.

An adequate battery of clinical chemistry parameters was evaluated in blood samples collected in Weeks 9, 13, and on the days of terminal or recovery necropsy.

Table 9: Solriamfetol-related Changes in Clinical Chemistry in the 6-month Rat Repeat Dose Study

Daily Dose (mg/kg/d): [a]	0 (Control)		29		253		505/379	
Toxicity Phase (No. of Animals)	**M: 30**	**F: 30**	**M:20**	**F: 20**	**M: 20**	**F: 20**	**M: 30**	**F: 30**
Serum Chemistry – Week 26								
Potassium (mmol/L)	–	4.1	–	1.073 ***	–	1.122 ***	–	1.122 ***
Calcium (mg/dL)	10.6	10.7	1.019 *	1.056 ***	1.019 *	1.056 ***	1.038 ***	1.065 ***
Inorg. phosphorus (mg/dL)	6.6	4.7	–	1.149 **	1.091 ***	1.447 ***	1.136 ***	1.638 ***
Total protein (g/dL)	–	7.1	–	–	–	0.972 *	–	0.958 **
Albumin (g/dL)	–	4.8	–	–	–	0.979 *	–	0.938 ***
Glucose (mg/dL)	–	106	–	–	–	0.849 **	–	0.774 ***
Triglycerides (mg/dL)	100	–	–	–	0.450 ***	–	0.500 ***	–
Urea nitrogen (mg/dL)	15.1	17.1	–	–	1.172 ***	–	1.146 ***	1.187 **
Creatinine (mg/dL)	–	0.32	–	–	–	0.906 **	–	0.875 ***
Total bilirubin (mg/dL)	0.11	–	–	–	1.182 *	–	1.273 ***	–
Alk. phosphatase (U/L)	65	26	–	–	–	1.308 **	1.169 *	1.731 ***
Aspartate aminotransferase (U/L)	148	138	–	–	1.081	0.754*	0.919	0.804

[Group mean values are presented for controls; for treated groups, multiples of controls/baselines are presented. Statistical significance is based on actual data; *, p< 0.05; **, p< 0.01; ***, p< 0.001; (-) no significant changes]

Urinalysis

Compared to controls, changes in urinary parameters were observed in MD and HD (Table 10), including increases in urinary volume (↑60% to 123%) with correlative slight decreases in specific gravity; slight decreases in pH (↓6% to 12%); slight to moderate decreases in ketones (↓51% to 76%); moderate increases in spermatozoa (↑98% at the terminal necropsy only) and squamous and cylindrical epithelial cell scores (↑140% to 193%); and slight decreases in occult blood, bacteria and triple phosphate crystal scores.

Changes in urinalysis parameters were generally more profound at earlier time point (Week 13) than at the terminal necropsy. Most changes were reversed at the end of the recovery period, except for slightly decreased pH in HDFs (pH 5.9 compared to pH 6.6 in controls), suggesting adaptation with drug treatment and recovery with treatment cessation.

An adequate battery of urinalysis was evaluated in urine samples collected in Week 13 and on the day of terminal or recovery necropsy (prior to necropsy).

Table 10: Solriamfetol-related Changes in Urinalysis Parameters in the 6-month Rat Repeat Dose Study

Daily Dose (mg/kg/d): [a]	0 (Control)		29		253		505/379	
Toxicity Phase (No. of Animals)	M: 30	F: 30	–	–	M: 20	F: 20	M: 30	F: 30
Urinalysis – Week 13:								
pH	7.6	6.6	–	–	0.895 ***	-	0.882 ***	0.955 *
Volume (mL)	13.8	18.8	–	–	1.899 *	1.649 **	2.123 ***	1.596 *
Specific gravity	1.027	1.020	–	–	0.996	0.995*	0.993***	0.996
Ketones	0.93	-	–	–	0.430 **	-	0.258 ***	-
Occult Blood	0.70	-	–	–	-	-	0.043 ***	-
Squamous epithelial cells	0.40	-	–	–	2.375 **	-	2.500 **	-
Cylindrical epithelial cells[b]	0.00	-	–	–	0.35 **	-	0.62 ***	-
Tripel phosphate crystals	2.07	0.87	–	–	0.556 ***	-	0.415 ***	0.195 **
Bacteria	2.3	2.00	–	–	0.579***	0.825*	0.549***	0.61***
Urinalysis – Week 26								
pH	7.3	–	–	–	-	-	0.918 **	-
Volume (mL)	12.2	–	–	–	-	-	1.402 *	-
Ketones	0.92	–	–	–	0.489 *	-	0.239 ***	-
Occult Blood	1.46	-	–	–	0.445 ***	-	0.301 ***	-
Spermatozoa	0.58	NA	–	NA	-	NA	1.983**	NA
Squamous epithelial cells	0.15	-	–	–	-	-	2.933 *	-
Bacteria	1.81	-	–	–	0.718*	-	0.635**	-

Daily Dose (mg/kg/d): [a]	0 (Control)		29		253		505/379	
Toxicity Phase (No. of Animals)	M: 30	F: 30	–	–	M: 20	F: 20	M: 30	F: 30
Urinalysis – Week 26								
pH	7.3	–	–	–	-	-	0.918 **	-
Volume (mL)	12.2	–	–	–	-	-	1.402 *	-
Ketones	0.92	–	–	–	0.489 *	-	0.239 ***	-
Occult Blood	1.46	-	–	–	0.445 ***	-	0.301 ***	-
Spermatozoa	0.58	NA	–	NA	-	NA	1.983**	NA
Squamous epithelial cells	0.15	-	–	–	-	-	2.933 *	-
Bacteria	1.81	-	–	–	0.718*	-	0.635**	-

[Group mean values are presented for controls; for treated groups, multiples of controls/baselines are presented. Statistical significance is based on actual data; *, p< 0.05; **, p< 0.01; ***, p< 0.001; (-) no significant changes]

Gross Pathology

At the terminal necropsy, cachexia (thin appearance), dehydration, rough haircoat, bone fracture, irritated mouth, crusty nose, and subcutaneous bleedings were observed in some of the rats. These were likely secondary to the drug-induced neurobehavioral (hyperactivity) changes and decreases in body weight.

Drug-related and dose-dependent gross pathological changes included pale (1 MDF and 2 HDFs) and swollen adrenal glands (6 HDFs); pale kidney (2 HDFs); more pronounced lobulation in the liver (1 LDF and 3 HDFs); and white stippling of the lungs (3 HDMs and 2 HDFs) and white focus in the lungs (3 LDFs, 1 MDM, 5 MDFs, and 9 HDFs, Table 11). These findings correlated with increased organ weight and histopathology changes in the adrenal gland, liver, kidney, and lung in the drug-treated animals.

In addition, dose-dependent increases in the incidence of skin alopecia were also observed in 1 LDF, 6 MDMs and 6 MDFs, and 13 HDMs and 7 HDFs, which could be due to the stimulant effects of the drug that caused excessive grooming.

At the end of the recovery period, swollen adrenal glands and a white focus in the lung persisted in 1 HDF each. Other gross pathology findings were not observed, suggesting recovery.

Table 11: Solriamfetol-related Gross Pathology Findings in the 6-month Repeat Dose Rat Study

Daily Dose (mg/kg/d): [a]	0 (Control)		29		253		505/379	
Toxicity Phase (No. of Animals)	M: 30	F: 30	–	–	M: 20	F: 20	M: 30	F: 30
Gross Pathology:								
Lungs: focus	0	0	0	3	1	5	0	9 **
Lungs: stippled, white	0	0	0	0	1	2	3	2
Liver: more pronounced lobulation	0	0	0	1	0	0	0	3
Kidneys: pale	0	0	0	0	0	0	0	2
Adrenal glands: pale	0	0	0	0	0	1	0	2
Adrenal glands: swollen	0	0	0	0	0	0	0	6 *
General: cachexia	1	0	1	0	0	1	3	3
Skin: alopecia	2	1	0	1	6	6	13 **	7 *

An adequate gross pathology was performed on all main study animals at terminal or recovery necropsy.

Organ Weights

At the terminal necropsy, compared to controls, increases in the absolute and relative organ weights were observed in the lung in MDFs and HDFs, liver in MDFs and HDFs, kidney in HDFs, adrenal gland in both sexes in MD and HD, ovary in MDFs and HDFs (Table 12). In addition, dose-dependent decreases in the absolute and relative thymus weight were observed in both sexes in MD and HD (Table 12). These changes correlated with gross pathology and/or histopathology findings.

A few other changes of the absolute organ weights were observed; however, these changes were likely secondary to decreased body weight without correlative histopathology or gross pathology findings.

At the recovery necropsy, compared to controls, HDFs still had increased absolute and relative lung weight and decreased absolute and relative adrenal gland weight. HDMs had no significant changes in organ weight relative to controls at the recovery necropsy.

Table 12: Solriamfetol-related Changes in Organ Weights in the 6-month Repeat Dose Rat Study

Daily Dose (mg/kg/day)	0 (control)		29 (LD)		253 (MD)		505/379 (HD)	
	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20	M: 20	F: 20
Body Weight (g)	521	317	514***	318***	440	270	423	272
Lungs (mg)	2230	1585	2097	1508	1976**	1558	1937**	2127
(mg/kg)	4231	5066	4099	4757	4496	5787	4615*	7766
Liver (mg)	13126	8237	12597	8875*	11066**	8571	11039**	8638
(mg/kg)	25608	26030	24568	27907**	25133*	31769***	25909**	31735***
Thymus (mg)	288	290	255	297***	183***	212***	188***	198***
(mg/kg)	553	915	496	927	417***	784**	440**	733**
Adrenals (mg)	58	77	54	79	65**	93***	66*	108***
(mg/kg)	114	248	107	250	149***	347***	160***	396***
Ovary (mg)		119		127		154***		148**
(mg/kg)		376		400		571***		548***

[Organ weight data are presented as absolute (mg) and relative (mg/kg) weight; *, p< 0.05; **, p< 0.01; ***, p<0.001]

An adequate list of organ weights was recorded on all main study animals at terminal or recovery necropsy.

Histopathology

At the terminal necropsy, compared to controls, drug-related histopathology findings were observed in multiple tissues/organs, primarily in MD and HD. Overall, females appeared to be more sensitive to the drug treatment than males, particularly in the HD. This difference could be due to higher exposure to the drug in females than in males. For a complete incidence and severity table of drug-related histopathology findings, see Appendix 12.1. Main drug-related findings are summarized below:

- adrenal gland: Dose-dependent increases in swelling of the zona fasciculata cells in MDFs and HDFs;
- kidney: Dose-dependent increases in swollen and vacuolated tubular cells in the papilla and/or medulla area in both sexes in MD and HD; and hypertrophic cortical tubules in MDFs and HDFs
- liver: Dose-dependent increases in hepatocellular hypertrophy, either localized in midzonal area or with a more diffusive pattern, in MDFs and HDFs;
- lung: Dose-dependent increases in foamy macrophages (usually multifocal) in LDFs, and both sexes in MD and HD; dose-dependent increases in presence of fibrinous material within the alveoli and bronchi in 1 MDF and HDM&Fs; and multi-focal alveolitis with presence of focal granulomatous inflammation or intraveolar giant cells primarily in HDM&Fs;
- skin: Dose-dependent increases in atrophy of the hypodermal adipose tissue in both sexes in MD and HD, and hypotrichosis (abnormal hair loss) in HDFs;
- thymus: dose-dependent increase in thymic involution in MDMs and HDMs;
- bone marrow: more prominent presence of granulocytes/granulopoiesis in the sternal bone marrow in HDFs;

- adipose tissue: slight and moderate atrophy of the hypodermal adipose tissue in both sexes in MD and HD; marginal atrophy of adipose tissue in the mesenterium in MDFs and both sexes in HD; marginal atrophy of adipose tissue and slight fibrosis in the mammary gland in HDFs; and marginally reduced number of adipose cells in the femoral bone marrow in both sexes in MD and HDMs;
- brain (only in pre-mature death animals): multifocal vacuolation of the cerebral cortex and presence of shrunken, dark-staining neurons in the hippocampus in 3 premature deaths animals in the HD group with perivascular edema in 2 of them (note: these histopathology findings may have been confounded by post-mortem conditions, see mortality section for details)
- ovaries: increase in eosinophilic corpora lutea in MDFs and HDFs with slight increases in tertiary follicles in HDFs and slight increases in cystic follicles in MDFs and HDFs;
- spleen: moderate increases in the presence of hemosiderin in MDMs and HDMs;
- Pancreas: marginal presence of halophenomenom in MDFs and HDFs;
- urinary bladder: slight increases in the presence of dilated lumen in HDMs;

Histopathology changes in the adrenal gland, liver, lung, kidney, and skin correlated with changes in organ weights and/or gross pathology findings. In addition, atrophy in adipose tissue was possibly secondary to the decreases in body weight and body weight gain. Dilated lumen in urinary bladder was likely in response to increased urine volume.

At the recovery necropsy, compared to controls, HDFs continued to show swelling of the adrenal zona fasciculata cells and foamy macrophages and multi-focal alveolitis with the presence of fibrinous material within the lung alveoli and bronchi. HDMs continued to show atrophy of the hypodermal adipose tissue. Changes in the lung could be ascribed to phospholipidosis; a follow up electron microscopy exam was done (see below). Other drug-related histopathologic changes in the bone marrow, kidney, liver, ovaries, pancreas, spleen, thymus, and adipose tissues were not observed in HD animals at the end of the recovery period, suggesting recovery in these tissues/organs.

An adequate battery of tissues/organs from the control and high dose animals was evaluated for histopathology. In addition, histopathology evaluation for gross lesions from all animals as well as premature death animals was conducted. No peer review statement was provided in the study report.

Special Evaluation

Prolactin level: Prolactin levels were determined in blood samples collected at the terminal or recovery necropsy. Compared to controls, there were no drug-related changes in prolactin levels at the terminal or recovery necropsy.

Electron microscopic (EM) examination: EM evaluation was performed on kidney, lung, and liver samples (either prepared by 3% glutaraldehyde perfusion or 10% formalin or 3% glutaraldehyde immersion) from the selected control and HD animals.

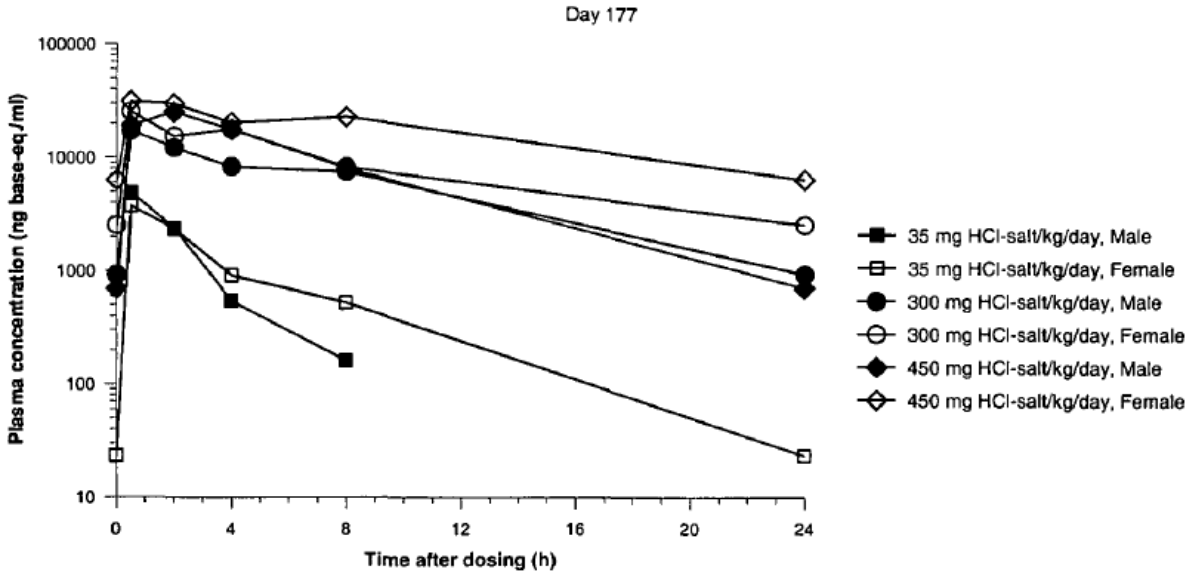
In the kidney samples from HDMs and HDFs, formation of large-sized vacuoles and inclusion bodies in the medullary collecting duct cells of the kidney and an increase in small cytoplasmic inclusion bodies with a crystalloid-like content were observed, which were reversible at the end of the recovery period, suggesting a potential adaptive change in response to increased urine volume. In the lung samples, increases in the number of lamellar inclusion bodies and whorls in type II pneumocytes, alveolar macrophages, and alveolar lumen were observed in 1 HDF, suggesting altered phospholipid turnover (phospholipidosis).

No change in cell ultrastructure was observed in the liver samples.

Toxicokinetics

After oral administration, solriamfetol was absorbed quickly with T_{max} values of 0.5 or 1 hour post-dose. The half-life ($T_{1/2}$) of solriamfetol in LD was about 3 hours. However, after repeat administration of solriamfetol at doses ≥ 253 mg/kg/day, the plasma levels of solriamfetol remained at a plateau level between 2 to 8 hours post-dose, followed by a slow decline between 8 and 24 hours (Figure 6). On Day 177, the $T_{1/2}$ of solriamfetol between 8 and 24 hours post-dose ($T_{1/2, 8\text{-}24h}$) were 5 and 9 hours for males and females at 253 mg/kg/day; and 4.5 and 8.7 hours for males and females at 379 mg/kg/day, respectively.

Figure 6: Mean Plasma solriamfetol Level versus Time on Day 177 in the 6-month Repeat Dose Rat Study



[Doses in the table are presented as the hydrochloride salt weight; the free base equivalent doses for the LD, MD, and HD groups were 29, 253, and 379 mg/kg/day]

The average C_{max} values were comparable between males and females whereas the AUC values were consistently higher in females with a female-to-male AUC ratio of ~ 1.5 (Table 1). In both sexes, the C_{max} increased slightly less than dose proportionally and the AUC increased slightly more than dose proportionally (Table 1).

Compared to the exposure after a single dose on Day 1, repeat administration of solriamfetol led to higher drug exposure (both C_{max} and AUC). The exposure levels on Day 62 were about 2-fold higher than Day 1 whereas no significant difference was observed in drug exposure between Day 62 and Day 177 (Table 13). (Reviewer's note*: the lower AUC values in the high dose group on Day 177 relative to Day 62 was due to dose reduction from 505 to 379 mg/kg/day on Day 93).

Table 13: Mean Toxicokinetic Parameters of solriamfetol in the 6-month Repeat Dose Rat Study

Daily Dose (mg//kg/d): [a]	0 (Control)		29		253		505/379 [g]	
Toxicokinetic Phase (No. of Animals)	M: 0	F: 0	M:6	F: 6	M: 6	F: 6	M: 6	F: 6
Died or sacrificed moribund	–	–	1 [b]	0	0	0	2	2
Day 0								
AUC_{0-24} (ng•h/mL)	–	–	6660	8691	68814	88238	166909	230847
C_{max} (ng/mL)	–	–	2277	2457	10340	9787	14767	18933
Day 62								
AUC_{0-24} (ng•h/mL)	–	–	7518	12560	127708	223286	309788	505827
C_{max} (ng/mL)	–	–	4413	2747	17700	21000	26933	36233
Day 177								
AUC_{0-24} (ng•h/mL)	–	–	10637	13740	127353	195386	176264	393830
C_{max} (ng/mL)	–	–	4870	3723	17100	25200	25000	31100

Limited TK sampling was performed on Day 92, the day before dose reduction from 505 to 379 mg/kg/day in the HD group. Dose reduction led to a proportional reduction in the AUC level of solriamfetol whereas the C_{max} values remained about the same.

Blood samples from TK animals were collected on Days 0, 62, 107 (only for HD animals) and 177 at 0.5, 1, 2, 4, 8, and 24 hours post-dose. In addition, on Day 92 (prior to dose reduction in the HD group), blood samples were collected from HD TK animals at 0 and 0.5 hours post-dose. TK parameters for solriamfetol were analyzed.

Dosing Solution Analysis

The concentration and stability of the dosing formulation were confirmed to be within the acceptable range (85% to 115%).

6.2.1.2 Repeat Dose Studies of Shorter Durations in the Rat

In addition to the 6-month repeat dose rat study, solriamfetol was also tested in repeat dose studies in the rat for shorter durations, including 90-, 28- and 14-day studies. In general, drug-related findings were similar to those observed in the 6-month rat study. Main findings from the individual studies are reviewed and summarized below.

90-Day Repeat Dose (Oral) Study in the Wistar Rat (Study No. [redacted] (b) (4) 0470RY01-001, GLP and Study No. [redacted] (b) (4) 96-07, GLP)

Wistar rats were orally treated with solriamfetol at 0 (vehicle control, saline), 29 (LD), 93 (MD), and 295 (HD) mg/kg/day, (n=20/sex/group). In addition, satellite TK groups (n=39/sex/group for solriamfetol treatment groups and n=12/sex for controls) were included at the same doses.

No mortality occurred in this study. Solriamfetol induced mild to moderate increases in activity, abnormal head movement, and constant searching within the cage in HDM&Fs, likely due to the pharmacology of the drug. Hair loss/alopecia was observed in one MDF and a few HDFs. Dose-dependent increases in the incidence of enlarged fecal pellets were observed in males at all doses and in MDFs and HDFs. Decreases in body weight (↓10%) and body weight gain (↓25% in total weight gain) were observed in HDMs only. Food consumption was initially decreased in HDM&Fs and MDFs but quickly recovered;

Target organs for toxicity included the liver (hypertrophy and increased liver weight in MD and HD), kidneys (tubular cell enlargement with vacuolation and increased kidney weight in HD), and ovaries (prominent corpora lutea and increased ovary weight in HDFs). No drug related effects in LD.

The toxicokinetic profiles of solriamfetol were determined in samples collected on Days 0, 28, and 89 (Table 14). On all three days, solriamfetol was quickly absorbed at all doses with a T_{max} of 0.25 to 2 hours. The AUC values increased close to or slightly more than dose proportionally whereas the C_{max} values increased slightly less than dose proportionally. On Days 0 and 28, females had higher drug exposures (AUC) than males; however, on Day 89 females had lower AUC than males. When dosed at 93 (MD) and 295 (HD) mg/kg/day, the drug exposure levels (AUC) were Day 28 > Day 89 > Day 0 in males and Day 28 > Day 0 > Day 89 in female rats (Table 14).

Table 14: Toxicokinetic Parameters of solriamfetol in the 90-day Repeat Dose (Oral) Rat Study

Male

Dose, mg/kg/day	35			110			350		
Day	0	28	89	0	28	89	0	28	89
N	3	3	3	3	3	3	3	3	3
Tmax, hr	0.25	0.25	0.25	0.25	0.25	0.25	0.25	1.00	1.00
Cmax, µg/mL	2.05	2.01	3.45	4.88	7.74	6.25	10.08	13.30	21.33
$AUC_{0\text{-last}}$, µg•hr/mL	5.99	6.50	7.07	18.50	40.24	34.47	79.63	156.13	131.64
$AUC_{0\text{-}\infty}$, µg•hr/mL	6.17	7.58	7.24	28.24	40.44	35.08	103.82	160.11	136.40
MRT, hr	2.47	3.93	1.99	7.42	4.84	5.43	15.61	6.71	6.19
t1/2, hr	1.60	2.79	1.54	5.20	3.21	4.17	11.80	4.91	5.11

Female

Dose, mg/kg/day	35			110			350		
Day	0	28	89	0	28	89	0	28	89
N	3	3	3	3	3	3	3	3	3
Tmax, hr	0.25	0.25	0.25	0.25	0.25	0.25	0.25	1.00	2.00
Cmax, µg/mL	2.52	2.66	1.39	5.07	7.39	4.73	8.31	20.74	12.88
$AUC_{0\text{-last}}$, µg•hr/mL	6.06	12.39	7.06	35.39	52.59	28.15	107.80	208.82	107.50
$AUC_{0\text{-}\infty}$, µg•hr/mL	6.25	12.98	11.36	35.47	53.27	30.75	210.22	241.94	115.88
MRT, hr	2.27	5.74	8.1	5.23	5.62	8.5	33.23	11.30	7.97
t1/2, hr	1.58	6.24	5.6	2.72	3.98	7.17	23.19	8.42	6.21

[Doses in the table are presented as the hydrochloride salt weight; the free base equivalent doses are 0, 29, 93, and 295 mg/kg/day]

Based on the histopathology and clinical signs the NOAEL is the low dose of 29 mg/kg/day. The corresponding exposure levels after 90 days of treatment are 3450 and 1390 ng/mL for C_{max}, and 7070 and 7060 h*ng/mL for AUC_{0-24h} in males and females, respectively.

Other Repeat Dose Oral Toxicity Studies in the Rat

Other repeat dose oral toxicity studies in the rat are listed in Table 15. Drug-related findings are generally similar to those in the 6-month and 90-day rat studies, including dose-dependent increases in CNS excitatory behaviors and decreases in body weight, body weight gain, and food consumption. Target organs of the drug included the adrenal gland, kidney, liver, skin and/or urinary bladder. In addition, in the 2-week and 14-day studies, the dose of 674/672 mg/kg/day exceeded MTD and caused rapid body weight loss and/or severe CNS clinical signs in the rat.

Table 15: Other Repeat Dose Oral Toxicity Studies in the Rat

Study No	Study Duration	Doses (mg/kg/day)	GLP	NOAEL (mg/kg/day)
(b) (4) 95-4	28-day, Wistar	0, 295	No	Not determined
(b) (4) 5651	2-week, SD	0, 29, 674/505	Yes	29
(b) (4) 95-1	14-day, Wistar	0, 50, 295, 672 (M)/483 (F)	No	50

2-Week Repeat Dose (Intravenous) Study in SD Rats (Study No. (b) (4) Tox-6677, GLP)

In a 2-week repeat dose IV toxicity study, SD rats were treated with IV bolus injections of 0 (vehicle control, saline), and solriamfetol at 29 (LD), 55 (MD), and 84 (HD) mg/kg/day (n=10/sex/group). In addition, satellite TK groups (n=6/sex/group for solriamfetol treatment groups only) were included at the same doses.

No drug-related mortality occurred in this study. Compared to controls, IV administration of solriamfetol induced dose-dependent increases in hyperactivity at all dose levels. Dose-dependent decreases in body weight gain and food consumption was observed in MD (↓26% in body weight gain and ↓10% in food consumption) and HD (↓33% in body weight gain and ↓13% in food consumption) males but not females.

Unlike oral repeat dose studies, IV administration of solriamfetol induced lower urinary volume with correlative higher specific gravity in MDMs and HDMs. Lower urinary pH was observed in both sexes in MD and HD. The cause for the differences in urine volume between IV and oral administration is unclear; but could be due to some liver metabolism of the drug after oral administration in rats. This conclusion could be supported by the studies in the dog where liver metabolism of solriamfetol is limited and no difference was observed on urine volume between IV and oral administrations

Drug-related histopathology findings included dose-dependent increases in hypodermal adipose tissue atrophy in both sexes in MD and HD.

On Day 14, the estimated $T_{1/2}$ ranged from 1.4 to 2.1 hours in males and 1.1 to 1.8 hours in females. The drug exposure increased approximately dose proportionally.

Females had slightly higher exposure levels (AUC) than males, with a female-to-male AUC ratio between 1.06 and 1.35-fold.

Based on the limited findings in the LD group, the NOAEL for this IV study is 29 mg/kg/day. The corresponding exposure levels after 14 days of IV administration are 9820 and 13300 h*ng/mL for $AUC_{0\text{-}24h}$ in males and females, respectively.

6.2.2 Repeat Dose Studies in the Dog

6.2.2.1 52 week oral (gavage) toxicity study in the beagle dog followed by a 13 week treatment-free period.

Study no.:	(b) (4) Tox-5706 and (b) (4) FK4453
Study report location:	EDR, SDN-1, 12/20/2017
Conducting laboratory and location:	(b) (4)
Date of study initiation:	04/23/2003
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Solriamfetol; Z (b) (4) PFA071, 99.4%

Key Study Findings

- Solriamfetol caused pharmacology-related and dose-dependent increases in hyperactivity/agitation, panting, and salivation at all doses. In MD and HD, the severity of drug-related clinical signs indicates adversity.
- Solriamfetol caused dose-dependent decreases in body weight and body weight gain with correlative decreases in food consumption, particularly during the first few weeks of treatment.
- Based on the limited drug effects on clinical signs and body weight in LD, the low dose of 8 mg/kg/day is considered to be the NOAEL. The corresponding exposure levels after 52 weeks of treatment are 1390/1440 ng/mL and 1390/1770 ng/mL for C_{max} and 15100 and 14100 h*ng/mL for $AUC_{0\text{-}24h}$ in males and females, respectively.

Methods

Doses:	0 (control), 8 (LD), 21 (MD), and 42 (HD) mg/kg/day, split into BID doses
Frequency of dosing:	twice daily (at approximately 6 hours apart)
Route of administration:	oral gavage
Dose volume:	2x 5 mL/kg (at approximately 6 hours apart)
Formulation/Vehicle:	demineralized water for injection
Species/Strain:	beagle dogs from (b) (4)
Number/Sex/Group:	4/sex/group for main study and an additional 2/sex for control and high dose groups for the recovery phase
Age:	approximately 5 months of age at treatment initiation
Weight:	M: 6.5 to 8.3 kg; F: 6.0 to 7.6 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None that significantly impacted the interpretation of study data.

Observations and Results

Mortality
There was no mortality in this study.

All animals were monitored for mortality at least twice daily.

Clinical Signs
Solriamfetol induced dose-dependent increases in hyperactivity/agitation, panting, and salivation at all doses. In MD and HD, during the first week of treatment, these clinical signs were sometimes accompanied with unsteady gait, subdued behavior/reduced activity, lying, weakness of hindquarters, crawling, barking, or stereotypical movement.

In addition, thin appearance was observed in a few MD and HD animals, which correlated with decreases in body weight and food consumption.

No drug-related clinical signs were observed during the recovery period.

All animals were monitored for clinical signs daily (at before and after dosing during the dosing period and at least once daily during the recovery period). Detailed clinical examination was performed before treatment initiation and during Weeks 4, 14, 26, 52, and 65.

Body Weights
Compared to controls, during the first 21 days of treatment, dose-dependent body weight loss was observed in MDMs and HDMs and females at all doses, with a mean body weight loss of -4 to -12% in MD and HD. In addition, dose-dependent decreases in

body weight gain were observed at all doses throughout the treatment period (Figure 7), which resulted in decreased mean body weight at all doses (Table 16). The decreases in body weight and body weight gain correlated with decreases in food consumption, particularly during the first week of treatment.

During the recovery period, compared to controls, HDM&Fs had higher body weight gain, suggesting recovery.

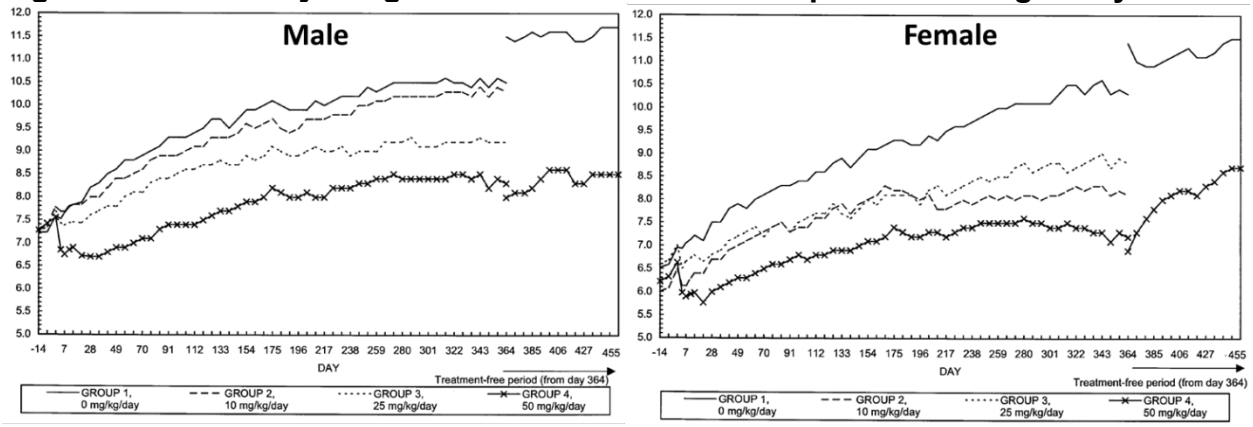
Body weights were recorded weekly during the treatment and recovery periods.

Table 16: Mean Body Weight Change (compared to Day 0), in the 52-week Repeat Dose Dog Study

Group		Day 4	Day 21	Day 182	Day 364	Day 455
Control	males	- 1%	+ 4%	+ 32%	+ 38%	+ 52% (+ 2%)
	females	- 1%	+ 1%	+ 33%	+ 47%	+ 65% (+ 1%)
10 mg/kg bw /day	males	- 1%	0%	+ 22%	+ 32%	/
	females	- 6%	- 2%	+ 26%	+ 25%	/
25 mg/kg bw /day	males	- 4%	- 4%	+ 17%	+ 19%	/
	females	- 7%	- 4%	+ 16%	+ 26%	/
50 mg/kg bw /day	males	- 9%	- 12%	+ 7%	+ 9%	+ 12% (+ 6%)
	females	- 9%	- 12%	+ 11%	+ 9%	+ 26% (+ 26%)

[Doses in the table are presented as the hydrochloride salt weight; the free base equivalent doses are 8, 21, and 42 mg/kg/day for LD, MD, and HD groups, respectively]

Figure 7: Mean Body Weight Curve in the 52-week Repeat Dose Dog Study

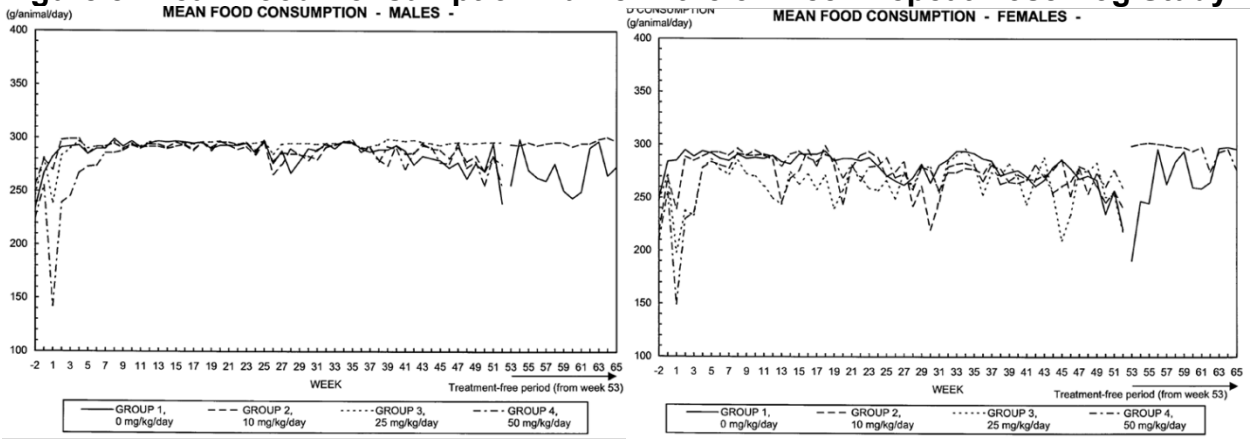


[Doses in the table are presented as the hydrochloride salt weight; the free base equivalent doses are 8, 21, and 42 mg/kg/day for LD, MD, and HD groups, respectively]

Food Consumption

During the first week of treatment, compared to controls, decreases in food consumption were observed at all doses, particularly in MD and HD, which correlated with decreases in body weight gain. Decreases in food consumption gradually recovered during the treatment period, with longer recovery time in higher doses groups (Table 8).

Figure 8: Mean Food Consumption Curve in the 52-week Repeat Dose Dog Study



[Doses in the table are presented as the hydrochloride salt weight; the free base equivalent doses are 8, 21, and 42 mg/kg/day for LD, MD, and HD groups, respectively]

Food consumption was measured daily during the treatment and recovery periods and reported as a weekly mean.

Ophthalmoscopy

There were no drug-related ophthalmic findings. At the end of the treatment period, 2/4 HDFs (Nos. 282, 286) and 1/2 HDF (No. 283) in the recovery group had unilateral focal corneal opacities. The opacity in animal No. 283 reversed at the end of the recovery period. Focal corneal opacity is common in dogs. Given the unilateral appearance and the reversibility of the focal corneal opacity, I consider this finding to be non-adverse.

Ophthalmic evaluation was conducted at pretest and during Weeks 26, 52, and 65.

ECG

Compared to controls and/or pre-test baseline values, there were no drug-related changes in PR, QRS duration, QT intervals, cardiac rhythm, or cardiac wave forms.

A mild increase in heart rate was observed in HDMs (142 beats/min compared to 113 beats/mins at baseline and 118 beats/min in controls) and HDFs (147 beats/min compared to 120 beats/mins at baseline and 128 beats/min in controls) on Day 1. After Day 1, there was a tendency towards slight decreases in the heart rate in MD and HD. Because of the small magnitude with no significant changes in other ECG parameters, these changes in the heart rate are not considered to be adverse.

Electrocardiography was performed at pre-test, before dosing on Day 1, and during Weeks 4, 13, 26, 39, 52, and 65.

Hematology
Compared to controls and/or pre-test baseline values, HDM&Fs had slightly decreased red blood cell counts (↓< 10%). Because of the small magnitude, this decrease is not considered to be adverse. No changes in hematology parameters were observed at the end of the recovery period.

An adequate battery of hematology parameters was evaluated in blood samples collected (under fast condition) at pre-test and during Weeks 4 (Day 23), 13 (Day 84), 26 (Day 179), 39 (Days 268 or 269), 52 (Days 357 or 358) and 65 (Day 451).

Clinical Chemistry
Compared to controls, HDFs had a slight decrease in calcium levels on multiple sampling days (↓~2% to 4% on Days 23, 84, 269, and 358). HDMs also had a similar trend towards slightly decreased calcium levels, but to a lesser degree. At the end of the recovery period, compared to controls, slightly lower calcium concentration was still observed in 1/2 HDM and HDF each. The mild decreases in calcium level in HD were unlikely to be adverse. Other changes in clinical chemistry parameters were of small magnitude or not dose-related, and therefore are considered to be incidental.

An adequate battery of clinical chemistry parameters was evaluated in blood samples collected (under fast condition) at pre-test and during Weeks 4 (Day 23), 13 (Day 84), 26 (Day 179), 39 (Days 268 or 269), 52 (Days 357 or 358) and 65 (Day 451).

Urinalysis
On Day 268, urinary excretion of all ions and creatinine were decreased in males at all doses, mainly due to decreased urine volumes. Dose-dependent decreases in urinary creatinine and creatinine clearance was still present at the end of the treatment period (Day 357, ↓14%, 21%, and 66% in LDMs, MDMs, and HDMs, respectively). Changes in creatinine clearance did not correlate with any gross pathology or histopathology findings in the kidney and there were no changes in serum creatinine level indicative of compromised glomerular filtration; therefore, the toxicological relevance of this finding is unclear. No other drug-related changes were observed in urinalysis parameters during the treatment period. No changes in urinalysis parameters were observed at the end of the recovery period.

An adequate battery of urinalysis parameters was evaluated in urine samples collected from animals in metabolic cages (animals deprived of food and water for approximately 15 hours).

Gross Pathology
At the terminal or recovery necropsy, compared to controls, no drug-related gross pathology findings were observed.

An adequate gross pathology was performed on all main study animals at terminal or recovery necropsy.

Organ Weights
At the terminal necropsy, compared to controls, no drug-related changes in organ weights were observed. A few changes in the absolute organ weights in HD were likely secondary to the decreases in body weights and therefore are not considered to be a direct drug effect.

At the recovery period, compared to controls, the absolute and relative kidney weight was increased in HDMs (↑20% and 59% in absolute and relative kidney weight, respectively). No correlative histopathology changes were observed in the kidney at the recovery period. Given the lack of similar changes at the terminal necropsy and the lack of correlative histopathology changes, I consider the increases in kidney weight to be incidental.

An adequate list of organ weights was recorded on all main study animals at terminal or recovery necropsy.

Histopathology
An adequate battery of tissues/organs was evaluated for histopathology from all animals. Peer review was conducted.

At the terminal necropsy, minimal multifocal bronchiolar/alveolar foamy macrophages in the lungs were observed in 1/4 LDF and 1/4 HDF. Additional electron microscopy examination of that HDF confirmed the presence of increased numbers of macrophages in the alveolar lumens and in the interstitium of the alveolar walls, containing increased amounts of lipid-like inclusion bodies and dispersed nuclear chromatin. No other ultrastructural abnormalities were detected by electron microscopy. The Applicant considered these findings in the lung to be incidental; however, because similar findings of foamy macrophages were also observed in the 6-month rat study, I consider these findings in the lung to be potentially drug-related phospholipidosis. In HDMs, atrophy of the adipose tissue was observed in the mammary gland region. Given the similar observations of adipose tissue atrophy in the 6-month rat study, I consider it to be drug-related. These histopathology changes did not correlate with any functional outcomes, and therefore did not appear to be overtly adverse.

At the recovery necropsy, no drug-related histopathology changes were observed.

Special Evaluation
Electron microscopic examination was conducted to further investigate the histopathology findings of foamy macrophages in the lung tissue in one HD female (See histopathology section above).

Toxicokinetics
On all three sampling days, orally administered solriamfetol was quickly absorbed, with a T_{max} of approximately 2 hours after both the first and the second daily dose. No significant sex difference was observed in drug exposure. Both C_{max} and AUC increased dose proportionally. Repeat dose of solriamfetol did not significantly alter its TK profiles (Table 17).

Table 17: Toxicokinetic Parameters of solriamfetol in the 52-week Repeat Dose Study in Beagle Dogs

TK Parameter	Dose (mg/kg/day)	Day 0		Week 13		Week 52	
		M	F	M	F	M	F
AUC (µg•h/mL)	8	13.8	16.4	14.1	14.0	15.1	14.1
	21	38.5	45.4	35.4	40.3	32.3	44.7
	42	92.5	78.4	67.7	56.6	69.7	63.1
C_{max1}/C_{max2} (µg/mL)	8	1.18/1.39	1.37/1.76	1.07/1.36	1.33/1.26	1.39/1.44	1.39/1.77
	21	2.61/3.98	2.97/4.53	2.99/3.28	3.10/3.69	2.99/3.15	4.08/5.10
	42	5.35/9.31	5.40/8.30	5.42/6.01	4.86/4.63	5.86/7.25	6.18/6.60

C_{max1}=maximum concentration achieved after first daily dose; C_{max2}=maximum concentration achieved after second daily dose.

Toxicokinetic profiles of solriamfetol were analyzed in blood samples collected on Day 0 and during Weeks 13 and 52 at pre-dose, 0.5, 1, 2, 4, 6 (before administration of the 2nd daily dose), 6.5, 8, and 24 hours after the first daily dose.

Dosing Solution Analysis

The concentration and stability of the dosing formulation were confirmed to be within the acceptable range (90% to 110%).

6.2.2.2 Repeat Dose Studies of Shorter Duration in the Dog

Other Repeat Dose Oral Toxicity Studies in the Dog

Other repeat dose oral toxicity studies in the dog are listed in Table 18. Drug-related findings are generally similar to those observed in the 52-week study, including dose-dependent increases in CNS excitatory behaviors and decreases in body weight, body weight gain, and/or food consumption. In the 14-day study, at 59 mg/kg/day, solriamfetol was not tolerated and caused paralysis of the hindlimbs and convulsion in the dog; the 29 mg/kg/day dose also exceeded the MTD due to severe CNS clinical signs in the dog; at 23 mg/kg/day, solriamfetol treatment slightly increased body temperature in dogs (↑0.4 to 0.9 °C relative to controls) during the first week of dosing but gradually diminished throughout the study. In addition, the BID dosing paradigm appeared to reduce the severity of CNS clinical signs, likely due to the reduction in C_{max} levels.

Table 18: Other Repeat Dose Oral Toxicity Studies in the Dog

Study No	Study Duration	Doses (mg/kg/day)	GLP	NOAEL (mg/kg/day)
(b) (4) 96-06	90-day, beagle	0, 8, 15, and 23	Yes	8
(b) (4) 96-04	14-day, beagle	0, 8, 15, 23/29, and 59	No	15
(b) (4) Tox-5704	5-day, beagle	0, 8, 21, and 42 (split into BID)	No	42

(b) (4) Tox-5743	single dose escalation followed by 5-day repeat dose	single dose: 42 and 84; repeat dose: 42 (split into BID)	No	Not determined

2-Week Repeat Dose (Intravenous) Study in beagle dogs (Study No. (b) (4) Tox-6574, GLP)

Beagle dogs were intravenously treated with solriamfetol as a slow bolus injection at 0 (vehicle control, saline), 4 (LD), 8 (MD), and 13 (HD) mg/kg/day (n=3/sex/group).

No mortality occurred in this study. IV injection of solriamfetol induced salivation and agitation in dogs at doses ≥ 8 mg/kg/day. Compared to controls, slight body weight loss was observed in both sexes at all doses (↓0.1 to 0.7 kg and ↓0.3 to 0.7 kg relative to pre-dose baseline in males and females, respectively), which correlated with decreases in food consumption during the first week (↓8-10% and 3- 25% decreases relative to controls in males and females, respectively). Dose-dependent decreases in red blood cell parameters were observed in males at all doses and females at ≥ 8 mg/kg/day. The changes in hematology parameters were of small magnitude, and did not appear to adversely affect the animals' overall health. At the doses ≥ 8 mg/kg/day, decreases in the absolute and relative organ weights were observed in thymus in MD and HD (↓~20%) and spleen in females (↓35% and 20% in MDFs and HDFs, respectively). Drug-related histopathology findings included minimal atrophy in adipose tissues in MD and HD; minimal white pulp atrophy in the spleen in HDFs; and marginal thymic involution/atrophy in MD and HD. No drug-related findings were observed in ophthalmology, ECG, clinical chemistry, urinalysis, or gross pathology evaluations.

After IV administration, plasma levels of solriamfetol declined in a largely monophasic pattern. The exposure levels (AUC and C_0) increased close to dose proportionally with no significant sex differences (Table 19). The volume of distribution at steady state (Vd_{ss}) was 3L/kg, suggesting extensive distribution into the tissues. Solriamfetol is cleared almost completely via renal excretion in dogs; and the clearance rate of 0.5 to 0.6 L/h/kg appeared to be higher than the normal glomerular filtration rate, suggesting potential active secretion.

Table 19: Toxicokinetic Parameters of solriamfetol after IV injection in the 2-week Repeat Dose IV Study in Beagle Dogs

Daily Dose (mg/kg/d): [a]	0 (Control)		4		8		13	
No. of Animals:	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3	M: 3	F: 3
Toxicokinetic Phase								
C_0 (ng/mL)	NA	NA	2020	2000	3870	4180	5520	5900
$AUC_{0\text{-}24h}$ (ng•h/mL)	NA	NA	6800	5510	16500	13300	24200	26800

Based on the limited findings in LD, the NOAEL is 4 mg/kg/day IV. The corresponding exposure levels ($AUC_{0\text{-}24h}$) are 6800 and 5510 h*ng/mL in males and females, respectively.

6.2.3 Repeat Dose Studies in the Mouse

The Applicant also conducted repeat dose studies of solriamfetol in the mouse, including a 3-month repeat dose oral toxicity study (Study No. (b) (4) Tox-6128, GLP) and

a 2-week repeat dose oral toxicity study (Study No. (b) (4) Tox-6052, non-GLP) in the Swiss mouse. These studies were conducted as dose range finding studies for the 2-year mouse carcinogenicity study (Reviewed in Section 8.1). These studies have been reviewed by Dr. Aisar Atrakchi at the time of Carcinogenicity Special Protocol Assessment (SPA) (b) (4). Findings are summarized below.

6.2.3.1 3-month Repeat Dose Oral Toxicity Study in the Swiss Mouse (Study (b) (4) 6128, GLP)

Swiss mice (CD-1) were orally treated with solriamfetol at 0 (vehicle control, demineralized water), 17 (LD), 168 (MD), and 505 (HD) mg/kg/day n=10/sex/group). In addition, satellite TK groups (n=9/sex/group for solriamfetol treatment groups only) were included at the same doses.

Drug-related mortality occurred in 2/10 HDMs in the main study and 2/9 HDMs in the TK study, indicating that 505 mg/kg/day exceeded the MTD. No drug-related mortality was observed at doses up to 505 mg/kg/day in females and 168 mg/kg/day in males. Drug-related clinical signs included dose-dependent increases in agitation in both sexes at all doses and tremors, ataxia, and salivation in HDFs and HDMs. These clinical signs were likely due to the pharmacology of the drug and were no longer present at 24 hours post-dose.

Compared to controls, decreases in body weight gain were initially observed in LD and MD during the first 2-3 weeks of the treatment (↓47% to 76% relative to controls), which gradually recovered afterwards. In HDM&Fs, body weight loss was observed during the first 1-2 weeks of the treatment (↓0.2 to 1.3 g body weight relative to pre-dose baseline). Body weight gain gradually recovered in HDFs whereas HDMs continued to have decreased body weight gain throughout the study (↓51% in HDMs at the terminal necropsy, relative to controls). Decreases in body weight gain in HDMs did not correlate with food consumption; instead, a mild increase was observed (↑24% relative to controls).

There were no drug-related changes in hematology, clinical chemistry, or gross pathology evaluations that are of toxicological significance. Compared to controls, MDMs and HDMs had slight increases in kidney weight (↑12% and 14% in MDMs and HDMs, respectively), which correlated with histopathology findings of multi-focal (≥3 foci) tubular basophilia (1/10 MDM, 3/10 HDMs, and 1/10 HDF) and higher incidence of protein cast in HDMs (7/8 in HDMs compared to 5/10 each in the control, LDMs, and MDMs) and females at all doses (5/10, 6/10, and 6/10 in LDFs, MDFs, and HDFs, respectively, compared to 1/10 in control). Other drug-related histopathology findings included decreased amount of glycogen at all doses and centrilobular hypertrophy in HDM&Fs in the liver; and decreased amount of fat in the panniculus of the skin in MD and HD.

Toxicokinetic analysis was performed on Day 86 (Table 20). Solriamfetol was quickly absorbed with a T_{max} value of 0.25 h in LDM&Fs, MDM&Fs, and HDMs, and ~ 4 hour in HDFs. The exposure levels ($AUC_{0\text{-}24h}$) increased close to dose proportionally whereas the C_{max} value increased less than dose proportionally. No significant sex differences were observed.

Table 20: Toxicokinetic Parameters of solriamfetol on Day 86 in the 3-month Repeat Dose Study in the Swiss Mouse

Day 86							
	Group	Low		Medium		High	
	Dose	20 mg HCl-salt/kg		200 mg HCl-salt/kg		600 mg HCl-salt/kg	
Time (h)	Sex	Male	Female	Male	Female	Male	Female
0.25		3033	3113	11463	13200	27100[1)]	18433
1		*762*	*988*	7227	8083	11167	19067
4		*157*	*61.5*[2)]	*4120*	*4350*	10120	23233
8		<40[1)]	<40	*167*	*982*	3405[1)]	9987
24		<40[1)]	<40	<40	<40	<40	<40[2)]
C_{max}	(ng/ml)	3033	3113	11463	13200	27100	23233
T_{max}	(h)	0.25	0.25	0.25	0.25	0.25	4.0
$t_{1/2}$[3)]	(h)	1.3	0.75	0.86	1.9	-[4)]	-[4)]
AUC_{0-t}[5)]	(ng.h/ml)	2760	2779	29838	36601	73429	142572
AUC_{0-24h}	(ng.h/ml)	3057	2846	30046	39232	-[4)]	-[4)]
Ratios							
C_{max}	female/male		1.0		1.2		0.86
AUC	female/male		0.93		1.3		1.9
C_{max}	vs. lower dose			3.8	4.2	2.4	1.8
AUC[6)]	vs. lower dose			9.8	14	2.5	3.9

1) n=2
2) median value
3) half-life calculated on values in italic
4) - = could not be calculated as extrapolation from data on 4, 8 h to 24 h would result in values higher than the LLOQ
5) where t denotes the time of the last measurable concentration, i.e. 4 or 8 h
6) AUC_{0-24h}-ratio for comparison of the medium *versus* low dosage groups, AUC_{0-8h}-ratio for comparison of the high *versus* medium dosage group

[Doses in the table are presented as the hydrochloride salt weight; the free base equivalent doses are 17, 186, and 505 mg/kg/day, respectively]

Based on the minimal findings in LD, the NOAEL is 17 mg/kg/day. After 86 days of repeat dosing, the corresponding exposure levels at the NOAEL are 3033 and 3113 ng/mL for C_{max} and 3057 and 2846 h*ng/mL for AUC_{0-24h} in males and females, respectively.

6.2.3.2 2-week Repeat Dose Oral Toxicity Study in the Swiss Mouse (Study 6052, non-GLP) (b) (4)

Swiss mice (CD-1) were orally administered with solriamfetol at 0 (vehicle control not specified), 17, 168, 505, or 1010 mg/kg/day (n=5/sex/group).

Mortality occurred in 2/5 males and 1/5 female at 1010 mg/kg/day, with moribund clinical signs of agitation, tremors, ataxia, prostration, ptosis, hypothermia, and/or spastic appearance. No mortality was observed at doses up to 505 mg/kg/day. Drug-related clinical signs included dose-dependent increases in agitation in females at all doses and in males at doses ≥ 505 mg/kg/day; and ataxia and/or tremors in females at ≥ 505 mg/kg/day and males at 1010 mg/kg/day. Compared to controls, initial decreases

in body weight were observed in males and females at doses of 168 and 505 mg/kg/day during the first week of treatment, which recovered during the second week. At 1010 mg/kg/day, both males and females had body weight loss during the study (↓1.2 to 1.8 g relative to pre-dose baseline). Slight decreases in food consumption were observed in males at ≥ 505 mg/kg/day. Food consumption was not affected in females.

No drug-related significant changes were observed in hematology parameters. Slight decreases in triglyceride were observed in males at ≥ 168 mg/kg/day and females at 1010 mg/kg/day. The liver weights were marginally decreased in both sexes at ≥ 168 mg/kg/day (↓~15% relative to controls with no clear dose relationship), which correlated with histopathology findings of a decrease or absence in hydropic appearance in the centrilobular and perilobular region of the liver at the same doses and a marginal increase in the incidence of hepatocellular hypertrophy in males at ≥ 168 mg/kg/day. Thymus weights were slightly decreased in females at ≥ 505 mg/kg/day (↓up to 25% relative to controls) with correlative thymic involution in the females at ≥ 505 mg/kg/day.

6.2.4 Repeat Dose Studies in the Rabbit

In a 7-day repeat dose study (Study No. (b) (4) 0440LY01-001, non-GLP), female New Zealand White rabbits were orally treated with solriamfetol at 0 (vehicle control, saline), 42, 84, 126, 168, and 210 mg/kg/day for 7 days (n=1/group, the control rabbit was dosed for 12 days). (Note*: this study was conducted as a DRF study for the rabbit embryo-fetal development toxicity study)

No mortality occurred in this study. Drug-related clinical signs occurred dose dependently at all doses, including constant movement of the lips, nasal twitching, and hair loss possibly due to excessive grooming. Other drug-related findings included constant chewing and abnormal head movement at ≥ 126 mg/kg/day; thin body condition at ≥ 168 mg/kg/day; and abnormal gait and stance, increased respiratory rate, body tremors, poor grooming and a soiled perianal region at 210 mg/kg/day. These clinical signs are likely due to the stimulant-like pharmacology of the drug.

Body weight loss occurred at doses ≥126 mg/kg/day (-0.2, -0.6, and -0.3 kg for 126, 168, and 210 mg/kg/day dose groups, respectively), which correlated with significant decreases in food consumption. At ≥ 126 mg/kg/day, less than 60 g of food intake was recorded, which is insufficient to maintain the overall health of the rabbit.

Based on the significant reduction in body weight and food consumption, 126 mg/kg/day exceeded the MTD in rabbits.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

7.1.1 *Ames/Salmonella-E. coli* Reverse Mutation Assay on Solriamfetol

Study no.:	(b) (4) 301-YU-001-95
Study report location:	EDR, SDN-1, NDA 211230
Conducting laboratory and location:	(b) (4)
Date of study initiation:	10/03/1995
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	YKP10A (solriamfetol), Lot # WQ-VI-51A, 99.69%

Key Study Findings

Solriamfetol was negative in a valid bacterial Ames assay.

Methods

Strains:	Salmonella typhimurium: TA1535, TA1537, TA98, TA100, and TA102; and E.Coli: $WP2_{uvrA}$
Concentrations in definitive study:	0, 42, 140, 420, 1400, 4200, and 8400 µg/plate
Basis of concentration selection:	Dose selection was based on a preliminary dose range finding study using both the pre-incubation and plate incorporation methods in tester strains TA1537, TA100, and $WP2_{uvrA}$. Solriamfetol was tested for cytotoxicity at the doses of 0(DMSO), 42, 140, 420, 1400, and 4200 µg/plate in the absence of S9. At 4200 µg/plate, solriamfetol induced cytotoxicity in TA100 using the pre-incubation method. No precipitation was observed at concentrations up to 4200 µg/plate.
Negative control:	dimethyl sulfoxide (DMSO), Lot #891856
Positive control:	-S9: sodium azide:10µg/plate for TA 1535 and TA100; 9-aminoacridine: 150 µg/plate for TA1537; 2-nitrofluorene: 5 µg/plate for TA98; mitomycin C: 2.5 µg/plate for TA102; N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) 2.0 µg/plate for $WP2_{uvrA}$. +S9: 2-aminofluorene: 30.0 µg/plate for TA 102; and 2-anthramine: 2.5 µg/plate for TA 1535, TA1537, TA98, TA100, and $WP2_{uvrA}$
Formulation/Vehicle:	DMSO
Incubation & sampling time:	The mutagenicity of solriamfetol was evaluated using both the pre-incubation and plate incorporation methods. The metabolic activation system consisted of a 6% (v/v) S-9 fraction prepared from Aroclor 1254-induced male Sprague-Dawley rat liver.

Study Validity
This study is valid. The tester strains and dose selections are adequate. Positive and negative controls generated expected responses. The S9 concentration is within acceptable range.

Results
Solriamfetol plate was not mutagenic in any of the tester strains in the presence or absence of metabolic activation.

No precipitation was observed at concentrations up to 8400 µg/plate. Solriamfetol was cytotoxic at ≥ 4200 µg/plate in all tester strains with or without S9, except for $WP2_{uvrA}$ with or without S9 under the pre-incubation assay and TA98 with S9 under the plate incorporation condition, for which solriamfetol was not cytotoxic at doses up to 8400 µg/plate.

7.2 *In Vitro* Assays in Mammalian Cells

Study title: Structural Chromosomal Aberration Assay In Human Lymphocytes on YKP10A

Study no.:	(b) (4) 0324FY01-001
Study report location:	EDR, SDN-1, 12/20/2017
Conducting laboratory and location:	(b) (4)
Date of study initiation:	03/19/1997
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	YKP10A (solriamfetol), 671-671-96-001, 99.85%

Key Study Findings
Solriamfetol was not clastogenic in a valid *in vitro* mammalian cell chromosome aberration assay.

Methods

Cell line:	human peripheral blood lymphocytes
Concentrations in definitive study:	Experiment 1: schedule I & II (see below): 420, 2100, and 4200 µg/mL + S9; schedule III: 421, 2100, and 4200 µg/mL - S9; schedule IV, 84, 210, 420, 840, 1680, 2100, and 4210 µg/mL –S9; and schedule V, 84, 210, 420, 840, 1680, 2100, and 4200 µg/mL – S9. Experiment 2: schedule I: 420, 2100, 3150, and 4200 µg/mL + S9; schedule II: 420, 2100, 3150, and 4200 µg/mL + S9; schedule III: 210, 1050, 2100, 2500, and 3150 µg/mL - S9; and schedule IV and V, 42, 84, 210, 420, 840 µg/mL –S9.

Basis of concentration selection:	Dose selection was based on a preliminary dose range finding study, in which 0.14, 0.42, 1.4, 4.2, 14, 42, 140, 420, 1400, and 4200 µg/mL solriamfetol was evaluated for cytotoxicity with or without S9.
Negative control:	di-H_2O
Positive control:	-S9: mitomycin C, 0.25 µg/mL; +S9: cyclophosphamide, 40.0 µg/mL
Formulation/Vehicle:	di-H_2O
Incubation & sampling time:	Schedule I: +S9, 5-hour treatment, 73-hour harvest; Schedule II: + S9, 5-hour treatment, 96-hour harvest; Schedule III: -S9, 5-hour treatment, 73-hour harvest; Schedule IV: -S9, 25-hour treatment, 73-hour harvest; Schedule V: -S9, 48-hour treatment, 96-hour harvest

Study Validity
Given the following evidence, I consider the study to be valid:

Two independent GLP-compliant experiments were conducted. Adequate number of cells was evaluated. The amount of S9 (2%) used in the study was on the low end of the recommended S9 concentration (1-10%). Because limited hepatic metabolism was observed in the dog and human *in vivo,* whereas higher hepatic metabolism was observed in rats, the 2% rat S9 likely provided adequate metabolism to assess the genotoxicity of potential metabolites.

The negative and positive control values were within the expected range of historical controls. The drug solutions did not significantly change the osmolality or the pH at the tested doses (up to 4200 µg/mL).

Results
At 4200 µg/mL, solriamfetol was cytotoxic and induced mitotic index inhibition of 40.9-100% in all five treatment schedules with or without S9.

In experiment 1, compared to the negative controls, solriamfetol did not induce any statistically significant or dose-dependent increase in the proportion of aberrant metaphases and did not induce any polyploidy at the tested doses.

In experiment 2, compared to the negative controls, solriamfetol induced statistically significant increases in the proportion of aberrant metaphases and the frequency of aberrations/cells at 210 µg/mL without S9 (schedules IV and V). However, the values in the treatment group were within historical control range and the statistical significance was mainly due to the low number of concurrent negative controls (0). No polyploidy was observed.

Given the overall negative findings, I conclude that the increases at 210 µg/mL are not biologically relevant and solriamfetol is not clastogenic in the mammalian chromosome aberration assay.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

7.3.1 *In Vivo* Micronucleus Test in Mouse Bone Marrow Erythropoietic Cells on YKP10A

Study no:	(b) (4) 0309FY01-001
Study report location:	EDR, SDN-1, 12/20/2017
Conducting laboratory and location:	(b) (4)
Date of study initiation:	09/22/1997
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	YKP10A (solriamfetol), Lot# 671-671-96-001, 99.85%

Key Study Findings

Solriamfetol did not induce any increase in micronuclei in the bone marrow following intraperitoneal (IP) administration in an *in vivo* mouse micronucleus assay. However, IP is not the clinical route of administration and there was no TK confirmation of drug exposure. The positive control value was lower than the historical values. High dose clearly exceeded the MTD. Therefore, I consider this study to be inadequate. A new in vivo micronucleus study should be performed.

Methods

Doses in definitive study:	0 (control), 50 (LD), 250 (MD), and 500 (HD) mg/kg; sacrifice at 24, 48, and 74 hours after treatment
Frequency of dosing:	a single injection
Route of administration:	intraperitoneal (IP) injection
Dose volume:	10 mL/kg
Formulation/Vehicle:	de-ionized water
Species/Strain:	Crl:CD-1 (ICR)BR mice from (b) (4)
Number/Sex/Group:	n=5/sex/group for control, LD, and MD groups; and n=8/sex for the HD group
Satellite groups:	No
Basis of dose selection:	Dose selection was based on a preliminary dose range finding study. In the DRF study, doses tested were 0, 210, 420, 630, 840, and 1680 mg/kg (n=2/sex/group). Drug-related clinical signs were observed at all doses. Mortality occurred at ≥ 630 mg/kg doses. Therefore, 630 mg/kg exceeded the MTD. No significant bone marrow toxicity was observed in all surviving animals as indexed by polychromatic to normochromatic erythrocytes (PCE/NCE ratio).
Negative control:	deionized water
Positive control:	cyclophosphamide (CP) 60 mg/kg, IP (n=5/sex, sacrificed 24 hours after treatment)

Study Validity

This study is inadequate for the following reasons:

The route of administration (ROA) used (IP) in this study is different from the clinical ROA (oral). There was no TK data to assess drug exposure in the study and none was available from other mouse studies. Mortality occurred at the high dose of 500 mg/kg, which clearly exceeded the MTD and induced some bone marrow toxicity. The CP positive control value (0.49 $\pm$ 0.165) was lower than the historical control value (2.263 $\pm$ 1.301). Values in the negative control group (0 or 0.1) were in the lower end of the historical control range (0.062 to 0.090 $\pm$ 0.09).

Results

In the definitive study, mortality occurred in 6 males and 3 females at 500 mg/kg, indicating that 500 mg/kg exceeded the MTD. Drug-related and dose-dependent clinical signs were observed at doses ≥ 250 mg/kg, including abnormal gait, partially closed eyes, quivering, twitching, and prostration. At 500 mg/kg, some bone marrow toxicity was observed as the PCE/NCE ratio was significantly decreased (1.453 $\pm$ 0.412 compared to 1.829 $\pm$ 0.444 in vehicle controls).

Compared to the vehicle control group, there were no dose-dependent increases in MPCE frequencies in the treatment groups. A few statistically significant increases in

MPCE frequencies were observed in some dose/time/sex groups, including 250 mg/kg at 48 hour time point (combined sex), 50 mg/kg at 72 hour time point (combined sex and females only), and 500 mg/kg at 72 hour time point (combined sex), likely due to the very low value in the concurrent vehicle controls (0).

Because the study was not adequately conducted, data generated from this study may be unreliable. A separate in vivo micronucleus study should be conducted.

7.3.2 *In vivo* micronucleus test on bone marrow cells of mice.

Study no:	(b) (4) TOX-5688
Study report location:	EDR, SDN-1, 12/20/2017
Conducting laboratory and location:	(b) (4)
Date of study initiation:	02/25/2003
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	(b) (4) /solriamfetol, Batch #: Z (b) (4) PFA051, 99.6 %

Key Study Findings

Solriamfetol, when orally administered at doses up to 250 mg/kg, was negative in a valid *in vivo* mouse micronucleus study.

Methods

Doses in definitive study:	0 (vehicle controls), 25 (LD), 84 (MD), and 250 (HD) mg/kg, at 24 and 48 hours after treatment.
Frequency of dosing:	single dose
Route of administration:	oral
Dose volume:	10 mL/kg
Formulation/Vehicle:	demineralized water
Species/Strain:	SPF albino Swiss (CD1) mice, from (b) (4)
Number/Sex/Group:	n=5/sex/group
Satellite groups:	n=6/sex/group (3 animals per time point, pooled)
Basis of dose selection:	Dose selection was based on two DRF studies. In the first DRF study, drug doses tested were 125, 250, 375, and 500 mg/kg. Drug-related clinical signs of hyperactivity were observed at ≥ 375 mg/kg at 6 hours after treatment. Animals were normal at 24 and 48 hours after treatment. In the second DRF study, doses tested were the same as the 1st DRF study. Drug-related hyperactivity occurred at ≥ 250 mg/kg at 6 hours post-dose and was not present at 12 or 24 hours post-dose. A large decrease in body temperature was observed ≥ 375 mg/kg at 3 hours post-dose (body temperature went below 33°C for some animals). The body temperature went back to normal from 6 hours after dosing onwards. Because induction of hypothermia was reported to induce micronuclei, 250 mg/kg, although not reaching the MTD, was selected as the high dose for the definitive study, because
Negative control:	demineralized water
Positive control:	cyclophosphamide (CP), 40 mg/kg

Study Validity

The study is valid. The negative and positive controls generated expected responses and were within the historical range at the test site. Dose selection was valid. Although MTD (defined by systemic toxicity) was not reached, the high dose of 250 mg/kg was properly selected to avoid complications from drug-induced hypothermia (observed in the DRF study at higher doses). Drug exposure was confirmed by the plasma concentration in the satellite TK group.

Results

No drug-related clinical signs were observed in the definitive study. Animals at 250 mg/kg had a slight body weight loss at 24 hours post-dose (-0.1 g compared to pre-treatment baseline, compared to +0.7 g in controls).

No bone marrow toxicity (as indicated by PCE%) was observed at drug doses up to 250 mg/kg. The positive control CP at 40 mg/kg induced statistically significant decreases in bone marrow proliferation (39% compared to 59% in vehicle controls for PCE%).

Drug exposure was confirmed in the TK animals. There was no sex difference in drug exposure. The plasma concentration increased slightly less than dose proportionally at 0.25 hours post-dose and greater than dose proportionally at 4 hours post-dose. At 250 mg/kg, the C_{max} of ~16000 ng/mL was approximately 10 times the human C_{max} at the MRHD of 300 mg.

Drug treatment at doses up to 250 mg/kg did not induce any increase in micronucleated PCEs at both 24 and 48 hours post-dose.

7.4 Other Genetic Toxicity Studies

(b) (4) (b) (4): reverse mutation in five histidine-requiring strains of Salmonella typhimurium.

Study no.:	(b) (4) (b) (4) 5648
Study report location:	EDR, SDN-1, 12/20/2017
Conducting laboratory and location:	(b) (4)
Date of study initiation:	02/10/2013
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	(b) (4) (solriamfetol) (b) (4), batch #: 01F03/F001, 101.6% (however, the lot expired at the time of the study)

Key Study Findings

The tested (b) (4) (solriamfetol) (b) (4) was not mutagenic in a bacterial Ames study. However, the validity of the study may be questionable due to the use of an expired lot of the test compound.

It should be noted that this study was performed in response to a finding of color change in (b) (4) in a clinical study (b) (4). The API (solriamfetol) has been tested to be negative in a separate Ames study (Study (b) (4) 301-YU-001-95). The proposed formulation for the current NDA 211230 is a film-coated immediate-release tablet, which is different from the capsules used in (b) (4). Therefore, findings from the (b) (4) have limited relevance to the current NDA.

Methods

Strains:	Salmonella Typhimurium: TA 98, TA 100, TA 1535, TA1537, and TA 102
Concentrations in definitive study:	0, 1.3, 6.7, 33.6, 168, 840, and 4200 µg/plate for experiment 1; and 66, 131, 263, 525, 1050, 2100, and 4200 for experiment 2.
Basis of concentration selection:	Dose selection was based on a dose range finding study in the TA 100 tester strain. Doses tested in the DRF study were 0, 1.3, 6.7, 33.6, 168, 840, and 4200 µg/plate using the plate incorporation method. No cytotoxicity or precipitation was observed at doses up to 4200 µg/plate.
Negative control:	DMSO
Positive control:	-S9: sodium azide:2 µg/plate for TA 1535 and TA100; 9-aminoacridine: 50 µg/plate for TA1537; 2-nitrofluorene: 5 µg/plate for TA98; glutaraldehyde: 25 µg/plate for TA102 +S9: 2-aminoanthracene: 5.0 µg/plate for TA 100, TA 1535, and TA 1537, and 20.0 µg/plate for TA 102; Benzo[a]pyrene: 10.0 µg/plate for TA 98
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Experiment 1 used the plate incorporation method, and experiment 2 used the pre-incubation method. Both experiments were conducted with and without 10% S-9 (prepared from Aroclor 1254-induced male SD rat liver.

Study Validity

The tester strain and dose selections are adequate. Positive and negative controls produced expected responses. The S9 concentration is within acceptable range. However, this study used an expired lot of the drug produced (expiration date: 01/31/2001 compared to the study initiation date of 02/10/2013). Therefore, the validity of this study may be questionable.

Results

The (b) (4) (solriamfetol) (b) (4) was not mutagenic any of the tester strains in the presence or absence of metabolic activation.

The (b) (4) (solriamfetol) (b) (4) was not cytotoxic and did not precipitate at doses up to 4200 µg/plate.

8 Carcinogenicity

The following final carcinogenicity studies have been reviewed with concurrence from the ECAC. The complete ECAC meeting minutes are attached in section 12.3.

Overall Comments on dose selection and the use of single vehicle group:

Comments on carcinogenicity study dose selection:
In the earlier dose range finding studies for the mouse and rat carcinogenicity study protocols, doses tested were based on the HCl-salt of solriamfetol. Subsequently, the same HCl-salt doses were used in the ECAC meeting minutes for dose recommendation. In the final carcinogenicity studies, the Applicant followed the ECAC recommended doses but used the free base equivalent weight. Therefore, the actual doses used in the carcinogenicity study were slightly higher than the recommended doses with a conversion factor of 1.19. Because the difference is of small magnitude, the actual doses used were slightly higher, and no other issues were identified with the mouse and rat carcinogenicity studies, I consider the doses used to be acceptable for the review.

Comments on the use of a single vehicle control group:
Identical dual vehicle control groups (n=60/group) were originally proposed in the Applicant's mouse and rat carcinogenicity study protocols, which were also recommended in the ECAC meeting minutes (faxed on 08/20/2004). The final study used a single vehicle control group of deionized water (n=76 for vehicle controls) for males and females in the mouse and rat carcinogenicity studies. Because deionized water is a common vehicle and is not expected to generate unexpected vehicle effect, I conclude that this deviation from the ECAC recommendation did not impact the data interpretation of the mouse and rat carcinogenicity studies and is acceptable for the review.

8.1 104-Week Mouse Carcinogenicity Study

Study no.:	(b) (4) 1301-011
Study report location:	EDR, SDN 1, 12/20/2017
Conducting laboratory and location:	(b) (4)
Date of study initiation:	06/02/2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	solriamfetol, Lot 00447457 with a purity of 98.8%; and Lot 1435H007 with a purity of 99.5%
CAC concurrence:	Yes[5]. See appendix for copy of meeting minutes.

[5] There are small deviations in dose selection and the use of single vehicle control group in the final mouse carcinogenicity study. However, these deviations do not impact the validity or adequacy of the carcinogenicity study.

Key Study Findings

- There were no drug-related neoplastic findings following oral daily administration of solriamfetol in male and female CD-1 mice for up to 104 weeks at doses of 20, 65, and 200 mg/kg/day. At 200 mg/kg/day, after 90 days of repeat dosing, the corresponding plasma exposure level (AUC) of solriamfetol was 66400 h*ng/mL, which is approximately 3.5 times the MRHD of 300 mg/day (based on human AUC value of 19070 h*ng/mL).

Adequacy of Carcinogenicity Study

Adequate. Slight deviations in dose selection (due to the weight difference between the salt and free base form) and the use of a single vehicle control group are acceptable. For details, see the overall comments.

Appropriateness of Test Models

The CD-1 mouse is an appropriate species and strain for long-term study with adequate historical control data.

Evaluation of Tumor Findings

An independent statistical review of tumor findings was conducted by Dr. Malick Mbodj from the Division of Biometrics. Dr. Mbodj's conclusion is in agreement with the Applicant's statistical analyses.

Methods

Doses:	0 (control), 20 (LD), 65 (MD), and 200 (HD) mg/kg/day for both males and females; in addition, a dose of 600 mg/kg/day in females was initially included in the study but was terminated following 26 weeks of treatment due to extensive mortality (carcinogenicity was not assessed for this group).
Frequency of dosing:	once daily
Dose volume:	5 mL/kg
Route of administration:	oral gavage
Formulation/Vehicle:	deionized water
Basis of dose selection:	Dose selection was based on a 3-month study in the CD-1 mice. The high dose was based on MTD (in males, mortality occurred at 600 mg/kg/day; and in females, clinical signs of agitation were seen at 200 mg/kg/day and doses in females up to 600 mg/kg/day were tolerated for up to 3 months of dosing). The doses used in the study were recommended by the ECAC.
Species/Strain:	Crl: CD1® (ICR) mice from (b) (4)
Number/Sex/Group:	n=60/sex/group for LD, MD, HD groups; n=76/sex for controls; and n=60 for the 600 mg/kg/day dose in females only.
Age:	~ 7 weeks of age at treatment initiation
Animal housing:	males: individually housed; females: pair housed
Paradigm for dietary restriction:	No dietary restriction; animals had access to diet and tap water *ad libitum*.
Dual control employed:	No
Interim sacrifice:	No; however, the 600 mg/kg/day dose group in females was terminated early after 26 weeks of dosing due to excessive mortality. This group was not evaluated for carcinogenicity.
Satellite groups:	Satellite TK groups were included in the study (n=12/sex/group for treatment groups and n=6/sex for controls). TK animals received the vehicle control or the drug at the same doses as the main study groups. Toxicokinetic assessment of solriamfetol was conducted on Day 90.
Deviation from study protocol:	None that significantly impacted the integrity or interpretation of the study.

Observations and Results

Mortality

Females in the 600 mg/kg/day group had excessive mortality within the first 26 weeks of dosing: 13/60 died within 13 weeks of dosing and an additional 7/60 died during Weeks 13 to 26. Mean body weights in females in this group were frequently decreased by more than 10% relative to vehicle controls and were considered adverse. Due to the excessive death, all surviving females in the 600 mg/kg/day were sacrificed on Day 183. Early termination of this group was performed prior to obtaining the Division's and the ECAC's concurrence but was later considered acceptable[6]. *No carcinogenicity or post-mortem evaluation was performed in this group.*

For all other groups, at the terminal necropsy, the number of surviving mice were 41, 22, 20, and 24 in the vehicle control, LD, MD, and HD groups in males, respectively (Figure 9 and Table 21); and 27, 25, 16, and 20 in the vehicle control, LD, MD, and HD groups in females, respectively (Figure 10 and Table 22). The number of surviving animals at the end of the study was adequate to allow for a statistical evaluation.

Statistical analysis was performed and reviewed by the statistical reviewer (Dr. Malick Mbodj). In the survival analysis, there were no significant increases in mortality across the vehicle control and the LD, MD, or HD groups in either males or females. Pairwise comparison in male mice showed a statistically significant increase in mortality in MD when compared to the vehicle control group (p=0.0087). Given that the difference only occurred in the MD male group with no dose-relationship and the overall non-significant finding in the survival analysis, I conclude that drug treatment at the doses up to 200 mg/kg/day did not increase mortality relative to the vehicle controls in both sexes.

[6] The Applicant terminated all surviving females in the 600 mg/kg/day group following 26 weeks of treatment due to excessive mortality and predicted lack of enough surviving animals at the end of the study. The Applicant did not obtain ECAC's concurrence prior to terminating the 600 mg/kg/day female group; but reported the early termination in the Annual report for IND 107203 (SDN 49, 02/13/2015). On 04/01/2016, the Applicant submitted a request for termination procedure for the rodent carcinogenicity studies (SDN 83, IND 107203) to the Division. In an email communicated to the Applicant on 04/13/2016, the review division (Division of Neurology Products) stated that the Division was in general agreement with the Applicant's criteria for early termination plan but suggested the Applicant to contact the Division for feedback prior to termination of any group or an entire study.

Figure 9: Survival Curve in the Mouse Carcinogenicity Study-Males

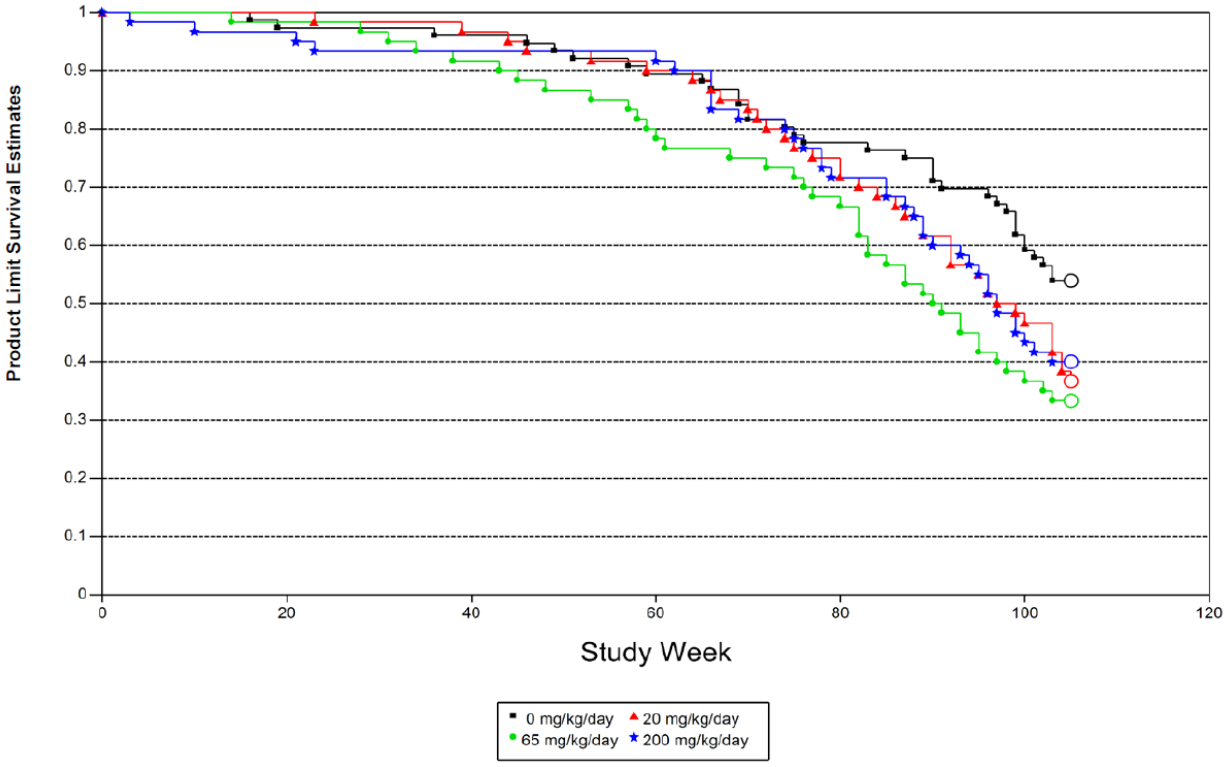


Figure 10: Survival Curve in the 104-Week Mouse Carcinogenicity Study-Females

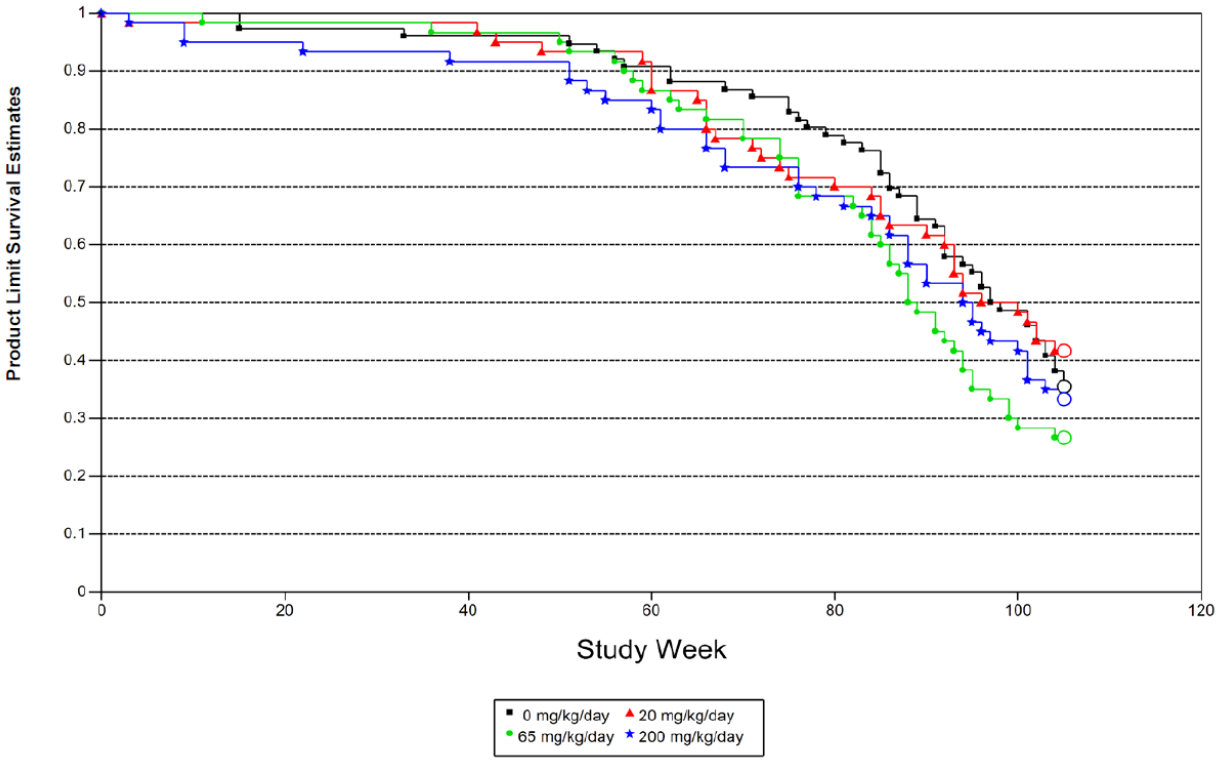


Table 21: Summary of Survival Estimates in the Mouse Carcinogenicity Study - Males

Dose (mg/kg/day)	0		20		65		200	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
1 - 13	.	.	.	.	.	.	2	3.33
14 - 26	2	3.33	1	1.67	1	1.67	2	6.67
27 - 39	1	5.00	1	3.33	4	8.33	.	.
40 - 52	3	10.00	2	6.67	3	13.33	.	.
53 - 65	3	15.00	3	11.67	6	23.33	2	10.00
66 - 78	8	28.33	8	25.00	5	31.67	10	26.67
79 - 91	6	38.33	8	38.33	12	51.67	8	40.00
92 - 105	12	58.33	15	63.33	9	66.67	12	60.00
Ter. Sac.	41	68.33	22	36.67	20	33.33	24	40.00
Total	76	100.00	60	100.00	60	100.00	60	100.00

[Table excerpted from Dr. Mbodj's statistical review of the Applicant's mouse carcinogenicity study]

Table 22: Summary of Survival Estimates in the Mouse Carcinogenicity Study - Females

Dose (mg/kg/day)	0		20		65		200	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
1 - 13	.	.	1	1.67	1	1.67	3	5.00
14 - 26	2	3.33	.	.	.	.	1	6.67
27 - 39	1	5.00	.	.	1	3.33	1	8.33
40 - 52	1	6.67	3	6.67	2	6.67	2	11.67
53 - 65	5	15.00	5	15.00	6	16.67	5	20.00
66 - 78	6	25.00	8	28.33	9	31.67	7	31.67
79 - 91	13	46.67	6	38.33	14	55.00	9	46.67
92 - 105	21	81.67	12	58.33	11	73.33	12	66.67
Ter. Sac.	27	45.00	25	41.67	16	26.67	20	33.33
Total	76	100.00	60	100.00	60	100.00	60	100.00

[Table excerpted from Dr. Mbodj's statistical review of the Applicant's mouse carcinogenicity study]

Clinical Signs

Compared to vehicle controls, a dose-dependent increase in the incidence of "sparse hair" occurred in males at all doses and was most profound in HDMs (Table 23). Alopecia with correlative histopathology of hypotrichosis was observed in previous

repeat dose studies in the rat and may be related with drug-induced hyperactivity and excessive grooming. In my opinion, mild hair loss does not significantly impact the health of study animals and is unlikely to affect the interpretation of carcinogenicity data. No other drug-related abnormal clinical signs were reported in this study.

Table 23: Sparse Hair in Males in the Mouse Carcinogenicity Study

Dose (mg/kg/day)	0	20	65	200	0	20	65	200
	incidence/number of times observed				total number of animals affected			
Weeks 1-52	93	128	172	386	5	8	11	17
Weeks 53-105	106	377	381	2096	11	20	9	25

*Reviewer's Notes: Given the pharmacology of solriamfetol, the drug is expected to induce some CNS signs, such as hyperactivity. In the 3-month repeat dose study in CD-1 mice, dose-dependent increases in agitation and/or hyperactivity were observed at the same doses of 20 and 200 mg/kg/day in both sexes for up to 6 hours post-dose. In the current carcinogenicity study, no drug-related CNS effect was reported. Adequate exposure to the drug was confirmed by TK data. It is possible that the lack of drug-related CNS clinical signs in the carcinogenicity study was due to the sparse schedule (weekly) of clinical observation.

Body Weights

Compared to the vehicle controls, drug-related decreases in body weight (↓~5-8%) were observed at multiple time points in males at 200 mg/kg/day and females at all doses (Table 24 and Figure 11). In addition, the mean body weight in females at 600 mg/kg/day was significantly decreased (↓10.1% relative to vehicle controls) at Week 26 (prior to early termination) and was considered adverse (Table 24). The decreases in body weights did not correlate with decreases in food consumption. In contrast, dose-dependent increases in food consumption were observed in both males and females.

Drug-related decreases in body weight gain, likely due to increased activity, were previously observed in the 3-month repeat dose study in CD-1 mice. In addition, existing literature also reported decreases in body weight associated with stimulants, such as amphetamine [7] or norepinephrine and dopamine reuptake inhibitors, such as bupropion[8]. Considering the stimulant-like pharmacology of solriamfetol, I conclude that with the exception of females at 600 mg/kg/day, the mild decreases in body weights (<10%) at all other doses did not adversely impact the overall health of the animals and did not confound the carcinogenicity data.

Food Consumption

Compared to the vehicle controls, there was a trend towards dose-dependent increases in food consumption in both sexes treated with solriamfetol (Table 25 and Figure 12), suggesting that the decreases in body weight gain may be due to drug-related changes in activity and metabolism rather than decreases in food intake.

[7] The effects of amphetamine on body weight and energy expenditure. Jones JR, Caul WF, and Hill JO. Physiol Behav. 1992 Mar; 51(3): 607-11

[8] Effects of bupropion on body weight. Harto-Truax N, Stern WC, Miller LL, Sato TL, Cato AE. J Clin Psychiatry. 1983 May; 44(5): 183-6

Figure 11: Mean Body Weight in the Mouse Carcinogenicity Study

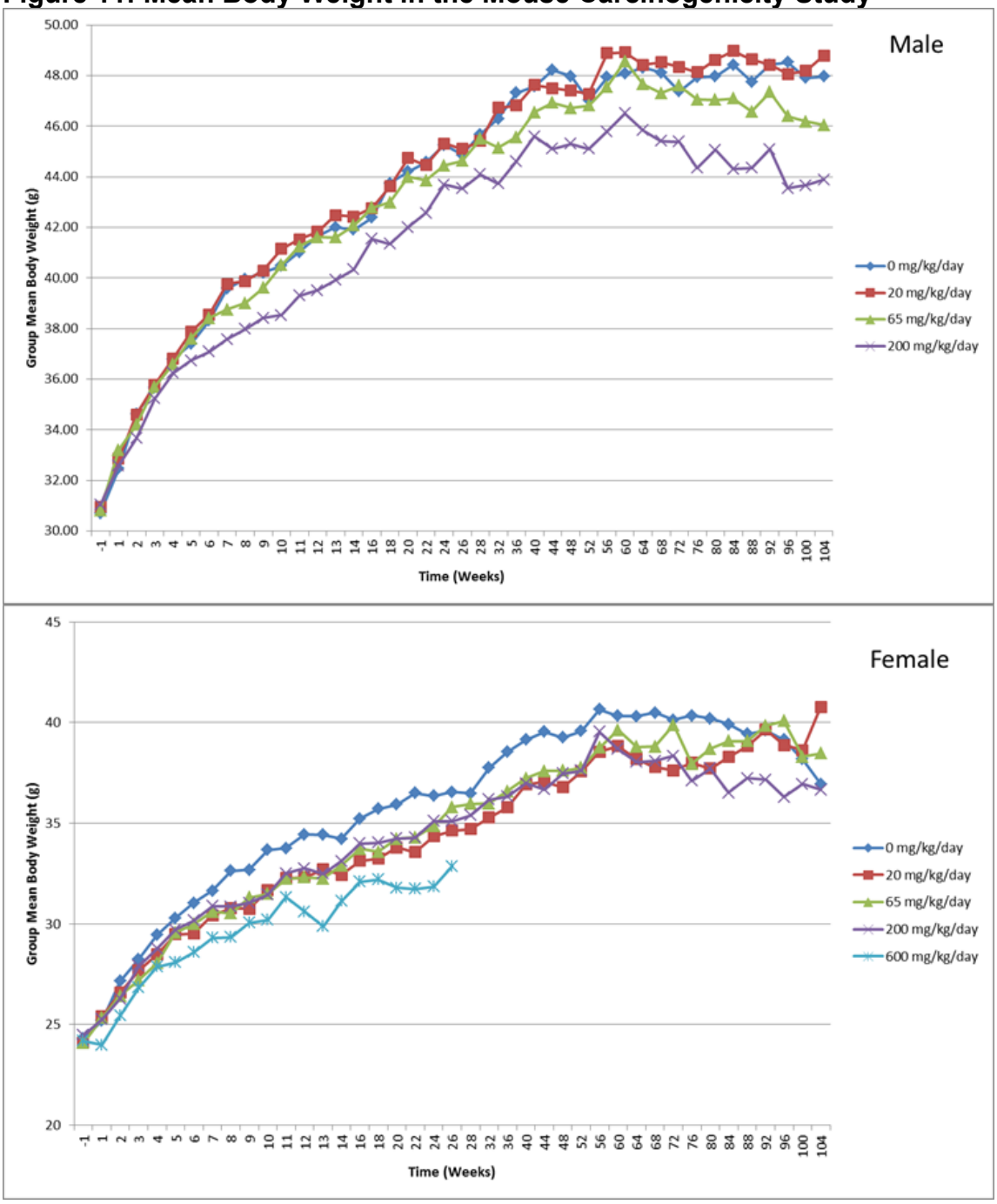


Table 24: Summary of Mean Body Weight in the Mouse Carcinogenicity Study

Table J. Summary of Group Mean Body Weight (g)								
Dose Level (mg/kg/day)	Main Study Males							
	Week 26	(%)	Week 52	(%)	Week 76	(%)	Week 104	(%)
0	44.9	NA	47.0	NA	47.9	NA	48.0	NA
20	45.1	(+0.4)	47.3	(+0.6)	48.1	(+0.4)	48.8	(+1.7)
65	44.6	(-0.7)	46.8	(-0.4)	47.1	(-1.7)	46.0	(-4.2)
200	43.5	(-3.1)	45.1	(-4.0)	44.3	(-7.5)	43.9	(-8.5)

(%) - Percent difference from vehicle control
NA – Not applicable

Table K. Summary of Group Mean Body Weight (g)								
Dose Level (mg/kg/day)	Main Study Females							
	Week 26	(%)	Week 52	(%)	Week 76	(%)	Week 104	(%)
0	36.6	NA	39.6	NA	40.4	NA	36.9	NA
20	34.6	(-5.5)	37.6	(-5.1)	38.0	(-5.9)	40.8	(+10.6)
65	35.8	(-2.2)	37.7	(-4.8)	38.0	(-5.9)	38.5	(+4.3)
200	35.1	(-4.1)	37.6	(-5.1)	37.1	(-8.2)	36.7	(-0.5)
600	32.9	(-10.1)	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]

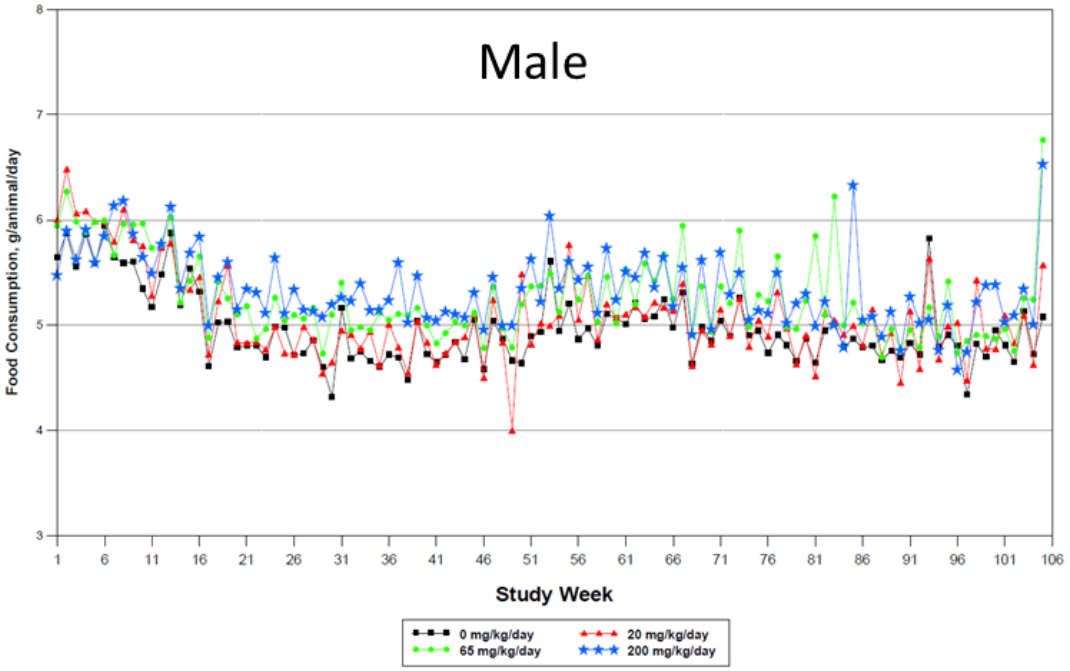
(%) - Percent difference from vehicle control
NA – Not applicable
[a] Females at 600 mg/kg/day were terminated following Week 26.

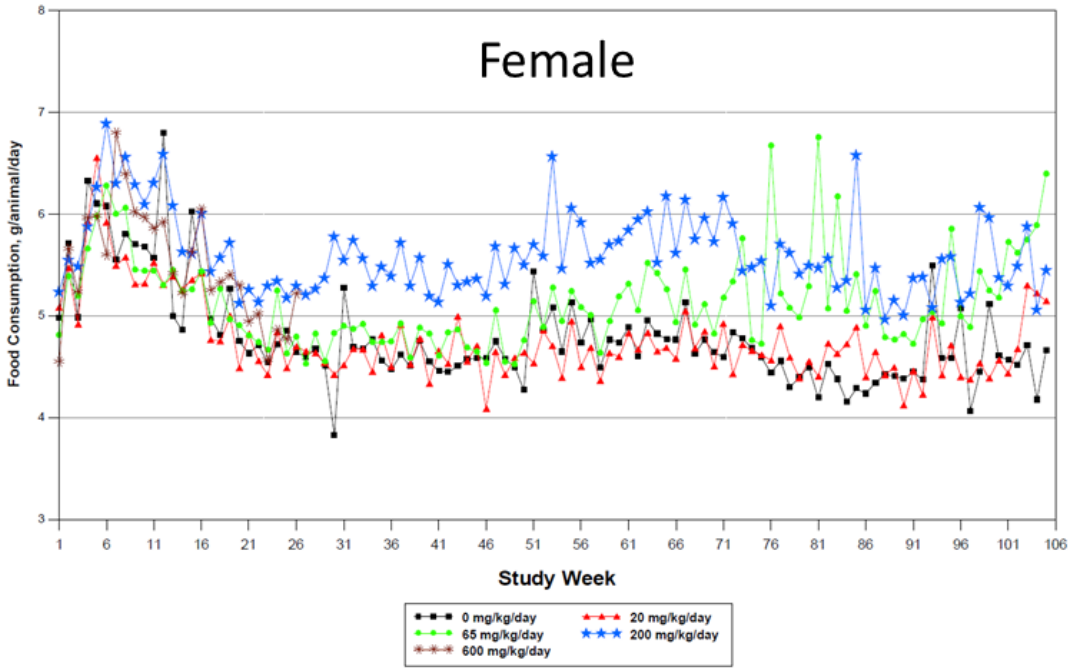
Table 25: Food consumption in the Mouse Carcinogenicity Study

Table L. Average Food Consumption; g/animal/day (Week 1 through Week 105)				
Dose Level (mg/kg/day)	Male		Female	
	Mean	(%) Difference from Vehicle Control	Mean	(%) Difference from Vehicle Control
0	4.97	NA	4.79	NA
20	5.08	(+2.2)	4.76	(-0.6)
65	5.27	(+6.0)	5.14	(+7.3)
200	5.34	(+7.4)	5.61	(+17.1)
600 [a]	NA	NA	5.50	(+14.8)

NA – Not applicable
[a] Females at 600 mg/kg/day were terminated following Week 26. % difference from vehicle control is based on control values at Week 26.

Figure 12: Mean Food Consumption in the Mouse Carcinogenicity Study





Gross Pathology

The female 600 mg/kg/day dose group that was terminated early at Week 26 was not evaluated. All other dose groups were included for carcinogenicity evaluation. There were no drug-related macroscopic findings in males or females euthanized in extremis, found dead, or survived to termination necropsy.

Histopathology

Peer Review: Peer review was conducted.

Neoplastic

The female 600 mg/kg/day group was terminated early at Week 26 and was not evaluated for neoplastic or non-neoplastic findings. For other groups, there were no-drug related increases in neoplastic findings in males or females at any doses.

Dr. Malick Mbodj from the Division of Biometrics conducted the statistical review. The following is an excerpt from Dr. Mbodj's review.

Reviewer's findings:

The tumor types with p-values less than 0.05 for dose response relationship and/or pairwise comparisons of vehicle control and treated groups are reported in Table 4.

Table 4: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons
Treated Groups and Vehicle Control Group in Mice
(lymphoma, leukemia on a per organ basis excluded)

Sex	Organ Name	Tumor Name	0 mg/Kg Veh. Cont. (N=76) P - Trend	20 mg/kg Low (N=60) P - VC vs. L	65 mg/kg Med (N=60) P - VC vs. M	200 mg/kg High (N=60) P - VC vs. H
Male	kidneys	ADENOMA, TUBULAR CELL	0/76 (58) 0.0461@	0/60 (42) NC	1/60 (37) 0.3895	2/60 (42) 0.1739
	stomach, glandular	ADENOMA	0/76 (58) 0.0461@	0/60 (42) NC	1/60 (37) 0.3895	2/60 (42) 0.1739

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
*: Statistically significant at 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship or 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.
@: not statistically significant at 0.025 and 0.05 level in rare tumor nor at 0.005 and 0.01 level in common tumor for tests of dose response relationship and pairwise comparison, respectively.

Following the multiple testing adjustment method described above, this reviewer's analyses showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased Solriamfetol dose in either sex of mice. The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in Solriamfetol treated groups, when compared to the vehicle control in either male or female mice.

Non Neoplastic

There were no-drug related increases in non-neoplastic findings in males or females.

Toxicokinetics

At the doses of 20, 65, and 200 mg/kg/day, no significant sex difference in the systemic exposure to solriamfetol was observed between males and females; therefore, TK analyses were performed with combined data from males and females. After 90 days of daily oral administration, the systemic exposure (AUC) to solriamfetol increased greater than dose proportionally whereas the C_{max} increased less than dose proportionally (Table 26). On Day 90, at the doses of 20, 65, and 200 mg/kg/day, the systemic exposure ($AUC_{0\text{-last}}$) to solriamfetol were 4460, 24500, and 66400 h*ng/mL, respectively and the C_{max} values were 3390, 6450, and 11000 ng/mL, respectively.

Table 26: Toxicokinetic Parameters of solriamfetol on Day 90 in the Mouse Carcinogenicity Study (Males and Females Combined)

Dose (mg/kg)	Day	C_{max} (ng/mL)	C_{max}/Dose (kg*ng/mL/mg)	T_{max} (hr)	T_{last} (hr)	AUC_{Tlast} (hr*ng/mL)	AUC_{Tlast}/Dose (hr*kg*ng/mL/mg)	AUC_{0-24hr} (hr*ng/mL)	AUC_{0-24hr}/Dose (hr*kg*ng/mL/mg)
20	90	3390	170	0.25	4	4460	223	NA[a]	NA
65	90	6450	99.2	0.25	24	24500	377	24500	377
200	90	11000	55.1	0.25	24	66400	332	66400	332
600[b]	90	40700	67.8	1	24	307000	511	307000	511

NA - Not applicable
a: AUC_{0-24hr} not calculated due to %AUCExtrap > 25%
b: No males were treated at 600 mg/kg

Blood samples were collected from TK animals under non-fasted condition on Day 90 at 0.25 hours postdose for controls and at 0, 0.25, 1, 2 (20 mg/kg/day dose group), 4, 8 (65, 200, and 600 mg/kg/day dose groups), and 24 hours postdose.

Dosing Solution Analysis
Adequate dosing formulation analyses were performed during the study. All samples were within the acceptance criteria for homogeneity, concentration, and stability.

8.2 101-Week Rat Carcinogenicity Study

Study no.:	(b) (4) 1301-012
Study report location:	EDR, SDN 1 and SDN 4
Conducting laboratory and location:	(b) (4)
Date of study initiation:	06/02/2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	solriamfetol, Lot 00447457 with a purity of 98.8%; and Lot 1435H007 with a purity of 99.5%
CAC concurrence:	Yes[9]. See appendix for copy of meeting minutes.

Key Study Findings

- There were no drug-related neoplastic findings following oral daily administration of solriamfetol in male and female SD rats at doses of 35, 80, and 200 mg/kg/day for up to 101 weeks. At 200 mg/kg/day, after 26 weeks of repeat dose, the corresponding plasma exposure level of solriamfetol was 177000 h*ng/mL, which is approximately 9.3 times the MRHD of 300 mg/day (based on human AUC value of 19070 ng*hr/mL).
- At the dose of 200 mg/kg/day, solriamfetol induced a ~20% decrease in body weight in both sexes, which may have confounded the interpretation of carcinogenicity data for this dose group.

Adequacy of Carcinogenicity Study

Adequate. Slight deviations in dose selection (due to the weight difference between the salt and free base form) and the use of a single vehicle control group are acceptable. For details, see the overall comments.

Appropriateness of Test Models

The SD rat is appropriate species and strain for long-term study with adequate historical control data.

Evaluation of Tumor Findings

An independent statistical review of tumor findings was conducted by Dr. Malick Mbodj from the Division of Biometrics. Dr. Mbodj's conclusion is in agreement with the Applicant's statistical analyses.

[9] There are small deviations in dose selection and the use of single vehicle control group in the final rat carcinogenicity study. However, these deviations did not impact the validity or adequacy of the carcinogenicity study.

Methods

Doses:	0 (vehicle controls), 35 (LD), 80 (MD), and 200 (HD) mg/kg/day for both sexes
Frequency of dosing:	once daily
Dose volume:	5 mL/kg
Route of administration:	oral gavage
Formulation/Vehicle:	deionized water
Basis of dose selection:	Dose selection was based on a 6-month study in the SD rat. The high dose was based on MTD (mortality occurred at 600 mg/kg/day in males and 450 mg/kg/day in females). The doses used in the study were recommended by the ECAC.
Species/Strain:	Crl:CD (SD) Sprague Dawley Rats from (b) (4)
Number/Sex/Group:	n=76/sex for vehicle controls; n=70/sex/group for treatment groups
Age:	~8 weeks at treatment initiation
Animal housing:	pair housed
Paradigm for dietary restriction:	No dietary restriction; animals had access to diet and tap water *ad libitum*.
Dual control employed:	No
Interim sacrifice:	No
Satellite groups:	Satellite TK groups were included in the study (n=4/sex/group). Toxicokinetic assessment of solriamfetol was conducted on Day 179.
Deviation from study protocol:	None that significantly impacted the integrity or interpretation of the study.

Observations and Results

Mortality

On Day 682 (Week 98), the number of surviving animals reduced to 20 in the HDM group, and dosing in the HDM group was stopped for the remainder of the study. On Day 683 (Week 98), the number of surviving animals reduced to 20 in the male vehicle control group and all remaining male groups in the study were terminated. On Day 687 (Week 99), the number of surviving animals reduced to 15 in the LDF group and the LDF group was terminated. Beginning on Day 706 (Week 101), all remaining female groups in the study were terminated because the number of surviving females in the vehicle group reduced to 20. These early termination procedures followed pre-specified guidelines and were consistent with the ECAC recommendation.

The causes for the unscheduled moribundity/mortality were consistent with common causes of death of aging rats and were comparable across all groups with no apparent relationship to solriamfetol treatment. The most frequent causes were pituitary gland tumors in both sexes and mammary gland tumors in females.

At the terminal necropsy, the number of surviving rats were 20, 26, 20, and 19 in the vehicle control, LD, MD, HD males (Table 27 and Figure 13), respectively, and 20, 15, 17, and 26 in the vehicle control, LD, MD, and HD females (Table 28 and Figure 14), respectively. The number of surviving animals at the end of the study was adequate to allow for a statistical evaluation.

Statistical analysis was performed and reviewed by the statistical reviewer (Dr. Malick Mbodj). No drug-related change in the mortality in either sex was observed in the survival analysis or pairwise comparisons.

Table 27: Intercurrent Mortality Rate in the Rat Carcinogenicity Study - Males

	0 mg|kg|day		35 mg|kg|day		80 mg|kg|day		200 mg|kg|day	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
1 - 13	1	1.32	.	.	.	.	.	.
14 - 26	1	2.63	.	.	.	.	.	.
27 - 39	1	3.95	1	1.43	1	1.43	2	2.86
40 - 52	6	11.84	4	7.14	4	7.14	3	7.14
53 - 65	12	27.63	11	22.86	9	20.00	5	14.29
66 - 78	14	46.05	6	31.43	6	28.57	13	32.86
79 - 91	11	60.53	15	52.86	18	54.29	14	52.86
91 - 98	10	73.68	7	62.86	12	71.43	14	72.86
Ter. Sac.	20	26.32	26	37.14	20	28.57	19	27.14
Total	76	100.00	70	100.00	70	100.00	70	100.00

Earlier terminal necropsies, Ter. Sac. = Week 98

[Table excerpted from Dr. Mbodj's statistical review of the rat carcinogenicity study]

Table 28: Intercurrent Mortality Rate in the Rat Carcinogenicity Study - Females

	0 mg|kg|day		35 mg|kg|day		80 mg|kg|day		200 mg|kg|day	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
1 - 13	.	.	.	.	1	1.43	.	.
14 - 26	1	1.32	.	.	.	.	1	1.43
27 - 39	.	.	.	.	.	.	2	4.29
40 - 52	2	3.95	4	5.71	2	4.29	3	8.57
53 - 65	8	14.47	9	18.57	4	10.00	6	17.14
66 - 78	13	31.58	10	32.86	17	34.29	7	27.14
79 - 91	18	55.26	25	68.57	19	61.43	18	52.86
92 - 101	14	73.68	7	78.57	10	75.71	7	62.86
Ter. Sac.	20	26.32	15	21.43	17	24.29	26	37.14
Total	76	100.00	70	100.00	70	100.00	70	100.00

Earlier terminal necropsies, Ter. Sac. = Week 101

[Table excerpted from Dr. Mbodj's statistical review of the rat carcinogenicity study]

Figure 13: Survival Curve in the Rat Carcinogenicity Study - Males

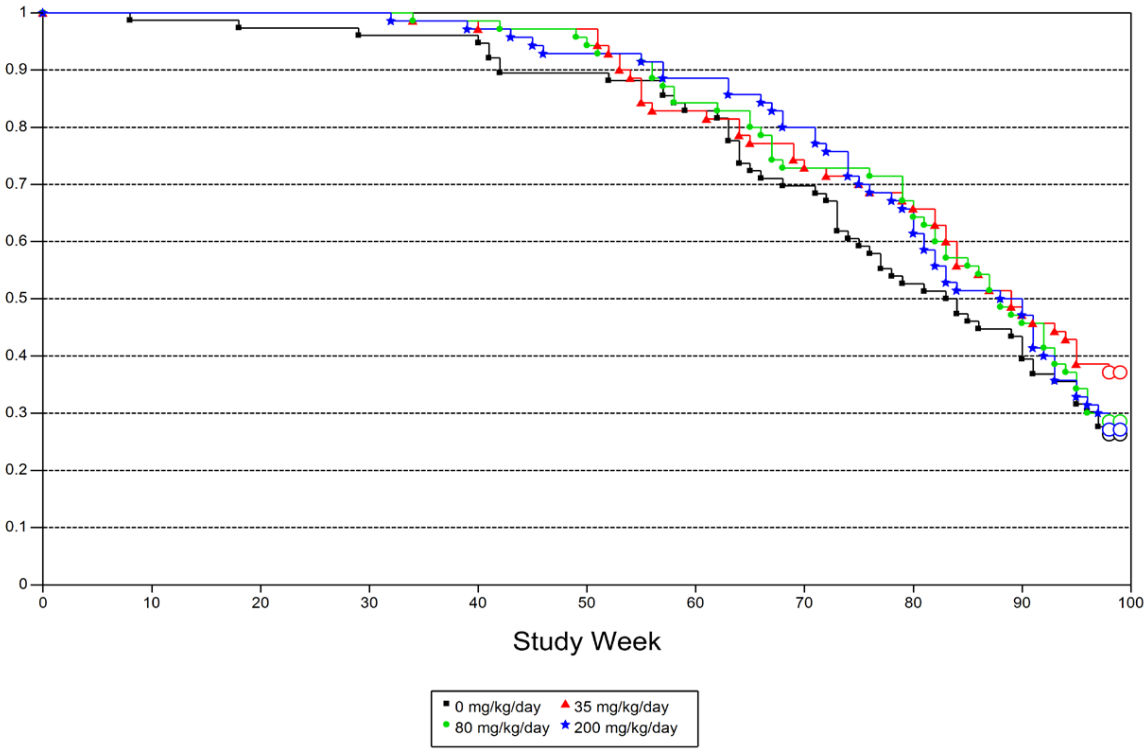
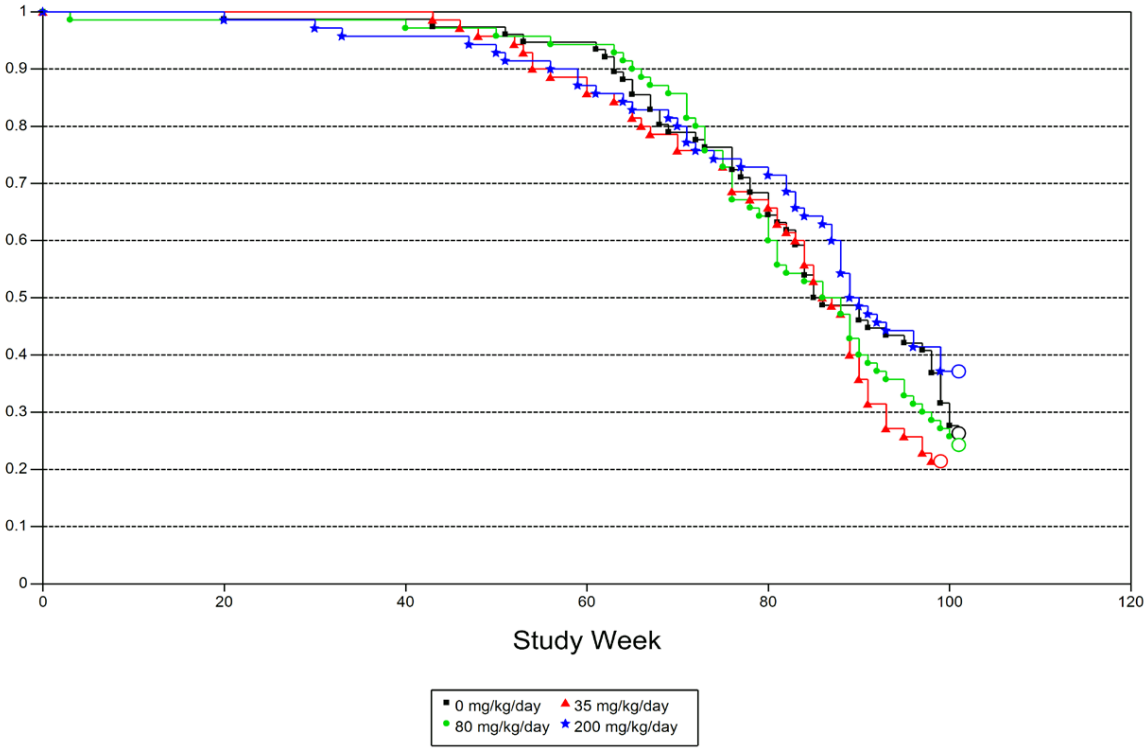


Figure 14: Survival Curve in the Rat Carcinogenicity Study - Females



Clinical Signs
Compared to vehicle controls, drug-related clinical signs were observed, including dose-dependent increases in activity, hypersensitivity to touch, and salivation in both sexes. These clinical observations were observed as early as Week 2 and continued throughout the study. Increased activity generally occurred at within 1 hour post-dose and last for several hours.

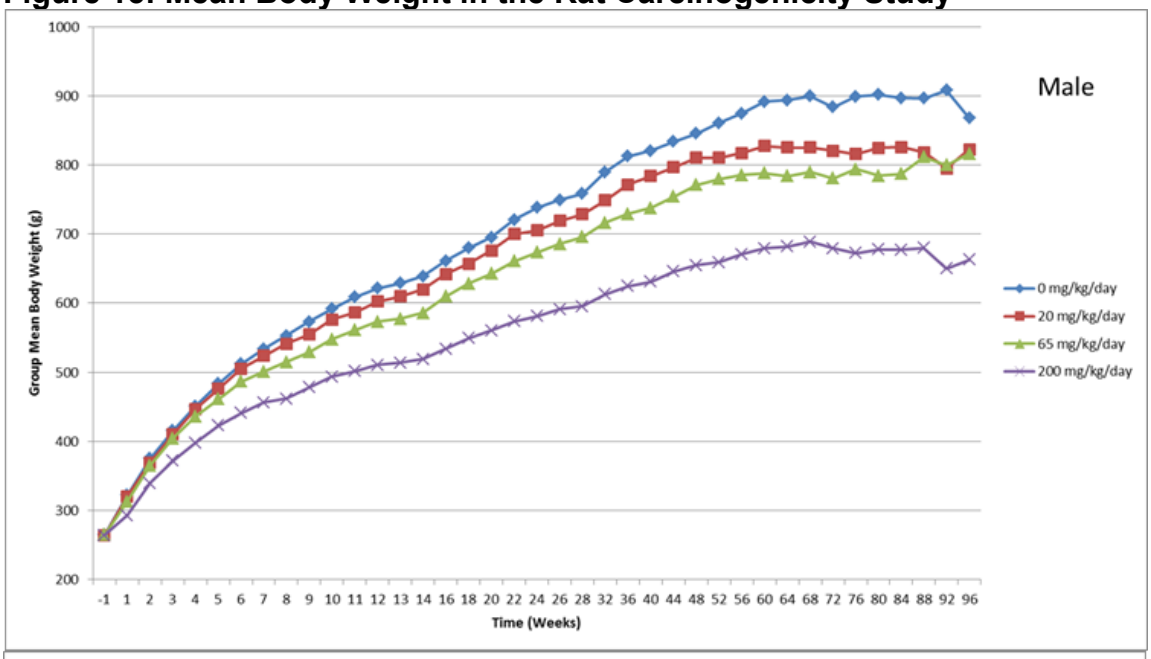
Similar CNS effects were previously observed in the 6-month repeat dose study in SD rats and are likely due to the pharmacology of the drug. Given that these CNS effects are expected and not severe in nature, I conclude that they do not adversely impact the health of the animals and do not affect the data interpretation of the carcinogenicity study.

Body Weights
Compared to the vehicle controls, drug-related and dose-dependent decreases in body weight were observed in both sexes at all doses and were most profound in HD (↓up to ~ 20% in HDM&Fs, relative to controls, Table 29 and Figure 15). The drug-related decreases in body weight did not correlate with any decreases in food consumption.

Decreases in body weight have been observed in previous repeat dose rat studies and are likely due to drug-induced hyperactivity. In addition, existing literature also reported decreases in body weight associated with stimulants, such as amphetamine [10] or norepinephrine and dopamine reuptake inhibitors, such as bupropion[11]. Because there were no correlative findings in histopathology or food consumption, the decreases in body weight did not appear to severely affect the health of animals. However, the ~20% decrease in body weight in HD may have confounded the interpretation of the carcinogenicity data, since lower body weight may affect tumorigenesis in rodents[12].

[10] The effects of amphetamine on body weight and energy expenditure. Jones JR, Caul WF, and Hill JO. Physiol Behav. 1992 Mar; 51(3): 607-11
[11] Effects of bupropion on body weight. Harto-Truax N, Stern WC, Miller LL, Sato TL, Cato AE. J Clin Psychiatry. 1983 May; 44(5): 183-6
[12] Comparison of Historical Control Tumor Incidence Rates in Female Harlan Sprague-Dawley and Fischer 344/N Rats From Two-Year Bioassays Performed by the National Toxicology Program. Gregg E Dinse, et al. Toxicol Pathol. 2010, Aug: 38(5): 765-775

Figure 15: Mean Body Weight in the Rat Carcinogenicity Study



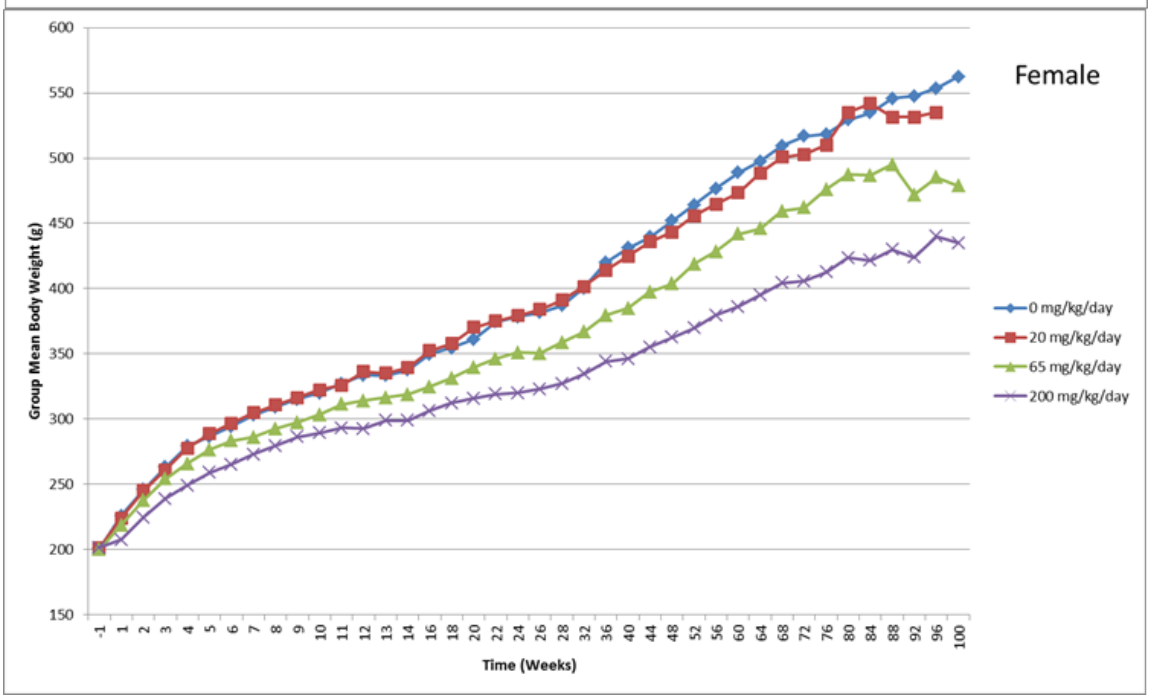


Table 29: Summary of Mean Body Weight in the Rat Carcinogenicity Study

Table J. Summary of Group Mean Body Weight (g)								
Dose Level (mg/kg/day)	Main Study Males							
	Week 26	(%)	Week 52	(%)	Week 76	(%)	Week 96	(%)
0	749.3	NA	861.0	NA	899.0	NA	867.5	NA
35	719.2	(-4.0)	810.6	(-5.9)	815.9	(-9.3)	822.6	(-5.2)
80	685.5	(-8.5)	779.3	(-9.5)	794.1	(-11.7)	816.3	(-5.9)
200	591.3	(-21.1)	658.8	(-23.5)	672.2	(25.2)	662.6	(-23.6)
(%) - Percent difference from vehicle control NA – Not applicable								

Table K. Summary of Group Mean Body Weight (g)								
Dose Level (mg/kg/day)	Main Study Females							
	Week 26	(%)	Week 52	(%)	Week 76	(%)	Week 100	(%)
0	381.7	NA	464.2	NA	518.4	NA	562.5	NA
35	384.1	(+0.6)	455.7	(-1.8)	510.0	(-1.6)	535.1[a]	(-3.3)[a]
80	350.3	(-8.2)	419.0	(-9.7)	476.0	(-8.2)	478.7	(-14.9)
200	323.0	(-15.4)	369.7	(-20.4)	412.5	(-20.4)	434.9	(-22.7)
(%) - Percent difference from vehicle control NA – Not applicable [a]Females at 35 mg/kg/day were terminated at Week 96. Percent difference from vehicle control was based on Week 96 control value of 553.6 grams.								

Food Consumption

Compared to vehicle controls, there were no drug-related changes in food consumption in either sex (Table 30). Food consumption did not correlate with the changes in body weight.

Table 30: Food Consumption in the Rat Carcinogenicity Study

Table L. Average Food Consumption; g/animal/day (Week 1 through Week 98 in males and 101 in females)				
Dose Level (mg/kg/day)	Male		Female	
	Mean	(%) Difference from Vehicle Control	Mean	(%) Difference from Vehicle Control
0	29.10	NA	19.60	NA
35	29.16	(+0.2)	20.72	(+5.7)
80	29.04	(-0.2)	21.15	(+7.9)
200	27.42	(-5.8)	19.99	(+2.0)
NA – Not applicable				

Gross Pathology
At the terminal necropsy, there were no drug-related macroscopic findings. The most common macroscopic findings included enlarged pituitary glands with correlative adenomas of the pars distalis and subcutaneous masses with correlative mammary tumors (fibroadenoma, adenoma, and adenocarcinoma) in the females and fibromas in the males. These macroscopic findings are comparable between controls and solriamfetol treatment groups and are consistent with background data in aging SD rats[13].

Histopathology
Peer Review: Peer review was conducted.

Neoplastic
There were no-drug related increases in neoplastic findings in males or females from any dose group. The most common tumors identified included pars distalis adenomas of the pituitary gland in both sexes and fibroadenomas and adenocarcinomas of the mammary gland in the females. The incidences of these neoplastic lesions were comparable between controls and solriamfetol treatment groups and therefore are not considered to be drug-related. Pairwise comparisons showed significant increase in the incidence of islet cell carcinoma (rare tumor, p=0.0333) in the pancreas in the LDMs and fibroadenoma in the mammary gland (common tumor, p=0.0093) in the LDFs; however, given the lack of significance in trend analysis and the lack of similar findings in MD or HD, the increases in LD are not considered to be drug-related.

Dr. Malick Mbodj from the Division of Biometrics conducted a statistical review. The following is an excerpt from Dr. Mbodj's review.

[13] Causes of death in rodent toxicity and carcinogenicity studies. Ettlin RA, Stirnimann P, and Prentice DE. Toxico Pathol. 1994; 22 (2): 167-178

Reviewer's findings:

The tumor types with p-values less than 0.05 for dose response relationship and/or pairwise comparisons of vehicle control and treated groups are reported in Table 2.

Table 2: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons

Treated Groups and Vehicle Control Group in Rats

Sex	Organ Name	Tumor Name	0 mg/Kg Veh. Cont. (N=76) P - Trend	35 mg/kg Low (N=70) P - VC vs. L	80 mg/kg Med (N=70) P - VC vs. M	200 mg/kg High (N=70) P - VC vs. H
Male	Pancreas	Carcinoma, Islet Cell	0/76 (37) 0.6801	5/70 (40) 0.0333*	1/70 (38) 0.5067	1/70 (38) 0.5067
	Thyroid Gland	Adenoma, C-Cell	2/76 (38) 0.0395@	2/70 (39) 0.7023	2/70 (39) 0.7023	6/70 (40) 0.1486

Sex	Organ Name	Tumor Name	0 mg/Kg Veh. Cont. (N=76) P - Trend	35 mg/kg Low (N=70) P - VC vs. L	80 mg/kg Med (N=70) P - VC vs. M	200 mg/kg High (N=70) P - VC vs. H
Female	Mammary Gland	Fibroadenoma	27/76 (55) 0.9318	38/70 (52) 0.0093*	31/70 (50) 0.1287	21/70 (48) 0.7702
	Thyroid Gland	Adenoma/Carcinoma C-Cell	4/76 (45) 0.0499@	2/70 (38) 0.8554	7/70 (41) 0.2087	8/70 (44) 0.1655

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;

NC = Not calculable

*: Statistically significant at 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship or 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

@: not statistically significant at 0.025 and 0.005 level in rare and common tumor, respectively, for tests of dose response relationship.

Following the multiple testing adjustment method described above, this reviewer's analyses showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased Solriamfetol dose in either sex of rats. The pairwise comparisons showed statistically significant increases in the low dose groups for the incidences of carcinoma, islet cell in the pancreas when compared to the vehicle control group in male rats (p-values =0.0333) since this tumor type was considered as rare tumors. Also, the pairwise comparisons showed statistically significant increases in the low dose groups for the incidences of fibroadenoma in the mammary gland when compared to the vehicle control group in male rats (p-values =0.0093) since this tumor type was considered as common tumors.

Non Neoplastic

There were no drug-related changes in non-neoplastic findings. The incidences of non-neoplastic findings were comparable across all groups with no dose-relationship and were consistent with the background changes in aging SD rats.

Toxicokinetics

At the doses of 35, 80, and 200 mg/kg/day, a slightly higher exposure to solriamfetol was observed in females than males; however, the difference was generally small with the female-to-male ratios for AUC and C_{max} less than 2-fold and did not reach statistical significance. Therefore, TK analyses were conducted with combined data from males and females.

After 26 weeks of daily oral administration, the systemic exposure (AUC) to solriamfetol increased slightly more than dose proportionally whereas the C_{max} increased dose proportionally (Table 31). On Day 179, at the doses of 35, 80, and 200 mg/kg/day, the systemic exposure ($AUC_{0\text{-last}}$) to solriamfetol were 17200, 56400, and 177000 h*ng/mL, respectively and the C_{max} were 3440, 7300, and 16300 ng/mL, respectively.

Table 31: Toxicokinetic Parameters of solriamfetol on Day 179 in the Rat Carcinogenicity Study (Males and Females Combined)

Dose (mg/kg)	Day	Statistic	C_{max} (ng/mL)	C_{max}/Dose (kg*ng/mL/mg)	T_{max} (hr)[a]	T_{last} (hr)[a]	AUC_{Tlast} (hr*ng/mL)	AUC_{Tlast}/Dose (hr*kg*ng/mL/mg)	$AUC_{0\text{-}24hr}$ (hr*ng/mL)	$AUC_{0\text{-}24hr}$/Dose (hr*kg*ng/mL/mg)
35	179	N	6	6	6	6	6	6	4	4
		Mean	3440	98.4	0.5	24	17200	492	19600	561
		SD	1230	35.1	(0.5 - 1)	(8 - 24)	6350	181	6340	181
		CV%	35.7	35.7	NA	NA	36.9	36.9	32.3	32.3
80	179	N	6	6	6	6	6	6	6	6
		Mean	7300	91.2	1	24	56400	705	56400	705
		SD	1790	22.4	(0.5 - 1)	(24 - 24)	19400	243	19400	243
		CV%	24.5	24.5	NA	NA	34.5	34.5	34.5	34.5
200	179	N	6	6	6	6	6	6	6	6
		Mean	16300	81.3	NA	24	177000	886	177000	886
		SD	3140	15.7	(0.5 - 1)	(24 - 24)	47200	236	47200	236
		CV%	19.3	19.3	NA	NA	26.6	26.6	26.6	26.6

NA - Not applicable

a: Median (minimum - maximum), median value only reported if actual collection interval

Blood samples were collected from TK animals under non-fasted condition on Day 179 (Week 26) at 0.5 hours postdose for controls and at 0, 0.5, 1, 4, 8 and 24 hours postdose for all treated groups.

Dosing Solution Analysis

Adequate dosing formulation analyses were performed during the study. All samples were within the acceptance criteria for homogeneity, concentration, and stability.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

9.1.1 Oral Female Fertility Study in the Rat

Study no.: (b) (4) Tox-5713
Study report location: EDR, SDN-1, NDA 211230
Conducting laboratory and location: (b) (4)
Date of study initiation: 04/08/2003
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: solriamfetol, Z (b) (4) PFA071, 99.4%

Key Study Findings

- Solriamfetol caused dose-dependent and pharmacology-related increases in CNS excitatory behaviors in MD and HD.

- Solriamfetol caused dose-dependent decreases in body weight gain, body weight, and food consumption in MD and HD with recovery during the treatment free period.
- A potentially drug-related increase in the number of corpora lutea was observed at all drug doses. Other female fertility parameters were not affected.
- Based on the minimal functional change in female fertility parameters, the high dose of 295 mg/kg/day is the NOAEL for female fertility, which is approximately 9.5 times the MRHD of 300 mg, based on mg/m^2 body surface area.

Methods

Doses:	0 (vehicle control), 15 (LD), 67 (MD), and 295 (HD) mg/kg/day
Frequency of dosing:	once daily
Dose volume:	10 mL/kg
Route of administration:	oral gavage
Formulation/Vehicle:	demineralized water
Species/Strain:	SPF Sprague-Dawley rats (Crl:CD) from (b) (4)
Number/Sex/Group:	n=24/group
Satellite groups:	None
Study design:	Female SD rats were orally dosed with solriamfetol at 15, 67, and 295 mg/kg/day for 14 days prior to mating, during mating (with untreated males), and up to Gestation Day (GD) 7 of pregnancy, inclusive (GD 0 = day of sperm positive smear). On GD 14, females were sacrificed. Parameters evaluated included clinical signs, body weights, food consumption, and female fertility parameters. Dose selection was based on the 90-day repeat dose studies in *Wistar rats*, in which 295 mg/kg/day was considered to be the MTD. At 295 mg/kg/day, solriamfetol induced excitatory behavioral signs, increased kidney and ovarian weight with correlative cortico-tubular cell enlargement in the kidney and prominent corpora lutea and para-ovarian cysts. In addition, increased alanine aminotransferase levels and enlarged hepatocytes were observed in the liver.
Deviation from study protocol:	None that significantly affected the study interpretation.

Observations and Results

Mortality

No drug-related mortality occurred in the study. 1/24 control female was sacrificed on GD 0 due to poor condition associated with urinary bladder stone. 1/24 HDF died on GD 6 due to gavage error (perforated esophagus).

Clinical Signs
Solriamfetol caused dose-dependent increases in the incidence and/or severity of excitatory behaviors (hyperactivity, agitation/aggression, tremors, and water wastage), alopecia, and excessive salivation in MD and HD. These clinical signs are likely due to the stimulant-like pharmacology of the drug. The severity of these drug-related clinical signs in MD was generally mild and considered to be non-adverse. LD was not affected.

Body Weight
During the pre-mating treatment period, compared to controls, body weight loss occurred in HD (- 8 to -18 g in HD compared to +2 - 4 g in controls), which led to decreases in body weight (253 - 263 g in HD compared to 273 - 275 g in controls, ↓~4-8%). Body weight gain and body weight were not affected in LD or MD. During the gestation treatment period (GD 0 to 7), compared to controls, MD and HD had decreases in body weight gain (25 and 26 g in respectively, compared to 32 g in controls, ↓~ 22%). During the treatment-free period (GD 8 to 13), recovery in body weight gains were observed in MD and HD (44 and 53 g respectively, compared to 36 g in controls, ↑~22 - 47%). Body weight changes correlated with food consumption.

Food Consumption
During the pre-mating treatment period, compared to controls, HD had decreases in food consumption (98 - 138 g in HD, compared to 145 - 149 g in controls, ↓~ 5 – 34%). MD also showed decreases in food consumption during Week1 but recovered during Week 2. LD was not affected. During the gestation treatment period (GD 0 to 7), compared to controls, MD and HD had decreases in food consumption (198 g compared to 211 g in controls, ↓~6%). During the treatment-free period (GD 8 to 13), recovery in food consumption were observed in MD and HD (187 and 214 g respectively, compared to 177 g in controls, ↑~6 – 21%). Changes in food consumption correlated with body weight and body weight gain. LD was not affected.

Toxicokinetics
Not performed

Dosing Solution Analysis
The concentration and stability of the dosing formulation were within the acceptable ranges.

Necropsy
At the terminal necropsy, compared to controls, HD had increases in the incidence of alopecia. Similar findings were consistently observed in general toxicology studies in the rat, and may be associated with the drug-induced hyperactivity and excessive grooming. Nevertheless, the severity of alopecia did not appear to affect the health of the animals.

No other drug-related gross pathology findings were observed.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)
Compared to controls, no drug-related effects were observed in estrous cycle, pre-coital intervals, copulation index, fertility rate, pre- and post-implantation losses, or mean litter size.

The number of corpora lutea was increased at all doses (16.7, 17.8, and 17.1 in LD, MD, and HD, respectively, compared to 15.8 in controls), which correlated with slight increases in the number of implantation and live embryos (Table 32). These numbers were within the historical control range; however, because similar findings of prominent corpora lutea were observed in the 90-day repeat dose study in Wistar rats, the possibility of a drug-induced change cannot be ruled out.

Table 32: Female Fertility Parameters in the Female Rat Fertility Study

Observation		Control 0 mg/kg	Low 18 mg/kg	Medium 80 mg/kg	High 350 mg/kg
FEMALE DATA					
Number of pregnant females/ terminally sacrificed	(2)	23/23	23/24	24/24	23/23
Copulation rate	(2)	23/23	24/24	24/24	23/23
Fertility rate	(2)	23/23	23/24	24/24	23/23
Body weight gain (d0 - d7)	(3)	32	33	25 **	26 **
Body weight gain (d8 - d13)	(3)	36	38	44 ***	53 ***
Weight gravid uterus	(3)	12.0	12.8	12.9	13.0 *
Corrected mean maternal weight gain	(3)	56.0	58.1	55.9	66.0 **
Food consumption (d0 - d7)	(3)	211	210	198 **	198 **
Food consumption (d8 - d13)	(3)	177	179	187 **	214 ***
LITTER DATA					
Number of live embryos/pregnant female	(3)	13.0	14.0	13.6	13.9
Mean litter size	(3)	13.0	14.0	13.6	13.9
Number of early resorptions/pregnant female	(3)	1.13	1.00	1.33	1.04
Total number of resorptions/pregnant female	(3)	1.13	1.00	1.33	1.04
Pre-implantation loss (%)	(3)	10.10	10.90	16.40	12.78
Post-implantation loss (%)	(3)	8.12	7.71	9.38	7.32
Number of implantations/pregnant female	(3)	14.1	15.0	15.0	15.0
Number of corpora lutea of pregnancy/pregnant female	(3)	15.8	16.7	17.8 **	17.1 *

Significances computed by Fisher Exact Test * : $p < 0.05$ ** : $p < 0.01$ *** : $p < 0.001$
(1) Right tail probability (Mid P Value)
(2) Left tail probability (Mid P Value)
(3) Significances computed by Mann-Whitney U test (two tailed)
Note : all weights are in gram
Reference group = Control
TerS12Reporter : Version 3.3.0

[Doses in the table are presented as the hydrochloride salt weight; the free base equivalent doses are 0, 15, 67, 295 mg/kg/day]

9.1.2 A Study of Male Fertility and Early Embryonic Development in Sprague Dawley Rats Administered solriamfetol Daily via Oral Gavage

Study no.:	(b) (4)-1301-014
Study report location:	EDR, SDN-1, NDA 21130
Conducting laboratory and location:	(b) (4)
Date of study initiation:	08/27/2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	solriamfetol, 00447457, 98.8%

Key Study Findings

- Solriamfetol caused decreases (~ 10%) in sperm count and sperm concentration in HD, but did not functionally affect the male fertility parameters.
- Solriamfetol caused dose-dependent and pharmacology-related increases in clinical signs of hyperactivity at all doses and decreases in body weight, body weight gain, and food consumption in MD and HD.
- Based on the decreases in sperm count and sperm concentration in the HD, the NOAEL is the mid-dose of 110 mg/kg/day, which is approximately 3.5 times the MRHD of 300 mg/day based on mg/m^2 body surface area.

Methods

Doses:	0 (vehicle control), 35 (LD), 110 (MD), and 350 (HD) mg/kg/day
Frequency of dosing:	once daily
Dose volume:	10 mL/kg
Route of administration:	oral gavage
Formulation/Vehicle:	deionized water
Species/Strain:	Sprague Dawley rats (Crl:CD) from (b) (4)
Number/Sex/Group:	n=22/group
Satellite groups:	None
Study design:	Male rats were orally administered with solriamfetol at 0, 35, 110, and 350 mg/kg/day doses for 28 days prior to mating with untreated females, and continued through the mating and post-mating period to terminal necropsy (approximately 8 weeks total). Parameters evaluated included clinical signs, body weights, food consumption, anatomical pathology, reproductive parameters, and sperm analysis. Dose selection was based on a 6-month repeat dose study in SD rats, in which 505 mg/kg/day was not tolerated and the doses were lowered to 379 mg/kg/day on Day 93. 379 which was the MTD with histopathology changes in the kidney, thymus, spleen, adipose, and lung in both sexes and in the adrenal glands and ovary in females only.
Deviation from study protocol:	none that significantly impacted the study interpretation

Observations and Results

Mortality
No mortality occurred in the study.

All males were observed for mortality, morbidity, injury twice daily.

Clinical Signs
Solriamfetol caused dose-dependent increases in activity in 5/22 MDMs and 22/22 HDMs, and salivation in 5/22 LDMs, 14/22 MDMs, and 16/22 HDMs, respectively. Vocalization and hypersensitivity to touch were also observed at all doses but without clear dose relationship. These clinical signs are due to the stimulant-like pharmacology of the drug and did not severely affect the health of the treated animals.

Detailed clinical observations were conducted in all males daily at 60 to 90 minutes post-dose during the dosing period. Untreated females for mating were observed prior to pairing and on Gestation Day 13.

Body Weight

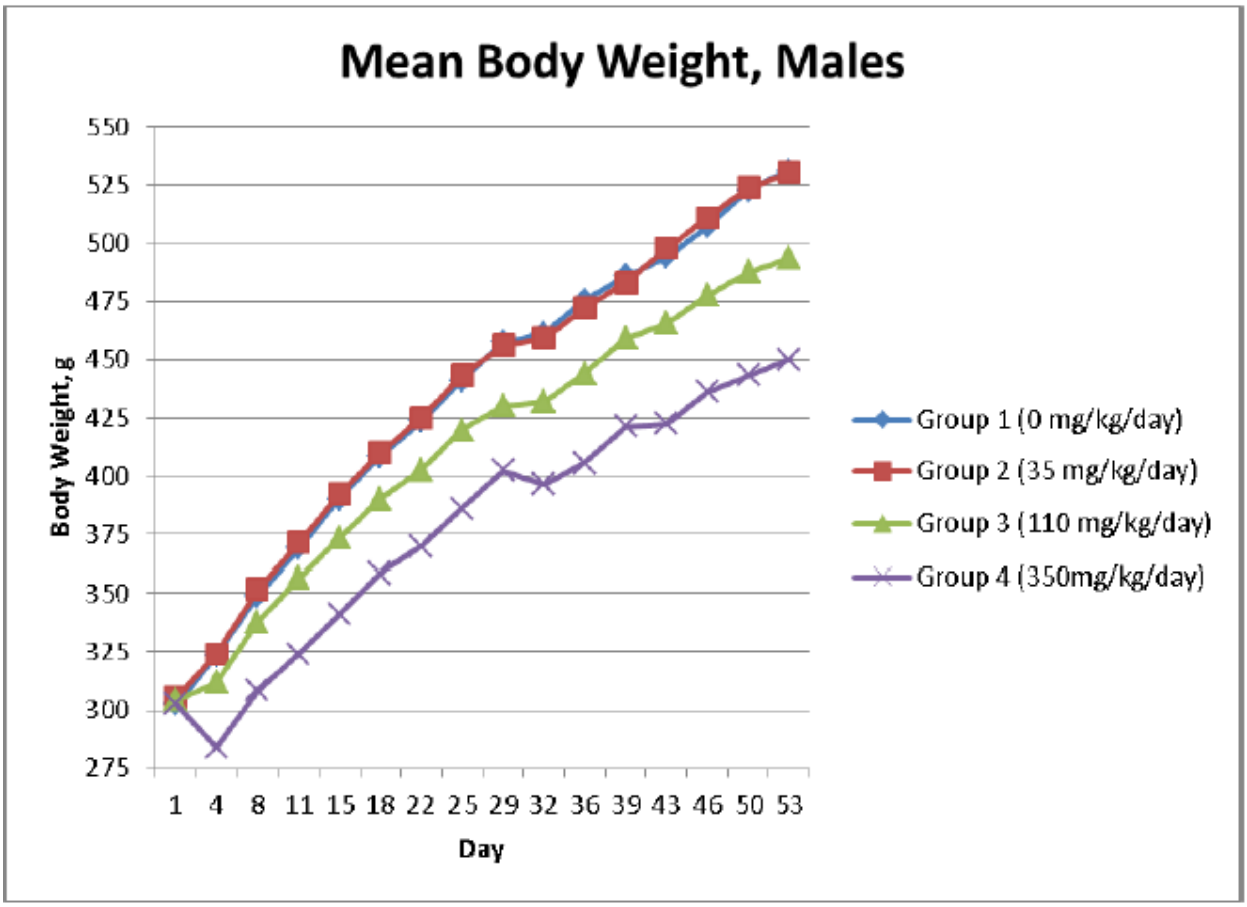
Compared to the vehicle controls, solriamfetol caused dose-dependent decreases in body weight gain and body weight with correlative decreases in food consumption in MD and HD during the pre-mating, mating, and post-mating periods (Table 33 and Figure 16). LD was not affected. Similar findings were also observed in general toxicology rat studies, and are likely related to the drug-induced hyperactivity.

Mean body weight and body weight gain in the untreated females were comparable across all groups.

Table 33: Solriamfetol Induced Decreases in Body Weight Gain in the Male Rat Fertility Study

Dose (mg/kg/day)	Pre-mating period (Day 1-29)		Mating period (Day 29- 43)		Post-mating period (Day 43-53)	
	BWG (g)	BW (g)	BW Gain	BW	BW Gain	BW
0 (Control)	154.8	457.4	36.9	494.3	36.9	531.2
35 (LD)	150.8	456.3	41.5	497.8	32.6	530.4
110 (MD)	125.8(↓17%)	430.1(↓17%)	35.5 (↓3%)	465.7(↓6%)	27.7/ ↓25%	493.5(↓7%)
350 (HD)	99.4 (↓36%)	402.1(↓12%)	20.4 (↓45%)	422.5(↓15%)	27.4/ ↓26%	450.0(↓15%)

Figure 16: Mean Body Weight Curve in the Male Rat Fertility Study



Body weights were recorded twice weekly.

Food Consumption
Compared to the vehicle controls, food consumption was decreased in MD and HD during Week 1 (↓12% and 30%, respectively) and in HD during Week 8 (↓8%). Decreases in food consumption correlated with decreases in body weight gain and/or body weight.

Food consumption was recorded weekly except during the pairing period.

Toxicokinetics
Not conducted.

Dosing Solution Analysis
The homogeneity, concentration, and stability of the dosing formulation were within the acceptable range.

Fertility Parameters
Compared to controls, no significant changes in male fertility parameters were observed. The mating index, fertility index, fecundity index, and copulatory interval (days to mating) were comparable across all groups (Table 34).

Table 34: Reproductive and Fertility Parameters in the Male Rat Fertility Study

Endpoint		Group 1 (0 mg/kg/day)	Group 2 (35 mg/kg/day)	Group 3 (110 mg/kg/day)	Group 4 (350 mg/kg/day)
No. Males on Study		22	22	22	22
No. Males Paired		22	22	22	22
No. Males Mated		21	22	22	21
No. Males Impregnating a Female		20	22	19	19
Male Mating Index (%)		95.5	100.0	100.0	95.5
Male Fertility Index (%)		90.9	100.0	86.4	86.4
Male Fecundity Index (%)		95.2	100.0	86.4	90.5
Females with Confirmed Mating Day		19	21	22	20
Copulatory Interval (Days)					
	Mean	4.3	3.4	4.5	3.7
	SD	4.21	2.31	4.32	3.29
	N	19	21	22	20

N - Number of measures used to calculate mean
SD - Standard Deviation
No. - Number

Sperm Analysis
Compared to the vehicle controls, HD had significant decreases in total sperm count (2.58 compared to 2.99 in controls, ↓14%) and sperm concentration (10.0 compared to

11.2 in controls, ↓11%, Table 35). The absolute values are close to the historical control range (2.6 to 3.9 for sperm count and 8.4 to 12.4 for sperm concentration). The fertility and fecundity index in HD were comparable to both concurrent vehicle controls and historical control data. The Applicant considered these decreases to be drug-related but not adverse. However, it should be noted that rats are highly fertile and a mild decrease (~10%) in sperm number is unlikely to affect the reproductive performance in rats, whereas in human the impact of a ~10% decrease in sperm count could be clinically relevant.

Compared to the vehicle controls, LD had an increase in percent abnormal sperm (6.05 compared to 2.66 in controls, Table 35). The increase was attributed to one male (No. 243) which had a 93.0% abnormal sperm with correlative findings of small testes and epididymis. This male successfully impregnated the female. Given the lack of similar finding at higher doses, I consider it to be incidental.

Table 35: Sperm Analysis Parameters in the Male Rat Fertility Study

	Group 1 (0 mg/kg/day)			Group 2 (35 mg/kg/day)			Group 3 (110 mg/kg/day)			Group 4 (350 mg/kg/day)		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Sperm % Motility	90.2	7.58	22	85.5	20.75	22	88.5	8.41	22	88.6	12.94	22
Total Sperm Count per Cauda Epididymis x 10^8	2.988	0.530	22	3.096	0.716	22	3.110	0.448	22	2.575[a]	0.384	22
Sperm Concentration per gram Cauda Epididymis x 10^8	11.229	1.698	22	10.775	1.727	22	11.069	1.112	22	10.023[a]	1.351	22
% Abnormal	2.66	1.990	22	6.05	19.494	22	2.55	2.075	22	5.39	5.416	22

N - Number of measures used to calculate mean
SD - Standard Deviation
[a]Significantly different from control; ($p<0.05$)

Gross Pathology

At the terminal necropsy, there were no drug-related gross pathology findings.

Organ Weights

There were no drug-related changes in organ weights. Decreases in the absolute weights of epididymis, prostate, and seminal vesicle with coagulating gland were observed in HD, which were likely secondary to decreases in body weight.

Female Cesarean Data

There were no drug-related changes in female cesarean data (Table 36).

Compared to vehicle controls, MD had decreases in viable embryos per dam (↓22%) and implantation sites per dam (↓18%), and increases in pre-implantation (22.79% vs 10.1 in controls) and post-implantation loss (12.12% vs 5.05% in controls). These values were also outside of the historical control range. Data from individual dams showed that the changes were mainly due to two females with 92.9% and 84.6% pre-implantation loss (Animal Nos. 339 and 341). Because no similar findings were observed in HD and because females were not drug-treated, these changes are considered to be incidental.

Table 36: Female Cesarean Data in the Male Rat Fertility Study

Endpoint		Group 1	Group 2	Group 3	Group 4
No. Females on Study		22	22	22	22
No. Not Pregnant		2	0	3	3
No. Pregnant		20	22	19	19
No. Females with Viable Embryos Day 13 Gestation		18	21	19	18
No. Pregnant Females with No Confirmed Mating Date		2	1	0	1
Corpora Lutea					
No. per Animal	Mean	16.4	15.5	15.4	16.3
	SD	1.54	1.44	3.31	2.68
	N	18	21	19	18
Implantation Sites					
No. per Animal	Mean	14.7	15.0	12.1	15.1
	SD	3.53	1.53	5.39	1.84
	N	18	21	19	18
Preimplantation Loss					
% per Animal	Mean	10.10	3.38	22.79	6.74
	SD	20.412	4.247	29.571	6.849
	N	18	21	19	18
Viable Embryos					
No. per Animal	Mean	13.9	14.0	10.8[a]	14.3
	SD	3.46	2.14	5.21	2.19
	N	18	21	19	18
Postimplantation Loss					
% per Animal	Mean	5.05	6.60	12.12	5.70
	SD	10.276	8.626	18.709	5.984
	N	18	21	19	18
Resorptions: Early + Late					
No. per Animal	Mean	0.8	1.0	1.3	0.8
	SD	1.72	1.20	1.77	0.86
	N	18	21	19	18

N - Number of measures used to calculate mean
SD - Standard Deviation
No. - Number
[a] Significantly different from control; ($p<0.05$)

9.1.3 Effects of solriamfetol on Lordotic Response of the Female Rat (Study No. SK8370, non-GLP)

In ovariectomized and estrogen treated female Long-Evans rats, subcutaneous administration (SC) of solriamfetol at 26 and 84 mg/kg caused significant increases in lordotic behavior relative to vehicle controls. The lordosis-promoting effects of solriamfetol were similar to quinelorane (a D2 receptor agonist, 25 µg/kg, SC) or bupropion (30 mg/kg, SC).

9.2 Embryonic Fetal Development

9.2.1 Study for Effects of solriamfetol (YKP10A) on Embryo-Fetal Development in Rats

Study no.:	(b) (4) 0328RY01-002
Study report location:	EDR, SDN-1, NDA 211230
Conducting laboratory and location:	(b) (4)
Date of study initiation:	08/27/1997
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	solriamfetol, 671-671-96-001, 99.85%

Key Study Findings

- Solriamfetol caused maternal toxicities of dose-dependent decreases in body weight, body weight gain, and food consumption in MD and HD.
- Solriamfetol caused fetal toxicities of increases in early resorption and post-implantation loss in MD and HD, and decreased in fetal weight in HD.
- Solriamfetol caused a small increase in fetal malformations in HD.
- Based on the decreases in body weight gain in the dams and the findings in the fetuses, the NOAEL for maternal toxicity and embryo-fetal toxicity is the low dose of 15 mg/kg/day, which is approximately 0.5 times the MRHD of 300 mg/day on a mg/m^2 basis.
- No malformation (teratogenicity) was observed at doses up to the MD of 67 mg/kg/day, which is approximately 2 times the MRHD of 300 mg based on mg/m^2 body surface area. Fetal malformation was observed at 295 mg/kg/day, which is approximately 9.5 times the MRHD based on mg/m^2 body surface area.

Methods

Doses:	0 (vehicle control, saline), 15 (LD), 67 (MD), and 295 (HD) mg/kg/day
Frequency of dosing:	once daily
Dose volume:	10 mL/kg
Route of administration:	oral gavage
Formulation/Vehicle:	saline (0.9% sodium chloride) for injection USP
Species/Strain:	Sprague Dawley (SD) rats from (b) (4)
Number/Sex/Group:	n=24/group
Satellite groups:	None
Study design:	Pregnant rats were orally administered with solriamfetol at 0, 15, 67, and 295 mg/kg/day from gestation Days (GD) 6 to 15, inclusive. Necropsy/cesarean was performed on GD 20. Parameters evaluated include mortality, clinical signs, body weight, food consumption, necropsy, and cesarean evaluation. No justification for dose selection is provided in the study report. In a 90-day general toxicology study in Wistar rats, 295 mg/kg/day was considered to be the MTD
Deviation from study protocol:	none that significantly impacted the study interpretation.

Observations and Results

Mortality

No mortality occurred in this study. There were no premature deliveries or abortions.

Clinical Signs

Drug-related clinical signs were observed in HD dams, including abnormal head movements, constant biting of the bottom of the cage or sipper, whole body tremors, labored breathing, hair loss (possibly due to excessive grooming), and swollen cranial regions (possibly due to self-mutilation). These effects were not observed in MD except for a lower incidence of hair loss. LD was not affected.

These drug-related clinical signs were similar to those observed in general toxicology studies and are likely due to the pharmacology of the drug. The severity in HD is adverse.

Body Weight

Compared to controls, cumulative body weight gain from GDs 0 to 20 was decreased by ~ 15% and 40% in MD and HD dams, respectively. No effects on body weight or body weight gain were observed in LD. The terminal body weights (corrected for gravid uterus and contents) were decreased by 3% and 8% in MD and HD, respectively (Table 37). Decreases in body weight and body weight gain correlated with decreases in food consumption in HD but not in MD.

Table 37: Body Weight and Body Weight Change in the Rat Embryo-Fetal Development Toxicity Study

Dose (mg/kg/day)		Gestation Day 14	15	16	17	18	19	20	Corrected Body Weight[a]	Corrected Body Weight Change[b]
0	$\bar{x}$	297	305	316	333	349	367	383	301	62
	S.D.	12.8	13.8	12.9	13.3	14.7	15.1	16.4	12.6	8.4
	N	24	24	24	24	24	24	24	24	24
18	$\bar{x}$	294	300	312	327	343	359	374	297	58
	S.D.	14.0	15.9	17.4	20.8	22.8	26.2	30.9	13.3	7.7
	N	21	21	21	21	21	21	21	21	21
80	$\bar{x}$	283**	289**	298**	313**	329*	344*	359*	292*	53**
	S.D.	14.3	15.3	17.6	21.9	27.1	32.1	36.4	13.9	12.5
	N	23	23	23	23	23	23	23	23	23
350	$\bar{x}$	272**	274**	280**	292**	309*	327*	347*	277**	37**
	S.D.	11.0	10.4	12.2	17.9	23.1	27.2	30.2	13.3	11.0
	N	22	22	22	22	22	22	22	22	22

[a] = Body weight after removal of gravid uterus and contents
[b] = Day 0 body weight subtracted from corrected body weight
* = P<0.05
** = P<0.01

[Doses in the table are presented as the hydrochloride salt weight; the free base equivalent doses are 0, 15, 67, 295 mg/kg/day]

Food Consumption

During the treatment phase (GDs 6 to 15), compared to controls, food intake was decreased in HD (↓up to ~ 30%), which correlated with decreases in body weight and body weight gain. Food consumption in the LD and MD was not affected.

During the treatment free phase (GDs 0 to 5 and 16 to 20), food consumption was not affected and the values were comparable across all groups.

Toxicokinetics
Not performed

Dosing Solution Analysis
The concentration and stability of the dosing formulation were confirmed to be within the acceptable range.

Necropsy
At the terminal necropsy, hair loss, scab formations and/or swollen regions of the body, particularly on the cranial region were observed in MD and HD. These observations were likely associated with drug-induced increases in activity. No other drug-related necropsy findings were observed. 1 MD dam had a fluid-filled uterus. Given the lack of similar findings at higher doses, this finding is considered to be incidental.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)
Compared to controls, MD and HD had increases in early resorption (1.3 and 1.4 respectively, compared to 0.8 in controls), total resorption (1.4 and 1.6 respectively, compared to 0.8 in controls), and post-implantation loss (19.1 and 14 respectively, compared to 5.8 in controls). In addition, fetal weights were decreased in HD (↓7% and 8% in HDM&F, respectively, Table 38). These changes suggest drug-related embryo-fetal toxicity in MD and HD. LD was not affected.

The male-to-female ratio was decreased in LD (5.3: 7.5 =0.7 compared to 7.4: 6.1=1.2 in controls). Given the lack of similar findings in MD or HD, this change is considered to be incidental.

Table 38: Cesarean Data in the Rat Embryo-fetal Development Toxicity Study

GROUP:		1	2	3	4
DOSE LEVEL (MG YKP10A/KG/DAY):		0	18	80	350
NUMBER OF GRAVID FEMALES		24	21	23	22
NUMBER OF CORPORA LUTEA	MEAN	17.6	16.7	16.0	17.2
	S.D.	2.5	3.5	4.6	2.7
NUMBER OF IMPLANTATIONS	MEAN	14.3	13.7	12.5	14.1
	S.D.	2.5	3.4	4.6	3.4
PERCENT PREIMPLANTATION LOSS	MEAN	17.8	17.7	24.0	18.5
	S.D.	14.5	17.0	21.7	17.7
NUMBER OF VIABLE FETUSES	MEAN	13.5	12.8	11.0	12.2
	S.D.	2.3	3.6	4.6	3.6
NUMBER OF NONVIABLE FETUSES	MEAN	0.1	0.0	0.0	0.3
	S.D.	0.4	0.2	0.2	0.6
NUMBER OF EARLY RESORPTIONS	MEAN	0.8	0.7	1.3	1.4
	S.D.	0.8	0.8	1.0	1.2
NUMBER OF LATE RESORPTIONS	MEAN	0.0	0.1	0.2	0.2
	S.D.	0.2	0.5	0.4	0.7
NUMBER OF TOTAL RESORPTIONS	MEAN	0.8	0.8	1.4*	1.6*
	S.D.	0.8	1.0	1.0	1.5
PERCENT POSTIMPLANTATION LOSS	MEAN	5.8	7.5	19.1*	14.0*
	S.D.	6.4	13.4	27.0	12.4
PERCENT TOTAL IMPLANTATION LOSS	MEAN	22.6	23.0	34.2	29.8
	S.D.	13.7	18.9	27.1	19.6
SEX: MALES / FEMALES[b]	MEAN	7.4 6.1	5.3 7.5	5.8 5.3	6.2 6.0
	S.D.	2.0 2.0	2.3 3.0	3.3 2.8	2.4 3.0
FETAL WEIGHT (g) (LITTER)[a,b]	MEAN	4.0	3.9	4.0	3.7*
	S.D.	0.2	0.3	0.3	0.5
(MALES)[a,b]	MEAN	4.1	4.1	4.2	3.8*
	S.D.	0.2	0.3	0.3	0.5
(FEMALES)[a,b]	MEAN	3.9	3.8	3.8	3.6*
	S.D.	0.2	0.3	0.3	0.6
GRAVID UTERUS WEIGHT (g)	MEAN	82	77	67*	70
	S.D.	13	22	27	20

[a] VALUE FOR EACH GROUP REPRESENTS THE MEAN OF THE INDIVIDUAL LITTER MEANS.
[b] DOES NOT INCLUDE DATA FROM DEAD FETUSES.
* SIGNIFICANTLY DIFFERENT FROM CONTROL ($p<0.05$).

[Doses in the table are presented as the hydrochloride salt weight; the free base equivalent doses are 0, 15, 67, 295 mg/kg/day]

Offspring (Malformations, Variations, etc.)

Compared to controls, HD had a slightly increased number of external, visceral, or skeletal malformations when counted by fetuses or by litters (Table 39). These malformations included single litter incidences of hindlimb rotation, situs inversus and bent limb bones; and two litters had one fetus each with severely mal-aligned sternebrae (Table 39). The Applicant considers these findings to be incidental; however, given the lack of historical control data and the significant increase in HD when counted both by litter and by fetus numbers, I conclude that solriamfetol potentially caused a small increase in the incidence of malformations in HD. LD and MD were not affected.

No drug-related fetal variations were observed. The numbers of fetuses or litters with fetal variations were comparable across all groups.

Table 39: Summary of Fetal Malformation Findings in the Rat Embryo-fetal Development Study

	FETUSES[a]				LITTERS			
GROUP:	1	2	3	4	1	2	3	4
DOSE LEVEL (MG YKP10A/KG/DAY):	0	18	80	350	0	18	80	350
NUMBER EXAMINED EXTERNALLY	325	269	255	268	24	21	21	22
HINDLIMB ROTATION	0	0	0	1	0	0	0	1
NUMBER EXAMINED VISCERALLY	158	133	122	129	24	21	21	22
SITUS INVERSUS	0	0	0	1	0	0	0	1
NUMBER EXAMINED SKELETALLY	167	136	133	139	24	21	21	22
STERNEBRA(E) MALALIGNED - SEVERE	0	1	1	2	0	1	1	2
BENT LIMB BONES	0	0	0	4	0	0	0	1
TOTAL MALFORMATIONS								
NUMBER WITH EXTERNAL MALFORMATIONS	0	0	0	1	0	0	0	1
NUMBER WITH VISCERAL MALFORMATIONS	0	0	0	1	0	0	0	1
NUMBER WITH SKELETAL MALFORMATIONS	0	1	1	6	0	1	1	3
TOTAL WITH MALFORMATIONS	0	1	1	8	0	1	1	5*

[a] DOES NOT INCLUDE INFORMATION FROM DEAD FETUSES.
* SIGNIFICANTLY DIFFERENT FROM CONTROL ($p<0.05$).

[Doses in the table are presented as the hydrochloride salt weight; the free base equivalent doses are 0, 15, 67, 295 mg/kg/day]

9.2.2 Study for Assessing the Effects of solriamfetol (YKP10A) on Embryo-Fetal Development in Rabbits

Study no.:	(b) (4) 0329LY01-002
Study report location:	EDR, SDN-1, NDA 211230
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11/12/1997
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	solriamfetol, 671-671-96-001, 99.85%

Key Study Findings

- Solriamfetol caused pharmacology-related clinical signs, body weight loss and decreases in food consumption in HD.
- Solriamfetol caused skeletal malformation (slight to moderate mal-aligned sternebrae) and decreased fetal weight in MD and HD.
- Based on the decreases in maternal body weight and food consumption, the NOAEL for maternal toxicity is the mid-dose of 38 mg/kg/day, which is approximately 2.5 times the MRHD of 300 mg based on mg/m^2 body surface area. Based on the fetal malformation and decreased fetal weight findings, the NOAEL for embryo-fetal toxicity is the low-dose of 17 mg/kg/day, which is approximately 1 time the MRHD based on mg/m^2 body surface area.

Methods

Doses: 0 (vehicle control), 17 (LD), 38 (MD), and 76 (HD) mg/kg/day

Frequency of dosing:	once daily
Dose volume:	3 mL/kg
Route of administration:	intubation and later switched to oral gavage due to excessive injury/death associated with intubation
Formulation/Vehicle:	saline (0.9% sodium chloride) for injection USP
Species/Strain:	New Zealand White Rabbits
Number/Sex/Group:	n=19/group
Satellite groups:	none
Study design:	Pregnant rabbits were orally administered with solriamfetol at 0, 17, 38, and 76 mg/kg/day once daily from Gestation Day (GD) 6 to 19, inclusive. Necropsy/cesarean was performed on GD 29. Parameters evaluated include mortality, clinical signs, body weight, food consumption, necropsy, and cesarean evaluation. Justification for dose selection was not provided. However, in a preliminary 7-day repeat dose study in non-pregnant rabbits, 126 mg/kg/day exceeded the MTD (Study No. (b) (4) 0440LY01-001).
Deviation from study protocol:	none that significantly impacted the study interpretation.

Observations and Results

Mortality

A total of 8 incidences of mortality occurred in the study (Table 40). In addition, 1 LD (No. 1730) and 1 HD (No. 1773) female aborted on GD 22 and 23, respectively and were subsequently sacrificed. Post-mortem necropsy showed lung perforation or ruptured stomach (Nos. 1715, 1737, 1746, and 1747); fractured spine (No. 1731); distended and thin wall in the stomach (No. 1742); dark discoloration or dark diffuse areas in the lung indicative of accidental aspiration of the drug (Nos. 1741 and 1730); and gastric obstruction due to trichobezoar (ingestion of hair, No. 1776). Therefore, except for the one HD female (No. 1773), other pre-mature deaths or abortion were likely due to dosing complication from intubation or trichobezoar rather than directly drug-induced toxicity: After the dosing route changed from intubation to gavage needle, no more mortality occurred.

The cause for abortion in the HD female (No. 1773) was unknown; a possible drug involvement cannot be ruled out.

Table 40: Mortality incidences in the Rabbit Embryo-fetal Development Toxicity Study

Group 1 0 mg/kg/day	Group 2 20 mg/kg/day	Group 3 45 mg/kg/day	Group 4 90 mg/kg/day
No. 1715 GD 9	No. 1731 GD 7 No. 1737 GD 14[b]	No. 1741 GD 21[a] No. 1742 GD 19 No. 1746 GD 11 No. 1747 GD 17	No. 1776 GD 26

[a] Animal Sacrificed
[b] Animal was nongravid.

[Doses in the table are presented as the hydrochloride salt weight; the free base equivalent doses are 0, 17, 38, 76 mg/kg/day]

Clinical Signs

Drug-related clinical signs included constant mouth movement (HD only), and dose-dependent increases in hair loss at all doses, likely due to excessive grooming. These clinical signs were also observed in non-pregnant female rabbits in a 7-day repeat dose study and other animal test species and are likely related to the stimulant-like pharmacology of the drug.

Body Weight

During the treatment period (GD 6 to 19), compared to controls, HD lost weight (-0.2 kg compared to +0.1 kg in controls, Table 41), which correlated with decreases in food consumption. Trend towards recovery in body weight gain occurred during the treatment free period (GD 20 to 29, + 0.3 kg compared to + 0.2 kg in controls, Table 41). Due to the body weight loss in the treatment period, the overall body weight gain for the entire gestation period (GD 0 to 29, inclusive) was slightly decreased in HD (0.2 kg compared to 0.3 kg in controls, Table 41).

Food Consumption

During the treatment period (GD 6 to 19), compared to controls, HD had decreases in food consumption (↓~ 35% relative to controls), which correlated with body weight loss in this period. During the treatment free period (GD 20 to 29), food consumption was comparable between HD and controls. Food consumption in LD and MD was not affected.

Table 41: Body Weight Changes in the Rabbit Embryo-fetal Development Toxicity Study

Dose (mg/kg/day)		Gestation Interval (Days) 0-6	6-19	19-29	6-29	0-29
0	$\bar{x}$	0.1	0.1	0.2	0.2	0.3
	S.D.	0.09	0.10	0.07	0.12	0.14
	N	18	17	17	17	17
20	$\bar{x}$	0.1	0.1	0.2	0.3	0.3
	S.D.	0.13	0.12	0.09	0.13	0.11
	N	16	15	14	14	14
45	$\bar{x}$	0.1	0.1	0.2	0.3	0.4
	S.D.	0.09	0.10	0.10	0.10	0.13
	N	19	17	15	15	15
90	$\bar{x}$	0.0	-0.2**	0.3**	0.1*	0.2**
	S.D.	0.09	0.15	0.09	0.15	0.18
	N	17	17	15	15	15

* = P<0.05
** = P<0.01

[Doses in the table are presented as the hydrochloride salt weight; the free base equivalent doses are 0, 17, 38, 76 mg/kg/day]

Toxicokinetics

Not conducted

Dosing Solution Analysis

The stability of the dosing formulation was confirmed to be acceptable. Samples were retained for potential homogeneity and concentration analysis; however, no detailed records of the homogeneity or concentration data were included in the study report. This deviation is unlikely to affect the data interpretation. Although TK is not performed, drug-related clinical signs and changes in body weight gain and food consumption were observed and were consistent with previous repeat dose studies in the rabbits, therefore qualitatively confirming drug exposure.

Necropsy

At the terminal necropsy, no drug-related differences were observed (Table 42). The pregnancy rate was 94.7%, 85.2%, 100.0%, and 89.5% in the control, LD, MD, and HD, respectively (data excluding pre-mature deaths and animals with early abortion).

Table 42: Summary of Necropsy Findings in the Rabbit Embryo-fetal Development Toxicity Study

GROUP:	1		2		3		4	
DOSE LEVEL (MG/KG/DAY):	0		20		45		90	
	No.	%	No.	%	No.	%	No.	%
FEMALES ON STUDY	19		19		19		19	
FOUND DEAD/EUTHANIZED	1	5.3	2[a]	10.5	4	21.1	1	5.3
PREMATURE DELIVERY/ABORTION	0	0.0	1	5.3	0	0.0	1	5.3
EXAMINED AT CESAREAN SECTION	18	94.7	16	84.2	15	78.9	17	89.5
NONGRAVID	1	5.6	2	12.5	0	0.0	2	11.8
GRAVID	17	94.4	14	87.5	15	100.0	15	88.2
WITH TOTAL RESORPTIONS	0	0.0	0	0.0	0	0.0	0	0.0
WITH LIVE FETUSES	17	100.0	14	100.0	15	100.0	15	100.0
TOTAL GRAVID FEMALES	18	94.7	16	85.2	19	100.0	17	89.5

[a] ANIMAL NO. 1737 WAS NONGRAVID.

GROUP:	1	2	3	4
DOSE LEVEL (MG/KG/DAY):	0	20	45	90
NUMBER OF FEMALES EXAMINED AT THE SCHEDULED GESTATION DAY 20 CESAREAN SECTION	18	16	15	17
NO ABNORMALITIES DETECTED	10	9	8	9
NONGRAVID	1	3	0	2
ABDOMINAL CAVITY				
-CONTAINS FLUID	2	2	0	0
OVARY(IES)				
-CYST(S)	5	3	4	4
HAIRLOSS				
-LEFT DORSAL ABDOMINAL	1	1	0	1
-RIGHT DORSAL ABDOMINAL	0	1	3	0
-LEFT VENTRAL ABDOMINAL	0	1	0	1
-LEFT DORSAL LUMBAR	1	1	0	1
-RIGHT DORSAL LUMBAR	1	4	3	1
-INGUINAL	0	1	0	0
-LEFT INGUINAL	0	0	0	2
-LEFT DORSAL CRANIAL	0	0	1	1

NOTE: DOES NOT INCLUDE FEMALES WHICH WERE SACRIFICED MORIBUND, FOUND DEAD OR ABORTED (SEE APPENDIX A FOR INDIVIDUAL FINDINGS).

[Doses in the table are presented as the hydrochloride salt weight; the free base equivalent doses are 0, 17, 38, 76 mg/kg/day]

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

Compared to controls, dose-dependent decreases in fetal weight were observed when tabulated by litter and separately by sex (Table 43). The decreases in fetal weight were most profound in MD and HD and were likely due to the decreases in maternal body weight gain and food consumption. Other cesarean parameters were not affected.

Table 43: Summary of Cesarean Data in the Rabbit Embryo-fetal Development Toxicity Study

GROUP:		1	2	3	4
DOSE LEVEL (MG/KG/DAY):		0	20	45	90
NUMBER OF GRAVID FEMALES		17	14	15	15
NUMBER OF CORPORA LUTEA	MEAN	13.4	11.3	10.9	12.9
	S.D.	3.7	1.4	3.2	2.6
NUMBER OF IMPLANTATIONS	MEAN	7.1	8.1	7.5	8.7
	S.D.	3.1	2.5	3.0	3.0
PERCENT PREIMPLANTATION LOSS	MEAN	45.0	29.7	32.8	32.4
	S.D.	27.0	21.7	18.9	18.4
NUMBER OF VIABLE FETUSES	MEAN	6.4	7.0	6.9	7.7
	S.D.	2.8	2.8	2.8	2.5
NUMBER OF NONVIABLE FETUSES	MEAN	0.0	0.1	0.2	0.3
	S.D.	0.0	0.3	0.6	0.7
NUMBER OF EARLY RESORPTIONS	MEAN	0.5	0.7	0.1	0.5
	S.D.	0.8	1.1	0.3	0.5
NUMBER OF LATE RESORPTIONS	MEAN	0.1	0.3	0.3	0.1
	S.D.	0.3	0.6	0.7	0.4
NUMBER OF TOTAL RESORPTIONS	MEAN	0.6	1.0	0.4	0.6
	S.D.	0.8	1.2	0.7	0.7
PERCENT POSTIMPLANTATION LOSS	MEAN	8.2	13.9	6.6	9.6
	S.D.	10.1	18.8	12.3	9.6
PERCENT TOTAL IMPLANTATION LOSS	MEAN	50.0	39.6	37.7	39.5
	S.D.	24.9	22.6	18.5	16.2
SEX: MALES / FEMALES[b]	MEAN	3.6 2.8	3.5 3.5	3.3 3.6	3.6 4.1
	S.D.	2.3 1.7	1.5 2.1	2.1 1.3	1.8 1.7
FETAL WEIGHT (g) (LITTER)[a,b]	MEAN	48.6[c]	45.7	44.3	43.2[c]
	S.D.	5.4	4.5	4.3	6.0
(MALES)[a,b]	MEAN	48.7	46.3	44.5	43.6[c]
	S.D.	4.5	4.8	4.8	5.7
(FEMALES)[a,b]	MEAN	47.5[c]	44.5	44.0	43.2
	S.D.	6.8	5.1	4.2	6.5
GRAVID UTERUS WEIGHT (g)	MEAN	442	468	458	485
	S.D.	156	178	147	120

[a] VALUE FOR EACH GROUP REPRESENTS THE MEAN OF THE INDIVIDUAL LITTER MEANS.
[b] DOES NOT INCLUDE DATA FROM DEAD FETUSES.
[c] DOES NOT INCLUDE ANIMAL 1706, FETUS 4 FOR WHICH A WEIGHT WAS NOT RECORDED.
[*] SIGNIFICANTLY DIFFERENT FROM CONTROL ($p<0.05$).

[Doses in the table are presented as the hydrochloride salt weight; the free base equivalent doses are 0, 17, 38, 76 mg/kg/day]

Offspring (Malformations, Variations, etc.)

Compared to controls, drug-related fetal malformations (slight-to-moderate mal-aligned sternebrae) were observed in MD and HD (Table 44). The Applicant considered it an incidental variation based on the commonly occurring nature of the observation. However, given the clear dose response in the MD and HD when counted by both litter and fetus, the lack of historical control data, and the similar finding of severely mal-aligned sternebrae in the rat study, I consider it to be a drug-related malformation.

All variations had comparable incidences across all groups including the control.

Table 44: Increases in Skeletal Malformations in the Rabbit Embryo-fetal Development Toxicity Study

	FETUSES*				LITTERS			
GROUP:	1	2	3	4	1	2	3	4
DOSE LEVEL (MG/KG/DAY):	0	20	45	90	0	20	45	90
STERNEBRA(E) MALALIGNED (SLIGHT-MODERATE)	5	9	11	14	4	4	9	10*

[Doses in the table are presented as the hydrochloride salt weight; the free base equivalent doses are 0, 17, 38, 76 mg/kg/day]

9.3 A Perinatal/Postnatal Developmental and Reproduction Study of solriamfetol by Oral (Gavage), Including a Postnatal Behavioral/Functional Evaluation

Study no.:	(b) (4)-20078502
Study report location:	EDR, SDN-1, NDA-211230
Conducting laboratory and location:	(b) (4)
Date of study initiation:	08/21/2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	solriamfetol, 1518H038, 98.8%

Key Study Findings

- Solriamfetol caused dose-dependent decreases in maternal body weight, body weight gain, and food consumption; and dose-dependent increases in clinical signs of hyperpnea and repetitive sniffing in MD and HD.
- HD had decreases in the number of pups delivered, increases in still-born pups. MD and HD had increases in the pup mortality during the lactation period.
- F1 generation in MD and HD had decreases in body weight and body weight gain; and delayed sexual maturation. F1 male and female rats in HD had decreased mating and fertility.
- Learning and memory in the F1 generation was not affected.
- Solriamfetol is present in the milk at approximately 3 to 4 times higher than in the plasma on post-partum day 15.
- The NOAEL for maternal toxicity and development toxicity of F1 generation is the low dose of 35 mg/kg/day, which is approximately 1 time the MRHD of 300 mg based on mg/m^2 body surface area.

Methods

Doses:	0 (vehicle control), 35 (LD), 110 (MD), and 350 (HD) mg/kg/day
Frequency of dosing:	once daily
Dose volume:	5 mL/kg
Route of administration:	oral gavage
Formulation/Vehicle:	deionized water
Species/Strain:	Sprague Dawley rats Crl:CD (SD)
Number/Sex/Group:	n=22/group
Satellite groups:	none
Study design:	Pregnant rats were orally treated with solriamfetol at 0, 35, 110, and 350 mg/kg/day from Gestation Day (GD) 6 to Post-partum Day /Lactation Day, LD) 20 (for rats that deliver a litter) or LD 24 (for rats that did not deliver a litter). Parameters evaluated include: for F0 generation: mortality, clinical signs, body weight, food consumption, parturition, lactation, maternal behavior, and macroscopic observations; for F1 generation: viability, clinical signs, body weight, food consumption, sexual maturation, learning and memory, reproductive capacity, macroscopic findings and organ weights, and ovarian and uterine contents. Milk and blood levels of solriamfetol were determined from F0 generation at 0.75 hours post dosing on LD 15. High dose of 350 mg/kg/day is selected based on findings from the 6-month repeat dose studies, in which 252 mg/kg/day was tolerated, whereas 505/379 mg/kg/day induced excessive and severe excitatory neurobehaviors and caused mortality.
Deviation from study protocol:	none that significantly impacted the study interpretation

Observations and Results (Optional Table)

F0 Generation:

Mortality
No mortality occurred in the dams.

Clinical Signs
Pharmacology-related clinical signs occurred dose-dependently during the gestation and lactation periods. They included hyperpnea at all doses; repetitive sniffing in MD

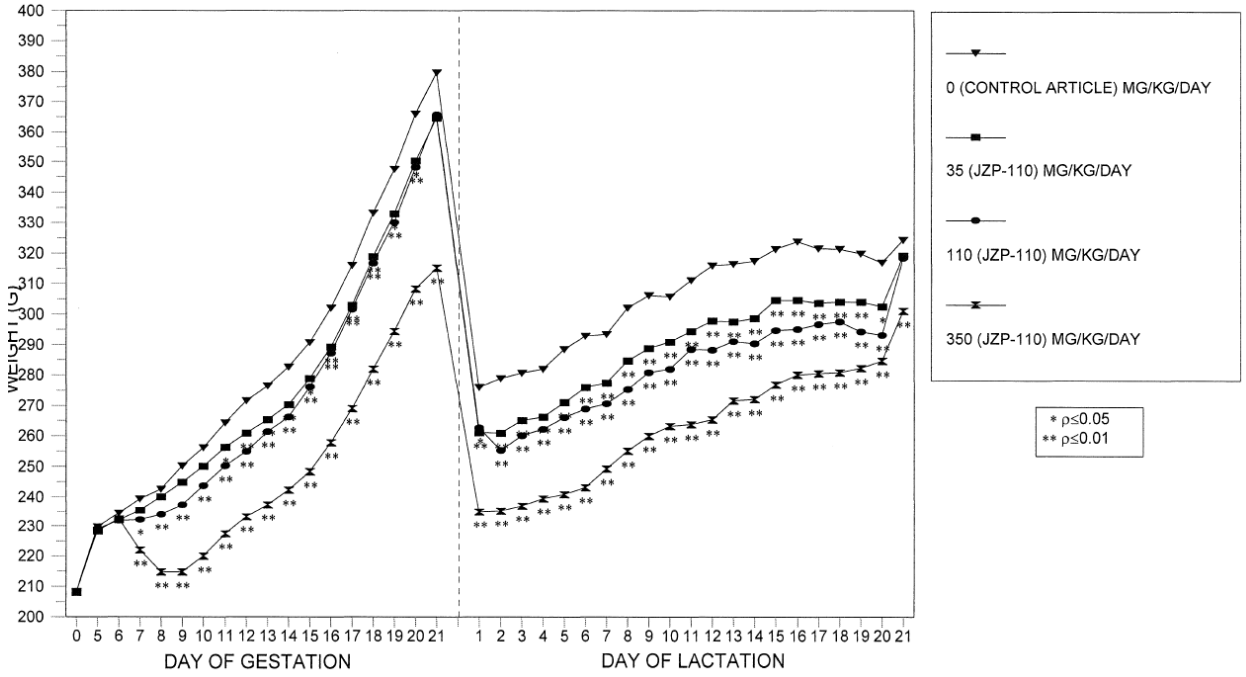
and HD; hunched posture, piloerection, hyperactivity to touch/sound, and mild dehydration in HD.

Body Weight

During the gestation period, compared to controls, dose-dependent decreases in body weight gain were observed. The cumulative body weight gain from GD 0 to 21 was decreased by 6.4%, 6.9%, and 37.3% in LD, MD, and HD, respectively. On GD 21, the mean body weight was also decreased by 4.0%, 3.7%, and 17.0% in LD, MD, and HD, respectively (Figure 17). Decreases in body weight gain and body weigh during the gestation period correlated with decreases in food consumption.

During the lactation period, compared to controls, drug-treated animals had comparable body weight gain, whereas the mean body weight on LD 21 was still decreased by 1.6%, 1.8%, and 7.2% in LD, MD, and HD, likely due to the decreases in body weight and body weight gain during the gestation period (Figure 17).

Figure 17: Body Weight Curve of the F0 Generation in the Rat Pre- and Post-natal Development Toxicity Study



Food consumption

During the gestation period, compared to controls, food consumption was decreased by 4.1%, 5.0%, and 24.6% in LD, MD, and HD, respectively, which correlated with decreases in body weight gain and body weight.

During the lactation period, compared to controls, food consumption was decreased by 18.5% in HD. LD and MD were not affected.

Maternal Necropsy
At the terminal necropsy (LD 21 or 25), no drug-related findings were observed in the dams.

Natural delivery and litter observations (Table 45)
No drug-related effects on any parameters were observed in the dams. In F1 generation, compared to controls, HD had decreases in the total number of pups and increases in still born pups. MD and HD had increases in the number of pups dying on Postpartum Day (PD) 1 and PD 2-4. The viability index was decreased in MD and HD and the lactation index was slightly decreased in HD. Dose-dependent decreases in average pup weights between PD 1-21 were observed in MD and HD.

In addition, HD had increases in the number of litters with adverse clinical observations in the pups, mainly dehydration, cold to touch, ungroomed coat, and no milk band (Table 45). No drug-related clinical signs were observed in LD or MD.

Table 45: Summary of Litter Observation in the Rat Pre- and Post-natal Development Toxicity Study

F0 generation female:	**0 mg/kg/day**	**35 mg/kg/day**	**110 mg/kg/day**	**350 mg/kg/day**
Number of Dams	22	22	22	22
Delivered litter	22	22	21	22
Gestation index	100%	100%	95%	100%
Mean No. of Implantations	13.5	13.3	14.0	13.1
F1 generation litters:	**0 mg/kg/day**	**35 mg/kg/day**	**110 mg/kg/day**	**350 mg/kg/day**
Number of pups	280	284	282	256
Number (%) of Live pups	280 (100%)	282 (99.3%)	281 (99.6%)	251 (98.0%)
Number (%) of Still born pups	0 (0%)	2 (0.7%)	1 (0.4%)	3 (1.2%)
unknown vital status[a]	0	0	0	2
Mean No. pups/Litter	12.7	12.9	13.4	11.6
Mean No. live pups/Litter	12.7	12.8	13.4	11.4
Number (%) of pups dying on Day 1	3/280 (1.1%)	1/282 (0.4%)	17/281 (6.0%)	8/251 (3.2%)
Number (%) of pups dying between Day 2 - 4	0/277 (0%)	2/281 (0.7%)	6/264 (2.3%)	54/243 (22.2%)
Viability Index	277/280 (98.8%)	279/282 (98.9%)	258/281 (91.8%)	189/251 (75.3%)
Lactation index	276/277 (99.6%)	279/279 (100%)	256/258 (99.2%)	184/189 (97.4%)
No of Total Litter Losses	0	0	1	4
Litter size (PD 1) (PD 21)	12.7 12.5	12.8 12.7	13.4 12.2	11.4 8.4

Pup weight (PD 1) (PD 21)	6.8 42.4	6.9 40.4 (↓4.7%)	6.5 36.1 (↓14.9%)	6.0 29.9 (↓29.5%)
Pup Sex Ratio (% males)	51.8%	48.9%	56.2%	53.0%
F1 Pups Clinical Observation	**0 mg/kg/day**	**35 mg/kg/day**	**110 mg/kg/day**	**350 mg/kg/day**
Litters examined	22	22	21	22
Dehydration	0/22	0/22	0/21	7/22
Cold to touch	0/22	0/22	0/21	6/22
Ungroomed coat	0/22	0/22	0/21	5/22
No milk band present	0/22	0/22	0/21	3/22

[a, maternal cannibalization or autolysis precluded identification of vital status at birth; Viability index: number of live pups on PD 4/number of live pups on PD 1; lactation index: number of live pups on PD 21/number of live pups on Day 4]

F1 Generation:

Mortality

Mortality occurred only in HD. After weaning, three mortalities occurred in the HD F1 generation (Nos. 481, 532, and 575). One male rat (No. 481) died on post-natal day (PND) 23 due to "its failure to thrive post weaning" with very low body weight of 22 grams on PND 22 (compared to 42 g in controls) and ungroomed coat, decreased motor activity, ataxia, ptosis, cold-to-touch, moderate dehydration, pale extremities, and scant feces. One female (No. 582) died on PND 23 with low body weight of 20 grams and ungroomed coat. The mortality of these two rats is considered to be drug-related decreases in body weight gain and growth.

One additional female (No. 575) rat was euthanized on PND 47 due to adverse clinical signs of enlarged eye and head tilt. Post-mortem necropsy did not observe any abnormal findings. Therefore, it is unknown whether this death was also drug-related or not.

All other F1 generation rats survived to scheduled euthanasia.

Clinical Observations

Compared to controls, ungroomed coat occurred in 5/22 HD F1 females. No other drug-related clinical signs were observed. F1 males were not affected.

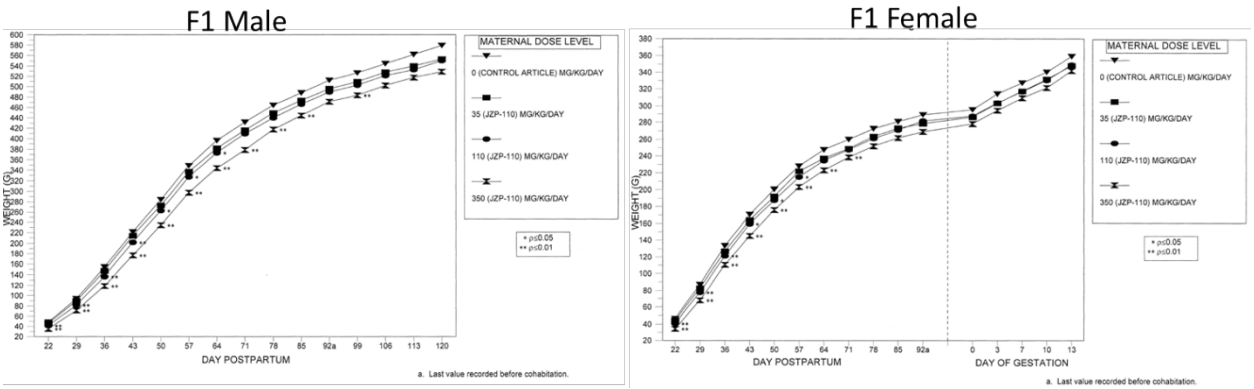
Body Weights (Figure 18)

Compared to controls, dose-dependent decreases in body weight and body weight gains were observed in the F1 generation at all doses. On PND 120, compared to controls, the average body weight of F1 males was decreased by 4.51%, 5.01%, and 8.69% in the LD, MD, and HD, respectively. From PNDs 22 to 92, the average body weight gain of F1 males was decreased by 2.93%, 3.17%, and 6% in the LD, MD, and HD, respectively. On PND 92, compared to controls, the average body weight of F1

females was decreased by 3.6%, 2.49%, and 6.89% in the LD, MD, and HD, respectively. From PNDs 22 to 92, the average body weight gain of F1 females was decreased by 3.38%, 0.58%, and 3.51% in the LD, MD, and HD, respectively. Decreases in body weight and body weight gain correlated with decreases in food consumption in F1 males but not F1 females.

During the gestation period, the body weight and body weight gain in F1 females were comparable across all groups, including the controls.

Figure 18: Body Weight Curve of the F1 Generation in the Rat Pre- and Post-natal Development Toxicity Study



Food Consumption

Compared to controls, food consumption from PND 29 to 92 was decreased in F1 males in MD and HD (↓7% and 9%, respectively), which correlated with the decreases in body weight and body weight gain.

Food consumption in F1 females was not affected during the growing and gestation period.

Sexual Maturation

Compared to controls, sexual maturation in the F1 generation was delayed in MD and HD (Table 46). The average day of preputial separation was increased in MD and HD F1 males (46.3 and 47.5 days respectively, compared to 44.1 days in controls). The average day of vaginal patency was increased in HD F1 females (34.0 days compared to 32.4 days in controls). The delay in sexual maturation in MD and HD is likely associated with the lower average body weight and growth retardation in the F1 generations. LD was not affected.

Table 46: Summary of Sexual Maturation in F1 Generation Rats in the Rat Pre- and Post-natal Development Toxicity Study

MATERNAL GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	JZP-110	JZP-110	JZP-110
MATERNAL DOSE LEVEL (MG/KG/DAY)		0	35	110	350
MALE RATS	N	22	22	22	21a
PREPUTIAL SEPARATION b	MEAN±S.D.	44.1 ± 1.9 [21]c	44.9 ± 1.9	46.3 ± 2.8* [21]d	47.5 ± 3.8**
BODY WEIGHT AT SEPARATION (G)e	MEAN±S.D.	230.2 ± 21.2 [21]c	230.0 ± 14.1	229.2 ± 24.5 [21]d	210.8 ± 18.8**
FEMALE RATS	N	22	22	22	21a
VAGINAL PATENCY f	MEAN±S.D.	32.4 ± 1.2 [21]c	32.4 ± 1.5 [19]c	32.6 ± 1.2	34.0 ± 1.7**
BODY WEIGHT AT VAGINAL PATENCY (G)g	MEAN±S.D.	109.0 ± 11.4 [21]c	104.4 ± 13.6 [19]c	99.2 ± 10.7*	96.8 ± 10.3**

[ ] = NUMBER OF VALUES AVERAGED
a. Excludes rats that were found dead or euthanized due to adverse clinical observations.
b. Average day postpartum that the prepuce was observed to be separated.
c. Excludes values for rats for which the exact day of maturity could not be determined.
d. Excludes values for rat 464, which did not have proper documentation of reaching sexual maturity.
e. Average body weight on day prepuce was first observed to be separated.
f. Average day postpartum that the vagina was observed to be patent.
g. Average body weight on day vagina was first observed to be patent.
* Significantly different from the control group value ($p \leq 0.05$).
** Significantly different from the control group value ($p \leq 0.01$).

Learning and Memory

Learning and memory were not affected by maternal dose of solriamfetol.

Transient, dose-dependent increases in the latency time in the passive avoidance test were observed in F1 males at all doses on PND 23±1. The difference was not present during the second test session one week later. Given the transient nature of this finding, it is likely due to the residual effects from lactational intake of solriamfetol in recently weaned pups, instead of a long-lasting drug effect on learning and memory. Water maze performance was comparable across all groups including the controls.

Mating and Fertility

Mating and fertility was compromised in HD F1 rats (Table 47). Compared to controls, HD had decreased mating index in F1 males (14/20 mated compared to 22/22 in controls) and females (15/20 mated compared to 22/22 in control). The fertility index was decreased in HD F1 males and females (82.4% and 78.9%, respectively, compared to 100% in controls). Because no drug-related effects were observed in the rat fertility studies at doses up to 350 and 295 mg/kg/day in males and females, respectively, the decreases in fertility in the F1 generation are likely secondary to the growth retardation in the F1 generation rather than a direct drug effect.

Mating and fertility in LD and MD F1 generation were not affected.

Table 47: Summary of Mating and Fertility in the F1 Generation in the Rat Pre- and Post-natal Development Toxicity Study

Male

MATERNAL GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	JZP-110	JZP-110	JZP-110
MATERNAL DOSE LEVEL (MG/KG/DAY)		0	35	110	350
RATS IN COHABITATION	N	22	22	22	20a,b
DAYS IN COHABITATION c,d	MEAN±S.D.	2.7 ± 1.0 [21]	2.5 ± 1.6 [21]	3.0 ± 1.3	3.6 ± 2.1
RATS THAT MATED d	N(%)	22(100.0)	21(95.4)	21(95.4)	17(85.0)
FERTILITY INDEX e,f	N/N	22/ 22	19/ 21	20/ 21	14/ 17
	(%)	(100.0)	(90.5)	(95.2)	(82.4)
RATS WITH CONFIRMED MATING DATES	N	21	20	21	17
MATED WITH FEMALE g DAYS 1-7	N(%)	21(100.0)	20(100.0)	21(100.0)	17(100.0)
RATS PREGNANT/RATS IN COHABITATION f	N/N	22/ 22	19/ 22	20/ 22	14/ 20
	(%)	(100.0)	(86.4)*	(90.9)	(70.0)**

[ ] = NUMBER OF VALUES AVERAGED
a. Excludes rat 481, which was euthanized on Day 23 postpartum due to adverse clinical observations.
b. Excludes rat 484, which was not assigned to cohabitation because there were no available female rats.
c. Restricted to rats with a confirmed mating date and rats that did not mate.
d. Includes only one mating for each male rat.
e. Number of pregnancies/number of rats that mated.
f. Includes only one pregnancy for each rat that impregnated more than one female rat.
g. Restricted to rats with a confirmed mating date.
* Significantly different from the control group value (p≤0.05).
** Significantly different from the control group value (p≤0.01).

Female

MATERNAL GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	JZP-110	JZP-110	JZP-110
MATERNAL DOSE LEVEL (MG/KG/DAY)		0	35	110	350
RATS IN COHABITATION	N	22	22	22	20a
DAYS IN COHABITATION b	MEAN±S.D.	2.7 ± 1.0 [21]	2.8 ± 2.6 [21]	3.3 ± 2.6	4.6 ± 4.2
RATS THAT MATED	N(%)	22(100.0)	22(100.0)	21(95.4)	19(95.0)
FERTILITY INDEX c	N/N	22/ 22	20/ 22	20/ 21	15/ 19
	(%)	(100.0)	(90.9)	(95.2)	(78.9)
RATS WITH CONFIRMED MATING DATES	N	21	21	21	19
MATED BY FIRST MALE d DAYS 1-7	N(%)	21(100.0)	20(95.2)	21(100.0)	17(89.5)
MATED BY SECOND MALE d DAYS 8-14	N(%)	0(0.0)	1(4.8)	0(0.0)	2(10.5)
RATS PREGNANT/RATS IN COHABITATION	N/N	22/ 22	20/ 22	20/ 22	15/ 20
	(%)	(100.0)	(90.9)	(90.9)	(75.0)

[ ] = NUMBER OF VALUES AVERAGED
a. Excludes values for rats that were found dead or euthanized due to adverse clinical observations.
b. Restricted to rats with a confirmed mating date and rats that did not mate.
c. Number of pregnancies/number of rats that mated.
d. Restricted to rats with a confirmed mating date.

Necropsy Observations

At the terminal necropsy, no drug-related findings were observed in F1 generation. The male organ weights of epididymis and testes were comparable across all groups, including the controls.

Cesarean Section Observations

No cesarean section or litter parameters were affected by maternal dose of solriamfetol. The average values for corpora lutea, implantations, litter size, and viable and non-viable embryos were comparable across all groups, including the controls. All placentas appeared normal.

Toxicokinetics

On post-partum day 15, solriamfetol was present in all milk and plasma samples collected from drug-treated dams (Table 48). Both the milk and plasma drug concentration increased approximately dose proportionally. Compared to the plasma, solriamfetol milk concentrations were higher with a milk-to-plasma ratio of 3.86, 4.25, and 3.30 for LD, MD, and HD groups, respectively.

Table 48: Milk and Plasma Levels of solriamfetol on Post-partum Day 15 in the Rat Pre- and Post-natal Development Toxicity Study

	Daily Dose (mg/kg/d):	0 (Vehicle)	35	110	350
F_0 Females:	Toxicokinetics (Day 15 postpartum) [b]:				
	Milk $C_{0.75}$ (ng/mL)	0	10000	28200	72900
	Plasma $C_{0.75}$ (ng/mL)	0	2570	6520	22000
	Milk / Plasma Ratio $C_{0.75}$	NC	3.86	4.25	3.30

10 Special Toxicology Studies

10.1 Juvenile Animal Study

A 14-day Dose Range Finding Study of solriamfetol by Oral (Gavage) in 21-Day old Juvenile Rats (Study No. (b) (4) 20083716, non-GLP)

In a 14-day oral toxicity study, juvenile rats (21-day old) were orally treated with solriamfetol at 0 (vehicle control, water), 35 (LD), 110 (MD), and 350 (HD) mg/kg/day for 14 days (n= 6/sex for controls, n=38 males for treatment groups, n= 9 females for LD group and n=7 females for MD and HD groups). Preliminary TK analyses were performed in plasma samples collected on Day 1 and Day 14 of dosing.

No mortality occurred in this study. Pharmacology-related stimulatory behavior occurred in HD. Compared to controls, dose-dependent decreases in body weight gain were observed in MD and HD (↓5%, 41.4%, 8.5%, and 29.2% in MDMs, HDMs, MDFs, and HDFs, respectively); HDFs had decreased femur length (↓~9%) whereas femur length in HDMs were not affected. Femur lengths in LD and MD were not affected.

On both sampling days, peak solriamfetol concentrations were observed between 0.5 and 4 hours post-dose. C_{max} increased less than dose proportionally whereas the AUC increased greater than dose proportionally. After 14 days of repeat dosing, the exposure to solriamfetol (AUC) decreased by approximately 50%. Accumulation ratios ranged from 0.45 to 0.57, suggesting that the exposure tended to be higher for the younger than adult rats at all doses. Other PK parameters in juvenile rat are generally similar to those in adult animals (based on repeat dose tox/TK studies).

Based on the limited findings in LD and MD groups, 110 mg/kg/day is considered to be the NOAEL in this juvenile animal study.

10.2 Phototoxicity

Calculation of the Extinction Coefficient for Solriamfetol Drug Substance (Study No. Jazz PD Memo 585.00)

The absorbance maximum of the solriamfetol drug substance was approximately 258 nm with no significant absorbance in the range of 290 to 700 nm. Therefore, solriamfetol is not considered to have significant direct phototoxicity potential.

10.3 Impurity

Computational Assessment and Evaluation of Potential Carcinogenicity and Genotoxicity of Solriamfetol and Seven Impurities with Case Ultra and DEREK/SARAH (Study No. (b) (4)-1291)

The Applicant submitted a computational assessment for potential carcinogenicity and genotoxicity of solriamfetol and seven impurities. The computational assessment included rodent carcinogenicity assays, bacterial gene mutation assays, *in vivo* micronucleus assays, *in vitro* mammalian gene mutation assays, and *in vitro* chromosomal aberration assays. For the current NDA review, a computational bacterial gene mutation assay was conducted by the FDA computational toxicology group and the findings are consistent with the Applicant's conclusion that these compounds are considered to be non-mutagenic and therefore are controlled as regular impurities. Other computational assays in the study report are not validated for regulatory submission and the regulatory decision was not based on these assays.

10.4 Other Toxicity Studies

Potential of Solriamfetol for Induction of Oxidative Stress/Reactive Metabolite-Responsive Genes (Study No. (b) (4) DS02126, non-GLP)

Male SD rats were treated with a single oral dose of solriamfetol at 0 (vehicle control, 0.5% methocel), 29 (LD), 92 (MD), and 294 (HD) mg/kg/day (n=3/group). The expression of liver oxidative stress or reactive metabolite-responsive genes was investigated.

Compared to vehicle controls, solriamfetol did not induce oxidative stress or reactive metabolite-responsive genes in the liver. These data suggest that oral treatment of solriamfetol had minimal effects on phase I or phase II drug metabolism genes.

3-Week Repeated Dose Oral Mechanistic Study in the Rat (Study No. (b) (4) Tox-6895, non-GLP)

To investigate the mechanisms of solriamfetol-induced changes in the kidney and fat tissue (lipid metabolism) observed in repeat dose studies, SD rats were orally treated with solriamfetol at 0 (vehicle control, water) and 378 mg/kg/day for 3 weeks (n=25/group).

In-life observations of drug-treated rats were similar to those observed in the repeat dose studies, including pharmacology-related stimulatory behaviors; decreases in body weight, body weight gain, and food consumption; decreased lipid synthesis likely due to decreased body weight gain; and changes in urinalysis parameters (↓pH, ↑urine volume, ↓specific gravity, ↓protein, ↓occult blood, ↓sodium/ potassium/chloride/ calcium/phosphate, ↓creatinine, and ↑ magnesium).

At the terminal necropsy, alopecia was observed in solriamfetol-treated rats. In addition, a few skin lesions (tail and lip sore, crusty nose) were observed, likely secondary to the

stimulatory neurobehavioral changes. Compared to controls, drug-related histopathology changes included:

- Adipose tissue: atrophy in the abdominal region (10/25), the adrenal gland (3/25), the kidney (5/25), the mammary gland (5/25), and the skin (18/25); no tissue adipose tissue atrophy was observed in any control animals
- Kidney: diffuse swollen vacuolated tubular cells in the papilla (22/25 rats) and medulla (9/25 rats) of the kidney, vacuolation of the pelvic epithelium overlying the papilla (12/25 rats), and multifocal dilated tubules (2/25 rats); and pronounced vacuolation in collecting duct cells in the medulla and papilla and of the epithelial cells of the pelvis (by electron microscopy);
- Skin: hypotrichosis and/or follicular atrophy (6/25 rats).
- None of the above findings were observed in control animals:

It should be noted that the histopathology changes in the kidney was not associated with any increase in α-GST, a marker for proximal tubule damage, or any changes in the kidney gene expression. Therefore, these data suggest that the solriamfetol induced histopathology changes in the kidney are likely to be a reactive/adaptive response to renal excretion of the drug or drug metabolites, instead of a degenerative or functional damage to the kidney.

Evaluation of the Cytotoxicity of Solriamfetol Using Human Hepatocyte Cultures (Study No. (b) (4) FK3911, non-GLP)

In human primary hepatocyte cultures, 24-hour incubation of solriamfetol at concentrations up to 1050 µM did not induce morphological changes or modify neutral red uptake, or increase cytotoxicity markers. In addition, solriamfetol had no impact on intracellular glutathione content.

11 Integrated Summary and Safety Evaluation

Solriamfetol is a new molecular entity under development for the treatment of excessive daytime sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA). The mechanism(s) of action of solriamfetol is unclear. However, its efficacy could be mediated through its activity as a dopamine and norepinephrine reuptake inhibitor. An adequate nonclinical package was submitted under NDA 211230 to allow for a thorough nonclinical safety assessment of solriamfetol. It should be noted that in some of the Legacy nonclinical study reports, the original doses were presented as solriamfetol hydrochloride salt. For consistency, the dosage information throughout this document is converted (when applicable) and presented as free base equivalent, unless stated otherwise.

Solriamfetol is a dopamine and norepinephrine reuptake inhibitor. Although its binding affinity is relatively low, the drug's neurobehavioral effects *in vivo* are similar to those of stimulants such as amphetamine. In general, the main drug adverse effects were extension of its pharmacology and included CNS clinical signs, effect on body weight and food intake, with target organs of the lung, adipose tissues, adrenal gland, liver and kidneys. Solriamfetol did not affect fertility but was teratogenic and caused fetal sternebrae mal-alignment in the rat and rabbit at maternally toxic doses. Solriamfetol

caused maternal and pup toxicities without affecting learning or memory of offspring (F1) pups. Solriamfetol was not genotoxic and was not carcinogenic in rat or mouse. Based on the overall assessment of the nonclinical results in rodent and nonrodent animals, there are no specific or additional monitoring recommended 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.

Pharmacology

Solriamfetol has relatively low binding affinities for the dopamine transporter (DAT) and norepinephrine transporter (NET, Ki=14,200 nM and 3700 nM, respectively) and minimal binding affinity for the serotonin transporter (SERT, Ki=81,500 nM) and the vesicular monoamine transporter 2 (VMAT2, Ki > 250 μM). In *in vitro* functional assays to evaluate monoamine kinetics, solriamfetol inhibited the reuptake of dopamine and norepinephrine but with relatively low potency (IC_{50}= 2900 nM and 4400 nM, respectively) relative to cocaine (IC_{50}= 385 nM and 194 nM, respectively). Solriamfetol, at therapeutically relevant levels (≤ 10 μM), did not stimulate the release of dopamine, norepinephrine, or serotonin and did not inhibit serotonin reuptake (IC_{50}> 100 μM); however, at higher concentration (30 μM), solriamfetol induced the release of dopamine and serotonin but not norepinephrine in rat brain synaptosomes.

Despite the low affinity for DAT and NET, in multiple *in vivo* studies in rats and/or mice, solriamfetol exhibited efficacy of enhancing dopaminergic and adrenergic transmission, whereas limited serotonergic effects were observed. When compared to different selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOs), or amphetamine (stimulants), the neurobehavioral effects of solriamfetol, albeit some differences, were mostly similar to those of amphetamine or dexamphetamine.

In mice and rats, solriamfetol treatment at 30 mg/kg IP increased active wakefulness and reduced the time in light sleep, deep sleep, and REM sleep but with a subsequent rebound increase in deep sleep time between 4 to 10 hours post-treatment. These effects on sleep-wake architecture were similar to those of amphetamine at 1 mg/kg IP. Solriamfetol enhanced wakefulness in both orexin-ablation narcoleptic and wild-type mice, indicating that wakefulness promoting effects of solriamfetol are not orexin-dependent.

The secondary pharmacology of solriamfetol was investigated as part of the primary pharmacology studies. In *in vitro* binding assays, solriamfetol showed weak affinity for 5-HT_{1A} receptor (IC_{50}= 1- 3 μM) but no affinity for 5-HT_{2A}, 5-HT_{2c}, D_1, D_2, or D_3 receptors (IC_{50} > 10 μM). Solriamfetol was a weak antagonist at the adrenergic α_{2A} and α_{2B} receptors (53.2% inhibition at 10 μM), and had no affinity or functional activity at the histamine H_1, H_2, H_3, orexin$_2$ receptors, or 89 G-protein coupled receptors (GPCRs). In a kinase screening assay against more than 100 kinases, solriamfetol did not show enzyme inhibition or activation activity at most kinases tested. In autoradiography studies in rodent brains, solriamfetol showed no significant occupancy at dopamine D_2, adrenergic α_{2A} or α_{2C} receptors.

The safety pharmacology of solriamfetol was evaluated in the cardiovascular, respiratory, and CNS systems. No severe adverse effects were identified at the clinically relevant doses. In one anesthetized dog (n=1/dose), an IV infusion solriamfetol at 84 mg/kg caused significant decrease in cardiac output (↓ >95%) and premature death. This dose corresponds to > 50-time the C_{max} at the MRHD of 300 mg; therefore, its clinical relevance is limited. Other drug-related effects included slight increases in heart rate and blood pressure, increases in locomotor activity, and, slight and transient increases in respiratory rate. These effects are expected as the extension of the drug's pharmacology and therefore, are not considered to be adverse.

Pharmacokinetics

Solriamfetol has high water solubility and permeability with a pKa value of 8.5 ± 0.1 and is expected to be positively charged at physiological range. In *in vivo* pharmacokinetic studies, no marked sex differences in exposure were noted in the species evaluated. The oral bioavailability after a single administration was moderate to high in rats (71.2%) and high in mice (101%) and dogs (86.5%) with a short T_{max} of 0.25-1.33 hours and relatively short half-life $T_{1/2}$ of 0.95 to 4.1 hours. The apparent volume of distribution of solriamfetol in test animal species exceeded total blood volume, indicating extensive tissue distribution beyond the vascular compartment. The plasma protein binding of solriamfetol was low in all species tested, with values of ~13% in mouse, rat, and human plasma; and ~ 8% in rabbit and dog plasma. In male rats, after a single subcutaneous dose, solriamfetol was present in the pre-frontal cortex and striatal regions of the brain at a level 2 to 3 times lower than in the plasma but remained relatively constant throughout the 6-hour sampling period. After a single oral administration of radioactive dose (autoradiography), the distribution of drug-related material appeared to be highest in the pigmented tissues of the eye (the viz, ciliary body, and choroid) whereas in non-pigmented tissues, the liver and kidney had the highest tissue distribution and the radioactivity was relatively low in the brain. In pregnant rats, after oral administration, solriamfetol was present in non-reproductive and reproductive tissues as well as the fetus; and the exposure in these tissues paralleled those in the blood.

Solriamfetol was not extensively metabolized in hepatocytes or liver preparations derived from the rat, mouse, rabbit, dog, or human. In rats *in vivo*, solriamfetol underwent both renal excretion and hepatic metabolism; however, in dogs and humans, limited hepatic metabolism was observed and the majority of the drug was excreted unchanged in urine. Therefore, the *in vivo* metabolism profiles of solriamfetol are similar between dogs and humans. *There was no unique or major human metabolite.* In lactating rats, following oral administration, solriamfetol was excreted in milk at concentrations 3 to 4-times higher in the milk than the plasma.

Solriamfetol was not a substrate of OAT1, OAT3, OATP1B1, OATP1B3, or MATE2-K in vitro. Solriamfetol appeared to be a low-affinity and non-selective substrate for multiple renal cation transporters such as OCT2, MATE1, OCTN1, and OCTN2. Solriamfetol did not significantly inhibit P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCTN1, or OCTN2. Solriamfetol showed weak inhibition of OCT2 (IC_{50}= 146 µM). These data indicate that solriamfetol is unlikely to cause clinically significant drug-drug

interactions with substrates for these transporters. In female rats, solriamfetol was a weak inducer of hepatic CYP3A enzymes and the effects were reversible after treatment cessation.

Toxicology

The nonclinical toxicology studies of solriamfetol included an adequate battery of genotoxicity studies; single- and repeat-dose general toxicology studies in the mouse for up to 3 months, rat for up to 6 months, and dog for up to 1 year; carcinogenicity studies in the mouse and rat; a complete battery of reproductive and developmental toxicology studies in the rat and/or rabbit; and special toxicity studies.

General toxicology

In all three species (mice, rats, and dogs), solriamfetol, due to its stimulant-like pharmacology, induced CNS signs of excitatory neurobehaviors, such as hyperactivity. The severity of these drug effects was dose dependent. In addition to effects on the CNS, solriamfetol caused dose-dependent decreases in body weight and/or body weight gain with correlative decreases in food consumption, particularly during the first few weeks after treatment initiation. At higher doses (≥ 253 mg/kg/day in rats, ≥ 21 mg/kg/day in dogs, and ≥ 168 mg/kg/day in mice), severe CNS signs, such as tremor, ataxia, convulsions, self-injury and premature death (in rats only), and decreases in body weight/body weight gain were observed.

In both rats and dogs, the target organ of toxicity was the lungs with increased macrophages and phospholipidosis-like inclusion bodies. In addition, atrophy was observed in adipose tissues, which was likely secondary to the decreases in body weight and food consumption.

In the rat and mouse, particularly the rat, additional findings of histopathology with correlative gross pathology and/or increases in organ weight were observed with solriamfetol treatment, including

- *adrenal gland*: Dose-dependent increases in swelling of the zona fasciculata cells
- *kidneys*: dose-dependent increases in swollen and vacuolated tubular cells in the papilla and/or medulla area with correlative diuresis
- *liver*: dose-dependent increases in hepatocellular hypertrophy

In general, females seemed to be more sensitive to the drug-induced toxicities, than male animals, likely due to the slightly higher exposure levels in the females.

In both rats and dogs, the drug-related toxicities were reversible or at least partially reversible during the recovery period. The phospholipidosis-like findings in the rat and dog were potentially due to solriamfetol being a cationic amphiphilic drug at physiological pH; however, the phospholipidosis did not correlate with any functional adversity and therefore is considered of limited safety concern. Dose-limiting toxicities were mainly due to exaggerated pharmacology of CNS over-stimulation and decreases in body weight gain.

At lower doses (29 mg/kg/day in rats, 8 mg/kg/day in dogs, and 17 mg/kg/day in mice), the drug-related CNS signs and/or decreases in body weight gain or body weight were generally mild and therefore these doses are considered to be the NOAEL. These doses correspond to 0.4, 0.8, and 0.15, respectively, times the clinical exposure level at the MRHD of 300 mg/day (Table 49). However, it should be noted that the dose limiting toxicities in animal studies were due to the pharmacology-related CNS signs and/or body weight decreases, which are clinically monitorable and were reversible upon treatment cessation. Therefore, these small safety margins do not impose unacceptable risks for the proposed indication and do not preclude the approval of solriamfetol.

Mutagenicity and Carcinogenicity

Solriamfetol was not genotoxic in an adequate battery of genotoxicity assays.

Daily oral administration of solriamfetol to mice at doses up to 200 mg/kg/day for up to 104 weeks did not induce drug-related neoplastic findings. At 200 mg/kg/day, after 90 days of repeat dosing, the corresponding plasma exposure level (AUC) of solriamfetol was 66400 h*ng/mL, which is approximately 3.5 times the MRHD of 300 mg/day (based on human AUC value of 19070 h*ng/mL at steady state).

Daily oral administration of solriamfetol to rats at doses up to 200 mg/kg/day for up to 101 weeks did not induce drug-related neoplastic findings. At 200 mg/kg/day, after 26 weeks of repeat dose, the corresponding plasma exposure level of solriamfetol was 177000 h*ng/mL, which is approximately 9 times the MRHD of 300 mg/day (based on human AUC value of 19070 ng*hr/mL at steady state).

Reproductive and Developmental Toxicity

In female and male rat fertility studies, similar to the general toxicology studies, solriamfetol caused dose-dependent and pharmacology-related increases in excitatory behaviors and decreases in body weight gain and food consumption. Fertility was not adversely affected by solriamfetol in either sex. In female rats, doses tested were 15, 67, and 295 mg/kg/day, which are approximately 0.5-, 2-, and 9.5- times the MRHD based on mg/m^2 body surface area. A potentially drug-related increase in the number of corpora lutea was observed at all doses; however, this change did not affect female fertility parameters. The NOAEL for female fertility is 295 mg/kg/day, which is approximately 9.5 times the MRHD, based on mg/m^2 body surface area. In male rats, doses tested were 35, 110, and 350 mg/kg/day, which are approximately 1-, 3,5-, and 11- times the MRHD, based on mg/m^2 body surface area. Solriamfetol did not affect fertility or sperm parameters at 35 and 110 mg/kg/day. However, at 350 mg/kg/day, solriamfetol caused a slight decrease (~10%) in sperm count and sperm concentration without affecting fertility. Because rats are highly fertile relative to humans, a 10% decrease in sperm count is unlikely to cause functional compromise in the rats; however, a decrease in sperm count or concentration in humans could be clinically meaningful. Therefore, the NOAEL for male fertility is considered to be 110 mg/kg/day, which is approximately 3.5 times the MRHD of 300 mg/day based on mg/m^2 body surface area.

The embryo-fetal developmental toxicity potential of solriamfetol was tested in rats and rabbits. Oral administration of solriamfetol during organogenesis caused maternal and fetal toxicities in rats and rabbits at doses ≥ 2 and 2.5 times- and was *teratogenic* at doses 9.5 and ≥ 2.5 times, respectively, the MRHD based on mg/m2 body surface area.

In the rat study, solriamfetol was administered orally to pregnant rats during the period of organogenesis at 15, 67, and 295 mg/kg/day, which are approximately 0.5-, 2-, and 9.5- times the MRHD based on mg/m^2 body surface area. Solriamfetol at ≥ 2 times the MRHD caused maternal toxicity that included hyperactivity, significant decreases in body weight, weight gain, and food consumption. Fetal toxicity at these maternally toxic doses included increased incidence of early resorption and post-implantation loss, and decreased fetal weight. Solriamfetol was teratogenic at 9.5 times the MRHD, it increased the incidence of fetal malformations that included two litters with severe sternebrae mal-alignment and single litter incidences of hind limb rotation, situs inversus, and bent limb bones. This dose was also maternally toxic. The no-adverse-effect level for malformation is 2 times and for maternal and embryofetal toxicity is approximately 0.5 times the MRHD based on mg/m^2 body surface area.

In the rabbit study, solriamfetol was administered orally to pregnant rabbits during the period of organogenesis at 17, 38, and 76 mg/kg/day, which are approximately 1-, 2.5-, and 5- times the MRHD based on mg/m^2 body surface area. Solriamfetol at 5 times the MRHD caused maternal toxicity of body weight loss and decreased food consumption. Solriamfetol was teratogenic at ≥ 2.5 times the MRHD, it caused fetal skeletal malformation (slight-to-moderate sternebrae mal-alignment) and decreased fetal weight. The no-adverse-effect level for malformation and fetal toxicity is approximately 1 time and for maternal toxicity is approximately 2.5 times the MRHD based on mg/m^2 body surface area.

In the pre- and post-natal developmental toxicity study, solriamfetol was administered orally to pregnant rats during the period of organogenesis from gestation day 7 through lactation day 20 post-partum, at 35, 110, and 350 mg/kg/day, which are approximately 1-, 3.5-, and 11- times the MRHD based on mg/m^2 body surface area. At ≥ 3.5 times the MRHD, solriamfetol caused maternal toxicity that included decreased body weight gain, food consumption, and hyperpnea. At these maternally toxic doses, fetal toxicity included increased incidence of stillbirth, postnatal pup mortality, and decreased pup weight. Developmental toxicity in offspring (F1) pups after lactation day 20 included decreased body weight, weight gain, and delayed sexual maturation. Mating and fertility of offspring pup were decreased at maternal doses 11 times the MRHD without affecting learning and memory. The no-adverse-effect level for maternal and developmental toxicity is approximately 1 time the MRHD based on mg/m^2 body surface area.

Summary of Safety Margins at the NOAELs from Pivotal Nonclinical Studies

The safety margins at the reviewer-determined NOAELs in pivotal nonclinical studies are summarized in Table 49.

Table 49: Safety Margins at the NOAEL from Pivotal Nonclinical Studies

Species	Study	NOAEL/NOEL (mg/kg/day)	AUC (ng.hr/mL, M/F)	Safety Margin (based on AUC)
Human, MRHD 300 mg, AUC: 19070 ng*hr/mL				
General Toxicology Studies				
Rat (PO)	6-month	29	6660/8691	~0.4
Dog (PO)	52-week	8	15100/14100	~0.8
Mouse (PO)	3-month	17	3057/2846	~0.15
Carcinogenicity Studies *				
Rat (PO)	101-week	200	66400	~ 3.5
Mouse (PO)	104-week	200	177000	~ 9.3
Reproductive and Developmental Toxicity Study (safety margins based on mg/m² body surface area)				
Rat Seg I fertility[a] (PO)	Female	295	ND	~ 10
	Male	110	ND	~ 3.5
Rat Seg II[a] (PO)	Maternal and embryo-fetal toxicity	15	ND	~ 0.5
	Teratogenicity	67	ND	~ 2
Rabbit Seg II[a] (PO)	Maternal toxicity	38	ND	~ 2.5
	Embryo-fetal	17	ND	~ 1
	Teratogenicity	17	ND	~ 1
Rat Seg III[a] (PO)	Maternal, perinatal, and F1 Development toxicity	35	ND	~ 1

[ND, not determined; *, doses where drug-related tumors were not observed; safety margins are calculated relative to the human steady state exposure level at the MRHD of 300 mg/day (AUC: 19070 ng*hr/mL); a, in the reproductive and developmental toxicity studies, safety margins are calculated based on mg/m^2 body surface area]

12 Appendix/Attachments

12.1 Appendix I: Detailed Drug-related Histopathology Table in the 6-month Repeat Dose Rat Study

2.6.7.7.4 Toxicology: Repeated-Dose Toxicity (Pivotal Study (b) (4)-TOX-5705) Test Article: JZP-110

Daily Dose (mg/kg/d): [a]	0 (Control)		29		253		505/379	
End-of-Dosing Phase (No. of Animals)	**M: 20**	**F: 20**	**M: 20**	**F: 20**	**M: 20**	**F: 20**	**M: 20**	**F: 20**
Histopathology:								
Adrenal gland †	19	19	1	19	0	19	19	19
Swollen cortical cells (zona fasciculate)	2	5	1	4	–	12 *	2	16 ***
Score 1[h]	2	3	1	3	–	12	2	9
Score 2	–	2	–	1	–	0	–	7
Bone marrow, femur†	19	19	19	19	19	19	19	19
Prominent granulocytes/granulopoiesis	–	2	–	1	–	3	–	5
Score 1	–	2	–	1	–	3	–	5
Reduced number of fat cells	0	2	1	1	5 *	7	4	3
Score 1	0	2	1	1	5	7	4	3
Bone marrow, sternum†	19	19	1	19	0	19	19	19
Prominent granulocytes/granulopoiesis	–	1	–	0	–	3	–	8 *
Score 1	–	2	–	0	–	3	–	8
Brain†	19	19	1	19	0	19	19	21 [f]
Vacuolation, multifocal (neocortex/hippocampus)	–	0	–	0		0	–	3
Score 1	–	0	–	0	–	0	–	1
Score 2	–	0	–	0	–	0	–	2
Shrunken/dark neurons (hippocampus)	–	0	–	0	–	0	–	3
Score 1	–	0	–	0	–	0	–	1
Score 2	–	0	–	0	–	0	–	2
Edema	–	0	–	0	–	0	–	2
Score 1	–	0	–	0	–	0	–	2

2.6.7.7.4 Toxicology: Repeated-Dose Toxicity (Pivotal Study (b) (4)-TOX-5705) Test Article: JZP-110

Daily Dose (mg/kg/d): [a]	0 (Control)		29		253		505/379	
End-of-Dosing Phase (No. of Animals)	**M: 20**	**F: 20**	**M: 20**	**F: 20**	**M: 20**	**F: 20**	**M: 20**	**F: 20**
Kidneys †	19	19	19	19	19	19	19	19
Hypertrophic tubule(s)	0	1	0	2	0	5	1	4
Score 1	0	1	0	2	0	4	1	1
Score 2	0	0	0	0	0	1	0	3
Swollen/vacuolated tubular cells (medulla)	0	0	0	0	1	1	14 ***	9 **
Score 1	0	0	0	0	1	1	10	9
Score 2	0	0	0	0	0	0	4	0
Swollen/vacuolated tubular cells (papilla)	0	0	0	0	4	3	11 ***	15 ***
Score 1	0	0	0	0	4	3	8	14
Score 2	0	0	0	0	0	0	3	1
Liver †	19	20	1	19	2	19	19	19
Hypertrophy	–	0	–	3	–	4 *	–	6 **
Score 1	–	0	–	3	–	4	–	5
Score 2	–	0	–	0	–	0	–	1
Hypertrophy, centrilobular	–	0	–	0	–	2	–	0
Score 1	–	0	–	0	–	2	–	0
Necrotic hepatocytes, (mult)focal to diffuse	–	0	–	0	–	0	–	4 *
Score 1	–	0	–	0	–	0	–	2
Score 2	–	0	–	0	–	0	–	1
Score 3	–	0	–	0	–	0	–	1
Lungs †	19	19	19	19	19	19	19	19
Alveolitis, (multi)focal	1	1	3	1	4	1	9 **	8 *
Score 1	1	1	3	1	4	1	7	6
Score 2	0	0	0	0	0	0	2	2

2.6.7.7.4 Toxicology: Repeated-Dose Toxicity (Pivotal Study (b) (4)TOX-5705) **Test Article: JZP-110**

Daily Dose (mg/kg/d): [a]	0 (Control)		29		253		505/379	
End-of-Dosing Phase (No. of Animals)	**M: 20**	**F: 20**	**M: 20**	**F: 20**	**M: 20**	**F: 20**	**M: 20**	**F: 20**
Fibrinous material (alveoli and/or bronchi)	0	0	0	0	0	1	3	8 **
Score 1	0	0	0	0	0	1	3	0
Score 2	0	0	0	0	0	0	0	2
Score 3	0	0	0	0	0	0	0	4
Score 4	0	0	0	0	0	0	0	2
Foamy macrophages	11	8	14	7	14	14	14	15 *
Score 1	10	8	13	3	10	13	6	6
Score 2	1	0	1	3	4	1	6	1
Score 3	0	0	0	1	0	0	2	7
Score 4	0	0	0	0	0	0	0	1
Giant cells (alveoli/bronchi) (w/ or w/o foreign material	0	0	0	0	0	0	2	0
Score 1	0	0	0	0	0	0	1	0
Score 2	0	0	0	0	0	0	1	0
Granulomatous inflammation, focal	0	0	0	0	3	0	2	1
Score 1	0	0	0	0	3	0	1	1
Score 2	0	0	0	0	0	0	1	0
Round cells, (mutlti)focal (perivascular)	0	0	1	0	0	0	4	6 *
Score 1	0	0	1	0	0	0	4	5
Score 2	0	0	0	0	0	0	0	1
Lymph node(s), mesenteric †	19	19	19	19	19	19	19	19
Atrophic adipose tissue	0	0	0	0	0	4	3	9 **
Score 1	0	0	0	0	0	3	2	6
Score 2	0	0	0	0	0	1	1	3

2.6.7.7.4 Toxicology: Repeated-Dose Toxicity (Pivotal Study (b) (4)TOX-5705) **Test Article: JZP-110**

Daily Dose (mg/kg/d): [a]	0 (Control)		29		253		505/379	
End-of-Dosing Phase (No. of Animals)	**M: 20**	**F: 20**	**M: 20**	**F: 20**	**M: 20**	**F: 20**	**M: 20**	**F: 20**
Mammary gland †	19	19	19	19	19	19	19	18
Atrophic adipose tissue	NA	0	NA	0	NA	0	NA	2
Score 1	NA	0	NA	0	NA	0	NA	1
Score 2	NA	0	NA	0	NA	0	NA	1
Fibrosis	NA	0	NA	0	NA	0	NA	5 *
Score 1	NA	0	NA	0	NA	0	NA	5
Ovaries †	NA	19	NA	19	NA	19	NA	19
Cystic follicle(s)	NA	0	NA	0	NA	3	NA	1
Score 1	NA	0	NA	0	NA	3	NA	1
Eosinophilic corpora lutea	NA	19	NA	18	NA	19	NA	19
Score 2	NA	2	NA	2	NA	0	NA	0
Score 3	NA	5	NA	3	NA	1	NA	3
Score 4	NA	8	NA	3	NA	4	NA	4
Score 5	NA	4	NA	10	NA	14	NA	12
Tertiary follices	NA	7	NA	11	NA	14 *	NA	9
Score 1	NA	6	NA	10	NA	13	NA	8
Score 2	NA	1	NA	1	NA	1	NA	1
Pancreas †	19	19	19	19	19	19	19	19
Halophenomenom	–	0	–	2	–	4	–	4
Score 1	–	0	–	2	–	4	–	4
Skin †	19	19	19	19	19	19	19	19
Atrophy (hypodermis)	0	0	0	0	5 *	5 *	8 **	8 **
Score 1	0	0	0	0	4	4	6	6
Score 2	0	0	0	0	1	1	1	1
Score 3	0	0	0	0	0	0	1	1

2.6.7.7.4 Toxicology: Repeated-Dose Toxicity (Pivotal Study (b) (4)TOX-5705) **Test Article: JZP-110**

Daily Dose (mg/kg/d): [a]	0 (Control)		29		253		505/379	
End-of-Dosing Phase (No. of Animals)	**M: 20**	**F: 20**	**M: 20**	**F: 20**	**M: 20**	**F: 20**	**M: 20**	**F: 20**
Hypotrichosis	0	0	1	0	1	1	2	5
Score 1	0	0	1	0	1	1	2	5
Spleen †	19	19	19	19	19	19	19	19
Hemosiderin	18	–	19	–	19	–	19	–
Score 1	3	–	1	–	0	–	1	–
Score 2	11	–	11	–	5	–	6	–
Score 3	4	–	7	–	13	–	11	–
Score 4	0	–	0	–	1	–	1	–
Thymus †	20	20	20	20	20	20	20	20
Involution	20	–	20	–	20	–	20	–
Score 1	4	–	1	–	1	–	0	–
Score 2	10	–	10	–	6	–	7	–
Score 3	6	–	8	–	12	–	12	–
Score 4	0	–	1	–	1	–	1	–
Urinary bladder †	19	19	19	1	19	2	18	19
Dilated lumen	1	–	1	–	3	–	7 *	–
Score 1	0	–	1	–	2	–	6	–
Score 2	1	–	0	–	1	–	1	–

12.2 ECAC Meeting Minutes for the Mouse and Rat Carcinogenicity Study Protocol

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs

FACSIMILE TRANSMITTAL SHEET

DATE: August 20, 2004

To: (b) (4)	**From:** Adele Seifried
Company: (b) (4)	HFD-024
Fax number: (b) (4)	**Fax number:** 301-480-8329
Phone number: (b) (4)	**Phone number:** 301-443-5344

Subject: Response to Carcinogenicity Special Protocol Assessment Request - Final CAC Report - (b) (4)

Total no. of pages including cover: 5

Comments:

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12.3 ECAC Meeting Minutes for the Final Mouse and Rat Carcinogenicity Studies

Executive CAC Final Study Minutes
Date of Meeting: June 19th, 2018

Committee: Karen Davis Bruno, PhD, OND IO, Chair
Paul Brown, PhD, OND IO, Member
Tim McGovern, PhD, OND IO, Member
Andrew Goodwin, PhD, DPARP, Alternate Member
Haleh Saber, PhD, DHOT, Alternate Member
Aisar Atrakchi, PhD, DPP, Pharm/Tox Supervisor
Jia Yao, PhD, DPP, Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA 211230
Drug Name: Solriamfetol/JZP-110
Sponsor: Jazz Pharmaceutical, LLC

Background
NDA 211230 was submitted on Dec. 20th, 2017 for market approval of solriamfetol to improve wakefulness and reduce excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea. The Sponsor submitted 2-year mouse and 2-year rat carcinogenicity studies with this NDA.

Mouse Carcinogenicity Study
CD-1 mice were orally administered solriamfetol at 20, 65, and 200 mg/kg/day doses in both males and females (n=60/sex/dose) for up to 104 weeks. An additional dose of 600 mg/kg/day was included in females only. The vehicle used was deionized water (n=76/sex). There was prior concurrence from the FDA ECAC for dose selection and study design. The final study contains a few slight deviations from the ECAC recommendations, including slightly higher doses used due to hydrochloride salt to free base equivalent conversion (conversion factor of 1.19) and a single vehicle control group instead of the identical dual control groups originally proposed. These deviations do not affect the study validity.

The 600 mg/kg/day female group was terminated early after 26 weeks of dosing due to excessive mortality. No carcinogenicity or post-mortem evaluation was performed in this group. This early termination did not impact the validity of the study since there are adequate doses evaluated.

Except for the early termination group, the survival rate was comparable across all groups including the controls. There were no drug-related neoplastic findings following oral daily administration of solriamfetol in male and female CD-1 mice at doses of 20, 65, and 200 mg/kg/day for up to 104 weeks.

Rat Carcinogenicity Study
SD rats were orally administered solriamfetol at 35, 80, and 200 mg/kg/day doses in both males and females (n=60/sex/dose) for up to 101 weeks. The vehicle used was deionized water

12.4 Statistics Review for the Final Carcinogenicity Review

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	NDA 211230
Drug Name:	Solriamfetol (JZP-110)
Indication(s):	To improve wakefulness and reduce excessive sleepiness in adult patients with narcolepsy or obstructive sleep apnea (OSA).
Studies	Two Year Oral Gavage Carcinogenicity Study in Rats and Mice.
Applicant:	Sponsor: Jazz Pharmaceuticals, Inc. 3180 Porter Drive, Palo Alto, California 94304 Test facility: (b) (4)
Documents Reviewed:	Electronic submission, dated: December 20, 2017 via SDN1 Electronic data submitted on February 1st, 2018 via SN0004.
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -VI
Statistical Reviewer:	Malick Mbodj, Ph.D.
Secondary Reviewer:	Hepei Chen
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Psychiatry Products (DPP)
Reviewing Pharmacologist:	Jia Yao, PhD
Project Manager:	Sarah H Seung, PharmD
Keywords:	Carcinogenicity, Dose response

Reference ID: 4280294

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/

JIA YAO
08/27/2018

AISAR H ATRAKCHI
08/28/2018