3.5.1.3.2 Animal Data

The pharmacology / toxicology review was referred to in order to see if preclinical data might shed light on the risk of pulmonary arterial hypertension with asenapine.

Table 8 shows a summary of fertility and early embryonic development studies from the April 30, 2008 Pharm/Tox Review. It is divided into 4 sections:

- Pilot Mating and Fertility Studies
- Mating, Fertility, and Teratogenicity Studies
- Embryo-fetal Development and Teratogenicity Studies
- Pre- and Post-Natal Development Studies

The table is largely self-explanatory. Comments include comments taken directly from the pharmacology and toxicology review and are shown in italics. Those comments that this reviewer believes are interest are highlighted in red or blue text. Where additional data or information elucidate the results they are also referred to in the comments section, and these tables immediately follow Table 8.

Pilot Mating and Fertility Studies

There was little effect of asenapine.

Mating, Fertility, and Teratogenicity (Early Embryonic Development) Studies

This study was considered inadequate however it's noteworthy that there's a congenital heart defect in one rat. It's noteworthy that there's a dose dependent post-natal mortality that occurs primarily in the first few days post partum and there's a high degree of cannibalism in the high dose group. This indicates potential issues with both late stage fetal development and possibly with breast feeding. These results are consistent with the suspected toxicities. It should be noted that in this study Wistar Rats were used, however with monocrotaline the risk of PAH is greatest with Sprague-Dawley Rats and might be due to differences in metabolic activation due to metabolism.

Embryo-fetal Development and Teratogenicity

There were 6 embryo-fetal development and teratogenicity studies where rats or rabbits were exposed to asenapine during the period of fetal development that corresponds to implantation to closure of the hard palette in rats or the period or organogenesis in rabbits.

What's striking is that in every one of these six studies there are indications of effects on bone formation and in some there are also indications of effects on connective tissue. Specifically there are dose dependent effects on bone ossification, including increases in poorly ossified and nonossified bone.

As has been seen with other drugs when a particular litter is effected the data is excluded from the analysis, even that this may indicate that is a borderline dose for the toxic effect and there may be increased exposure to parent drug or metabolite in that particular dam.

These studies were initially conducted in Sprague-Dawley and Wistar/HAN rats with PO administration and later in 2005 in Sprague-Dawley Rats with IV administration. In addition 3 different rabbit strains were used. The fact that effects were seen in two different species and all strains, were dose dependent and were even seen when conditions would be expected to minimize finding effects, significantly raises the level of concern that these effects are based on a mechanism that is common across a variety of species and will be seen in humans. In addition the suspected mechanism indicates that connective tissue effects will be seen not only in neonates but also in older individuals where bone remodeling is ongoing, such as growing children whose skeletons are constantly reforming as they grow.

A high incidence of bone malformations were seen in rabbits at doses of 30 mg/kg/day (see Table 8 and Section 0 (
Appendix 3 – Skeletal Exams in Chinchilla Rabbits - Study SDG RR 2914) however even at low doses likely to produce exposures only a few fold higher than in humans effects on bone ossification were seen.

Other findings include brain malformation and an umbilical hernia and repeated findings include effects on the eye, and hydronephrotic kidneys in both rabbits and rats. Particularly worrisome is the evidence of pulmonary effects in rabbits and that for several experiments the examinations appear designed to avoid detecting certain problems, i.e. visceral and soft tissue findings, in spite of the fact that the sponsor appears to be looking specifically for skeletal problems.

Based on these studies there is no margin of safety relative to the human dose in Sprague-Dawley Rats. Plus in Chinchilla and New Zealand White Rabbits there is a 2 – 3 fold increased risk for major visceral malformations at asenapine exposures only double those in humans.

Pre- and Post-Natal Development Studies

There were 5 pre- and post-natal development studies in Sprague-Dawley Rats.

Two of these, including one conducted in 1992, were fostering studies where pups either exposed or not exposed in utero were fostered by dams either exposed or not exposed to asenapine. This is highly unusual unless the sponsor is looking for a specific effect such as toxicity due to breast feeding. Also troubling is that all but one of these studies utilized IV dosing which would minimize the formation of any toxic metabolites. The IV pilot studies that appear to be primarily for dose selection purposes for the second fostering study clearly show that there is an increase in mortality due to exposure in utero late in pregnancy, as would be expected with a drug causing PAH. Having both an IV and PO fostering allow comparisons and although the IV dose was 1/10 the PO dose the pup mortality was still increased in the first 4 days post-partum, (20% - 25%), as compared to 3% in the control group, but what is amazing is that this increased mortality was seen even when the pups were only exposed by breast feeding.

Although 2 of these studies noted that pups were bluish and this was explained as hypothermia, the fact that this also occurred on the heads and snouts and is consistent with the mechanism suggests that it may actually be due to cyanosis.

Table 9 Results of Fertility and Early Embryonic Development in Wistar Rats - Study SDG RR 3115

Group		Control	Low Dose	Mid Dose	High Dose
Dose mg/kg bid (Maleate salt)		0	0.5	2.5	15
Number of Births		122	106	65	32
# Pups found dead at first litter check		0	0	2	1
# Pups found alive at first litter check (Survival)		122	106	63	31
# Pups Alive at Day 4		122	102	58	24
# Pups Alive at Day 21		120	102	56	23
% Survival at:	First Litter Check Day 1 Post Partum	100%	100%	96.9%	96.9%
	Day 4 Post Partum	100%	96.2%	89.2%	75.0%
	Day 21 Post Partum	98.4%	96.2%	86.2%	71.8%

Table 10 Asenapine Toxicokinetics in New Zealand White Rabbits – Study SDG RR 4428

Dose (mg/kg/day)	t½ (min)	AUC (0-24) (ng.h/ml)	Normalized AUC (0-24) (ng.h/ml)/(mg/kg)	CL (ml/min/kg)	V.central (l/kg)
0.025	46.60	4.88*	192.56*	115.05	2.73
0.125	52.35	41.53	327.51	51.07	1.93
0.625	58.90	179.02	285.43	59.02	2.25

n = 5 rabbits per dosing group.
* As the AUC could not be calculated up to 24 h for the 0.025 mg/kg/day group, it was calculated up to and including the last measurable concentration (AUC 0-t).

Table 11 Rate of Major Visceral Defects with Asenapine in New Zealand White Rabbits – Study SDG RR 4428

Dose mg/kg/day	0.0	0.025	0.125	0.625
N	177	111	97	164
Visceral Major Defects	1	2	1	4
%	0.6	1.8	1.0	2.4

N.B. There's approximately a 2 – 3 fold increased risk at exposures twice human exposures.

Table 12 Design and Results of PO Asenapine Fostering in Sprague-Dawley Rats - Study SDG RR 4299

		Group		
		1	2	3
Dose mg/kg BID PO	Dose Prenatal	0	0	15
	Dose Postnatal	0	15	15
Fostered Post-natally		No	Yes	No
Comments			Delivered by C-section	
Survival 1st 24 hrs (%)[a]		100.0%	70.7%	14.3%
Survival on Day 7 (%)		92.7%	28.3%	7.15%
% Change in Survival from end of Day 1 to Day 7		7.3%	42.4%	50%

a Largely died by cann balization within 4 hours of birth

Table 13 Design and Results of Pilot Lactation Study in Sprague-Dawley Rats - Study NL0012545

		Group		
Dose mg/kg/day IV	Dose Prenatal	0	0.3	3
	Dose Postnatal	0	0	0
Survival 1st 24 hrs (%)		99.2%	96.7	57.3%
Survival at End of Lactation (%)		98.3%	94.6%	37.2%

Table 14 Design and Results of Pilot Lactation Study in Sprague-Dawley Rats - Study NL0048584

Dosage Group	LD	MD	HD
Dose mg/kg/day IV	0.5	1	2
Live Births	100%	100%	100%
Survival at Day 4	98%	88%	71%%
Survival at End of Lactation (%)	98.3%	94.6%	37.2%

Table 15 Survival in Pre-and Postnatal in Sprague-Dawley Rats - Study NL0052638

Group		Control	LD	MD	HD
Dose mg/kg /day IV		0	0.3	0.9	1.5
Implantations (Births)		292	293	310	321
Post Implantation Losses		6	29	48	35
Total Number Pups at First Litter Check		286	264	262	286
# Dead Pups at First Litter Check		0	0	1	1
# Living Pups	First Litter Check	286	264	262	285
	Day 1 Post Partum	286	259	254	271
	Day 2 Post Partum	276	254	240	225
	Day 3 Post Partum	275	253	239	219
	Day 4 Post Partum			238	215
	Day 5 Post Partum				216
	Day 6 Post Partum	274			217
	Day 7 Post Partum		251		
	Day 13 Post Partum			237	
	Day 26 Post Partum	273			
% Loss Birth to First Litter Check		2.1%	9.9%	15.8%	11.2%
% Survival	Birth to First Litter Check	97.9%	90.1%	84.5%	88.8%
	Day 1 Post Partum	97.9%	88.4%	81.9%	84.4%
	Day 2 Post Partum	94.5%	86.7%	77.4%	70.1%
	Day 3 Post Partum	94.2%	86.3%	77.1%	68.2%
	Day 4 Post Partum			76.8%	67.0%
	Day 5 Post Partum				67.3%
	Day 6 Post Partum	93.8%			67.6%
	Day 7 Post Partum		85.7%		
	Day 13 Post Partum			76.5%	
	Day 26 Post Partum	93.5%			

Table 16 Study Design in IV Asenapine Sprague-Dawley Rat Fostering Study – Study INT00000051

Cross foster groups	Exchange of litters (dam/litter)	Dam from	Litter from
Vehicle/vehicle	V/V (exchange of litter from vehicle treated dams)	Group 1	Group 1
Vehicle/high dose	V/HD (vehicle treated dam with litter from test-item-treated dam)	Group 1	Group 2
High dose/vehicle	HD/V (test item-treated dam with litter from vehicle-treated dam)	Group 2	Group 1
High dose/high dose	HD/HD (exchange of litters from vehicle-treated dam)	Group 2	Group 2
Control groups	**No exchange of litters**		
Vehicle control	V Control		
High dose control	HD Control		

Table 17 Postnatal Mortality in IV Asenapine Sprague-Dawley Rat Fostering Study – Study INT00000051

Period Post Partum	Statistics	V/V	V/HD	HD/V	HD/HD	V Control	HD Control
Days 1-4	Pup loss (%)	2.8	19.4	3.3	25.8	0.7	20.2
	No. of litters affected	3	7	2	9	1	6
Day 5-10	Pup loss (%)	0	0	2.8	0.9	2.1	6.0
	No. of litters affected	0	0	3	1	3	1

Table 18 Lack of Postnatal Suckling in IV Asenapine Sprague-Dawley Rat Fostering Study – Study INT00000051

No Milk in Stomach	V/V	V/HD	HD/V	HD/HD	V Control	HD Control
No. of pups affected	0	2	0	28	1	34
No. of litters affected	0	1	0	5	1	8

3.5.1.3.3 Neonatal Effects of Cis-Asenapine

Even more problematic is the Pharm/Tox review conclusions regarding a single oral dose embryo-fetal development study of Org 5033, (cis-asenapine).

"Moreover, a 9-fold increase in the incidence of malformations, and signs of embryotoxicity demonstrated as a 2-fold increase in post-implantation loss, were observed in fetuses of female rabbits dosed with Org 5033 at 80 mg/kg/day during the period of organogenesis in this non-GLP pilot study."

It should be noted that although cis-asenapine is dosed at 80 mg/kg/day in these animal toxicology studies which is likely much greater than any human doses it is possible that this study could be used as a surrogate toxicology study for other species with higher exposures in humans. Table 19 shows an example of how it could hypothetically be done, so that this data could be used to more fully inform us of the human toxicity of other circulating species. However, presently this can not be done without the receptor binding and metabolism information requested.

Table 19 Example of How Requested Mass Balance, Receptor Binding and Toxicology Data could Hypothetically be used to Evaluate Potential Safety Issues with Asenapine

Chemical Species of Interest	Relative 5HT2B Binding		Agonist or Antagonist	Dosage (mg/kg/day)		Relative Toxicologic Exposures	
	Humans	Rabbits		Humans	Rabbits	Humans	Rabbits
Cis-Asenapine	1	0.01	Agonist	0.0004	80	0.0004	0.8
Hypothetical Toxic Asenapine Metabolite	0.8		Agonist	1		0.8	