Dosage: 30, 100 (MD), 350 (MD2) or 1250 mg/kg/day
600 (MD3) or 900 (MD4) mg/kg/day (separate dosing; no statistical evaluation)
Schedule: daily for 13 weeks
Route: oral (via feed)
(Observations)

Mortality (daily)	HD ♂ 4/10 (Days 70, 76) HD ♀ 5/10 (Days 72, 75, 78, 80, 89)
Clinical Obs. (daily)	Ruffled fur: approx 50% HD at week 5 and all HD animals after wk 7 Pale mucosa last 3 weeks

Body weights (wkly)		HD	MD4	MD3	MD2
Relative to control D90/91	♂	↓ 65%	↓ 39%	↓ 14%	↓ 8%
See graphs below	♀	↓ 56%	↓ 7%	↑ 9%	

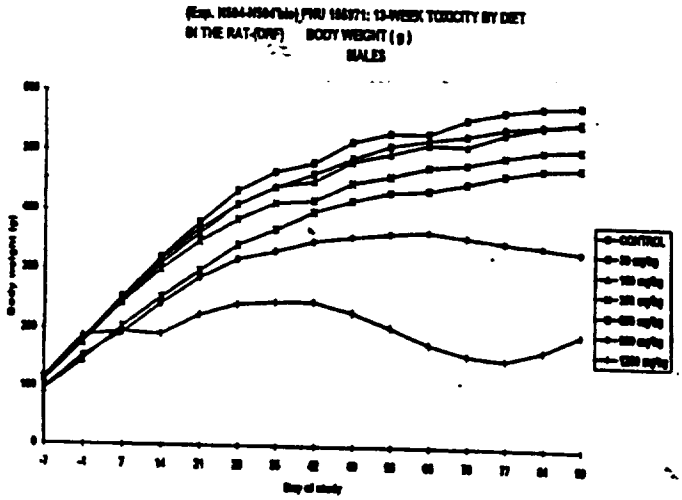
Food consumption (wkly)	↓ HD D 7-90 ♂ 19% (D90); ♀ 27% (D 90) ↓ MD4 D 49-70 ♂ 30% (D90)			
Hematology (wk 13)	HD ♂	HD ♀	MD4 ♂	
↓ WBC	48%	41%	38%	
↓ lymphocytes	64%	67%	42%	
↑ platelets	87%	52%		
↓ Hbg	9.2%	16%		
↓ Hematocrit		11%		
↓ MCV		12%		
↓ MCH	6%	17%		
↓ MCHC	5%	5%		
Clinical chemistry (week 13)	HD ♂	HD ♀	MD4 ♂	MD4 ♀
↑ AST	129%	216%		
↑ ALT	87%	247%		
↑ AP	72%	119%	100%	166%
↑ TG	175%	40%		
↑ Chol	115%	89%		
↑ Phospholipids	153%	63%		
↓ Tot Prot	14%	26%	8%	14%
↓ Albumin	15%	33%	19%	27%
Urinalysis (week 13)	Unremarkable			

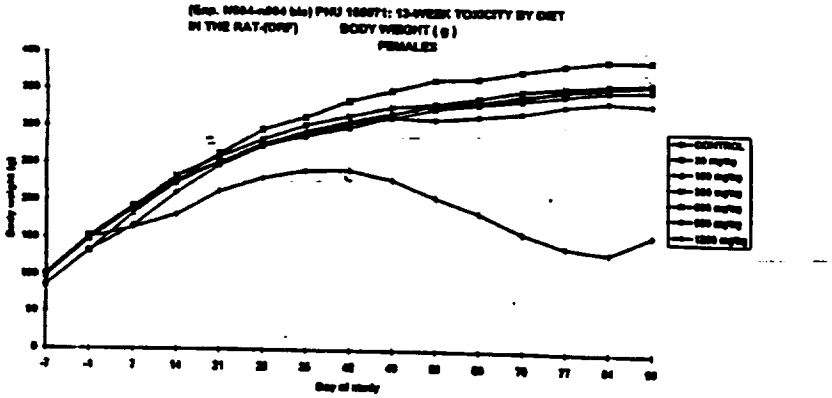
Organ weights	HD♂	HD♀	MD4♂	MD4♀	MD3♂	MD3♀	MD2♂	MD2♀
Absolute:								
Adrenals ↓	48%	55%	27%	40%	11%			12%
Brain ↓	15%	13%	10%					
Epididymides ↓	57%		21%					
Heart ↓	51%	45%	32%		9%		10%	
Kidneys ↓	46%	29%	34%		17%		8%	
Ovaries ↓		76%						
Pituitary ↓	44%	56%	29%	29%				
Prostate ↓	66%		49%					
Spleen ↓	58%	66%	45%	21%				
Testes ↓	74%		16%					
Thymus ↓	77%	86%	51%	32%		9%		25%
Relative:								
Adrenals ↑	70%							
Brain ↑	160%	115%	52%					
Epidydimides ↑	32%							
Heart ↑	43%	35%						
Kidneys ↑	60%	72%						
Pituitary ↑	70%							

Liver ↑	157%	207%	76%	55%	32%	19%	19%	
Uterus ↑		63%						
Ovaries ↓		42%						
Thymus ↓	42%	68%	21%	26%		18%		26%

Gross Pathology	HD ♂	HD ♀	MD4 ♂	MD4 ♀
Scheduled:				
General condition: fairly good to poor	6/6	5/5	5/10	2/10
Liver: moderately enlarged	2/6	5/5		
Prostate: moderately small	3/6			
Spleen: markedly small	1/6	2/5		
Testes: moderately small/flaccid	5/6			
Thymus: small/not found	5/6	5/5		
Unscheduled:				
General condition: poor/autolytic changes	4/4	5/5		
Prostate: moderately small	3/4			
Seminal vesicles: moderately small	3/4			
Spleen: moderately small	4/4	4/5		
Testes: moderately small	2/4			
Thymus: small/not found	4/4	5/5		

Histopathology Limited tissues/doses	Scheduled: Kidneys: tubular basophilia HD ♂ 1/6 Liver: hepatocytic hypertrophy/brown pigment/hyperchromasia of hepatocytes: ♂ HD 6/6, MD4 6/10, MD3 9/10, MD2 5/10; ♀ HD 5/5, MD4 8/10, MD3 9/10, MD2 3/10, MD1 2/10 Ovaries: hypoplasia HD 5/5 Unscheduled: Kidneys: moderate selective tubular degeneration HD ♂ 2/4 Liver: hepatocytic hypertrophy/brown pigment/hyperchromasia of hepatocytes: HD ♂ 4/4 ♀ 5/5 Ovaries: hypoplasia HD 5/5
PK/TK	Study no. 818i, summarized in IND review no. 2.





FCE 24304: 52-week oral toxicity study in female beagle dogs followed by a 6-week recovery period. Study no. 416i. Study initiated June 18, 1990. Report dated March 19, 1993. Study no 416i. Conducted by [redacted] according to GLPs. The sponsor chose to use only female dogs as FCE 24304 is intended to be used only in women.

Conclusion: The HNSTD for this study is at least 480 mg/kg/day, the highest dose tested. No significant toxicological effects were observed at 30 mg/kg/day. Target organ for toxicity was the liver and gall bladder. Exemestane effects on reproductive tissues and the mammary gland were likely related to its pharmacological properties.

Species: female beagle dogs
n: 6/dose
Age/weight: 7-8 months/7.1-10.2 kg
Drug: FCE 24304
Batch # 9002 G226; purity 97.8%
Dosage: 30, 120 or 480 mg/kg/day
Schedule: daily for 52 weeks
Route: oral gavage
Formulation: 5% Methocel/0.4% Tween 80
Volume: 2 mL/kg
(Observations)

Mortality (daily)	None
Sacrifice – planned	52 weeks – 4/dose 58 weeks – 2/dose
Clinical Obs. (daily)	Feces: diarrhea: HD 5/6, MD 4/6 LD 3/6 Feces: traces of white substance: HD 6/6; MD 6/6 Sialorrhea, slight to marked: HD 6/6 MD 3/6 Vomiting, slight: HD 6/6, MD 6/6, LD 3/6
Body weight (wkly)	HD ↓ 11% at 52 weeks (not statistically different from control)
Food consumption (daily)	Unremarkable
Ophthalmoscopic (Pretest, D 180, 359, 403)	Unremarkable
ECG (pretest, D 86, 178, 262, 354, 400)	Unremarkable
Hematology (pretest, D 25, 92, 183, 358, 400)	Unremarkable

Clinical Chemistry (pretest, D 25, 92, 183, 358, 400)	ALT: ↑ HD D 92, 358 (52%)
Urinalysis (pretest, D 25, 92, 183, 358, 400)	Unremarkable
Gross Pathology	Unremarkable
Organ Weights	Absolute: 52-week sacrifice Liver: ↑ HD 28% Ovaries: ↑ HD 51% Uterus: ↓ LD-HD 43-67% (not dose dependent) Recovery sacrifice: unremarkable Relative (bw): Similar to absolute
Histopathology	52-week sacrifice Gall Bladder: slight epithelial hyperplasia: HD 2/4, MD 3/4 Liver: slight biliary proliferation: HD 3/4 Reproductive tract/mammary gland: inhibition of normal cyclical changes: HD 4/4 MD 4/4 Recovery sacrifice: Reproductive tissues: HD 1/2 animals anestrus
PK/TK	Report 809i., reviewed in Pharmacokinetics above

TOXICOLOGY SUMMARY

Acute Dose Studies

Acute dose toxicity studies for mice, rats and dogs were previously reviewed (IND Review No. 1). The oral LD_{50} for mice and rats was greater than 3000 and 5000 mg/kg, respectively, and approximately 3000 mg/kg for dogs. Clinical signs in mice included lung congestion, sedation, prostation, staggering gait, dypsnea, salivation and tonic convulsions. Congestion and erosions in the GI tract, vomiting, ataxia, muscular tremors, sedation and convulsions were seen in dogs.

Repeat Dose Studies

The main target organs for toxicity in repeat dose studies were the liver in rats, mice and dogs and rodent kidney. Exemestane effects on reproductive organs appear to be extensions of its pharmacological activity. The major acute effect was signs of CNS stimulation in mice, rats and dogs, including convulsant activity that was observed in mice and dogs (study not reviewed).

Summary of repeat dose studies (including IND reviews 1-3)

Species	Dose (mg/kg/d)	Schedule	Rev. #	Target Organ/Significant findings
Mice	100, 300, 1000 (feed)	4 week	NDA #1	None
Mice (♀)	15, 50, 150, 450	13 week	IND #3	Reproductive tissues, kidney, liver
Mice	30, 100, 350, 1250 (feed)	13 week	IND #3	Reproductive tissues, liver, kidney
Rat	100, 300, 1000 (feed)	4 weeks	NDA #1	None
Rat	30, 150, 750, 3750	4 weeks	IND #1	Liver, kidneys, lymphopoietic tissue, stomach gonads; 100% mortality first 14 days at 3750 mg/kg/d
Rat[1]	1000, 2000	4 weeks		Liver, kidney, lymphoid depletion, reproductive organs; mortality at 2000 mg/kg/d
Rat	30, 100, 350, 600, 900, 1250 (feed)	13 week	NDA #1	Reproductive organs, liver, thymus; possibly pituitary, spleen, adrenals; at 1250 mg/kg/d mortality and severe bw depression
Rat	30, 180, 1080	26 week	IND #1	Thymus, adrenal and gonads at all dose levels; at 1080 mg/kg/d significant mortality, liver and kidney toxicity
Rats	20, 50, 125, 315	52 weeks	IND #2	Reproductive organs, liver, kidney

Dog	30, 90, 270, 810	4 week	IND #1	Slight hyperplasia of the interstitial cells of the testes; ovarian follicular cysts
Dog	30, 150, 750	26 week	IND #1	Minor toxicity in GI, liver, kidney, adrenal gonads from 30-150 mg/kg/d; at 750 mg/kg/d mortality, toxicities to CNS, liver, kidney, thymus, adrenal and gonads
Dog (♀)	30, 120, 480	52 week	NDA #1	Reproductive tissues, liver, gall bladder

[1] study was not reviewed for NDA or IND

Histopathology Inventory for NDA 20,753

Study	T-910-90-002	9650370	N505-Q1295	9850371	21784F	416i	
Species	rat	Rats[1]	Mouse[1]	Mouse[2]	Mouse	Dog[2]	
Study Duration	52 wk gavage	13 week oral by diet	13 weeks oral by diet	13 wk gavage	13 week oral (feed)	52 week gavage	
Adrenals	X			X		X	
Aorta	X			X		X	
bone marrow smear				X		X	
bone (femur)				X			
Brain	X			X		X	
Cecum	X			X		X	
Cervix	X			X			
Colon	X			X		X	
Duodenum	X			X		X	
Epididymis	X						
Esophagus	X			X		X	
Eye	X			X		X	
fallopian tube							
gall bladder				X		X	
gross lesions	X		X	X	X		
harderian gland	X			X			
Heart	X			X		X	
ileum	X			X		X	
injection site							
jejunum	X			X		X	
kidneys	X	X	X	X	X	X	
lachrymal gland						X	
larynx							
liver	X	X	X	X	X	X	
lungs	X			X		X	
lymph nodes, cervical							
lymph nodes mandibular							
lymph nodes submaxillary				X		X	
lymph nodes, mesenteric	X			X		X	
mammary gland	X					X	
nasal cavity							

optic nerves	X			X		X	
ovaries	X	X	X	X	X	X	
pancreas	X			X		X	
parathyroid	X			X		X	
peripheral nerve							
pharynx							
pituitary	X			X		X	
prostate	X		X		X		
rectum	X			X		X	
salivary gland	X			X		X	
sciatic nerve	X			X		X	
seminal vesicles	X		X		X		
skeletal muscle	X			X		X	
skin	X			X		X	
spinal cord	X			X		X	
spleen	X			X		X	
sternum	X			X		X	
stomach	X		X	X	X	X	
testes	X		X		X		
thymus	X			X		X	
thyroid	X			X		X	
tongue	X			X		X	
trachea	X			X		X	
urinary bladder	X			X		X	
uterus	X		X	X	X	X	
vagina	X			X		X	
zymbal gland							

[1] inventory for study modified from summary review under IND [2] Females only

REPRODUCTIVE TOXICOLOGY

Dosage-range finding study of FCE 24304 administered orally via gavage to CDBR VAF/Plus rats (pilot study for segment I and segment III). Report no 418i. Sponsor's study no Q1135. study no 901-006P. Report dated August 27, 1991. Conducted by according to GLPs.

Conclusion: Treatment of females with exemestane reduced mating performance (200 mg/kg/d) and increased delivery complications (e.g., mortality in dams ≥ 10 mg/kg/d; increased duration of gestation ≥ 10 mg/kg/d; and increased duration of parturition at 200 mg/kg/d). Exemestane reduced the percentage of pregnancies resulting in birth of live litters (≥ 5 mg/kg/d). Increased still births (≥ 5 mg/kg/d); increased pup deaths (≥ 10 mg/kg/d); and reduced pup viability on both days 4 and 7 postpartum (≥ 10 mg/kg/d) was also observed. Pup deaths potentially related to drug exposure occurred at 5 mg/kg/day, with a clear increase in pup deaths occurring at 10 mg/kg/day.

The sponsor states that there was a reduction in the live litter size at weighing on day 1 and a reduction in the number of surviving pups per litter, starting at 5 mg/kg/day. A trend to decreased live litter size was also observed at 2 mg/kg/day on D1, and again at weighings at day 4 and 7 postpartum (data not presented). The sponsor provided no explanation for the exclusion of the 2 mg/kg/day group or the inclusion of the 5 mg/kg/day group in this finding. The biological relevance of the data from these groups is uncertain (see data table below). A similar conclusion can be reached regarding the number of surviving pups per litter.

Untreated females mated to males treated with ≥ 500 mg exemestane/kg/d showed decreased fertility. Pups born to these dams appeared normal. The effect of exemestane on sperm morphology/viability was not assessed.

Species: CD BR VAF/Plus rats
n: 8/group
Age/weight: 72-74 days; 254-327 g (M) and 186-240 g (F)
Drug: PNU-155971
batch nos. 9001G226 and 9002G226; purity 98.2 and 97.8%, respectively
Dosage: ♂: 125 (LD), 250 (LMD), 500 (HMD) or 1000 (HD) mg/kg/d
♀: 2 (LD), 5 (MD1), 10 (MD2), 40 (MD3) or 200 (HD) mg/kg/d
Schedule: ♂: 80 days (63 days prior to mating with untreated ♀ to sacrifice)
♀: 43-56 days (14 days prior to mating with untreated ♂ to scheduled sacrifice on day 25 of presumed gestation or day 7 postpartum)
volume: 10 mL/kg
Route: oral (gavage)
(observations)

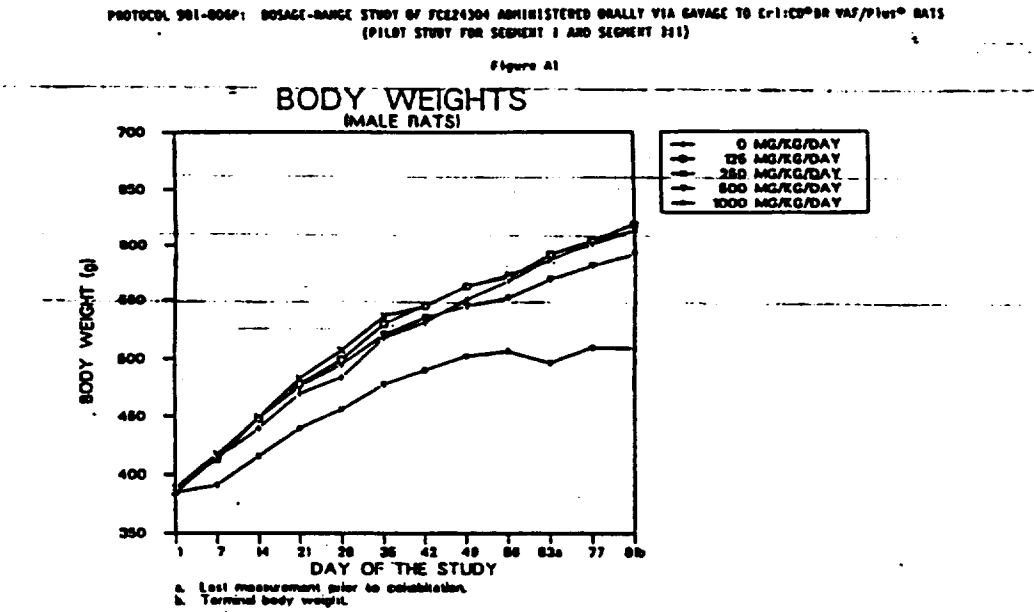
Mortality (daily)	♂ HD 2/8[a]	HD ♀[b]	MD3 ♀[b]	MD2 ♀[b]
		1/8	1/8	2/8
	[a] one attributed to intubation accident; one treatment related death on day 65 [b] difficulty in delivery			
Clinical Obs. (daily)	♂: LD-HD: excess salivation and reddish salivation; LMD-HD: chromorrhinorrhea; HD: urine-stained abdominal fur and ungroomed coat; HD decedant: cold to touch, pale, emaciated appearance; red-black substance around nose, mouth and front paws ♀: delivery complications in MD2-HD; including prolonged gestation, prolonged parturition and/or failure to survive delivery; prolonged prepartum bleeding			
Body weights (daily)	♂ See graph below; HD ↓ 17% on D81 ♀ unremarkable			
Food consumption (wkly)	Unremarkable			
Mating	↓ ♂ HD 2/6 mated; HMD 4/8 mated ↓ ♀ HD 6/8 mated; MD3 7/8 mated			
Estrus cycle	HD: Decreased estrus stages (0.8/14 day period) relative to control (3/14 day period) due to prolonged diestrus (≥ 6 days; 0/8 C and 6/8 HD). Average days in cohabitation increased from 2.8 (C) to 5.6			
Fertility	♂ ↓ (mated to untreated ♀: HD 2/8 pregnant; HMD 4/8 pregnant) ♀: unremarkable			

Birth record	HD	MD3	MD2	MD1	LD	C
Pregnant	6/8	7/8	8/8	7/8	7/8	7/8
Delivered litters	4	5	6	6	7	7
Dams with pregnancy confirmed at sacrifice (D25)	1	1		1		
Dams found dead with some pups delivered	1	1	1			
Dams found dead; pregnancy confirmed at necropsy			1			
Gestation index[a]	1/5[b]	3/6[b]	6/8	6/7	7/7	7/7
Mean duration of gestation in days	25.5	24.2	23.7	23.2	23.0	23.0
Mean duration of parturition in days	↑ in HD: mean days 2 vs 1.3 (C)					
Dams with ≥ 1 stillborn pup	2/3[b]	3/4[b]	2/6	5/6	0/7	1/7
Dams with all still born pups	0	1	0	0	0	0
Dams with all pups dying day 1-4 postpartum	0	2	0	0	0	0
Dams with all pups dying before 7 days postpartum	2	3	0	0	0	0
Mean no. live births/litter	1.3	5.0	11.3	12.5	12.4	13.0
Mean no. stillborn/litter	2.7	3.5	0.5	2.2	0	0.1

Live litter size at weighing D1 (mean ± SD)	1.0 ± 0.0	8.0 ± 8.5	10.2 ± 3.1	12.2 ± 3.1	12.4 ± 2.8	13.0 ± 5.2
Pups dying D1 (% of total liveborn)	75%	20.0%	10.3%	2.7%	0	0
Pups dying D 2-4 (% of total)	0	12.5%	9.8%	2.7%	2.3%	1.1%
Viability index D4[c]	25.0%	70.0%	80.9%	94.7%	97.7%	98.9%
Viability index D7	25.0%	70.0%	80.9%	94.7%	96.6%	98.9%
Surviving pups D1/litter	4.0	6.7	11.3	12.5	12.4	13.0
Surviving pups D4/litter	1.0	4.7	9.2	11.8	12.1	12.8
Pup bw (mean/litter)	↓ postpartum in HD on days 4 (26%) and day 7 (26%)					

[a] pregnancies resulting in birth of live litters; [b] excludes dam that was observed delivering but pups were missing and presumed cannibalized prior to litter observations; [c] % liveborn pups surviving to D4

Gross Pathology	Unscheduled: F_0 generation HD ♂: lack of body fat, gas-filled stomach and intestines and gastric erosions MD2 ♀: gastric erosions, dark red substance in vagina, pale internal organs, one black-red edematous fetus Scheduled: HD ♂: small and flaccid testes and epididymides (1/8) MD2 ♂: brown fluid in bladder; hydronephrosis (1/8) HD ♀: thickened uterine horn adhered to abdominal wall, retained placenta (1/8) MD3 ♀: autolyzed fetus in uterine horn (1/8) MD1 ♀: brown fluid in uterus (1/8) Pups: unscheduled deaths (# pups with finding/# in litter; # litters affected/# litters examined) HD: no milk in stomach (3/4; 1/1) MD3: no milk in stomach (4/12; 1/2) MD1: gas filled stomach (2/14; 1/6) Scheduled: unremarkable
Pregnancy	Unscheduled deaths: HD ♀: delivered 5 conceptuses (2 pups and 3 canabalized); 11 fetuses in utero MD3 ♀: delivered 2 pups, 1 fetus in uterine cervix and 10 fetus in utero MD2 ♀: one black-red edematous fetus and 3 early resorptions (of 23 implantation sites); in second dam, one pup delivered, one fetus in uterine cervix and 19 fetuses present in utero. Scheduled: MD1 ♀: resorption of litter (1/8) ; retained placenta; 2 pups stillborn and 2 additional dead on day 2 postpartum (1/8)



Fertility and general reproduction (including a "behavioral" postnatal evaluation) of FCE24304 administered orally by gavage to :CDBR VAF/Plus female rats (segment I evaluation). Final report dated February 9, 1993. Sponsor's study no. Q1231. Report no. 417i. Conducted by according to GLPs.

Conclusion: Treatment with exemestane caused delivery complications, prolonged gestation, and resulted in grossly visible changes in the placenta at ≥ 20 mg/kg/day. Significantly increased placental weights were observed in all dosage groups, attributed to possible anabolic action of exemestane. Effects on fetuses included reduction in litter size, delays in ossification and reduced body weight. Estrous cycling and mating were unaffected by up to 100 mg/kg/day exemestane. The effect of 100 mg/kg/d exemestane on fertility was uncertain due to the low pregnancy rate in this group and in controls. Some findings (e.g., wavy ribs in 4 mg/kg/d fetuses) may be indicative of maternal toxicity.

The sponsor states, and I concur, that the developmental NOEL for this study is less than 4 mg/kg/d, based on increased placental weights, a parameter affected by both the dam and conceptus. Alternatively, the sponsor calculates a NOEL of 4 mg/kg/d based on findings classically associated with the fetus. I do not concur with this analysis. The number of fetal variations, while not significantly different from control, increased in this group without apparent maternal toxicity. Secondly, to discount the possibility that the fetus is not impacted by the anabolic activity of exemestane at 4 mg/kg/d would require additional studies. Finally, the number of litters examined for effects is about one-half considered adequate for statistical purposes (ICH guideline "Detection of Toxicity to Reproduction for Medicinal Products").

A maternal NOEL of 4 mg/kg/d was observed in this study, based on deaths, clinical and necropsy findings, and reproductive effects at the higher doses.

The pregnancy rate in control animals was very low (56.7%), barely within the historic range of this strain of rats (56-100%) as published by MARTA (September, 1993). The pregnancy rate for the 4-100

mg/kg/d groups was 80%, 80% and 66.7%, respectively. The reason for the low rates in control and 100 mg/kg/d animals was not clear to the sponsor. However, it was not considered drug related.

Species: CD BR VAF/Plus female rats

Mating data	HD	MD	LD	C
Rats in cohabitation	30	30	30	30
Rats pregnant	20	24	24	17
# pregnant rats in Caesarian group	8	10[a]	11[b]	8
# pregnant rats in natural delivery group	12	14	13	9
# rats in natural delivery group found dead	3	1	0	0
# of rats that delivered litters	8[c]	13	13	9

[a] one dam sacrificed D 19 of gestation; [b] mating day incorrectly identified for one dam that delivered normal litter on presumed D 4 of gestation; [c] one rat with confirmed pregnancy at sacrifice on D25 did not deliver

Age/weight: 67 days; 190-234 g
Drug: PNU-155971
batch no. 9001G226; purity 98.2%
Dosage: 4, 20 and 100 mg/kg/day
Schedule: 14 days premating through 21 days of cohabitation until day 20 of presumed gestation (Caesarian group) or day 15 of presumed gestation (natural delivery group); dosing resumed for days 1-21 of lactation
volume: 10 mL/kg
Route: oral (gavage)
(observations)

Mortality (daily)	Natural Delivery group HD: 3/15 natural delivery group (Days 23, 24, and 25 of gestation) MD: 1/15 natural delivery group (Day 24 of gestation) Caesarian: none
Clinical Obs. (daily)	Natural delivery group: Decedents: MD-HD: delivery complications (prolonged gestation, dystocia and placental changes); red perivaginal/vaginal substance (3/3 HD); decreased motor activity, pale and cold to touch (1/3 HD) HD: pale (1/12) MD pale (1/14) Caesarian Section group: unremarkable
Body weights (daily)	Unremarkable
Food consumption (wkly)	Unremarkable
Mating	Unremarkable
Estrus cycle	Unremarkable
Fertility	Uncertain in HD due to low pregnancy rate in HD and controls

Birth record: Caesarian group	HD	MD	LD	C
Dams with resorptions/# pregnant: ↑ HD	8/8	7/10	6/11	6/8
Mean # resorptions: ↑ MD-HD	3.8	2.6	1	1.5
Resorbed conceptus/litter (%):↑ MD-HD	22.8	15.5	5.4	8
Mean litter size: ↓ MD-HD	13	12.9	16.5	16.4
Placental weights: ↑ vs. C	72%	72%	13%	—
Live fetal bw (g/litter): ↓ vs C	4.2%	9.9%		—
♂	0%	8.7%		
♀	5.4%	10.5%		
Fetal alterations: Caesarian group				
# litters with any variation/# evaluated	4/8	3/9	3/10	0/8
Fetuses with any variation (* p = 0.01)	6 (5.85)*	8 (7.3%)*	4 (2.4%)	0
Fetuses with any variation/litter	6.4%	7.5%	2.4%	0%

The following are litter incidences (%)	HD	MD	LD	C
Renal: moderate dilation pelvis	0	0	10	0
Vertebrae: bifid thoracic centrum	12.5	22.2	0	0
vertebral lumbar arch incomplete ossification	12.5	0	0	0
Ribs: incomplete ossification	12.5	0	10	0
Ribs: wavy	12.5	0	10	0
Sternebrae: including incomplete/unossified	12.5	11.1	0	0
Pelvis: unossified pubes and ischia	0	11.1	0	0
Birth record: Natural delivery group (NDG)				
Dams with early resorption:[a]	1			
Implantation sites per delivered litter (mean):	16.2	15	15.5	12.3
Dams with all stillborn/cannibalized pups at birth:	2/8	0/13	0/13	0/9
Dams with stillborn pups	8/8	5/13	3/13	0/9
Dams with all pups dying day 1-4 postpartum:	3/6	3/13	1/13	1/8
Mean no. liveborn pups/litter	4.7	5.9	13.5	11.4
Mean no. stillborn pups/litter:	4.5	1.8	0.3	0
Pup weight at birth: ↓ relative to control	8.5%	3%		
Pups dying D1 (mean %/litter)	35.7%	18.2%	1.7%	0.0%
Pups dying D2-4 (mean %/litter)	22.2%	4.8%	3.4%	1.0%

[a] dam sacrificed Day 25 because it did not deliver; 5 early resorptions *in utero* found at necropsy

Viability index (# pups alive D 7/D 1) (NDG)	46.4%	77.9%	94.3%	97.1%
Lactation index (# pups alive D21/D7) (NDG)	100%	100%	100%	100%
Gestation mean no. days (NDG)	24.6	24.2	23.2	23.2

Gross Pathology	Unscheduled: Natural delivery group HD: red brown fluid in uterus and large, mottled placenta (2/3 unscheduled deaths natural delivery group) MD: red brown fluid in uterus and stomach; large, mottled placenta Scheduled: Natural delivery: Unremarkable Scheduled: Caesarian section group: Uterus: red brown fluid (MD, HD each 1/15)
Postweaning behavior	Unremarkable

Preliminary teratogenesis study by oral route in rats. Report dated March 16, 1989. RPM experiment no. 880018. Report no. 406i. Conducted by (no GLP statement).

Conclusion: Under the conditions tested, no effects on the dams were observed. Fertility problems were observed at the highest dose used (810 mg/kg/day) and may be due to interference of the test article with implantation. Slight embryo/fetotoxicity was observed at ≥ 90 mg/kg/day as manifested by increased early and late resorptions.

Species: :CD (Sprague Dawley) BR VAF/Plus female rats
n: 8 dams/group
Age/weight: 9-10 weeks old, 200-225 g
Drug: PNU-155971
batch no. A16003; purity 97.7%
Dosage: 30, 90 (LMD), 270 (HMD) or 810 mg/kg/day
Dosing period: Days 6-17 of pregnancy

volume: 10 mL/kg
Route: oral (gavage)
(observations)

Mortality (daily)	None					
Clinical Obs. (daily)	HD: metrorrhagia (1/8, pregnancy D 15) HMD: metrorrhagia (1/8, pregnancy D 15)					
Body weights: (D 0, 6, 10, 15 18 and 20 of gestation)	Unremarkable					
Food consumption (D 6, 10, 15, 18 and 20 of gestation)	Unremarkable					
Fertility index (# pregnant/# with positive vaginal smears)	HD: ↓ (3/8 vs. 7/8 in control)					
Gross Pathology (F_0)	Unremarkable					
Reproductive effects		HD	HMD	LMD	LD	C
	Dams with early resorptions	2/3		4/8		2/7
	Dams with late resorptions		1/7	1/8		0/7
	Dams with dead fetuses		1/8			
	Dams with only viable fetuses	1/3	4/7	3/8		5/7
	Post implantation loses	11.61%				3.36%
	Mean placenta weight (↑ vs. C)	20%	43%	55%	33%	
Fetal alterations (external evaluation)	LMD fetus: omphalocele (1/13 fetuses) HMD fetus: dead; omphalocele, absence of bone structure and ablepharia (1/9 fetuses)					

Teratogenesis study of FCE-24304 by oral route in rats. Report dated April 15, 1992. Report no. 414i. Conducted by according to GLPs (OECD). In addition to teratogenesis, compound-related effects on the physical and behavioral development of the offspring as well as their reproductive performance was assessed.

Conclusion: Exemestane was well tolerated in pregnant dams at doses up to 810 mg/kg/day administered on days 6 to 17 of gestation. No signs of general toxicity or gross lesions were observed in the dams. Mortality due to dystocia was observed in some dams at all dose levels in the natural delivery group. An increase in the number of dams with resorptions was found in ≥ 10 mg/kg/d animals, related to a lower number of dams with only viable fetuses. Of particular note was the increasing number of dams with late resorptions. An increase in mean fetal body weight per litter was observed in from 10-250 mg/kg/d animals (statistically significant at 50 and 250 mg/kg/d), and slightly reduced at 810 mg/kg/d. The mean number of live births decreased from 50 mg/kg/d. Pup weight at birth was decreased at 810 mg/kg/d animals but was greater than control in all other dose groups on days 1-21 (significant on day 12 for both males and females). The sex difference in live fetuses seen in the Casearean section group (i.e., decreased mean number of female live births per litter from 50 mg/kg/d) was not seen in the natural delivery group.

The principal adverse effect of exemestane was a prolongation of the gestation period (statistically significant in all dose groups) with dystocic parturition in all dose groups, which caused delivery complications and death in some dams allowed to deliver. No specific drug-related or dose-dependent anomalies were observed in the conceptus.

The sponsor notes the dose-relationship observed in resorptions ≥ 10 mg/kg/d animals but states that for 10 mg/kg/d animals it is ..ot statistically significant and falls within the range for colony data. While not conclusive, the increase in both the number of dams with resorptions and the mean number of resorptions per litter in low dose animals, coupled with a dose-response trend, is indicative of a possible increase in

resorptions in the 10 mg/kg/d animals which cannot be discounted.

Species: CD (Sprague Dawley) BR VAF/Plus female rats

	HD	HMD	LMD	LD	C
Total rats	40	40	40	40	40
# rats pregnant	34	34	36	30	34
# rats Caesarian (planned)	25	25	25	25	25
# pregnant	21	22	23	21	20
Incidental delivery	1		1		
# Caesarean sectioned	20	22	22	21	20
# rats natural delivery (planned)	15	15	15	15	15
# pregnant	13	12	13	9	14
# with only implantations			1		
# rats delivering	13	12	12	9	14

Age/weight: 9-10 weeks old, 200-225 g
Drug: PNU-155971
batch no. 2/88; purity 97.7%
Dosage: 10, 50 (LMD), 250 (HMD) or 810 mg/kg/day
Dosing period: Daily days 6-17 of pregnancy
volume: 10 mL/kg
Route: oral (gavage)
(observations)

Mortality (daily)	No. Dead (day of death)	HD 2 (23, 25)	HMD 2 (24, 24)	LMD 4 (24, 25, 25, 27)	LD 1 (24)	C 0
	Caesarean group – no unscheduled deaths					
Clinical Obs. (daily)	Dystocia: 1 LD, 4 LMD, 2 HMD, 2 HD; all animals except LD died unable to deliver fetuses; LD dam died after complete expulsion					
Body weights (days 0, 6, 10, 15 18 and 20 of gestation; weekly during lactation)	Unremarkable					
Food consumption (days 6, 10, 15, 18 and 20 of gestation)	Unremarkable					
Fertility index (# ♀ pregnant/# with positive vaginal smears)	Unremarkable					

	Caesearean group	HD	HMD	LMD	LD	C
Reproductive effects	Dams with early + late resorptions/gravid	10/20	9/22	9/22	6/21	4/20
	Dams with early resorptions	6	6	6	4	4
	Dams with late resorptions	6	6	4	2	0
	Dams with only viable fetuses	10	13	13	15	16
	# early resorptions (mean/litter)	.80	.50	.32	.29	.20
	# late resorptions (mean/litter)	.55	.64	.68	.10	.00
	Early + late resorptions (mean/litter)	1.35	1.14	1.00	.38	.20
	Dead fetuses (mean/litter	0	0	0	0	0
	Live fetuses (mean/litter)	12.80	12.77	13.45	14.24	14.55
	Live male fetuses (mean/litter)	7.60	7.59	7.82	7.14	6.95
	Live female fetuses (mean/litter)	5.20	5.18	5.64	7.10	7.60
	Post-implantation loses (mean/litter)	10.23%	8.18%	7.09%	2.45%	1.25%
	Live fetal mean weight: ↑ (↓) vs C	(2.7%)	5.6%	3.8%	3.2%	—
	♂	(2.9%)	5.8%	2.1%	3.7%	
	♀	(3.0%)	4.9%	3.0%	2.7%	
	Live placental mean weight/litter: ↑ vs. C	32.7%	38.5%	42.3%	19.2%	—
	Live female fetuses (mean/litter)	5.20	5.18	5.64	7.10	7.60
	Live male fetuses (mean/litter)	7.60	7.59	7.82	7.14	6.95

	Natural delivery group					
	Parturitions	13	12	12	9	14
	Dams with live pups at birth	11	10	8	9	14
	Gestation index (%)	84.62	83.33	61.54	100	100
	Dams with stillborn pups	2	1	1	2	1
	Dams with all stillborn pups	0	0	0	0	0
	Dams with live pups at weaning	11	10	7	8	14
	Liveborn (mean/litter)	13.27	11.50	11.38	13.50	13.71
	Stillborn pups (mean/litter)	0.36	0.10	0.13	0.25	0.17
	Postimplantation losses (mean %/litter)	12.23	18.69	29.52	9.50	5.26
	Gestation days (mean/litter)	23.00	22.80	23.13	22.88	22.21
Fetal alterations	↑ incidence of convoluted ureter, in all dose groups (30-100% higher than control); no dose dependency ↑ incidence of dilation of renal pelvis (2-5% frequency in dose groups vs. 0% in control; no dose dependency)					
Pup examination	Pup wt. at birth (♂, ♀) ↓ in HD group (↓ of 10 and 9% relative to control) Pup weight D1-21 (♂, ♀): ↑ in all dose groups vs. C, significant on D 12 in HMD-HD (~15-17% vs C) Precocious appearance of eruption of incisors and eye opening in all treated groups; no apparent dose dependency					
Physical and behavioral development	Unremarkable					

Preliminary teratogenesis study of compound FCE 24304 given orally to the rabbit. Study initiated January 13, 1988. Study report completed September 15, 1989. Report no. 407i. Conducted by (non-GLP).

Conclusion: Exemestane had clear effects on the dams treated at 270 mg/kg/d and 810 mg/kg/d in this study. Gastric effects were seen in all animals that died unexpectedly and may have contributed to death in 3 of the 810 mg/kg/d animals and total litter loss in 2 females in the 270 mg/kg/d group. Resorptions, abortions and post implantation losses were higher in the 270 mg/kg/d and 810 mg/kg/d groups compared to control values, indicating that exemestane was toxic in this species at the test doses. The decrease in mean number of viable fetuses in the 270 mg/kg/d group can be attributed to the two dams in this dose group that had either resorptions only or a total abortion. An increase in the number of non-specific anomalies in viable fetuses was observed at the 270 mg/kg/d level, but the relationship of this finding to treatment is uncertain because of the few litters, the low number of viable fetuses examined, and the absence of serious morphological changes.

Species: New Zealand White HY/CR outbred female rabbits
n: 5/dose
Age/weight: 7-8 months old,
Drug: FCE 24304
batch no. A16002; purity 95.9%
Dosage: 30, 90 (LMD), 270 (HMD) or 810 mg/kg/day
Dosing period: Days 6-18 of pregnancy
volume: 4 mL/kg
Route: oral (gavage)
(observations)

Mortality (daily)	HD: 3/5 (days 21 and 24) LMD: 2/5 (attributed to intubation error at 4th and 12th dosing) LD: 2/5 (attributed to intubation error at 9th and 13th dosing)

Clinical Obs. (daily)	HD: loss of appetite, hypoactivity and loss of fur (all animals, dose dependent); pale feces (3/5); hypothermia, metrorhagia and weakness (1/5); poor nutritional status (5/5) HMD: loss of appetite (2/5), loss of fur (2/5) and hypoactivity (5/5); pale feces (1/5); vaginal discharge of mucus (1/2 dams with total litter loss) and fetal expulsion in late pregnancy (2nd dam with total litter loss); poor nutritional status (2/5)
Body weights (daily)	HD: progressive ↓ in body weight until sacrifice (D 28) relative to pretreatment (25% decrease, no live fetuses in the 2 HD animals); ↓ 29% vs. D 28 C HMD: ↓ 10% vs. D28 C
Food consumption (daily)	HD: marked inhibition in food intake from 1st dosing; only 5% of control during days 11-14 (nadir), recovery thereafter, reaching 65% of control during days 25-28.
Fertility	Unremarkable

Gross Pathology F_0	Unscheduled: Gall bladder: slight (2/3 HD) to markedly enlarged (1/3 HD) Gastrointestinal: lesions in 3/3 HD animals that died, including hemorrhagic or necrotic ulcers and deep erosion of gastric mucosa; blood and fur in gastric content; flatulence or liquid feces and intestinal enlargement in all HD animals. Hemorrhagic or necrotic points in 2/2 LMD; dilated vessels and blood in 1/2 LD Reproductive (tubes and ovaries): cysts, congestion of tubes, brownish points on ovaries: some animals all treatment groups, no dose response Thoracic and pulmonary hemorrhage in lower dose animals with intubation errors Scheduled Gall bladder: slight (1/5 HMD) to markedly enlarged (1/2 HD) Reproductive (tubes and ovaries): cysts, congestion of tubes, brownish points on ovaries: some animals all treatment groups, no dose response; Uterus: hyperplasia and hyperemic, no dose response Amniotic fluid scant and brown, yolk sac brown and thick (1/5 HMD)

Reproductive effects	Summary of maternal survival and pregnancies					
		HD	HMD	LMD	LD	C
	Total # dams	5	5	5	5	5
	# Dams pregnant	5	5	4	5	4
	# Pregnant dams surviving to D29	2	5	2	3	4
	Dams at scheduled sacrifice					
		HD	HMD	LMD	LD	C
	Dams with only viable fetuses	0/2	2/5	1/2	2/3	1/4
	Dams with resorptions/dead fetuses only	2	1			
	Dams with total or partial abortion		1			
	Dams with viable fetuses, resorptions, dead fetuses	0	1	1	1	3
	Mean no. viable fetuses/litter	0	4	7.5	7.33	6.5
	Post implantation loss (mean %/litter)	100[1]	42[1]	7.14	5.56	13.68

[1] includes dams showing nidation

	Unscheduled					
	Dams with resorptions only	3/3				
	Dams with fetuses only			1/2	1/2	
	Dams with fetuses and resorptions			1/2	1/2	

Fetal alterations in viable fetuses		HD	HMD	LMD	LD	C
	# Litters	0	3	2	3	4
	Total # fetuses examined	0	20	15	22	26
	Total # fetuses with malformations[1]		0	1[3]	0	0
	Total # fetuses with anomalies[1]		6[3]	1	0	2[3]
	Irregular palatine shelves		c, e[2]			b
	Marked concavity of palate		E			b
	Double left subclavian artery		B	b		
	Bilobate gallbladder		A			
	Misshapen spleen		D			
	moderate kidney hypoplasia		c			
	ovarian cyst		f			
	irregular ovarian vascularization		f			
	Microsomia			a		
	moderate acrocephaly			a, b		a

[1] includes visceral and external examination; [2] letters refer to individual animals; [3] animals a and b; c and d; and e and f are from same litter

Assessment of possible embryotoxic or teratogenic effects in rabbits by the oral route (includes Amendment 1). Final report dated April 30, 1991. Report no. 411i. Study no. 4745 RSL (No. Q1017). Conducted by [redacted] according to GLPs. Females were artificially inseminated in this study.

Conclusion: The sponsor states that the 3 dams in the 90 mg/kg/d group and 1 in the 270 mg/kg/d group found dead during the treatment period were due to misdosing. However, in three of these animals (two 90 mg/kg/d and one 270 mg/kg/d) this appears speculative as no significant observations were noted at necropsy. In 270 mg/kg/d dams, there was a marked increase in rates of resorptions and post-implantation losses, and abortions were observed in 3 dams (2 drug related) at this dose. The increased incidence of reduced ossification of the hyoid bone was not discussed by the sponsor except to indicate that the value in 270 mg/kg/d animals was within the range of historical control data. Findings of reduced ossification are indicative of delayed development that may be linked to reduced body weight, particularly in dams treated with 270 mg/kg/d exemestane. Exemestane did not show any teratogenic effects at doses up to 270 mg/kg/day in this study.

Species:	New Zealand White HY/CR outbred female rabbits
n:	18/group
Age/weight:	16-18 weeks old, 3.6 kg
Drug:	FCE 24304
	batch no. 2/88; purity 97.7%
Dosage:	Females: 30, 90, or 270 mg/kg/day
Dosing period:	Daily days 6-18 of pregnancy
volume:	2 mL/kg
Route:	oral (gavage)
(observations)	

Mortality (daily)	Found dead: HD 1/18 (day 7, attributed to misdosing) MD: 3/18 (day 7, 14, 16, attributed to misdosing) Control: 1/18 (day 18; cause unidentified) Sacrificed early for abortion: HD: 3/18 (D14, 15, 20) MD 1/18 (D17; purulent lungs)

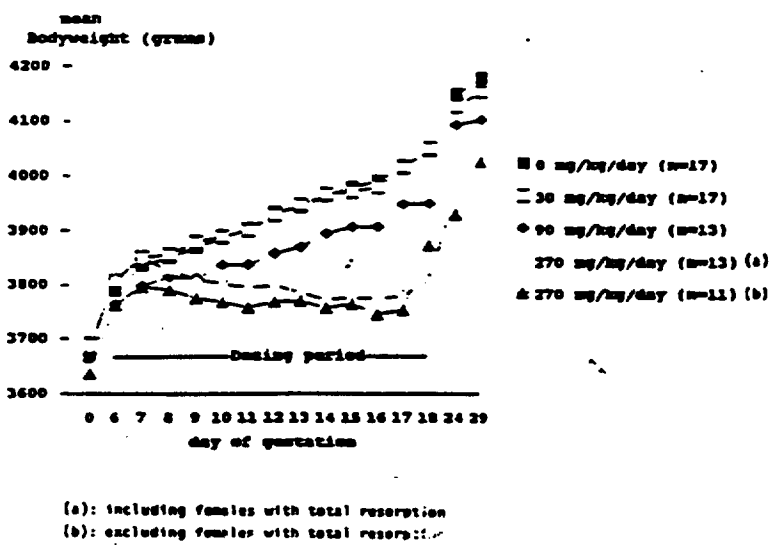
Clinical Obs. (daily)	HD: startle and stretching (2/18, one of which died) MD: startle, stretching (2/3 animals which died; 1/3 animals sacrificed for abortion); tremors, lying on side, paleness of extremities, dypsnea (1/3 animals which died); noisy respiration, blood in bedding (1/3 animals which died); paleness of extremities; ocular damage LD: tremors, startle and dyspnea, lying on side (1/18)
Body weights (daily to day 18, days 24 and 29)	See graph below. ↓ 2.4% and 5.8% in MD and HD vs D18 C (nadir) ↓ in D6-18 body weight gain vs C (dose dependent) during treatment period; HD (net weight loss), MD 27.5% , LD 5.1%
Food consumption (weekly)	↓ during dosing period in MD (25%) and HD (50%) relative to controls
Fertility	Unremarkable
Gross Pathology	Unscheduled (dead and sacrificed): Lungs: test substance (1/3 MD); purulent (1/1 MD sacrificed) Thymus red spots (1/3 MD) Vagina: sacrificed animals had blood in vagina (3/3 HD, 1/1 MD) Scheduled Unremarkable

Reproductive effects		HD	MD	LD	C
	Dams with abortion/# pregnant[1]	3/17	1/17	0/17	0/18
	Dams with total resorptions	2			
	Dams with viable fetuses at term	11	13	17	17
	Post-implantation loss (% sites/animal)	35.2	0	0	6.9
	Live mean placental wt ↓ vs. C	14.7%	14.7%		
	Mean no. live fetuses: (% sites/animal)	76.6	100	100	93.1
	Mean bw of viable ♂ fetuses: ↓ vs. C	13.8%			
	Mean bw of viable ♀ fetuses: ↓ vs C	14.4%			

Fetal alterations in viable fetuses	External observations: Unremarkable Skeletal observations: 13th thoracic rib: ↓ litter incidence in LD (76.5%) and HD (72.7%) compared to control (94.1%) Reduced ossification of Hyoid bone: ↑ fetal incidence in HD relative to control (9.5% vs. 0%); dose dependent ↑ in litter incidence of 0%, 5.9%, 7.7% and 18.2%, control-HD

[1] One each HD and MD considered not drug-related.

Maternal



(a): including females with total resorption
(b): excluding females with total resorp::

SUMMARY OF REPRODUCTIVE TOXICOLOGY

The doses selected for all studies were acceptable and demonstrate clear toxic effects without demonstrating observable teratologic effects.

Study	Species	Doses (mg/kg/d)	Findings
Seg I/III pilot	Rat	♂ 125, 250, 500, 1000 ♀ 2, 5, 10, 40, 200 Dosing: ♂: 63 days premating through cohabitation ♀: 14 days premating to day 7 of lactation)	♂ ↓ fertility in untreated females mated with males dosed with ≥ 500 mg/kg/d ♀ ↑ in mean days parturition at 200 mg/kg/d; ↑ duration of gestation ≥ 10 mg/kg/d; mortality in dams due to delivery ≥ 10 mg/kg/d; ↓ gestation index ≥ 5 mg/kg/d; ↓ estrous stages at 200 mg/kg/d; ↑ in stillbirths ≥ 5 mg/kg/d; ↑ % pup deaths ≥ 10 mg/kg/d; ↓ pup viability day 4 and 7 postpartum ≥ 10 mg/kg/d; ↓ live litter size on weighing postpartum days 1, 4 and 7 at ≥ 10 mg/kg/d; ↓ pup bw at 200 mg/kg/d; gross lesions with pup deaths ≥ 5 mg/kg/d
Segment I	Rat	♀ 4, 20, 100 Dosing: 14 days premating through 21-day cohabitation period to D20 gestation (Caesarean group) or D15 of gestation and resuming on D1-21 of lactation (natural delivery group)	↑ mean # days gestation ≥ 20 mg/kg/d; dystocia, with dam mortality ≥ 20 mg/kg/d; no effect of estrus cycling or mating; uncertain effect on fertility at 100 mg/kg/d; ↓ litter size, fetal body weights and delayed ossification ≥ 20 mg/kg/d; ↑ placental weight ≥ 4 mg/kg/d; ↑ stillborn pups ≥ 4 mg/kg/d; ↑ resorption ≥ 20 mg/kg/d; ↓ mean liveborn pups/litter ≥ 20 mg/kg/d; ↑ pup mortality D 1 postpartum ≥ 20 mg/kg/d; ↓ pup viability D 1-7 postpartum ≥ 20 mg/kg/d; gross placental changes ≥ 20 mg/kg/d
Seg II pilot	Rat	♀ 30, 90, 270, 810 Dosing: D 6-17 of gestation	↓ fertility at 810 mg/kg/d; ↑ resorptions ≥ 90 mg/kg/d; ↑ placental weight ≥ 30 mg/kg/d
Seg II	Rats	10, 50, 250, 810 Dosing: D 6-17 of gestation	Dystocia ≥ 10 mg/kg/d, with dam mortality; ↑ gestation period ≥ 10 mg/kg/d; ↓ gestation index ≥ 50 mg/kg/d; ↓ mean #/litter liveborn 50-250 mg/kg/d; ↑ placental weight ≥ 10 mg/kg/d; ↑ in resorptions, particularly late resorptions ≥ 10 mg/kg/d; ↑ mean fetal bw 50-250 mg/kg/d; ↓ mean fetal bw 810 mg/kg/d; ↑ mean pup weight D1-21 ≥ 10 mg/kg/d; ↓ mean number of live female fetuses (C-section group) ≥ 250 mg/kg/d; no teratologic findings
Seg II pilot	Rabbits	30, 90, 270, 810	Maternal GI/ovarian/uterine toxicity ≥ 30 mg/kg/d, no dose response; ↑ in abortions/resorptions/post implantation losses at 270 mg/kg/d; ↑ in non-specific fetal anomalies at 270 mg/kg/d but the finding is uncertain due to few litters and no serious morphological changes observed
Seg II	Rabbits	30, 90, 270	↑ in abortions/resorptions at 270 mg/kg/d; ↑ post-implantation loss at 270 mg/kg/d; ↓ fetal bw at 270 mg/kg/d; ↓ placental wt ≥ 90 mg/kg/d; ↑ litter incidence of reduced ossification of hyoid bone ≥ 30 mg/kg/d; no teratogenic potential noted

GENETIC TOXICOLOGY:

The following studies were previously reviewed (see Review #1). Additional information not captured in the original review is presented below.

Gene mutation in *Salmonella typhimurium* on FCE 24304 (Ames test). Study initiated November 16, 1987. Study concluded February 23, 1988. Report no 303i. Conducted by according to GLPs.

Conclusion: FCE 24304 was not mutagenic with or without metabolic activation in the bacterial strains tested. The study incorporated S. typhimurium strain TA 1538 into the battery of test strains. TA1538, which assays frameshift mutations in the his D gene, is not considered part of the necessary core battery defined by ICH guideline S2A. In report no. 307i, the sponsor reported the results of a study in which the mutation potential of FCE 24304 in E. coli strain CM 891 (WP2 uvrA pKM101) was assessed (reviewed in IND review no. 2, dated 12/15/98). The results indicated that FCE 24304 was also negative as a genotoxic agent in that strain. Thus, these studies together provide the complete set of strains suggested for mutagenesis analysis according to ICH guideline S2A.

Mean number of revertants/plate in 5 strains of *Salmonella typhimurium* without metabolic activation.

Compound	Amount (µg/plate)	Exp. no.	TA 1535	TA1537	TA 1538	TA 98	TA 100
methanol		1	12.3	7.8	12.7	27.8	104.5
		2	10.5	8.0	14.2	29.2	107.8
FCE 24304	125	1	12.3	6.7	13.0	28.3	101.3
		2	9.3	7.3	15.0	29.7	108.0
	250	1	10.0	4.3	12.3	31.0	108.3
		2	11.3	6.7	24.3	23.7	100.3
	500	1	13.3	7.3	11.7	27.0	97.7
		2	10.7	6.0	15.0	20.7	93.0
	1000	1	9.3	4.7	9.0	31.7	97.7
		2	7.0	8.3	14.3	30.0	84.7
	2000*	1	5.3	4.0	8.0	17.3	57.0
		2	5.3	4.0	10.0	15.3	73.3
Sodium azide	5	1	1482.7				811.7
		2	1185.7				819.3
9-aminoacridine	70	1		1091.3			
		2		956.0			
2-nitrofluorene	10	1			979.7	762.7	
		2			1030.0	462.3	

*Reduction to background lawn to less than 50% of control.

Mean number of revertants/plate in 5 strains of *Salmonella typhimurium* with metabolic activation.

Compound	Amount (µg/plate)	Exp. no.	TA 1535	TA1537	TA 1538	TA 98	TA 100
methanol		1	16.5	8.8	33.8	47.0	131.0
		2	12.2	9.7	31.2	39.0	125.5
FCE 24304	125	1	18.0	7.0	33.7	39.0	123.3
		2	14.3	11.0	35.0	46.3	132.3
	250	1	18.3	5.7	30.3	44.3	130.0
		2	13.7	8.7	30.3	41.0	122.0
	500	1	13.3	8.7	31.7	41.0	123.3
		2	8.3	8.8	30.3	41.3	133.3
	1000	1	14.7	7.0	28.7	42.7	117.3
		2	10.3	7.7	23.3	41.3	117.7
	2000*	1	8.3	3.0	25.3	29.0	82.3
		2	6.0	4.0	21.7	27.7	86.3
2-aminoanthracene	10	1	419.3	366.7	3127.0	2346.3	2776.0
		2	360.3	308.3	2121.7	1916.7	2780.3
2-acetylaminofluorine	50	1			1968.7	1559.7	
		2			1676.3	1242.0	
benzo[a]pyrene	10	1			269.0	255.3	475.7
		2			118.3	151.7	329.7

*Reduction to background lawn to less than 50% of control.

DNA repair test with FCE 24304 in rat hepatocyte primary cultures. Study initiated November 4, 1987. Study concluded February 16, 1988. Report no 302i. Conducted by according to GLPs. Net nuclear grain count was determined by subtracting the highest cytoplasmic count from the nuclear count. Grain counts were performed on 20 nuclei/slide from 3 different slides.

Conclusion: FCE 24304 did not increase the net nuclear grain count over control levels at nontoxic doses tested. FCE 24304 did not induce DNA repair in primary rat hepatocytes.

Species: Male Fisher rats as hepatocyte source
Age/weight: 10-13 weeks old; 200-300 g

Mean of 60 net nuclear grain counts obtained from triplicate slides.

Compound	Concentration (µg/mL)	Net nuclear grain count
cell control	-	-2.4
methanol	-	-6.0
FCE 24304	3.125	-5.3
	6.25	-4.8
	12.5	-6.4
	25	-4.9
	50	-4.2
	100*	-
	200*	-
2-aminofluorine	0.9	42.5
	1.8	47.2

*toxic concentration

Micronucleus test in mouse bone marrow cells after oral administration of FCE 24304. Study initiated September 28, 1987. Study concluded January 18, 1988. Report no 301i. Conducted by [redacted] according to GLPs.

Conclusion: FCE 24304 was not genotoxic in the mouse bone marrow micronucleus test.

Species: CD-1 mice
n: 5/sex/dose/timepoint
Age/weight: 5 weeks old; 25 g (M) and 24 g (F)
Drug: FCE 24304
purity 95.9%
Pos. control: cyclophosphamide 50 mg/kg i.p.
Dosage: 0, 625, 1250 and 2500 mg/kg
suspension of 0.5% Methocel and 0.4% Tween 80
Timepoints: 24, 48 and 72 hours post dosing of FCE 24304
Schedule: single
volume: 0.2 mL/ 10 g body weight
Route: oral, via gavage

			Micronucleated polychromatic erythrocytes (%)			Ratio polychromatic/normochromatic erythrocytes		
compound	dose (mg/kg)	hours post dosing	males	females	pool	Males	females	pool
Vehicle	--	24	0.08	0.08	0.08	0.75	0.79	0.77
		48	0.12	0.08	0.10	0.74	0.72	0.73
		72	0.10	0.06	0.08	0.77	0.66	0.72
FCE 24304	625	24	0.06	0.08	0.07	0.74	0.52	0.63
		48	0.06	0.12	0.09	0.76	0.71	0.73
		72	0.04	0.06	0.05	0.62	0.64	0.63
	1250	24	0.14	0.04	0.09	0.75	0.61	0.68
		48	0.18	0.04	0.11	0.87	0.70	0.78
		72	0.04	0.02	0.03	0.65	0.68	0.66
	2500	24	0.10	0.06	0.08	0.65	0.63	0.64
		48	0.16	0.04	0.07	0.62	0.65	0.64
		72	0.08	0.08	0.08	0.55	0.89	0.72
Cyclophos phamide	50	24	3.11	2.99	3.05	0.56	0.52	0.54

SUMMARY OF GENETIC TOXICOLOGY

Exemestane was negative in most genotoxicity assays (see summary table below). Exemestane was a positive clastogen *in vitro* in human lymphocytes without metabolic activation.

Test	Findings	
Ames test – mutation analysis	Negative	In vitro
E coli – mutation analysis	Negative	In vitro
V79 Chinese hamster cells – mutation analysis	Negative	In vitro
Mouse bone marrow – micronucleus	Negative	In vivo
Primary rat hepatocyte – DNA repair	Negative	In vitro
Human lymphocytes – chromosome analysis	Clastogenic without activation; clear dose response	In vitro
Mouse bone marrow – chromosome analysis	Negative	In vivo

OVERALL SUMMARY AND EVALUATION

Exemestane is an irreversible aromatase inhibitor structurally related to the natural substrate, androstenedione, differing by the presence of a C6 methylene group in the inhibitor. This cytochrome P450 enzyme catalyzes the conversion of C19 androgens (androstenedione and testosterone) to C18 estrogens (estrone and estradiol). In postmenopausal women, most estrogen synthesis occurs in peripheral tissue that is not subject to feedback stimulation by gonadotropins. Thus, inhibition of aromatase in postmenopausal women should reduce estrogen synthesis and lead to decreased tissue and serum estrogen levels.

Pharmacology: Exemestane is capable of inhibiting aromatase activity in both stromal and epithelial breast cells *in vitro*, consistent with literature reports of the presence of aromatase in both cell populations. In PMSG-primed rats, exemestane inhibited ovarian aromatase with an oral EC_{50} of 3.7 mg/kg. The major metabolites of exemestane identified to date were less potent aromatase inhibitors than the parent compound. The most potent metabolite, FCE 25071 (17-hydroexemestane), was 2.6 fold less potent in inhibiting placental aromatase compared to the parent compound (69 and 27 nM, respectively). This metabolite binds to the androgen receptor with 100 times greater affinity compared to parent exemestane (27% and 0.28%, respectively). Exemestane does not inhibit P450s involved in drug metabolism, including human CYP 1A2, 2C9, 2D6, 2E1 and 3A4, or other enzymes of the steroidogenic pathway. *In vitro*, $\geq$ 93% of exemestane was bound to serum albumin and α_1-acid glycoprotein, and to approximately the same extent, but the relative affinities of exemestane for each protein was not assessed.

Safety Pharmacology: In mice, no effect on locomotor activity was noted at up to 100 mg/kg (p.o.). Exemestane affected behavior in a mixed dose-dependent pattern. At lower doses (100-200 mg/kg) in mice and rats, slight excitation was noted whereas behavioral depression was noted from 400 mg/kg. Mice appeared more sensitive than rats to CNS effects of exemestane. In mice, respiratory depression, tremors and clonus were observed at 400-800 mg/day. Additionally, exemestane showed a marked, dose-related proconvulsant activity through interaction with pentylenetetrazole. Hypothermia was noted in mice from 400 mg/kg but was not observed in rats up to 1600 mg/kg. At 1600 mg/kg, respiratory depression resulted in the deaths of all treated mice. No mortality was observed in rats at this dose.

Pharmacokinetics:

General pharmacokinetic parameters

After a single dose of exemestane in female rats (oral gavage), normalized AUC of parent compound exhibited dose proportionality from 20-125 mg/kg; however, a major deviation was observed at 315 mg/kg. After repeat dosing, normalized AUCs declined 2-fold for 50-125 mg/kg/d and 7-fold for 315 mg/kg/d. This suggests saturation of a metabolic process that is counterbalanced by induction of metabolic processes with repeat administration. Sex differences were observed in AUC of male and female rats, but as most studies used only female animals, the nature of sex differences is uncertain.

In mice, normalized AUC after single and repeat dosing increased with increasing dose (oral gavage) to 50 mg/kg; in the range of 50-450 mg/kg, normalized AUC was dose proportional. Normalized AUC decreased with repeat dosing compared to a single dose except at the lowest dose tested (15 mg/kg/day), where an increase was observed. In oral feeding studies, normalized AUC decreased with increasing dose, and no major differences between days 7 and 28 were observed. No deviations were observed in dose proportionality in humans up to 50 mg/kg/day. Comparisons of C_{max} and AUC for exemestane in mice and rats (gavage) and humans after single and repeat oral dosing are presented in the tables below.

Plasma pharmacokinetic parameters[a] after a single dose of exemestane.

Mice			Rats			Human[b]		
Dose mg/kg	C_{max} ng/mL	AUC ng hr/mL	Dose mg/kg	C_{max} ng/mL	AUC ng hr/mL	Dose mg	C_{max} ng/mL	AUC after chronic dosing ng hr/mL
15	20	27	20	24	57	50	27	—
50	349	605	50	123	275	200	221	566
150	1410	2477	125	171	540	400	343	907
450	3102	6853	315	591	5332	800	414	1081

Plasma pharmacokinetic parameters[a] after chronic dosing of exemestane.

Mice			Rats			Human[b]		
Dose mg/kg/day	C_{max} D90 ng/mL	AUC D90 ng hr/mL	Dose mg/kg/day	C_{max} D28 ng/mL	AUC D28 ng hr/mL	Dose mg/day	C_{max} ng/mL	AUC after chronic dosing ng hr/mL
15	41	38	20	26	59	2.5	2.8	11
50	240	282	50	61	136	10	7.6	36
150	946	1126	125	53	289	25[c]	14.9	105
450	1036	2762	315	97	742	50	27.1	207

[a] parent drug only; [b] data from Clinacal Pharmacology and Biopharmaceutics Review of Pre NDA package; [c] proposed human dose

Plasma levels of the androgenic metabolite FCE-25071 in female beagle dogs were 18 ng/mL one hour after receiving an oral dose of 30 mg/kg exemestane, 25% of the plasma concentration of the parent compound (73 ng/mL). In rats, approximately 3.7% of total radioactivity in plasma after a radiolabeled dose of 125 mg/kg exemestane was found to be FCE 25071; unchanged parent compound was 11.2% of total radioactivity (study not reviewed). In humans, plasma levels of FCE 25071 were less than 1/10 of the corresponding unchanged drug levels (CPB review of Pre-NDA).

Absorption

The t_{max} of parent exemestane is reached 0.5-1 hour after oral administration in rats and dogs, indicating that the drug is rapidly absorbed from the GI tract. Human t_{max} is reported at 1.9 hr. Species differences include a C_{max} and AUC that are higher in dogs than rats. The AUC, C_{max} and t_{max} of total radioactivity in non-fasted female rats was 58% and 43% of that observed in fasted female rats, respectively, indicating that food delays absorption of exemestane. Bioavailability of parent exemestane in female rats and female dogs, respectively, was calculated at 1.9% and 3.53% after a single oral dose of 1 mg/kg, and 4.4% and 4.97% after a single oral dose of 30 mg/kg (dog study not summarized).

Distribution

Exemestane is characterized by a large volume of distribution (in rats, Vd_{SS} 21 L/kg), substantially larger than total body water, suggesting extensive distribution into tissues. In female rats, the level of radiolabeled drug (parent and metabolites) was particularly high in liver, adrenals, kidneys and the GI tract. The blood to plasma ratio of drug indicated some uptake of drug material into blood cells. In all species tested, a significant portion of exemestane was bound to serum protein (> 89% in rats, rabbits, dogs, humans and monkeys). Serum albumin and α_1-acid glycoprotein both bind exemestane *in vitro*.

Radioactivity was also found to substantially distribute to the rat fetuses, with fetal liver concentrations higher than maternal blood concentration. As expected by the lipophilic nature of exemestane, levels of drug in milk of lactating rats was higher than observed in maternal plasma. The maternal ovary of the pregnant rat also had substantially elevated levels of total radioactivity (693% 6 hours postdosing) compared to the non-pregnant rat.

Metabolism

Extensive first-pass metabolism of exemestane was suggested by comparison of AUC ratios (oral:i.v.) of total radioactivity (24% rats, 21% dogs) vs. parent compound (< 5% in both species). A large number of metabolites was observed in all biological samples examined. Most metabolites have decreased biological potency compared to the parent compound, with the exception of the androgenic activity of 17-hydroexemestane. The rapid metabolism of exemestane probably accounts for its low oral bioavailability, approximately 5% at a dose of 30 mg/kg in female rats. A decrease in bioavailability and/or increase in systemic clearance were observed with repeat dosing. In rats, the clearance was 126 mL/min/kg after a 3 mg/kg i.v. dose, or approximately 2-fold higher than hepatic blood flow (~ 70 mL/min/kg). This suggests the involvement of extrahepatic clearance; the sponsor proposes that ubiquitous reductases present in blood are responsible for this activity.

Most conjugation was found to be with glucuronic acid as arylsulfatase had little effect on the metabolite profile (data not submitted). Based on structural knowledge of identified metabolites, biotransformation of exemestane probably occurs through reduction of the 17-keto group and/or epoxidation of the 6-exo double bond followed by hydrolysis and rearrangement. A number of metabolites have not yet been structurally identified. In the urine, metabolites that comigrate with known standards account for 43-47% of excreted radioactivity in humans, rats and monkeys and approximately 18% in dogs (studies not reviewed).

Elimination

Dogs appear to have a higher urinary and lower fecal rate of elimination compared to rats. Exemestane is subject to enterohepatic circulation. In rats and dogs, fecal elimination was the most common route of elimination. Most of the administered dose appears in the feces within 48 hours post administration. The plasma half-life of total radioactivity of the terminal phase was 5.3-7.1 hours for rats and 12 hours for dogs. A plasma half-life of parent exemestane in the terminal phase of elimination of 13 hours was observed in rats.

Toxicology: The main target organs were the livers of rats, mice and dogs and rodent kidney. The major acute effect was sign of CNS stimulation in mice, rats and dogs, including convulsant activity that was observed in mice and dogs. Exemestane effects on reproductive organs appear to be extensions of its pharmacological activity.

Summary of repeat dose study findings

Species	Dose (mg/kg/d)	Schedule	Rev. #	Target Organ/Significant findings
Mice	100, 300, 1000 (feed)	4 week	NDA #1	Palatability study; slight ↓ bw ♂ from 1000 mg/kg/d
Mice (♀)	15, 50, 150, 450	13 week	IND #3	Liver (↑ wt at 450 mg/kg/d; ↑ incidence hepatic vacuolation at 450 mg/kg/d); kidney (↑ wt ≥ 15 mg/kg/d; minimal papillary mineralization at 450 mg/kg/d); reproductive tissues (↑ epithelial mucinification and keratinization of cervix and vagina ≥ 15 mg/kg/d;↓ ovarian wt ≥ 50 mg/kg/d;

				↑ tertiary follicles and ↓ corpora lutea in ovaries ≥ 15 mg/kg/d; ↑ apoptotic cells in uterus, not dose-dependent)
Mice	30, 100, 350, 1250 (feed)	13 week	IND #3	Liver (↑ wt ≥ 350 mg/kg/d; hepatocyte hypertrophy ≥ 350 mg/kg/d); kidney (↑ wt ≥ 30 mg/kg/d; tubuloepithelial hyperplasia at 1250 mg/kg/d); reproductive tissues (prostate: ↓ wt 1250 mg/kg/d; ovaries:↓ wt ≥ 30 mg/kg/d; tubulostromal hyperplasia ≥ 30 mg/kg/d; ↑ # lutein cysts ≥ 100 mg/kg/d; ↑ atretic follicles ≥ 30 mg/kg/d; ↓ corpora lutea ≥ 100 mg/kg/d; brown pigment in interstitial cells ≥ 100 mg/kg/d; uterus: ↓ wt 1250 mg/kg/d; stromal hypoplasia ≥ 100 mg/kg/d; testes flaccid 1250 mg/kg/d); slight anemia in ♀ (1250 mg/kg/d); slight ↓ bw ♂ (1250 mg/kg/d);
Rat	100, 300, 1000 (feed)	4 weeks	NDA #1	Palatability study; ↓ bw (≥ 300 mg/kg/d)
Rat	30, 150, 750, 3750	4 weeks	IND #1	Liver (↑ wt 750 mg/kg/d; enlarged with focal or multifocal necrosis and inflammation at 3750 mg/kg/d); kidneys (pale, with necrosis of proximal tubular epithelial at 3750 mg/kg/d); reproductive organs ↓ wt (prostate, sv, ovaries at 3750 mg/kg/d); lymphopoietic tissue (↑ platelets at 750 mg/kg/d; at 3750 mg/kg/d, ↓ wt thymus and spleen, lymphoid depletion); GI (erosions at 3750 mg/kg/d); ↑ bw ♀ (30-750 mg/kg/d); 100% mortality first 14 days, anorexia, marked ↓ bw (3750 mg/kg); ↑ bw ♀ (≥ 30 mg/kg/d)
Rat[1]	1000, 2000	4 weeks		Liver, kidney, lymphoid depletion, reproductive organs; mortality at 2000 mg/kd/d
Rat	30, 100, 350, 600, 900, 1250 (feed)	13 week	NDA #1	Liver (↑ relative liver weight ≥ 350 mg/kg/d; hepatocyte hypertrophy ≥ 100 mg/kg/d; ↑ transaminases ≥ 1250 mg/kg/d); kidney (tubular basophilia at 1250 mg/kg/d); reproductive tissues (↓ wt of organs, ovarian hypoplasia ≥ 900 mg/kg/d), hemolymphopoietic (↓ wt spleen and thymus ≥ 900 mg/kg/d, ↓ WBC/lymphocytes ≥ 900 mg/kg/d); mortality (at 1250 mg/kg/d); ↓ bw (≥ 350 mg/kg/d); adrenals (↓ wt ≥ 600 mg/kg/d)
Rat	30, 180, 1080	26 week	IND #1	liver (hepatocyte vacuolation ≥ 30 mg/kg/d, hypertrophy ≥ 180 mg/kg/d; ↑ wt, hemorrhage and necrosis at 1080 mg/kg/d); kidney (tubular nephropathy ≥ 30 mg/kg/d); GI (erosions at 1080 mg/kg/d); reproductive (mucoid epithelial hyperplasia in cervix and vagina ≥ 30 mg/kg/d; interstitial cell hyperplasia of testes; ↓ wt prostate, sv at 1080 mg/kg/d); hemolymphopoietic (↓ wt ♀ thymus ≥ 30 mg/kg/d; ↓ WBC at 1080 mg/kg/d); mortality (at 1080 mg/kg/d); ↑ ♀ bw gain (≥ 30 mg/kg/d); ↓♂ bw gain (at 1080 mg/kg/d); adrenals (↓ wt ≥ 180 mg/kg/d)
Rats	20, 50, 125, 315	52 weeks	IND #2	Liver (↑ ♀ wt ≥ 20 mg/kg/d)); kidney (↑ wt, nephropathy at 315 mg/kg/d); reproductive organs (↓ prostate, testes wt ≥ 20 mg/kg/d; ↑ ovary wt ≥ 20 mg/kg/d; follicular cysts at 315 mg/kg/d); adrenal (↓ wt ≥ 50 mg/kg/d); ↓ bw ♂ (≥ 50 mg/kg/d); ↑ bw ♀ (≥ 20 mg/kg/d)

Dog	30, 90, 270, 810	4 week	IND #1	testes (hyperplasia of the interstitial cells ≥ 30 mg/kg/d); ovary (follicular cysts ≥ 30 mg/kg/d); liver (↑ wt ≥ 30 mg/kg/d); vomiting (at 810 mg/kg/d)
Dog	30, 150, 750	26 week	IND #1	Liver (↑ ALT, wt ≥ 150 mg/kg/d); kidney (↑ ♂ wt); GI (vomiting, nausea, diarrhea at 750 mg/kg/d); hemolymphopoietic (↓ wt thymus ≥ 30 mg/kg/d; ↓ ♂ WBC/neutrophils ≥ 30 mg/kg/d); reproductive (↑ wt/hypertrophy of prostate, ovaries ≥ 30 mg/kg/d; hyperplasia of testicular interstitial cells ≥ 30 mg/kg/d; ovarian cysts and prominent secondary follicles ≥ 30 mg/kg/d); CNS (posture, tremors and convulsions at 750 mg/kg/d); adrenal (↓ wt ≥ 30 mg/kg/d); mortality (750 mg/kg/d);
Dog (♀)	30, 120, 480	52 week	NDA #1	Liver (↑ wt, ALT at 480 mg/kg/d; biliary proliferation at 480 mg/kg/d); gall bladder (epithelial hyperplasia ≥ 120 mg/kg/d); reproductive (inhibition of normal cycle ≥ 120 mg/kg/d); GI (vomiting, diarrhea ≥ 30 mg/kg/d)

[1] study was not reviewed for NDA or IND

Reproductive toxicology: The doses selected for all studies were acceptable. In a preliminary study, fertility in male rats was examined at doses from 125-1000 mg/kg/day. Males treated for 63 days prior to mating to untreated females showed reduced fertility at doses from 500 mg/kg/day. Sperm morphology/vitality was not assessed. In the preliminary study, the principal effect of exemestane on treated females was deaths at doses ≥ 10 mg/kg/day due to complications during parturition and prolonged gestation. In the main Segment I study, prolonged gestation and grossly visible changes occurred in the placenta ≥ 20 mg/kg/day. Increased placental weights were observed in all dosage groups, possibly due to an anabolic action of exemestane or its metabolites. Fetal effects included reduction in litter size, an increase in resorptions, an increase incidence in delayed ossification and reduced fetal body weights.

Estrous cycling and mating were unaffected in rats by up to 100 mg/kg/day exemestane. The effect of 100 mg/kg/d exemestane on fertility was uncertain due to the low pregnancy rate in this group and in controls. In the pilot study in rats, exemestane decreased estrus stages at 200 mg/kg/d, principally due to prolonged diestrus, and days in cohabitation increased in this treated group. Fertility was decreased in rats treated in the Segment II pilot study at 810 mg/kg/day, but did not appear affected at lower doses. In toxicology studies, changes were observed in the reproductive tissues of mice, rats and dogs. Findings include ovarian follicular or luteal cysts in mice (≥ 100 mg/kg/d), rats (315 mg/kg/d); and dogs (≥ 30 mg/kg/d); and a decrease or absence of corpora lutea in mice (≥ 15 mg/kg/d). Changes in vaginal and cervical secretions were also noted in mice (≥ 15 mg/kg/d) and rats (≥ 30 mg/kg/d). Ovarian tubulostromal hyperplasia was noted in mice (≥30 mg/kg/d). Inhibition of normal cyclical changes was seen in beagles at ≥ 120 mg/kg/d.

In rats and rabbits, exemestane did not show any signs of teratogenesis at up to 810 mg/kg/day and 270 mg/kg/day (a clearly maternotoxic dose), respectively.

The extensive metabolism of exemestane in all species examined leads to many as yet unidentified metabolites with unknown biological activity. Little pharmacokinetic data are available for rabbits, including the metabolite profile and the AUC and C_{max} for parent exemestane. Additionally, deviation from dose-proportionality for the AUC was observed in mice at 15 mg/kg/d after single and repeat

dosing and at 315 mg/kg/d for rats at 315 mg/kg/d after a single dose. Dose proportionality at higher doses has not been assessed. For these reasons, use of AUC for cross-species comparisons in reproductive toxicology studies is precluded.

Study	Species	Doses (mg/kg/d)	Findings
Seg I/III pilot	Rat	♂ 125, 250, 500, 1000 ♀ 2, 5, 10, 40, 200 Dosing: ♂: 63 days premating through cohabitation ♀: 14 days premating to day 7 of lactation)	♂ ↓ fertility in untreated females mated with males dosed with ≥ 500 mg/kg/d ♀ ↑ in mean days parturition at 200 mg/kg/d; ↑ duration of gestation ≥ 10 mg/kg/d; mortality in dams due to delivery ≥ 10 mg/kg/d; ↓ gestation index ≥ 5 mg/kg/d; ↓ estrous stages at 200 mg/kg/d; ↑ in stillbirths ≥ 5 mg/kg/d; ↑ % pup deaths ≥ 10 mg/kg/d; ↓ pup viability day 4 and 7 postpartum ≥ 10 mg/kg/d; ↓ live litter size on weighing postpartum days 1, 4 and 7 ≥ 10 mg/kg/d; ↓ pup bw at 200 mg/kg/d; gross lesions with pup deaths ≥ 5 mg/kg/d
Segment I	Rat	♀ 4, 20, 100 Dosing: 14 days premating through 21-day cohabitation period to D20 gestation (Caesarean group) or D15 of gestation and resuming on D1-21 of lactation (natural delivery group)	↑ mean # days gestation ≥ 20 mg/kg/d; dystocia, with dam mortality ≥ 20 mg/kg/d; no effect of estrus cycling or mating; uncertain effect on fertility at 100 mg/kg/d; ↓ litter size, fetal body weights and delayed ossification ≥ 20 mg/kg/d; ↑ placental weight ≥ 4 mg/kg/d; ↑ stillborn pups ≥ 4 mg/kg/d; ↑ resorption ≥ 20 mg/kg/d; ↓ mean liveborn pups/litter ≥ 20 mg/kg/d; ↑ pup mortality D 1 postpartum ≥ 20 mg/kg/d; ↓ pup viability D 1-7 postpartum ≥ 20 mg/kg/d; gross placental changes ≥ 20 mg/kg/d
Seg II pilot	Rat	♀ 30, 90, 270, 810 Dosing: D 6-17 of gestation	↓ fertility at 810 mg/kg/d; ↑ resorptions ≥ 90 mg/kg/d; ↑ placental weight ≥ 30 mg/kg/d
Seg II	Rats	10, 50, 250, 810 Dosing: D 6-17 of gestation	Dystocia ≥ 10 mg/kg/d, with dam mortality; ↑ gestation period ≥ 10 mg/kg/d; ↓ gestation index ≥ 50 mg/kg/d; ↓ mean #/litter liveborn 50-250 mg/kg/d; ↑ placental weight ≥ 10 mg/kg/d; ↑ in resorptions, particularly late resorptions ≥ 10 mg/kg/d; ↑ mean fetal bw 50-250 mg/kg/d; ↓ mean fetal bw 810 mg/kg/d; ↑ mean pup weight D1-21 ≥ 10 mg/kg/d; ↓ mean number of live female fetuses (C-section group) ≥ 50 mg/kg/d; no teratologic findings
Seg II pilot	Rabbits	30, 90, 270, 810	Maternal GI/ovarian/uterine toxicity ≥ 30 mg/kg/d, no dose response; ↑ in abortions/resorptions/post implantation losses at 270 mg/kg/d; ↑ in non-specific fetal anomalies at 270 mg/kg/d but the finding is uncertain due to small # of litters in this study and lack of serious morphological changes
Seg II	Rabbits	30, 90, 270	↑ in abortions/resorptions at 270 mg/kg/d; ↑ post-implantation loss at 270 mg/kg/d; ↓ fetal bw at 270 mg/kg/d; ↓ placental wt ≥ 90 mg/kg/d; ↑ litter incidence of reduced ossification of hyoid bone ≥ 30 mg/kg/d; no teratogenic potential noted

Genetic toxicology: Exemestane was negative in most genotoxicity assays (see summary table below). Exemestane was a positive clastogen *in vitro* in human lymphocytes without metabolic activation. Carcinogenicity protocols for mice and rats for exemestane have been evaluated by the Executive Carcinogenicity Advisory Committee.

Test	Findings	
Ames test – mutation analysis	Negative	In vitro
E coli – mutation analysis	Negative	In vitro
V79 Chinese hamster cells – mutation analysis	Negative	In vitro
Mouse bone marrow – micronucleus	Negative	In vivo
Primary rat hepatocyte – DNA repair	Negative	In vitro
Human lymphocytes – chromosome analysis	Clastogenic without activation; clear dose response	In vitro
Mouse bone marrow – chromosome analysis	Negative	In vivo

RECOMMENDATION: The pharmacology/toxicology data supports approval of exemestane for the treatment of advanced breast cancer.

Label comments to follow.

/S/ 10/1/99

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