Group	N/sex	Drug concentration	Dosage (mg/kg)	Dosing volume (ml/kg)
3	3	0.2%	10	5
4	2	Placebo for 1.0%	0	10
5	2	1.0%	50	5
6	2	1.0%	100	10

Rats (3/sex/group) were intravenously given 5, 10, 50 and 500 mg/kg AGN 192024 or vehicle control qd for 7 days. The day of the first dosing was designated as Day 0. Toxicity was assessed as shown below.

Mortality – Daily
Clinical Signs – At least 4 times daily
Body Weights – Days 0, 3 and 7
Clinical Pathology – Day 7
TK Assay – See Pharmacokinetics section
Necropsy (Including Histopathology) – All animals were terminated on day 7 and received a complete necropsy examination. All tissues listed in the following table from all animals were processed and microscopically examined.

Brain	Duodenum	Adrenal	Testes and epididymides
Lungs	Jejunum	Kidneys	Thyroid
Heart	Ileum	Liver	Tail
Spleen	Cecum	Ovaries	
Stomach	Colon	Uterus and vagina	

Results:

Mortality and clinical signs: No mortality was observed. No abnormal clinical signs were noted in both control groups and in 5 and 10 mg/kg dose groups during the study period. In 50 and 100 mg/kg/day groups, many clinical signs were observed that included decreased motor activity, dyspnea, cyanotic tail, soft stool, ataxia, gasping, ptosis, lethargy and piloerection. The onset of the clinical signs occurred immediately following dosing with an approximately 2 hr duration.

Body weights: Decreased body weight gain was noted in the male animals treated at 50 and 100 mg/kg/day of AGN 192024 (see table below). No toxicologically significant findings were noted in other groups.

Body weight changes in animals treated with AGN 192024 (g)

	Males		
Dosage (mg/kg)	Vehicle	50	100
Body weights			
Day 0	159±21.2	169±5.0	173±2.8
Day 3	189±11.3	169±10.6	168±5.0
Day 7	204±25.5	188±9.9	192±2.8
Body weight gain (Days 0-7)	45	19	19
% control		42.2	42.2

Hematology: No treatment-related changes in hematology examination were noted.

Blood chemistry: No treatment-related changes in blood chemistry were noted in the 5 and 10 mg/kg dose groups and their corresponding control group. The blood samples collected from the other 3 groups were milky white. Several parameters could not be measured or could only be measured for isolated animals because the values were out of the instrument range. These

parameters included: creatinine (> 25 mg/dl), total bilirubin (no reaction), AP, ALT, AST (> 412 iu/l) and triglyceride (> 531 mg/dl). In addition, the sponsor indicated that the parameters summarized in the table below were lower (Na, Cl, Ca, protein and albumin) or higher (cholesterol) than the normal range. These changes were considered to be induced by the placebo for 1.0% AGN 192024.
[Reviewer's Comments: The sponsor did not provide "normal range" data.]

Clinical pathological findings in animals treated with AGN 192024

	Males			Females		
Group	**4**	**5**	**6**	**4**	**5**	**6**
Dosage (mg/kg)	**Vehicle**	**50**	**100**	**Vehicle**	**50**	**100**
Sodium (mmol/l)	118±0.7	136±2.8	123±0	121±7.1	133±3.5	127±3.5
Chloride (mmol/l)	84±2.1	98±2.1	89±1.4	88±4.9	96±0.7	92±3.5
Calcium (mg/dl)	8.1±0.28	9.5±0.14	8.7±0.14	8.2±0.57	9.2±0.42	9.0±0.71
Protein (g/dl)	5.9±1.98	4.5±0.21	5.5±0.57	4.6±0.42	4.7±0.14	5.0±0.28
Albumin (g/dl)	2.4±0.57	2.3±0.07	2.4±0.14	2.2±0.35	2.4±0.28	2.2±0
Cholesterol (mg/dl)	442±78.5	368±35.4	484±36.8	445	384±45.3	476±16.3

Gross necropsy: No drug-related gross pathological changes were observed in any animal of any group.

Histopathological evaluation: No drug-related, biologically relevant findings were noted in Groups 1,2 and 3 animals. In Groups 4,5 and 6 animals treated with AGN 192024 formulated [redacted] in the spleen was noted (see table below). Since this lesion was present in all animals that received 1% of placebo, it was regarded as a placebo-induced lesion. There were no other toxicologically significant histopathological findings.

Histopathological findings in rats treated with AGN 192024

	Males						Females					
Group	1	2	3	4	5	6	1	2	3	4	5	6
Dosage (mg/kg/day)	0	5	10	0	50	100	0	5	10	0	50	100
N	3	3	3	2	2	2	3	3	3	2	2	2
Spleen, foamy histiocyte infiltration												
Minimal	0	0	0	1	0	0	0	0	0	0	0	0
Moderate	0	0	0	2	2	2	0	0	0	2	2	0

In summary, Sprague Dawley rats were treated intravenously with AGN 192024 at 5, 10, 50 and 100 mg/kg/day for 7 days. At dose levels of 5 and 10 mg/kg/day, no local and systemic toxicity was observed. However, when AGN 192024 was administered as [redacted] at dose levels of 50 and 100 mg/kg/day, clinical signs such as decreased motor activity, dyspnea, cyanotic tail, soft stool, ataxia, gasping, ptosis, lethargy and piloerection were noted. Body weight gain was decreased in male rats. These changes were considered AGN 192024-related. In addition, there were a number of clinical chemistry changes and histological changes in the spleen [redacted] in animals treated with AGN 192024 1.0% (50 and 100 mg/kg/day) and its corresponding placebo. These changes were regarded as the effects of the 6% poloxamer contained in the placebo.

15. AGN 192024: 2-week intravenous injection safety study in Sprague Dawley rats. Vol. 24, Page 237

Study N^{o}: TX97009
Study Site: Allergan, Inc., 2525 Dupont Drive, Irvine, CA 92713-9534

Study Purpose: To determine the potential systemic toxicity of AGN 192024 at various ophthalmic concentrations following daily iv injection for 14 days in rats
Compound: AGN 192024 0.001% solution
AGN 192024 0.01% solution
AGN 192024 0.1% solution
Vehicle:
Dose: 0, 0.03, 0.3 and 1 mg/kg/day (Dosing volume = 3, 3, 3 and 1 ml/kg)
Route: Intravenous injection
Animal: Sprague Dawley rats, 6-7 weeks old, 150-230 g for ♂ and 140-220 g for ♀, 10/sex/group
Study Initiation: January 24, 1995
GLP/QAU: Yes
Study Design: Rats (10/sex/group) were intravenously given 0.03, 0.3 and 1 mg/kg AGN 192024 or vehicle control qd for 14 days. The day of the first dosing was designated as Day 1. Toxicity was assessed as shown below.

Clinical Observations – 3 times daily
Body Weights – Semiweekly
Clinical Pathology – At termination
TK Assay – See Pharmacokinetics section
Necropsy (Including Histopathology) – All animals were terminated at the end of the treatment period and received a complete necropsy examination. All tissues listed in the following table from the animals of control and high dose groups were processed and microscopically examined. Organs denoted with * from all animals were weighted at the scheduled necropsy.

Adrenal*	Jejunum	Ovaries*	Sternum
Aorta	Cecum	Pancreas	Thymus
Bone/Marrow (femur)	Colon	Pituitary*	Thyroid/Parathyroid
Brain*	Heart*	Prostate	Tongue
Diaphragm	Kidneys*	Salivary Glands	Trachea
Epididymides	Liver*	Sciatic Nerve	Urinary Bladder
Eyes with Optic Nerve and Adnexa	Lungs	Seminal vesicle	Uterus and cervix
Esophagus	Cervical lymph node	Skeletal Muscle	Vagina
Stomach	Mesenteric Lymph Nodes	Spinal Cord	
Ileum	Mediastinal Lymph Nodes	Spleen*	
Duodenum	Mammary Gland	Testes*	

Results:

Mortality: One male rat at 0.3 mg/kg group was found dead 2 hr after dosing on Day 4. No abnormal clinical signs were noted. Necropsy and histopathological examinations showed no abnormal findings. The reason of the death was unknown.

Clinical observations: No abnormal findings in clinical observations were noted.

Body weights: No treatment-related differences in body weight changes were observed.

Hematology: No biologically relevant abnormal findings in hematology examination were noted.

Blood chemistry: No treatment-related changes in blood chemistry were noted.

Gross necropsy: No drug-related gross pathological changes were observed in any animal of any group.

Organ weights: No treatment-related organ weight changes were noted.

Histopathological evaluation: No drug-related, biologically relevant findings were noted.

In summary, Sprague Dawley rats were treated intravenously with AGN 192024 at 0.03, 0.3 and 1.0 mg/kg/day for 14 days. No local and systemic toxicity was observed. NOAEL was determined as 1.0 mg/kg/day in this study.

16. AGN 192024: 1-month intravenous injection safety study in Sprague Dawley rats. Vol. 25, Page 001

Study Nº: TX98014
Study Site: Allergan, Inc., 2525 Dupont Drive, Irvine, CA 92713-9534
Study Purpose: To determine the toxicity of AGN 192024 following daily iv injection for 1 month in rats
Compound: AGN 192024 0.2% solution [redacted]
Vehicle: [redacted]
Dose: 0, 0.1, 0.3 and 1 mg/kg/day x 1 month
Route: Intravenous injection
Animal: Sprague Dawley rats, 8-9 weeks old, 210-310 g for ♂ and 160-260 g for ♀, 12/sex/group
Study Initiation: March 11, 1998
GLP/QAU: Yes
Study Design:

Group	N/sex (main)	N/sex (TK)	Drug concentration	Dosage (mg/kg)	Dosing volume (ml/kg)
1	12	3	Placebo	0	0.5
2	12	3	0.02%	0.1	0.5
3	12	3	0.06%	0.3	0.5
4	12	3	0.2%	1.0	0.5

Rats (12/sex/group) were intravenously given 0.1, 0.3 and 1 mg/kg AGN 192024 or vehicle control qd for 1 month. The day of the first dosing was designated as Day 0. Toxicity was assessed as shown below.

Mortality – Daily
Clinical Observations – At least 3 times daily
Body Weights – Weekly
Food Consumption – Weekly
Ophthalmoscopy – Pretest and prior to the end of treatment (direct ophthalmoscopy, main animals only)
Clinical Pathology – Blood samples were collected on the day of scheduled sacrifice.
Urinalysis – Urine samples were collected at the end of the treatment.
TK Assay – See Pharmacokinetics section
Necropsy (Including Histopathology) – All animals were terminated at the end of the treatment period and received a complete necropsy examination. All tissues listed in the following table from the animals of control and high dose groups were processed and microscopically examined. The reproductive organs from the 0.1 and 0.3 mg/kg/day groups of females were also examined

microscopically. Organs denoted with * from all animals were weighted at the scheduled necropsy.

Adrenal*	Jejunum	Ovaries*	Sternum
Aorta	Cecum	Pancreas	Thymus
Bone/Marrow (femur)	Colon	Pituitary*	Thyroid/Parathyroid
Brain*	Heart*	Prostate	Tongue
Diaphragm	Kidneys*	Salivary Glands	Trachea
Epididymides	Liver*	Sciatic Nerve	Urinary Bladder
Eyes with Optic Nerve and Adnexa	Lungs	Seminal vesicle	Uterus and cervix
Esophagus	Cervical lymph node	Skeletal Muscle	Vagina
Stomach	Mesenteric Lymph Nodes	Spinal Cord	
Ileum	Mediastinal Lymph Nodes	Spleen*	
Duodenum	Mammary Gland	Testes*	

Results:

Mortality: No mortality occurred.

Clinical observations: No abnormal findings in clinical observations were noted.

Body weights: There were no drug-related differences in body weights and body weight gain in the treated animals when compared to the placebo controls throughout the study period.

Food consumption: No treatment-related differences in food consumption were noted.

Ophthalmoscopy: There were no drug-related ocular lesions.

Hematology: No biologically relevant abnormal findings in hematology examination were noted.

Blood chemistry: No treatment-related changes in blood chemistry were noted.

Urinalysis: There were no treatment-related effects observed in the urinalysis values.

Gross necropsy: No drug-related gross pathological changes were observed in any animal of any group.

Organ weights: No treatment-related organ weight changes were noted.

Histopathological evaluation: No drug-related, biologically relevant findings were noted in males at any doses. In females, the only treatment-related changes were increased corpora lutea (minimal to mild) in the ovary of 11 of the 12 rats treated at 1 mg/kg/day. The changes were interpreted as an altered regression of corpora lutea, such that there was an increased prominence of all intermediate stages, with prominent end stage (vacuolated) corpora lutea. There was no impact upon normal ovarian cycling because there were no treatment-related alterations in the uterus, vagina or other endocrine glands. No other abnormal findings in histopathological examination were noted.

In summary, Sprague Dawley rats were treated intravenously with AGN 192024 at 0.1, 0.3 and 1.0 mg/kg/day for 1 month. No local and systemic toxicity was observed in male rats. In female rats, decreased regression of corpora lutea, evidenced by increased corpora lutea in the ovary,

was observed at 1 mg/kg/day. NOAEL was determined as 1.0 mg/kg/day for males and 0.3 mg/kg/day for females.

17. 4-week intravenous safety evaluation study of AGN 192024 in cynomolgus monkeys. Vol. 31, Page 239

Study Nº: 6177-112
Study Site: [redacted]
Study Purpose: To determine the toxicity of AGN 192024 following daily iv injection for 4 weeks in cynomolgus monkeys
Compound: AGN 192024 0.2% solution (Lot #: 9123X-11268, purity = 100%)
Vehicle: [redacted]
Dose: 0, 0.1, 0.3 and 1 mg/kg/day x 4 weeks
Route: Intravenous injection
Animal: Cynomolgus monkeys (Macaca fascicularis), 2-3-year old, 1.8-2.7 kg for ♂ and 1.8-2.6 kg for ♀, 3/sex/group
Study Initiation: February 12, 1998
GLP/QAU: Yes
Study Design:

Group	N/sex	Drug concentration	Dosage (mg/kg)	Dosing volume (ml/kg)
1	3	Placebo	0	0.5
2	3	0.2%	0.1	0.05
3	3	0.2%	0.3	0.15
4	3	0.2%	1.0	0.5

Monkeys (3/sex/group) were intravenously given 0.1, 0.3 and 1 mg/kg AGN 192024 or vehicle control qd for 4 weeks. Toxicity was assessed as shown below.

Clinical Observations – Twice daily
Body Weights – Weekly
Ophthalmoscopy – Pretest and week 4 (indirect ophthalmoscopy and slit lamp biomicroscopy)
ECG, Heart Rate, Respiratory Rate, Temperature and Blood Pressure – Pretest, Weeks 1 and 4
Clinical Pathology – Pretest and Week 4
TK Assay – See Pharmacokinetics section
Necropsy (Including Histopathology) – All animals were terminated at the end of the treatment period and received a complete necropsy examination. All tissues listed in the following table from all animals were processed and microscopically examined. Organs denoted with * from all animals were weighted at the scheduled necropsy.

Adrenal*	Jejunum	Ovaries*	Sternum
Aorta	Cecum	Pancreas	Skin
Bone/Marrow (femur)	Colon	Pituitary*	Thymus*
Brain*	Heart*	Prostate*	Thyroid/Parathyroid*
Diaphragm	Kidneys*	Salivary Glands	Trachea
Epididymides*	Liver*	Sciatic Nerve	Urinary Bladder
Eyes with Optic Nerve and Adnexa	Lungs*	Seminal vesicle	Uterus and cervix*
Esophagus	Rectum	Skeletal Muscle	
Stomach	Mesenteric Lymph Nodes	Spinal Cord	Gall Bladder
Ileum	Mandibular Lymph Nodes	Spleen*	Injection Site
Duodenum	Mammary Gland	Testes*	Lesions

Results:

Mortality: No mortality occurred.

Clinical observations: No drug-related abnormal findings in clinical observations were noted.

Body weights: No drug-related effects on body weights were noted.

Ophthalmoscopy: No ophthalmoscopic abnormalities were noted during the study period.

ECG, heart rate, respiratory rate, temperature and blood pressure: No drug-related abnormalities were noted.

Clinical pathology: No biologically relevant abnormal findings in hematology, clinical chemistry and urinalysis examinations were noted.

Post-mortem examinations: No drug-related abnormal findings in gross necropsy, organ weights and histopathology examinations were observed in any animal of any group.

In summary, cynomolgus monkeys were treated intravenously with AGN 192024 at 0.1, 0.3 and 1.0 mg/kg/day for 4 weeks. The drug was well tolerated at all doses. No local and systemic toxicity was observed. NOAEL was determined as 1.0 mg/kg/day in this study.

18. 17-week intravenous safety evaluation study of AGN 192024 in cynomolgus monkeys. Vol. 32, Page 001

Study N^{o}: 6177-113
Study Site: [redacted]
Study Purpose: To determine the toxicity of AGN 192024 following daily iv injection for 17 weeks followed by a 12-week recovery period in cynomolgus monkeys
Compound: AGN 192024 0.2% solution [redacted]
Vehicle: [redacted]
Dose: 0, 0.01, 0.1 and 1 mg/kg/day x 4 weeks
Route: Intravenous injection
Animal: Cynomolgus monkeys (*Macaca fascicularis*), 4-year old, 2.3-3.6 kg for ♂ and 1.9-3.1 kg for ♀, 6/sex/group
Study Initiation: December 21, 1998
GLP/QAU: Yes
Study Design:

Group	N/sex (main study)	N/sex (recovery)	N/sex (total)	Drug concentration	Dosage (mg/kg)	Dosing volume (ml/kg)
1	6	2	6	Placebo	0	0.5
2	6	2♂3♀	6	0.002%	0.01	0.5
3	6	2	6	0.02%	0.1	0.5
4	6	2	6	0.2%	1.0	0.5

Monkeys (6/sex/group) were intravenously given 0.01, 0.1 and 1 mg/kg AGN 192024 or vehicle control qd for 17 weeks. Toxicity was assessed as shown below.
Clinical Observations – At least twice daily

Body Weights – Weekly
Food Consumption – Daily
Ophthalmoscopy – Pretest and Weeks 9, 18 and 27 (indirect ophthalmoscopy and slit lamp biomicroscopy)
ECG, Heart Rate, Respiratory Rate and Blood Pressure – Pretest, Weeks 13 and 17
Clinical Pathology – Pretest and Weeks 4, 13, 17 and 30
TK Assay – See Pharmacokinetics section
Necropsy (Including Histopathology) – All animals were terminated at the end of the treatment period (Days 121 and 122) or recovery period (Day 205) and received a complete necropsy examination. All tissues listed in the following table from all animals were processed and microscopically examined. Organs denoted with * from all animals were weighted at the scheduled necropsy.

Adrenal*	Jejunum	Ovaries*	Sternum
Aorta	Cecum	Pancreas	Skin
Bone/Marrow (femur)	Colon	Pituitary	Thymus*
Brain*	Heart*	Prostate*	Thyroid/Parathyroid*
Diaphragm	Kidneys*	Salivary Glands	Trachea
Epididymides*	Liver*	Sciatic Nerve	Urinary Bladder
Eyes and Adnexa	Lungs*	Seminal vesicle	Uterus and cervix*
Esophagus	Rectum	Skeletal Muscle	Vagina
Stomach	Mesenteric Lymph Nodes	Spinal Cord	Gall Bladder
Ileum	Mandibular Lymph Nodes	Spleen*	Injection Site
Duodenum	Mammary Gland	Testes*	Lesions

Results:

Mortality: A 0.01 mg/kg/day female was sacrificed in extremis on Day 99 (Week 15). The animal had diarrhea in the 16 days preceding its death. Histological examination showed gastroenteritis and renal tubular dilatation with cast formation, which likely contributed to the moribund condition, but might not be drug-related effects.

Clinical observations: No drug-related abnormal findings in clinical observations were noted.

Body weights: No drug-related effects on body weights were noted.

Food consumption: No drug-related effects on food consumption were noted.

Ophthalmoscopy: A drug-related increase in the prominence of the periocular sulci which resulted in a widening of the palpebral fissure of both eyes was noted in treated animals (see table below) at the end of the treatment period. The incidence of severity of this change decreased during the recovery period. Ophthalmic examinations conducted in Week 27 (10 weeks following the cessation of treatment) showed the similar findings in only 1 male at 0.1 mg/kg/day group and 1 male and 1 female at 1 mg/kg/day group. These effects were considered pharmacological effects of this pharmacological class since monkeys given other PG analogues showed similar effects.

Number of animals with prominence of the periocular sulci and widening of the palpebral fissure

	Males				Females			
Dosage	**Control**	**0.01 mg/kg**	**0.1 mg/kg**	**1 mg/kg**	**Control**	**0.01 mg/kg**	**0.1 mg/kg**	**1 mg/kg**
N	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**
Affected	**0**	**1**	**4**	**6**	**0**	**2**	**3**	**5**

ECG, heart rate, respiratory rate, temperature and blood pressure: No drug-related abnormalities were noted.

Clinical pathology: No biologically relevant abnormal findings in hematology, clinical chemistry and urinalysis examinations were noted.

Post-mortem examinations: No drug-related abnormal findings in gross necropsy, organ weights and histopathology examinations were observed in any animal of any group.

In summary, cynomolgus monkeys were treated intravenously with AGN 192024 at 0.01, 0.1 and 1.0 mg/kg/day for 17 weeks. A reversible increase in the prominence of the periocular sulci and widen palpebral fissure in both eyes were noted in all treated groups. These changes were considered pharmacological effects of this pharmacological class since monkeys given other PG analogues showed similar effects. Similar changes were also noted in 1-year ocular toxicity study with AGN 192024 in monkeys. No systemic toxicity was observed at any dose.

Ocular toxicity studies

1. AGN 192024: 3-day ocular safety study in New Zealand white and Dutch Belted rabbits. Vol. 25, Page 243

Stusy №: TX97003
Study Aim: To determine the local ocular effects of 0.03% AGN 192024 ophthalmic solution following multiple topical ocular administration to New Zealand white rabbits and Dutch Belted rabbits (35 µl, left eyes, qid at 2 hr intervals) for 3 days
Compound/Vehicle: 0.03% AGN 192024 ophthalmic solution (Lot #: 9106X-R3883/150); the composition of AGN 192024 and vehicle is listed in the following table. The formulation of the drug used in this study was the same as the clinical formulation.

Ingredient (% w/v)	Vehicle	0.03% AGN 192024

Dose & Route: 1 drop (35 µl)/eye, left eye only, qid x 3 days (2 hr intervals)
Animals: Female New Zealand white rabbits and Dutch Belted rabbits, 3.5-4-month old, weighing 1.5-3.0 kg; 4/sex/group
Study Location: Allergan, 2525 Dupont Drive, P.O.Box 19534, Irvine, CA 92612-1531
Compliance with GLP/QAU: No
Study Date: 8/5/97-8/7/97
Study Design: AGN 192024 or vehicle was applied to left eye of each rabbit qid for 3 days as shown in the following table. The right eye remained untreated as control.

Group	AGN 192024 Treatment	Nº of Animals	Treatment Volume (μl)/eye	Treatment Frequency	Animals
1	0 (Vehicle Control)	4/sex/group	35	Qid at 2 hr interval	New Zealand White rabbits
2	0.03% AGN 192024		35		New Zealand White rabbits
3	0 (Vehicle Control)		35		Dutch Belted rabbits
4	0.03% AGN 192024		35		Dutch Belted rabbits

The following parameters were monitored.
Mortality – Daily
Clinical Observations – Daily
Gross Ocular Examinations – Following each installation, and before the first and last daily instillations
Biomicroscopic Examination – At pretest (screening examination) and 1 hr after the last instillation on the last day of the treatment

Results:

Mortality: No mortality occurred.

Clinical observations: All animals remained in good health throughout the study period.

Gross ocular examinations: No abnormal findings were noted in animals in Groups 1, 3 and 4. In three Group 2 animals (New Zealand white rabbits treated with AGN 192024 0.03%), slight, transient hyperemia in the conjunctiva was noted on Day 1 (see table below).

Gross ocular findings in Group 2 animals (NZW rabbits treated with AGN 192024 0.03%)

Animals number	1			2			3			4		
Days	1	2	3	1	2	3	1	2	3	1	2	3
Pre-instillation observations (24 occurences)												
No findings	2	2	2	2	2	2	1	2	2	1	2	2
Slight tranisent hyperemia	0	0	0	0	0	0	1	0	0	1	0	0
Post-instillation observations (48 occurrences)												
No findings	3	4	4	4	4	4	1	4	4	1	4	4
Slight tranisent hyperemia	1	0	0	0	0	0	3	0	0	3	0	0

Slit lamp examination: No abnormal ocular findings were noted in any animals.

In summary, New Zealand white rabbits and Dutch Belted rabbits were topically treated (qid) with 0.03% AGN 192024 ophthalmic solution or vehicle solution for 3 days. Only slight transient conjunctival hyperemia was noted in treated non-pigmented rabbits on Day 1.

2. AGN 192024: A 1-month ocular and systemic safety study in Dutch Belted rabbits. Vol. 25, Page 269

Stusy №: TX97032
Study Aim: To determine the ocular and systemic toxicity of 0.03% AGN 192024 ophthalmic solution following multiple topical ocular administration to Dutch Belted rabbits (35 μl, left eyes, bid at a 6 hr interval) for 1 month
Compound/Vehicle: 0.03% AGN 192024 ophthalmic solution (Lot #: 9106X-11179, purity = 99.97%); the composition of AGN 192024 and vehicle is listed in the following table. The formulation of the drug used in this study was the clinical formulation.

Ingredient (% w/v)	Vehicle	0.03% AGN 192024
Lot number	[redacted]	[redacted]

Dose & Route: 1 drop (35 μl)/eye, left eye only, bid x 1 month (at a 6 hr interval)
Animals: Dutch Belted rabbits, 3-month old, weighing 1.2-1.5 kg for ♂ and 1.1-1.7 kg for ♀; 10/sex/group
Study Location: Allergan, 2525 Dupont Drive, P.O.Box 19534, Irvine, CA 92612-1531
Compliance with GLP/QAU: Yes
Study Date: 8/19/97-9/19/97
Study Design: AGN 192024 or vehicle was applied to left eye of each rabbit bid for 1 month as shown in the following table. The right eye remained untreated as control.

Group	AGN 192024 Treatment	N° of Animals	Treatment Volume (μl)/eye	Treatment Frequency	Dose (μg/day)
1	0 (Vehicle Control)	10/sex/group	35	bid at a 6 hr interval	0
2	0.03% AGN 192024		35		21

The following parameters were monitored.
Mortality – Daily
Clinical Observations – Daily
Gross Ocular Examinations – Following the first and last installations during the 1st week, once weekly thereafter, and before the first and last daily instillations during the 1st week and once weekly
Biomicroscopic Examination – At pretest (screening examination) and at the end of the treatment period
Direct Ophthalmoscopic Examination - At pretest (screening examination) and at the end of the treatment period
Body Weights – Weekly
PK/TK – See Pharmacokinetics section
Clinical Pathology (Blood Chemistry & Hematology) – During the final week of the treatment
Necropsy (Organ Weights & Histopathology) - All animals were terminated at the end of the treatment period and received a complete necropsy examination. All tissues listed in the following table from all animals were processed and microscopically examined. Organs denoted with * from all animals were weighted at the scheduled necropsy.

Adrenal*	Jejunum	Ovaries*	Sternum
Aorta	Cecum	Pancreas	Thymus
Bone/Marrow (femur)	Colon	Pituitary*	Thyroid/Parathyroid
Brain*	Heart*	Prostate	Tongue
Diaphragm	Kidneys*	Salivary Glands	Trachea
Epididymides	Liver*	Sciatic Nerve	Urinary Bladder
Eyes with Optic Nerve and Adnexa	Lungs		Uterus and cervix
Esophagus	Cervical lymph node	Skeletal Muscle	Vagina
Stomach	Mesenteric Lymph Nodes	Spinal Cord	Gall bladder
Ileum	Mediastinal Lymph Nodes	Spleen*	
Duodenum	Mammary Gland	Testes*	

Results:

Mortality: No drug-related mortality occurred.

Clinical observations: No treatment-related clinical findings were observed.

Gross ocular examinations: No abnormal findings were noted.

Ophthalmoscopy: No compound-related abnormalities of the lens, vitreous, or retina were noted.

Slit lamp examination: No treatment-related abnormal ocular findings were noted in any animals.

Body weights: All animals showed a comparable body weight gain during the treatment period.

Clinical pathology: No toxicologically significant differences from the control group were found for any hematology and clinical chemistry parameters at the end of the treatment period.

Necropsy: No treatment-related lesions were noted in any animals.

Organ weights: There were no biologically relevant differences in absolute and relative organ weights between control and treated animals.

Histopathology: No treatment-related histopathological findings were noted.

In summary, Dutch Belted rabbits were topically treated (bid) with 0.03% AGN 192024 ophthalmic solution or vehicle solution for 1 month. The treatment produced no ocular irritation in rabbit eyes. No toxicologically significant systemic or ocular toxicities were observed.

3. 1-month ocular and systemic safety study of hypotensive lipid (AGN 192024) in New Zealand white rabbits. Vol. 26, Page 001

Stusy №: 1012C-2968-58
Study Aim: To determine the ocular and systemic toxicity of 0.001%, 0.01% and 0.1% AGN 192024 ophthalmic solutions following multiple topical ocular administration to rabbits (35 µl, left eyes, qid for 1 month) with a 14-day recovery period.
Compound/Vehicle: 0.001% AGN 192024 ophthalmic solution [redacted] purity = 99.99%); 0.01% AGN 192024 ophthalmic solution [redacted] purity = 99.99%); 0.1% AGN 192024 ophthalmic solution (Lot #: [redacted] purity = 99.90%); the composition of AGN 192024 and vehicle ([redacted] 8705X-10691A) is listed in the following table. The formulations used in this study were similar to the clinical formulation except for the presence of a [redacted] and preservative (benzalkonium chloride).

Ingredient (% w/v)	Vehicle	0.001% AGN 192024	0.01% AGN 192024	0.1% AGN 192024
Lot number	[redacted]			

Dose & Route: 1 drop (35 µl)/eye, left eye only, qid x 1 month

Animals: New Zealand white rabbits, weighing 2-3 kg; 10/sex/group
Study Location: Allergan, 2525 Dupont Drive, P.O.Box 19534, Irvine, CA 92612-1531
Compliance with GLP/QAU: Yes
Study Date: 2/20/95-4/6/95
Study Design: AGN 192024 or vehicle was applied to left eye of each rabbit qid for 1 month followed by a 2-week recovery period. The right eye remained untreated as control.

Group	N/sex (main study)	N/sex (recovery)	N/sex (total)	Treatment	Daily dosage
1	8	2	10	AGN 192024 placebo	qid
2	8	2	10	AGN 192024 0.001%	qid
3	8	2	10	AGN 192024 0.01%	qid
4	8	2	10	AGN 192024 0.1%	qid

The following parameters were monitored.
Mortality – Daily
Clinical Observations – Daily
Gross Ocular Examinations – Following each installation during the treatment period and once daily during the recovery period
Biomicroscopic Examination – At pretest (screening examination), on Day 8, and at the end of the treatment and recovery periods
Direct Ophthalmoscopic Examination - At pretest (screening examination) and at the end of the treatment and recovery periods
Body Weights – Weekly
Clinical Pathology (Blood Chemistry & Hematology) – Pretest, and at the end of the treatment and recovery periods
Necropsy (Organ Weights & Histopathology) - All animals were terminated at the end of the treatment and recovery periods and received a complete necropsy examination. All tissues listed in the following table from control and high dose animals, and all ocular tissues from all groups were processed and microscopically examined. Organs denoted with * from all animals were weighted at the scheduled necropsy.

Adrenal*	Jejunum	Ovaries*	Sternum
Aorta	Cecum	Pancreas	Thymus
Bone/Marrow (femur)	Colon	Pituitary*	Thyroid/Parathyroid
Brain*	Heart*	Prostate	Tongue
Diaphragm	Kidneys*	Salivary Glands	Trachea
Epididymides	Liver*	Sciatic Nerve	Urinary Bladder
Eyes with Optic Nerve and Adnexa	Lungs	Seminal vesicle	Uterus and cervix
Esophagus	Cervical lymph node	Skeletal Muscle	Vagina
Stomach	Mesenteric Lymph Nodes	Spinal Cord	Gall bladder
Ileum	Mediastinal Lymph Nodes	Spleen*	
Duodenum	Mammary Gland	Testes*	

Results:

Mortality: No drug-related mortality occurred.

Clinical observations: No treatment-related clinical findings were observed.

Gross ocular examinations: Slight ocular discomfort lasting up to 30 sec in duration was the principal finding in all 4 groups and occurred at 23-35% of the instillations. Regarding ocular irritation, slight conjunctival hyperemia was found in all 4 groups and occurred at 2-14% of the instillations (see table below). Average Draize score in every group was lower than 0.3, which was graded as non-irritating.

Total incidence of conjunctival hyperemia following instillation

			Males				Females			
Group	Treatment	N/ sex	Total observations	1*	2	3	Total observations	1	2	3
1	AGN 192024 placebo	10	1160	91 (8%)	0	0	1160	20 (2%)	0	0
2	AGN 192024 0.001%	10	1156	127 (11%)	0	0	1160	168 (14%)	0	0
3	AGN 192024 0.01%	10	1100	67 (6%)	0	0	1160	101 (9%)	0	0
4	AGN 192024 0.1%	10	1160	87 (8%)	0	0	1160	116 (10%)	0	0

* 1 = slight, 2 = moderate, 3 = severe

Ophthalmoscopy: No compound-related abnormalities in the lens, vitreous, or retina were noted.

Slit lamp examination: No treatment-related abnormal ocular findings were noted.

Body weights: All animals showed a comparable body weight gain during the treatment period.

Clinical pathology: No toxicologically significant differences from the control group were found for any hematology and clinical chemistry parameters at the end of the treatment period.

Necropsy: No apparent treatment-related lesions were noted in any animals at the end of treatment or recovery periods.

Organ weights: There were no biologically relevant differences in absolute and relative organ weights between control and treated animals.

Histopathology: No treatment-related histopathological findings were noted in ocular and non-ocular tissues.

In summary, New Zealand white rabbits were topically treated (qid) with 0.001%, 0.01% and 0.1% AGN 192024 ophthalmic solutions or vehicle solution for 1 month followed by a 2-week recovery period. The drug was considered non-irritating to the rabbit eyes. No toxicologically significant systemic or ocular toxicities were observed.

4. AGN 192024: 6-month ocular safety study in Dutch Belted rabbits with a 1 month recovery period. Vol. 27, Page 001

Stusy №: TX98004

Study Aim: To determine the ocular and systemic toxicity of 0.03% and 0.1% AGN 192024 ophthalmic solutions following multiple topical ocular administration to rabbits (35 µl, left eyes, qid for 1 month) with a 1-month recovery period

Compound/Vehicle: 0.03% AGN 192024 ophthalmic solution (Lot #: 9106X-11240B); 0.1% AGN 192024 ophthalmic solution (Lot #: 9131X-11242); the composition of AGN 192024 and vehicle is listed in the following table. The formulation of the drug used in this study was the same as the clinical formulation except for the concentration of the active ingredient, AGN 192024.

Ingredient (% w/v)	Vehicle	0.03% AGN 192024	0.1% AGN 192024
Lot number	9105X-10239B	9106X-11240B	9131X-11242

Dose & Route: 1 drop (35 μl)/eye, left eye only, qd or bid x 6 months
Animals: Dutch Belted rabbits, 6-7 months old, weighing 1.7-2.8 kg; 15/sex/group
Study Location: Allergan, 2525 Dupont Drive, P.O.Box 19534, Irvine, CA 92612-1531
Compliance with GLP/QAU: Yes
Study Date: 2/5/98-9/2/98
Study Design: AGN 192024 or vehicle was applied to left eye of each rabbit qd or bid (at a 6 hr interval) for 6 month followed by a 1-month recovery period. The right eye remained untreated as control.

Group	N/sex	N/sex (recovery)	N/sex (total)	Treatment	Daily dosage	Dosing frequence
1	15	5	15	AGN 192024 placebo	0	bid
2	15	5	15	AGN 192024 0.03%	10.5 µg/day	qd
3	15	5	15	AGN 192024 0.03%	21.0 µg/day	bid
4	15	5	15	AGN 192024 0.1%	70 µg/day	bid

The following parameters were monitored.
Mortality – Daily
Clinical Observations – Daily
Gross Ocular Examinations – Daily following each installation during the 1st week of the treatment, and once weekly thereafter
Biomicroscopic Examination – At pretest (screening examination), in Weeks 4 and 13, and at the end of the treatment and recovery periods
Direct Ophthalmoscopic Examination - At pretest (screening examination), in Weeks 4 and 13, at the end of the treatment and recovery periods
Body Weights – Weekly during the 1st month, and biweekly thereafter
Clinical Pathology (Blood Chemistry & Hematology) – Pretest, at the end of week 1, during Week 12, and at the end of the treatment and recovery periods
TK – See Pharmacokinetics section
Necropsy (Organ Weights & Histopathology) - All animals were terminated at the end of the treatment and recovery periods and received a complete necropsy examination. All tissues listed in the following table from control and high dose animals, and all ocular tissues from all groups were processed and microscopically examined. Tissues and organs from recovery rabbits were not examined microscopically because there were no significant findings at the end of the treatment period. Organs denoted with * from all animals were weighted at the scheduled necropsy.

Adrenal*	Jejunum	Ovaries*	Sternum
Aorta	Cecum	Pancreas	Thymus
Bone/Marrow (femur)	Colon	Pituitary*	Thyroid/Parathyroid
Brain*	Heart*	Prostate	Tongue
Diaphragm	Kidneys*	Salivary Glands	Trachea
Epididymides	Liver*	Sciatic Nerve	Urinary Bladder
Eyes with Optic Nerve and Adnexa	Lungs	Seminal vesicle	Uterus and cervix
Esophagus	Cervical lymph node	Skeletal Muscle	Vagina
Stomach	Mesenteric Lymph Nodes	Spinal Cord	Gall bladder
Ileum	Mediastinal Lymph Nodes	Spleen*	Skin
Duodenum	Mammary Gland	Testes*	

Results:

Mortality: No mortality occurred.

Clinical observations: No treatment-related clinical findings were observed.

Gross ocular examinations: No ocular irritation and clinically significant discomfort occurred during the 6-month treatment period. Following dosing, occasional transient slight ocular discomfort lasting no more than 30 sec was observed in 3♂ and 5♀ in Group 4, and in 1♂ each in Groups 1, 2 and 3. Tearing was noted in 1 ♀ in Group 4 prior to and following instillation, which was not considered toxicologically significant because it was noted in only 1 rabbit.

Ophthalmoscopy: No compound-related abnormalities of the lens, vitreous, or retina were noted.

Slit lamp examination: No treatment-related abnormal ocular findings were noted.

Photographic documentation: Photographs taken after 6 months of dosing showed no changes in iris pigmentation when compared to pre-study photographs in all groups.

Body weights: There were no toxicologically significant differences in body weights or body weight gain between control and treated animals.

Clinical pathology: No toxicologically significant differences from the control group were found for any hematology and clinical chemistry parameters.

Necropsy: No apparent treatment-related lesions were noted in any animals at the end of treatment or recovery periods.

Organ weights: There were no biologically relevant differences in absolute and relative organ weights between control and treated animals.

Histopathology: No treatment-related histopathological findings were noted in ocular and non-ocular tissues.

In summary, Dutch Belted rabbits were topically treated (qd or bid) with 0.03% and 0.1% AGN 192024 ophthalmic solutions or vehicle solution for 6 month followed by a 1-month recovery period. The drug was considered non-irritating to the rabbit eyes. No systemic or ocular toxicities were observed.

5. AGN 192024: 1-month ocular and systemic safety study in dogs. Vol. 29, Page 152

Stusy №: 1012C-3137-5
Study Aim: To determine the ocular and systemic toxicity of 0.001%, 0.01% and 0.1% AGN 192024 ophthalmic solutions following multiple topical ocular administration to dogs (35 µl, left eyes, qid for 1 month)
Compound/Vehicle: 0.001% AGN 192024 ophthalmic solution [redacted] purity = 99.99%); 0.01% AGN 192024 ophthalmic solution [redacted] purity = 99.99%); 0.1% AGN 192024 ophthalmic solution (Lot #: [redacted] purity = 99.90%); the composition of AGN 192024 and vehicle [redacted] is listed in the following table. The formulations used in this study were similar to the clinical formulation except for the presence of a [redacted] and preservative (benzalkonium chloride).

Ingredient (% w/v)	Vehicle	0.001% AGN 192024	0.01% AGN 192024	0.1% AGN 192024
Lot number				
[redacted]				

Dose & Route: 1 drop (35 µl)/eye, left eye only, qid x 1 month
Animals: Beagle dogs [redacted] 10-12-month old, weighing 11-15 kg for ♂ and 7-14 kg for ♀; 3/sex/group
Study Location: Allergan, 2525 Dupont Drive, P.O.Box 19534, Irvine, CA 92612-1531
Compliance with GLP/QAU: Yes
Study Date: 3/28/95-4/28/95
Study Design: AGN 192024 or vehicle was applied to left eye of each dog qid (at 2 hr intervals) for 1 month. The right eye remained untreated as control. The day of the 1st dosing was designated as Day 0.

Group	N/sex	Treatment	Daily dosage
1	3	AGN 192024 placebo	qid
2	3	AGN 192024 0.001%	qid
3	3	AGN 192024 0.01%	qid
4	3	AGN 192024 0.1%	qid

The following parameters were monitored.
Mortality – Daily
Clinical Observations – Daily
Physical Examinations – During the pretest screening and last week of treatment period
Gross Ocular Examinations – Following each installation during the 1st week and twice weekly thereafter
Biomicroscopic Examination – At pretest (screening examination) and at the end of the treatment period
Direct Ophthalmoscopic Examination - At pretest (screening examination) and at the end of the treatment period
Body Weights – Weekly
Food Consumption – Daily
Clinical Pathology (Blood Chemistry & Hematology) – Pretest and Week 4

Urinalysis – Pretest and Week 4
ECG and Blood Pressure – pretest and Week 4
Necropsy (Organ Weights & Histopathology) - All animals were terminated at the end of the treatment period and received a complete necropsy examination. All tissues listed in the following table from all animals were processed and microscopically examined. Organs denoted with * from all animals were weighted at the scheduled necropsy.

Adrenal*	Jejunum	Ovaries*	Sternum
Aorta	Cecum	Pancreas	Thymus
Bone/Marrow (femur)	Colon	Pituitary*	Thyroid/Parathyroid
Brain*	Heart*	Prostate	Tongue
Diaphragm	Kidneys*	Salivary Glands	Trachea
Epididymides	Liver*	Sciatic Nerve	Urinary Bladder
Eyes with Optic Nerve and Adnexa	Lungs	Seminal vesicle	Uterus and cervix
Esophagus	Cervical lymph node	Skeletal Muscle	Vagina
Stomach	Mesenteric Lymph Nodes	Spinal Cord	Gall bladder
Ileum	Mediastinal Lymph Nodes	Spleen*	
Duodenum	Mammary Gland	Testes*	

Results:

Mortality: No mortality occurred in this study.

Clinical observations: No treatment-related clinical findings were observed.

Physical examinations: All animals were observed to be in good health condition.

Gross ocular examinations: The positive findings are summarized in the table below. Slight ocular discomfort lasting less than 30 sec in duration was noted in all 4 groups. Slight conjunctival hyperemia was also found in all 4 groups. Average Draize score was lower than 0.85 in all 4 groups, which was within the practically non-irritating range (0.5-2.5). Miosis was observed in all AGN 192024-treated left eyes, which was an expected canine-specific pharmacological effect.

Gross ocular findings

			Males (n=3)		Females (n=3)	
Group	**Treatment**	**Total observations**	**Slight discomfort incidence (%)**	**Slight (+1) hyperemia incidence (%)**	**Slight discomfort incidence (%)**	**Slight (+1) hyperemia incidence (%)**
1	AGN 192024 placebo	156	58(37)	0	49(31)	0
2	AGN 192024 0.001%	156	94(60)	10(6)	77(49)	5(3)
3	AGN 192024 0.01%	156	135(87)	60(39)	147(94)	66(42)
4	AGN 192024 0.1%	156	140(90)	61(39)	140(90)	52(33)

Ophthalmoscopy: No compound-related abnormalities of the lens, vitreous, or retina were noted.

Slit lamp examination: No treatment-related abnormal ocular findings were noted.

Body weights: All animals showed a comparable body weight gain during the treatment period.

Food consumption: No drug-related differences in food consumptions were noted.

Clinical pathology: No toxicologically significant differences from the control group were found for any hematology and clinical chemistry parameters at the end of the treatment period.

Urinalysis: There were no treatment-related effects observed in the urinalysis values.

ECG and blood pressure: No treatment-related effects on ECG and blood pressure were observed.

Necropsy: No apparent treatment-related lesions were noted in any animals.

Organ weights: There were no biologically relevant differences in absolute and relative organ weights between control and treated animals.

Histopathology: No treatment-related histopathological findings were noted in ocular and non-ocular tissues.

In summary, beagle dogs were topically treated (qid) with 0.001%, 0.01% and 0.1% AGN 192024 ophthalmic solutions or vehicle solution for 1 month. The drug was considered practically non-irritating to the dog eyes. No toxicologically significant systemic or ocular toxicities were observed.

6. 52-week ocular safety study with AGN 192024 in cynomolgus monkeys. Vol. 30, Page 001

Stusy №: 6177-110
Study Aim: To evaluate ocular and systemic toxicity of AGN 192024 ophthalmic solutions in cynomolgus monkeys when administered ocularly for at least 29 or 52 weeks followed by a 24- or 20-week recovery period
Compound/Vehicle: AGN 192024 - 0.03% (Lot Nº 9106X-11240B) and 0.1% (Lot Nº 9131X-11242); Vehicle (Lot Nº 9105X-11239B). The composition of AGN 192024 and vehicle is listed in the following table. The formulation of the drug used in this study was the same as the clinical formulation except for the concentration of the active ingredient, AGN 192024.

Ingredient (% w/v)	Vehicle	0.03% AGN 192024	0.1% AGN 192024
Lot number	9105X-11239B	9106X-11240B	9131X-11242

Dose & Route: 1/drop/eye (35 µl), right eye only, bid (0.03% and 0.1%) or qd (0.03%). The left eye remained untreated as control.
Dosing Duration: 29 or 52 weeks
Animals: Cynomolgus monkeys, 3-5 years old, weighing 1.9-2.7 kg for ♂ and 1.9-2.5 kg for ♀, 6/sex/group
Study Location:
Compliance with GLP/QAU: Yes
Study Date: 12/7/1997 –5/8/2000

Study Design: AGN 192024 or vehicle was applied to right eye of each monkey qd or bid for 1 year. The left eye remained untreated as control.

Group	Daily dosage	N/sex (total)	Early sacrifice	Early recovery	Terminal sacrifice	Terminal recovery	Treatment
1	bid	6	1/sex	0	3/sex	2/sex	AGN 192024 placebo
2	qd	6	0	0	4/sex	2/sex	AGN 192024 0.03%
3	bid	6	1/sex	1/sex	3/sex	1/sex	AGN 192024 0.03%
4	bid	6	1/sex	1/sex	3/sex	1/sex	AGN 192024 0.1%

One monkey/sex in Groups 1, 3 and 4 was sacrificed during Week 29. In addition, one monkey/sex in Groups 3 and 4 began a post-treatment recovery period (24-week recovery period).

The following parameters were monitored during the study.
Mortality and Clinical Observations - 2x/day
Body Weights – Twice pre-dose, and weekly thereafter
Ophthalmoscopic Examinations (indirect ophthalmoscopy and slit-lamp biomicroscopy) – Prior to the initiation of the study, in Weeks 6, 13, 26, 35, 44, 53, 62 and 71
Gross Ocular Grading – Treated and control eyes of all monkeys, daily during the 1st week, weekly during the 1st month, and monthly thereafter
ECG, Heart Rate (HR), Respiratory Rate (RR) and Blood Pressure (Bp) – Pre-dose, Weeks 2, 13, 26 and 52
PK/TK – see Pharmacokinetics section
Clinical Pathology – Pre-dose, Weeks 12, 25, 51 and 72 (blood samples) and weeks 13, 26, 53 and 72 (urine samples)
Necropsy (Including Organ Weights & Histopathology) – One monkey/sex in Groups 1, 3 and 4 was sacrificed during Week 29. One monkey/sex in Groups 3 and 4 began a post-treatment recovery period. After 24 weeks recovery following the early sacrifice, the Group 3 animals and Group 4 female were euthanized. The Group 4 male was held in recovery for 44 weeks and terminated at the 2nd post-recovery sacrifice. After 52-week treatment, 3 monkeys/sex in Groups 1, 3 and 4, and 4 monkeys/sex in Group 2 were euthanized. The remaining animals were terminated after 20-week recovery following the 52-week treatment. All tissues and organs were examined grossly. Organs denoted with * from all animals were weighed at the scheduled necropsy. All tissues from all animals listed in the following table and gross lesions were processed for microscopic examination.

Adrenal*	Cecum	Mesenteric Lymph Nodes	Skeletal Muscle
Aorta	Colon	submandibular Lymph Nodes	Spinal Cord
Bone (Long)	Rectum	Mammary Gland and Skin	Spleen*
Bone Marrow	Testes*	Ovaries*	Tongue
Brain*	Heart*	Pancreas	Thymus*
Epididymis*	Kidneys*	Peripheral Nerve (Sciatic)	Thyroid/Parathyroid*
Eyes with Optic Nerve and Adnexa		Pituitary	Trachea
Esophagus	Liver*	Prostate*	Urinary Bladder
Stomach	Gall Bladder	Stem	Uterus with cervix*
Ileum	Jejunum	Salivary Glands	Any Gross Lesions
Duodenum	Lungs*	Seminal Vesicle	

Results:

Mortality and Clinical Observations – No deaths occurred. There were no treatment-related, toxicologically significant clinical signs. In the AGN 192024 treated eyes, dark iris and prominent sulcus were noted (see table below), which were also noted in monkeys with other PG analogues.

Clinical observations in monkeys treated with AGN 192024

	Males				Females			
Group	1	2	3	4	1	2	3	4
N	6	6	6	6	6	6	6	6
Eye (treated): Iris appeared dark	0	1	4	5	0	4	2	5
Palpebral/conjunctiva (treated eye): prominent sulcus	0	0	5	6	0	2	5	6

Body Weights – No treatment-related effects in body weights were noted.

Ocular Examination – Starting from Day 87, increased iridal pigmentation was noted in AGN 192024-treated eyes in several monkeys (see table below). Starting from Day 178, periocular findings (a widening of the palpebral fissure and/or prominent palpebral sulci) were noted in all treated animals. These findings were also observed in monkeys with other PG analogues (including latanoprost) and were considered to be related to this pharmacological class. No functional or anatomic ocular abnormalities were noted. The increased iridal pigmentation did not reverse in any affected animals; however, the periocular findings completely resolved by the end of the recovery period.

AGN 192024-induced ocular changes

	Males				Females			
Group	1	2	3	4	1	2	3	4
N	6	6	6	6	6	6	6	6
↑ iridal pigmentation (treated eye)	0	1	3	4	0	3	2	5
↑ prominence of the periocular sulci (treated eye)	1	6	6	6	2	6	6	6
Eyelids, palpebral fissure widened (treated eye)	0	6	4	5	0	4	3	4

Gross ocular grading: There were no drug-related, biologically relevant changes.

ECG, HR, RR and Bp: There were no drug-related changes during the study.

Clinical Pathology – No toxicologically significant, biologically relevant effects of AGN 192024 on clinical chemistry, hematology and urine analysis were observed.

Organ Weights - There were no drug-related, toxicologically significant changes in absolute & relative organ weight examination.

Gross Pathology – No drug-related abnormal findings were noted.

Microscopic Examination –No positive findings related to the drug effects were noted.

In summary, cynomolgus monkeys were topically treated with 0.03% and 0.1% AGN 192024 ophthalmic solution once or 2 times a day for 1 year to determine the ocular and systemic toxicity of the drug. Clinical observations and ocular examinations showed increased iridal pigmentation and periocular changes characterized by a prominent upper and/or lower sulcus and/or widening of the palpebral fissure in the treated eyes. No functional or anatomic ocular abnormalities were noted. The periocular findings were completely reversed by the end of the recovery period, while the increased iridal pigmentation was not reversible. These findings were also observed in monkeys with other PG analogues (including latanoprost) and were considered to be related to this pharmacological class. No systemic toxicity was observed at any dose.

7. 3-month ocular adjunctive study of 0.03% AGN 192024 and 0.5% timolol in Dutch Belted rabbits with a 1 month recovery period. Vol. 28, Page 197

This study is not reviewed.

Reproductive toxicity studies

1. Oral (gavage) fertility and general reproduction study of AGN 192024 in rats. Vol. 34, Page 127

Study №: 1801-013
Study Aim: To determine the toxic effects of AL06221 on fertility and general reproductive performance in male and female Sprague-Dawley rats
Compound: AGN 192024 0.2% solution (Lot#s: 9123X11246 and 9124X11268)
Vehicle Control: [redacted]
Dose/Route/Duration: 0, 0.1, 0.3 and 0.6 mg/kg, oral gavage, qd
Animals: Sprague Dawley rats, ♂: 11-week old, 344-380 g, ♀: 12-week old, 231-249 g, 25/sex/group
Study Location: [redacted]
GLP/QAU: Yes
Study Initiation: March 1998
Study Design: Four groups of male rats (25/group) were treated with 0, 0.1, 0.3 and 0.6 mg/kg/day AGN 192024 by oral gavage for 10 weeks, then cohabitated with female rats (25/group) given similar dose for 15 days. Cohabitation was on a 1:1 ratio and continued until evidence of mating (copulatory plug or sperm in the estrus smear) was observed. The day on which evidence of copulation was observed was designated as Day 0 of gestation. Dosing was continued in males until evidence of copulation was observed, and in female rats until gestation Day 7. Males were sacrificed folloiwing cohabitation and females were sacrificed on gestation Day 10 for caesarean-section. Toxicity was assessed as shown below.
Clinical Observations – At least once daily
Body Weights – Daily
Food Consumption – Weekly
Uterine and Ovarian Examinations – On Day 10 of gestation, all females were euthanized and viable and nonviable embryos, early resorptions, the number of total implantations and corpora lutea were recorded.
Postmortem Evaluations – A necropsy examination was performed on all treated male and female animals. For the males euthanized at the study termination, the testes, seminal vesicles, prostate and epididymides were weighted and examined histopathologically. The concentration and motility of the sperm were measured.

Results:

Clinical Signs – During the study period, no drug-related mortality was noted, and no remarkable clinical signs attributable to the treatment were noted.

Body Weights – No treatment-related body weight changes were noted in male and female animals.

Food Consumption – No drug-related changes in food consumption were noted.

Cohabitation Data – Mating results are summarized in the table below. No toxicologically significant, treatment-related changes were noted.

Copulation index and fertility index in male and female rats

Dose	Number of females			Copulation index*	Fertility index*
	Females				
(mg/kg/day)	Paired	Inseminated	Pregnant	%	%
0	25	25	24	100	96
0.1	25	25	24	100	96
0.3	25	25	24	100	96
0.6	25	25	24	100	96
Historical					94.0
	Males				
(mg/kg/day)	Paired	With ♀ inseminated	With ♀ pregnant	%	%
0	25	25	24	100	96
0.1	25	25	24	100	96
0.3	25	25	24	100	96
0.6	25	25	24	100	96

* Copulation index = (# inseminated/# paired x 100); Fertility index = (# pregnant/# inseminated x 100)

Estrous Cycle Examination – No treatment-related changes were noted.

Uterine and Ovarian Examinations – The results are summarized in the table below. No toxicologically significant changes were noted. At 0.6 mg/kg, one animal had a litter of 3 nonviable embryos. However, this was a single case, and the total incidence of nonviable embyros was still within the historical range, hence it was not considered treatment-related.

Uterine and ovarian examination

(µg/kg/ day)	pregnant	Corpora lutea (#/dam)	Implantations (#/dam)	Pre-implantation loss (#/dam)	Litter size (#/dam)	Viable embyros (#/dam)	nonviable embryos (#/dam)	Dams with all nonviable embryos
0	24	16.9±2.3	15.8±1.8	1.1	15.8±1.9	15.8±1.9	0±0.2	0
0.1	24	16.8±2.0	15.2±2.5	1.6	15.0±2.6	15.0±2.6	0.2±0.5	0
0.3	24	17.5±4.2	15.3±3.3	2.2	15.2±3.4	15.2±3.4	0.1±0.3	0
0.6	24	16.4±2.5	14.4±3.2	2.0	14.2±3.7	14.2±3.7	0.2±0.6	1
Historical		15.2-21.0	12.9-18.0	1.7	11.8-17.0		0-1.6	

Necropsy examinations – No treatment-related changes were noted in male and female treated rats.

Organ weights and histopathology – No treatment-related differences were noted.

Sperm analysis – No drug-related abnormal findings were observed.

In summary, Sprague Dawley rats (25/sex/group) were given 0.1, 0.3 and 0.6 mg/kg AGN 192024 or vehicle control via daily oral (gavage) administration. Dosing to males began 10 weeks prior to cohabitation and to females 15 days prior to cohabitation. Dosing was continued through gestation Day 7 for females. Cohabitation was on a 1:1 ratio and continued until evidence of mating (copulatory plug or sperm in the estrus smear) was observed. No parental toxicity or adverse effects on fertility or general reproduction were observed in rats treated with AGN 192024 at the doses up to 0.6 mg/kg/day.

2. Oral (gavage) dosage-range developmental toxicity study of AGN 192024 in mice. Vol. 33, Page 142

Study №: TX 99020
Study Aim: To provide dose selection information for a study to determine the toxic effects of AL06221 on pregnant mice and embryo/fetal development
Compound: AGN 192024 0.2% solution (Lot#: 11459A)
Vehicle Control: [redacted]
Dose/Route/Duration: 0, 0.3, 1.0, 4.0 and 16 mg/kg, oral gavage, qd, gestation Days 6-15
Animals: Presumed pregnant Crl:CD-1 (ICR)BR mice, 8/group
Study Location: [redacted]
GLP/QAU: Yes
Study Initiation: March 1999
Study Design: Presumed pregnant mice (8/group) were given 0.3, 1.0, 4.0 and 16 mg/kg AGN 192024 or vehicle control via daily oral (gavage) administration from Day 6 of gestation to Day 15 of gestation. On Day 18 of gestation each female was euthanatized and caesearean-sectioned. Toxicity was assessed as shown below.
Clinical Observations – Daily
Body Weights – Daily
Gross necropsy – On Day 18 of gestation, all animals were euthanized and caesearean-sectioned. A gross necropsy of the thoracic, abdominal and pelvic viscera was performed.
Uterine and Ovarian Examinations – The number of implantation sites and corpora lutea, early and late resorptions, and live and dead fetuses were recorded.
Teratologic Evaluations – Fetuses were weighted, sexed and examined for external malformations and variations.

Results:

Clinical Observations – Deaths occurred in one mouse at 4 mg/kg (gestation Day 10) with emaciation and one mouse at 0.3 mg/kg (gestation Day 9). The causes of the deaths were not known. Abortion occurred in 1 mouse at 1 mg/kg (gestation Day 16), 2 mice at 4 mg/kg (gestation Days 14 and 16) and 1 mouse at 16 mg/kg (gestation Day 16). A perivaginal substance was seen in 2 mice and one mouse in the 4 and 16 mg/kg groups, respectively.

Body Weight – Decreased body weight gain was noted in animals at 1.0, 4.0 and 16.0 mg/kg groups (see table below).

Body weight changes in mice treated with AGN 192024 (g)

Dose (mg/kg)	Day of gestation	Control	0.3	1.0	4.0	16.0
Body weights	6	30.8±2.0	30.6±1.6	31.7±0.6	33.3±1.2	32.0±1.4
	16	47.7±4.2	47.8±4.3	44.7±7.6	36.5±3.5	35.5±3.5
% control			100	93.7	76.5	74.4
Body weight gain	6-16	16.8±2.5	17.0±4.1	13.0±7.9	2.5±3.5	3.5±2.1
% control			100	77.3	14.9	20.8

Necropsy examinations – No treatment-related changes were noted

Uterine and Ovarian Examinations – The results are summarized in the table below. The pregnant rates were low in 1.0, 4.0 and 16.0 mg/kg groups. Total resorption was noted in 4.0 and 16.0 mg/kg groups. The fetal body weights were low in 1.0 mg/kg group. These changes were considered treatment-related.

Uterine and ovarian examination

(mg/kg/ day)	Pregnant N(%)	Caesarean sectioned	Corpora lutea (#/dam)	Implantations (#/dam)	Litter size (#/dam)	Resorptions (#/dam)	Live fetuses (#/dam)	Live fetal body weights (g/litter)	Live male fetuses/litter (%)
0	6(75)	6	13.0±1.4	12.2±1.5	11.7±2.2	0.5±0.8	11.7±2.2	1.34±0.08	43.2±15.2
0.3	8(100)	7	13.3±2.7	11.3±2.9	9.8±3.6	1.4±1.8	9.8±3.6	1.37±0.10	65.8±14.8
1.0	3(37.5)	2	13.5±0.7	12.5±0.7	12.0±0.0	0.5±0.7	12.0±0.0	1.24±0.03	45.8±5.9
4.0	3(37.5)	1	18.0±0.0	15.0±0.0	0	15.0±0.0			
16.0	2(25)	1	15.0±0.0	13.0±0.0	0	13.0±0.0			
Historical			11.8-15.4	10.8-14.1		0.4-1.1	10.3-13.0	1.28-1.42	45.8-61.4

Fetal examinations – All fetuses appeared normal at gross external observation.

In summary, pregnant Crl:CD-1®(ICR)BR mice (8/group) were orally treated with AGN 192024 from gestation Days 6-15 with doses of 0, 0.3, 1.0, 4.0 and 16.0 mg/kg. Animals were terminated on Day 18 of gestation and examinations on the uterine and fetuses were performed. Maternal toxicities (deaths, abortions and decreased body weights) were noted in animals at the doses ≥ 0.3 mg/kg/day. Increased resorption was noted at 0.3 mg/kg, while total resorption was noted at 4.0 and 16.0 mg/kg. Decreased fetal body weights were observed at 1.0 mg/kg/day.

3. Oral (gavage) dosage-range developmental toxicity study of AGN 192024 in rats. Vol. 34, Page 001

Study №: 1801-013P
Study Aim: To provide dose selection information for reproductive toxicity studies in rats
Compound: AGN 192024 0.2% solution (Lot#: 9124X-11246) [redacted]
Vehicle Control: [redacted]
Dose/Route/Duration: 0, 0.1, 0.3, 1.0 and 3.0 mg/kg, oral gavage, qd, gestation Days 7-17
Animals: Presumed pregnant Sprague Dawley rats, 8/group, 11-12 weeks old, 220-233 g
Study Location: [redacted]

GLP/QAU: Yes
Study Initiation: February 1998
Study Design: Presumed pregnant rats (8/group) were given 0.1, 0.3 1.0 and 3.0 mg/kg AGN 192024 or vehicle control via daily oral (gavage) administration from Day 7 of gestation to Day 17 of gestation. On Day 20 of gestation each

female was euthanatized and caesearean-sectioned. Toxicity was assessed as shown below.

Clinical Observations – At least twice daily

Body Weights – Daily

Food Consumption – Gestation Days 0, 7, 10, 12, 15, 18 and 20

Gross necropsy – On Day 20 of gestation, all animals were euthanized. A gross necropsy of the thoracic, abdominal and pelvic viscera was performed.

Uterine and Ovarian Examinations – The number of implantation sites and corpora lutea, early and late resorptions, and live and dead fetuses were recorded.

Teratologic Evaluations – Fetuses were weighted, sexed and examined for external malformations and variations.

Results:

Clinical Observations – No mortality was noted. Abortion occurred in 5 rats each at 1 mg/kg and 3 mg/kg doses during gestation Days 17-19. One rat at 1.0 mg/kg delivered on gestation Day 20. Perivaginal substance was seen in 1 rat at 1.0 mg/kg and 6 rats at 3.0 mg/kg. No other drug-related clinical observations were noted.

Body Weight – Decreased body weight gain was noted in animals at 1.0 and 3.0 mg/kg groups (see table below).

Body weight changes in rats treated with AGN 192024 (g)

Dose (mg/kg)	Day of gestation	Control	0.1	0.3	1.0	3.0
Body weights	7	225.1±4.8	225.6±4.9	224.9±4.0	224.9±4.4	225.1±4.2
	18	355.0±18.3	357.4±8.4	363.9±12.7	343.4±19.6	276.0±46.8
% control			100	100	96.7	77.7
Body weight gain	7-18	86.6±9.7	86.1±10.7	92.1±7.3	79.5±19.2	5.0±41.6
% control			100	100	92.3	5.8

Food Consumption – Daily food consumption was lower in rats at 3.0 mg/kg (18.5-21.7 g/day) than in the control animals (23.2-27.8 g/day).

Necropsy Examinations – No treatment-related changes were noted

Uterine and Ovarian Examinations – The results are summarized in the table below. All rats at 3 mg/kg either aborted or totally resorbed their litter. Only 2 dams at 1.0 mg/kg had viable litters. AGN 192024 at the doses up to 0.3 mg/kg/day produced no effects on any parameters evaluated at caesarean-section.

Uterine and ovarian examination

(mg/kg/ day)	Pregnant N(%)	Caesarean sectioned	Corpora lutea (#/dam)	Implantations (#/dam)	Litter size (#/dam)	Resorptions (#/dam)	Live fetuses (#/dam)	Live fetal body weights (g/litter)	Live male fetuses/litter (%)
0	8 (100)	8	15.8±2.5	15.0±1.4	14.4±1.5	0.6±0.8	14.4±1.5	3.58±0.24	42.8±10.4
0.1	8(100)	8	15.0±1.4	13.9±2.4	13.5±2.4	0.4±0.7	13.5±2.4	3.73±0.21	47.7±13.5
0.3	8(100)	8	15.8±1.5	14.9±1.4	14.5±1.2	0.4±0.7	14.5±1.2	3.71±0.21	54.9±18.9
1.0	8(100)	2	11.5±9	8.0±9.9	7.5±9.2	0.5±0.7	7.5±9.2	3.98±0.34	32.2±45.5
3.0	8(100)	3	17.3±4.9	14.3±1.5	0	14.3±1.5	0		
Historical			15.2-21.0	12.9-18.0		0-1.6	11.8-17.0	3.10-3.78	42.1-57.0

Fetal examinations – All fetuses appeared normal at gross external observation.

In summary, pregnant Sprague Dawley rats (8/group) were orally treated with AGN 192024 from gestation Days 7-17 with doses of 0, 0.1, 0.3, 1.0 and 3.0 mg/kg. Animals were terminated on Day 20 of gestation and examinations on the uterine and fetuses were performed. Maternal toxicities evidenced by abortions, prematural delivery and decreased body weights and food consumption were noted in animals at the doses ≥ 1.0 mg/kg/day. A decrease in implantation, litter size and live fetuses per litter was seen at 1.0 mg/kg, while total resorption was noted at 3.0 mg/kg. NOAEL was considered as 0.3 mg/kg/day for both dams and fetuses.

4. Oral (gavage) developmental toxicity study of AGN 192024 in mice. Vol. 33, Page 253

Study №: TX 99038
Study Aim: To determine the toxic effects of AL06221 on pregnant mice and embryo/fetal development
Compound: AGN 192024 0.2% solution (Lot#: 11482)
Vehicle Control: [redacted]
Dose/Route/Duration: 0, 0.1, 0.3 and 0.6 mg/kg, oral gavage, qd, gestation Days 6-15
Animals: Pregnant female Crl:CD-1 (ICR)BR mice, 11-week old, 25-29 g, 25/group
Study Location: [redacted]
GLP/QAU: Yes
Study Initiation: June 1999
Study Design: Pregnant mice (25/group) were given 0.1, 0.3 and 0.6 mg/5 ml/kg AGN 192024 or vehicle control via daily oral (gavage) administration from Day 6 of gestation to Day 15 of gestation. The day on which evidence of copulation was observed was designated as Day 0 of gestation. On Day 18 of gestation each female was euthanatized and caesearean-sectioned. Toxicity was assessed as shown below.
Clinical Observations – Twice daily
Body Weights – Daily
Gross necropsy – On Day 18 of gestation, all animals were euthanized and caesearean-sectioned. A gross necropsy of the thoracic, abdominal and pelvic viscera was performed.
Uterine and Ovarian Examinations – The number of implantation sites and corpora lutea, early and late resorptions, and live and dead fetuses were recorded.
Teratologic Evaluations – Fetuses were weighted, sexed and examined for external malformations and variations. One-half of the fetuses were examined for soft tissue defects. The other half of the fetuses were examined for skeletal anomalies.

Results:

Clinical Observations – Abortion occurred in 1 mid dose mouse (gestation Day 17) and 3 high dose mice (gestation Days 16 and 17). In addition, premature deliveries were noted in 3 high dose mice on gestation Day 18. The abortion and premature deliveries were considered treatment-related. Post-mortem examinations showed no abnormal findings in dams or fetuses.

Body Weight – No treatment-related body weight changes were noted.

Necropsy examinations – No treatment-related changes were noted

Uterine and Ovarian Examinations – The results are summarized in the table below. There were one and two dead fetuses in the 0.3 and 0.6 mg/kg groups, which was within the historical control ranges and was not considered treatment-related.

Uterine and ovarian examination

(mg/kg/ day)	Pregnant	Caesarean sectioned	Corpora lutea (#/dam)	Implantations (#/dam)	Litter size (#/dam)	Resorptions (#/dam)	Live fetuses (#/dam)	Live fetal body weights (g/litter)	Live male fetuses/litter (%)
0	24	24	13.4±2.6	11.8±2.3	11.4±2.3	0.3±0.7	11.4±2.3	1.37±0.09	52.9±13.8
0.1	23	23	13.1±2.0	12.3±1.7	11.9±1.9	0.4±0.7	11.9±1.9	1.36±0.09	54.8±15.6
0.3	25	24	13.5±2.0	12.6±2.0	12.4±2.1	0.2±0.5	12.4±2.2	1.37±0.09	54.0±18.6
0.6	23	17	13.5±2.1	12.5±1.7	12.0±1.4	0.5±0.9	11.9±1.5	1.36±0.07	48.6±16.2
Historical			**11.8-15.4**	**10.8-14.1**		**0.4-1.1**	**10.3-13.0**	**1.28-1.42**	**45.8-61.4**

Fetal examinations – Positive external, visceral and skeletal findings are summarized in the table below. These findings were common in this species and strain, were within the historical control ranges, were not dose-dependent, and were not considered drug-related.

Summary of fetus/litter incidence of external, visceral and skeletal effects

Dose (µg/kg)	Class	Control	0.1	0.3	0.6	Historical range
Litters evaluated		**24**	**23**	**24**	**17**	
Fetuses evaluated		**275**	**273**	**299**	**205**	
Litters with fetuses with any alterations		**20 (80.3%)**	**20 (87%)**	**22 (91.7%)**	**16 (94.1%)**	
Fetuses with any alterations observed		**62 (22.5%)**	**57 (20.9%)**	**61 (20.5%)**	**47 (23.3%)**	
External exam: Number of fetuses/litters		**275/24**	**273/23**	**299/24**	**205/17**	
Cleft palate	Malformation	2/2	1/1	1/1	**0/0**	
Visceral exam: Number of fetuses/litters		**129/24**	**130/23**	**142/24**	**98/17**	
Heart: large	Malformation	0/0	1/1	0/0	0/0	
Heart: situs inversus	Malformation	0/0	1/1	0/0	1/1	
Skeletal exam: Number of fetuses/litters		**146/24**	**143/23**	**157/24**	**107/17**	
Skull: palate, incompletely ossified	Malformation	2/2	1/1	1/1	0/0	
Skull: frontals, contain an interfrontal	Variation	51/19	42/18	41/18	35/16	
Cervical vertebrae: cervical rib present at 7th cervical vertebra	Variation	20/10	18/11	30/14	20/9	
Sternal centra: fused	Variation	0/0	1/1	2/2	0/0	
Sternal centra: asymmeteric	Variation	1/1	0/0	1/1	0/0	

In summary, pregnant Crl:CD-1®(ICR)BR mice (25/group) were orally treated with AGN 192024 from gestation Days 6-15 with doses of 0, 0.1, 0.3 and 0.6 mg/kg. Animals were terminated on Day 18 of gestation and examinations on the uterine and fetuses were performed. Dose-related abortion and early delivery occurred in the 0.3 and 0.6 mg/kg/day groups. Necropsy examination revealed no drug-related abnormalities. No developmental toxicities were noted at any dose groups. In conclusion, AGN 192024 was not considered to be teratogenic under the conditions of this study. NOAEL was considered as 0.1 mg/kg/day and 0.6 mg/kg/day for dams and fetuses, respectively.

5. Oral (gavage) development toxicity study of AGN 192024 in rats. Vol. 35, Page 001

Study №: 1801-018

Study Aim: To determine the toxic effects of AL06221 on pregnant rats and embryo/fetal development
Compound: AGN 192024 0.2% solution (Lot#: 9124X-11246)
Vehicle Control: [redacted]
Dose/Route/Duration: 0, 0.1, 0.3 and 0.6 mg/kg, oral gavage, qd, gestation Days 7-17
Animals: Pregnant female Sprague Dawley rats, 14-week old, 229-328 g, 25/group
Study Location: [redacted]
GLP/QAU: Yes
Study Initiation: May 1998
Study Design: Pregnant rats (25/group) were given 0.1, 0.3 and 0.6 mg/1.5 ml/kg AGN 192024 or vehicle control via daily oral (gavage) administration from Day 7 of gestation to Day 17 of gestation. The day on which evidence of copulation was observed was designated as Day 0 of gestation. On Day 20 of gestation each female was euthanatized and caesearean-sectioned. Toxicity was assessed as shown below.
Clinical Observations – At least twice daily
Body Weights – Daily
Food Consumption – Gestation Days 0, 7, 10, 12, 15, 18 and 20
TK – See Pharmacokinetics Section
Gross necropsy – On Day 20 of gestation, all main study animals were euthanized and caesearean-sectioned. A gross necropsy of the thoracic, abdominal and pelvic viscera was performed.
Uterine and Ovarian Examinations – The number of implantation sites and corpora lutea, early and late resorptions, and live and dead fetuses were recorded.
Teratologic Evaluations – Fetuses were weighted, sexed and examined for external malformations and variations. One-half of the fetuses were examined for soft tissue defects. The other half of the fetuses were examined for skeletal anomalies.

Results:

Clinical Observations – Abortion occurred in 2 rats at 0.6 mg/kg/day on gestation Day 19. Necropsy of these rats revealed no gross lesions. Localized alopecia was noted in 8 dams in the 0.6 mg/kg/day group vs. 4 in the control group. Five of the 8 dams had alopecia on the ventral surface while none in the control group. This was considered treatment-related. No other toxicologically significant abnormal findings were noted in clinical observations.

Body Weights – Body weights were not affected by the treatment.

Food Consumption – Food consumption was not affected by the drug during the treatment period.

Necropsy examinations – No treatment-related changes were noted

Uterine and Ovarian Examinations – The results are summarized in the table below. No toxicologically significant, biologically relevant findings were observed.

Uterine and ovarian examination

(mg/kg/ day)	Pregnant	Caesarean sectioned	Corpora lutea (#/dam)	Implantation (#/dam)	Litter size (#/dam)	Resorptions (#/dam)	Live fetuses (#/dam)	Dead fetuses (#/dam)	Live fetal body weights (g/litter)	Live male fetuses/litter (%)
0	25	24	15.9±3.1	14.1±1.9	13.6±1.9	0.5±0.8	13.6±1.9	0	3.44±0.28	45.1±12.6
0.1	24	24	15.7±3.6	14.0±3.6	13.9±3.7	0.2±0.5	13.8±3.7	0±0.2	3.50±0.24	47.4±16.3
0.3	25	25	17.0±2.3	15.3±1.6	14.4±2.5	0.9±1.7	14.4±2.5	0	3.57±0.21	53.5±15.5
(mg/kg/ day)	Pregnant	Caesarean sectioned	Corpora lutea (#/dam)	Implantation (#/dam)	Litter size (#/dam)	Resorptions (#/dam)	Live fetuses (#/dam)	Dead fetuses (#/dam)	Live fetal body weights (g/litter)	Live male fetuses/litter (%)
0.6	23	21	16.6±3.2	14.1±3.3	13.7±3.3	0.4±0.6	13.7±3.3	0±0.2	3.57±0.20	54.4±15.5
Historical			15.2-21.0	12.9-18.0	11.9	0-1.6	11.8-17.0	0-1.1	3.10-3.78	42.1-57.0

Fetal examinations – Positive external, visceral and skeletal findings are summarized in the table below. These findings were common in this species and strain, were within the historical control ranges, were not dose-dependent, and were not considered drug-related.

Summary of fetus/litter incidence of external, visceral and skeletal effects

Dose (µg/kg)	Class	Control	0.1	0.3	0.6	Historical range
Litters evaluated		24	24	25	21	
Fetuses evaluated		326	333	361	288	
Litters with fetuses with any alterations		12 (50%)	12 (50%)	12 (48%)	12 (47.6%)	
Fetuses with any alterations observed		26 (8%)	23 (6.9%)	18 (5.0%)	18 (6.3%)	
External exam: Number of fetuses/litters		326/24	333/24	361/25	288/21	
Incomplete twin joined at the ventral chest	Malformation	0	1/1	0	0	
Umbilical hernia	Malformation	0	0	1/1	0	
Depressed eye bulge, protruding tongue, short snout and dark red fluid-filled areas on the left side of the head, surface of the nose and between the eyes	Malformation	0	0	0	1/1	
Visceral exam: Number of fetuses/litters		157/24	160/24	174/25	137/20	
Umbilical artery descended to the left of urinary bladder	Variation	0/0	1/1	0/0	0/0	
Skeletal exam: Number of fetuses/litters		169/24	173/24	187/25	151/21	
Thoracic vertebrae: centrum, bifid	Variation	4/3	5/3	4/4	0	
Cervical vertebrae: cervical rib present at 7th cervical vertebra	Variation	0	0	2/1	1/1	
Ribs:wavy	Variation	2/2	0	0	1/1	
Sternal centra summarization	Variation	9/7	8/7	3/3	3/3	
Sternal centra: 1st, incompletely ossified	Variation	8/6	8/7	2/2	2/2	
Sternal centra: 1st, not ossified	Variation	1/1	0/0	1/1	0/0	
Sternal centra: 2nd, incompletely ossified	Variation	0	0	1/1	1/1	
Pelvis summarization	Variation	16/7	13/8	10/5	13/6	
Pelvis: pubis, incompletely osscified	Variation	16/7	12/8	9/5	11/5	
Pelvis: ischium, incompletely osscified	Variation	4/2	0	4/3	3/3	
Pelvis: pubis, not osscified	Variation	0	1/1	0	0	

In summary, pregnant Sprague Dawley rats (25/group) were orally treated with AGN 192024 from gestation Day 7 to Day 17 with doses of 0, 0.1, 0.3 and 0.6 mg/kg. Animals were terminated on Day 20 of gestation and examinations on the uterine and fetuses were performed. Two abortions occurred in the 0.6 mg/kg/day group. At the same dose, increased incidence of alopecia was noted. Necropsy examination revealed no drug-related abnormalities. No developmental toxicities were noted at any dose groups. In conclusion, AGN 192024 was not considered to be teratogenic under the conditions of this study. NOAEL was considered as 0.3 mg/kg/day and 0.6 mg/kg/day for dams and fetuses, respectively.

6. Oral (gavage) developmental and perinatal/postnatal reproduction toxicity study of AGN 192024 in rats, including a postnatal behavioral/functional evaluation. Vol. 35, Page 206

Study №: 1801-020 (TX 99057)
Study Aim: To determine the toxicity potential of AL06221 in the pregnant/lactating females and in the development of the offspring following exposure of the female from implantation through weaning
Compound: AGN 192024, 0.2% (Lot#: 9124X-11482)
Vehicle Control: [redacted]
Dose/Route/Duration: 0, 0.05, 0.1, 0.3 and 0.6 mg/kg/day, oral (gavage), qd, from gestation Day 7 to lactation Day 20
Animals: Female mated Sprague Dawley rats, 10 weeks old, 200-224 g, 25/group
Study Location: [redacted]
Compliance with GLP/QAU: Yes
Study Initiation: August 1999
Study Design: Pregnant rats (25/group) were given 0.05, 0.1, 0.3 and 0.6 mg/kg/day AGN 192024 or vehicle control via daily oral (gavage) administration from Day 7 of gestation to Day 20 of lactation. The day on which evidence of mating was observed was designated as Day 0 of gestation. The day of birth was defined as Day 1 of lactation. Toxicity was assessed as shown below.
Clinical Observations – At least twice daily
Body Weights – Daily
Food Consumption – Days 0, 7, 10, 12, 15, 18 and 20 of gestation and on Days 1, 4, 7, 10 and 14 of lactation
F_0 parturition and F_1 litter observations – The pregnant animals were allowed to deliver and the duration of gestation, litter size and viability were examined. All pups in a litter were individually weighted. During pre-weaning observations, each litter was evaluated for viability twice daily. Clinical observations were recorded once daily and body weights were measured weekly.
F_1 postweaning observations – Selected F_1 generation rats from 0, 0.05, 0.1 and 0.3 mg/kg/day groups were observed for viability (twice daily), clinical observations (weekly), body weights and food consumption (weekly). Beginning at 24 days postpartum, one male and one female from each litter were evaluated in a passive avoidance test for learning, short- and long-term retention. Beginning at day 28 postpartum, females were evaluated for the age of vaginal patency. Beginning at day 39 postpartum, males were evaluated for the age of preputial separation. Beginning at 70 days postpartum, one male and one female from each litter were evaluated in a water-filled M-maze for overt coordination, swimming ability, learning and memory.
F_1 Reproduction Assessment – At approximately 90 days of age, the F_1 generation rats within each dosage group were assigned to cohabitation, one male rat per female rat, with the exclusion of sibling matings. Female rats with sperm observed in a smear of the vaginal contents and a copulatory plug observed were considered to be at Day 0 of gestation and assigned to individual housing.
F_0 Necropsy – After the 21-day postpartum period, female rats were euthanized and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed. The number and distribution of implantation sites were recorded.
F_1 Necropsy – Pups found dead were examined for gross lesions. All pups culled on Day 21 of lactation were examined for gross lesions. Male F_1 rats selected for reproduction assessment were

terminated after cohabitation period and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed. On gestation Day 21, female rats were sacrificed and caesarean-sectioned, and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed. The female rats were examined for the number of corpora lutea, implantation sites, live and dead fetuses and early and late resorptions.
F_2 fetuses – Each fetus was weighted and examined for sex and internal alternations.

Results:

F_0: Maternal Observations – No treatment-related mortality and clinical signs were noted.

F_0: Maternal Body Weight – Prior to gestation Day 18, maternal body weight gain was comparable among different groups. The average body weights from gestation Days 18 to 20 was reduced in the 0.6 mg/kg group, which was 91.7% of the body weights in control animals. The decrease was attributed to the litter loss (dead or resorbed conceptuses) in this group. During lactation period, maternal body weights were comparable among the groups.

F_0: Maternal Food Consumption – Food consumption was comparable among different groups during gestation and lactation periods.

F_0: Maternal Necropsy Findings – No abnormal findings were noted.

F_0: Reproductive Parameters – Reproductive parameters of F_0 dams are summarized in the table below. In 0.6 mg/kg group, 3 dams were not observed to have delivered a litter by gestation Day 25. Post mortem examination showed that 2 of these rats had early resorptions and the other one delivered the litter without observations. In 0.3 mg/kg and 0.6 mg/kg groups, the duration of gestation was reduced, peri- and postnatal pup mortality was increased.

Summary of reproductive parameters of F_0 dams

Dose (mg/kg)	Control	0.05	0.1	0.3	0.6
Number of dams assigned to study	25	25	25	25	25
Pregnant	24	21	25	25	24
Dams delivering litters	24 (100%)	21 (100%)	25 (100%)	25 (100%%)	21 (87.5%)
Included in analysis	24	21	25	24	15
Gestation length (days)	22.8±0.5	22.8±0.4	22.8±0.5	21.8±0.8	21.1±0.8
Implantation sites/dam	14.0±1.2	16.3±2.4	13.9±1.3	14.3±1.4	14.4±2.1
Dams with stillborn pups	2(8.3%)	3 (14.3%)	4 (16.0%)	12 (50%)	12 (80%)
Dams with all stillborn	0	0	0	3	5
Gestation index*	100%	100%	100%	87.5%	66.7%
Dams with all pups dying days 1-4 postpartum	0	0	0	5(23.8%)	6 (60%)

* gestation index: # of rats with live offspring/# of pregnant rats

F_1: Offspring Viability and Survival – F_1 offspring viability data are summarized in the table below. Treatment-related changes included decreases in the number of pups per litter at birth, the number of live born pups per litter, the percentage of pups surviving after 1 and 4 days, and pup weights during the preweaning period at 0.3 and 0.6 mg/kg/day.

Summary of F_1 offspring survival

Dose (mg/kg)	Control	0.05	0.1	0.3	0.6
Number of litters with liveborn pups delivered	24	21	25	21	10
Number of pups delivered /litter	13.4±1.3	15.6±2.2	13.2±1.6	13.0±2.3	10.3±4.4
Number of live pups delivered /litter	13.3±1.4	15.4±2.2	13.0±1.6	11.8±3.7	7.4±5.3
Number of stillborn pups delivered /litter	0.1±0.3	0.1±0.4	0.2±0.4	1.1±2.0	2.7±2.6

Dose (mg/kg)	Control	0.05	0.1	0.3	0.6
Pups found dead or presumed cannibalized					
Day 1	0	2/323 (0.6%)	0	18/248(7.2%)	13/70 (18.6%)
Days 2-4	1/320 (0.3%)	7/321(2.2%)	3/326(0.9%)	26/230(11.3%)	18/57(31.6%)
Viablity index*	99.7	97.2	99.1	82.2	55.2
Pup weights/litter (g) Day 1	6.6±0.4	6.3±0.6	6.9±0.5	5.6±1.0	5.1±1.3
Pup weights/litter (g) Day 7	13.3±1.2	14.9±2.0	13.8±1.3	11.9±1.2	11.1±3.4
Pup weights/litter (g) Day 21	38.9±4.2	34.7±4.6	41.3±5.0	36.7±4.0	35.6±10.9

*# of live pups on day 4 postpartum/# of live born pups on day 1 postpartum

F_1: Observations – No treatment-related mortality and clinical signs were noted during premating period and during gestation period.

F_1: Body Weights – Postweaning and gestation body weights and body weight gain for the F_1 generation male and female rats were not affected by administration of AGN 192024 to the F_0 generation dams.

F_1: Food Consumption – No toxicologically significant changes in food consumption were observed.

F_1: Sexual Maturation – The average day on which preputial separation was evident in males and vaginal patency was evident in females were comparable between control and treated groups.

F_1: Behavioral Evaluation – No biologically relevant, toxicologically significant differences in the values for learning, short-term retention, long-term retention or response inhibition were noted in the F_1 generation male and female rats.

F_1: Necropsy Observations – No treatment-related, toxicologically significant findings were noted. In the males, the terminal body weights, testes and epididymides weights were comparable among different groups.

F_1: Cohabitation Data and Reproductive Parameters – The cohabitation data and reproductive parameters are summarized in the table below. It seemed that in 0.3 mg/kg/day group, the number of days in cohabitation was increased and the fertility index was slightly decreased.

Summary of cohabitation data and reproductive parameters of F_1 dams

Dose (mg/kg)	Control	0.05	0.1	0.3
Number of males placed with females	25	25	25	25
Days in cohabitation	3.1±2.3	3.4±3.0	2.6±2.6	4.8±4.1
Number of males mated	25 (100%)	25 (100%)	24 (96%)	23 (92%)
Fertility index*	24/25 (96%)	22/25 (88%)	22/24 (91.7%)	19/23 (82.6%)
Number of females placed with males	25	25	25	25
Days in cohabitation	3.1±2.3	3.0±2.0	2.9±3.9	5.0±4.6
Number of females inseminated	25 (100%)	25 (100%)	24 (96%)	25 (100%)
Fertility index*	24/25 (96%)	22/25 (88%)	22/24 (91.7%)	20/25 (80%)
Number of corpora lutea/dam	18.1±2.2	19.2±3.1	17.7±1.7	18.8±3.2
Number of implantation/dam	15.8±2.2	16.0±2.8	16.0±2.1	15.9±2.8
Number of live fetuses/litter	15.4±2.0	15.2±2.4	15.4±2.2	15.0±2.4
Resorptions/dam	0.4±0.5	0.9±0.9	0.6±0.7	1.0±0.9
Live fetal body weights (g/litter)	5.06±0.29	5.28±0.42	5.06±0.25	5.00±0.30

* Fertility index: # of pregnancies/# of rats that mated

F_2: Fetal External Observations – No treatment-related abnormal findings were noted.

In summary, pregnant Sprague Dawley rats (25/group) were given 0.05, 0.1, 0.3 and 0.6 mg/kg AGN 192024 or vehicle control via daily oral (gavage) administration from gestation Day 7 to lactation Day 20. Dams were allowed to give birth. Selected F_1 offspring were mated for assessment of breeding and reproductive effects. No treatment-related mortality, clinical signs of toxicity, body weight and food consumption changes were noted in F_0 rats. At $\geq$ 0.3 mg/kg/day, the duration of gestation was reduced and peri- and postnatal pup mortality was increased. Drug-related effects included decreases in the number of pups per litter at birth, the number of liveborn pups per litter, the percentage of pups surviving after 1 and 4 days, and pup weights during the preweaning period at 0.3 and 0.6 mg/kg/day. Sexual maturation and behavioral evaluations showed no abnormal findings in F_1 generation rats in any dosage groups. In mating and fertility assessment in F_1 generation, rats from 0.3 mg/kg group showed a slight increase in the number of days required for mating, and a slight decrease in the fertility index. The NOAEL was determined as 0.1 mg/kg/day in this study.

The following 2 dose-range finding studies are not reviewed.

7. TX 97055: AGN 192024: Four-day oral (gavage) range finding study in New Zealand white rabbits. Vol. 37, Page 001

8. 1801-012P: Oral stomach tube dosage range developmental toxicity study of AGN 192024 in rabbits. Vol. 37, Page 048

Genotoxicity Studies

1. In vivo mouse micronucleus assay with AGN 192024. Vol. 37, Page 183

Study N^{o}: 19471-0-455OECD
Compound: AGN 192024, 0.2% (Lot#: 9123X-11268)
Vehicle: [redacted]
Dose level: 0, 5, 10 and 20 mg/kg
Route: Intravenous injection
Dosing Regimen: Single dose
Animal: Male Crl:CD-1 (ICR)BR mice, 8 weeks old, 30.4-36.8 g
Study Initiation: April 22, 1998
Study site: [redacted]
GLP/QAU: Yes

Treatment protocol

Compound	Dosage (mg/kg)	Dosing volume (ml/kg)	N (24 hr harvest)	N (48 hr harvest)
Vehicle (iv)	0	10	6	6
AGN 192024 (iv)	5	10	6	
AGN 192024 (iv)	10	10	6	
AGN 192024 (iv)	20	10	6	6
Cyclophosphamide (po)	80.0	10	6	

* Only 5 mice were used for preparation of slides.

The purpose of this study was to evaluate the in vivo clastogenic activity of AGN 192024. The bone marrow was harvested 24 and 48 hr after dosing. The frequency of

micronucleated cells was expressed as percent micronucleated polychromatic erythrocytes (MNPCE).

Results:

In dose range finding assay, 3 mice/sex/dose were intravenously treated with a single dose of AGN 192024 at 5, 10 and 20 mg/kg and were observed for toxicity for 2 days. All animals appeared normal throughout the 2-day observation period. Based on this assay, the high dose of 20 mg/kg, the maximum dose possible with the concentration limit of 0.2%, was determined.

In micronucleus assay, all animals appeared normal. The results of mouse micronucleus assay are shown in the table below. NCE = normochromatic erythrocyte. PCE = polychromatic erythrocytes.

Results of micronucleus assay

Compound	Dosage (mg/kg)	PCE/NCE (24 hr)	MNPCE % (24 hr)	PCE/NCE (48 hr)	MNPCE % (48 hr)
Vehicle (iv)	0	0.29±0.05	0.02±0.01	0.59±0.07	0.06±0.01
AGN 192024 (iv)	5	0.41±0.07	0.07±0.04		
AGN 192024 (iv)	10	0.45±0.03	0.06±0.03		
AGN 192024 (iv)	20	0.41±0.03	0.02±0.01	0.47±0.03	0.02±0.01
Cyclophosphamide (po)	80.0	0.46±0.06	3.39±0.47		

AGN 192024 induced no signs of clinical toxicity and was not cytotoxic to the bone marrow. AGN 192024 did not induce a significant increase in micronucleated PCEs over the levels observed in the vehicle controls at any harvest timepoints. Therefore, AGN 192024 was not clastogenic under the present testing conditions.

2. Salmonella/Escherichia coli mutagenicity assay. Vol. 37, Page 225

Study Nº: G95BN52.503003
Study Site: [redacted]
Compound: AGN 192024 (Lot #: 91184)
Vehicle: [redacted]
Bacteria: *Salmonella typhimurium* strains TA98, TA100, TA1535, TA 1537, *Escherichia colistrains* WP2*uvr*A and WP2
Dose Level: 33, 100, 333, 1000, 5000 µg/plate
GLP/QAU: Yes

The objective of this study was to evaluate the mutagenic potential of AGN 192024 by measuring its ability to induce reverse mutations at selected loci of several strains of *Salmonella typhimurium* and two strains of *E. coli* in the presence or absence of S9 activation.

Positive control

Strain	S9 activation	Positive control	Concentration (µg/plate)
All *Salmonella* strains	+	2-aminoanthracene	1
WP2 *uvrA*			10
WP2		Sterigmatocystin	100
TA98	-	2-nitrofluorene	1
TA100, TA1535		Sodium azide	1
TA1537		9-aminoacridine	75
Both *E. coli* Strains		Methyl methanesulfonate	1,000

Criteria for the positive results were 1) a dose-related increase in the mean revertants per plate of at least one tester strain with a minimum of two increasing concentrations of test article and 2) the increase in mean revertants at the peak of the dose response is equal to or greater than three times (TA1535 and TA1537) or two times (TA98, TA 100, WP2 and WP2uvrA) the mean vehicle control value.

Results and Discussion:

In both prelimary toxicity assay and mutagenicity assay, neither precipitate nor appreciable toxicity was observed. AGN 192024 at the concentrations of 33, 100, 333, 1000, and 5000 µg/plate did not induce any positive response with any of the strains in the presence and absence of S9 fraction. These results indicated that AGN 192024 was not mutagenic under these experiment conditions.

3. Reduced volume L5178Y/TK$^{+/-}$ mouse lymphoma mutagenesis assay. Vol. 37, Page 270

Study N^{o}: G95BN52.702005
Project N^{o}: 1893
Study Site: [redacted]
Compound: AGN 192024 (Lot #: 91184)
Dose Level: 50-900 µg/ml
Indicator Cells: L5178Y cells, clone 3.7.2C
(+) Control: Ethyl methanesulfonate (0.25 and 0.5 µl/ml); 7,12-dimethylbenz (-) anthracene (2.5 and 4.0 µg/ml)
(-) Control: DMSO
GLP/QAU: Yes

The objective of this study was to evaluate mutagenic potential of AGN 192024 based on quantitation of forward mutations at the thymidine kinase locus of L5178Y mouse lymphoma cells. The study included a preliminary toxicity assay and a mutagenicity assay. The results would be considered as positive if a concentration-related increase in mutant frequency was observed and more than one dose level with 10% or greater total growth exhibited a mutant frequency two-fold greater than the solvent control. A doubling above background at one or more dose levels with 10% or greater total growth with no evidence of a dose-response would be considered equivocal. Test articles not producing a doubling above background at one or more dose levels with 10% or greater total growth were concluded to be negative.

Results:

In the preliminary assay, suspension growth relative to the solvent controls was 0% at 1000 and 5000 µg/ml with and without S9 activation. Based on the results of the toxicity assay, the doses chosen for the mutagenicity assay ranged from 50 to 900 µg/ml for both the non-activated and S9-activated cultures. In mutagenicity assay, cytotoxicity was evidenced by the inhibition of the total growths to 28% for the non-activated cultures at concentration of 452 µg/ml and 10% for S9-activated cultures at concentration of 472 µg/ml. No concentration-related increase in mutant frequency was observed. Under the conditions of this study, AGN 192024 did not produce a positive response in the non-activated and S9-activated systems.

Special Studies

1. Guinea pig sensitization – Maximization test. Vol. 37, Page 307

Study Nº: TX 99052 (0423XA08.001)
Study purpose: To evaluate the potential for a delayed dermal contact hypersensitivity response to AGN 192024 in guinea pigs
Compound: AGN 192024, 0.2% (Lot#: 11461)
Vehicle: [redacted]
Animal: Hartley guinea pigs, 4-week old, 347-375 g for dose-range finding studies (2/sex/group), and 305-396 g for main study animals (5/sex for vehicle control, 10/sex for AGN 192024 and 3/sex for positive control)
Study site: [redacted]
GLP/QAU: Yes
(+) Control: 0.1% 1-chloro-2,4-dinitrobenzene (DNCB)
Study Initiation Date: August 1999
Study Design: The study was divided into 4 phases.

Phase 1. Dose-range finding studies: Four guinea pigs (2/sex) were injected intradermally with concentrations of 0.01, 0.03, 0.06 and 0.1 mg/ml AGN 192024 and graded for skin response 24 hr later. Additional 4 animals were topically exposed to AGN 192024 for 24 hr at 0.5, 1.0, 1.5 and 2.0 mg/ml.

Phase 2. Intradermal induction: Main study animals were injected intradermally on Day 0 at 6 sites. Two sites received 0.1 ml of each solution listed in the table below.

Solutions for intradermal induction

Site	Vehicle control	AGN 192024	Positive control
1-2	FCA (Freund's Complete Adjuvant , 1:1)	FCA	FCA
3-4	0.9% NaCl	0.1 mg/ml AGN 192024	0.1% DNCB (in saline)
5-6	5% NaCl (in 1:1 FCA)	0.1 mg/ml AGN 192024 (in 1:1 FCA)	0.1% DNCB (in 1:1 FCA)

Phase 3. Topical induction: On Day 7, the animals were exposed topically to AGN 192024 (2 mg/ml) or control solutions applied using an occlusive patch. The patches were removed 48 hr later.

Phase 4. Challenge: Topical application: Two weeks after topical induction, all animals were topically challenged at a naive skin site with the respective test or control solution using occlusive patches. The patches were removed 24 hr later, and application sites were scored 24 and 48 hr after application.

The test sites were graded using the following scale:
0 = no reaction
1 = slight patch mild redness
2 = moderate and diffuse redness
3 = intense redness and swelling
4 = severe erythema and edema; skin damage

Results:

During the dose range finding phase, no treatment-related reactions were noted. Based on these results, the concentrations of 0.1 mg/ml and 2 mg/ml were chosen for the intradermal induction and topical induction, respectively.

No skin reactions were observed at the AGN 192024 or saline treated sites. The positive control group exhibited the anticipated positive response at challenge. In conclusion, AGN 192024 intradermally induced at 0.1 mg/ml and topically induced and challenged at 2.0 mg/ml did not elicit a dermal sensitization response.

2. Antigenicity study in guinea pigs: systemic anaphylaxis and passive cutaneous anaphylaxis reactions. Vol. 38, Page 001

Study Nº: TX 99053 (0742AA08.002)
Study purpose: To evaluate the potential antigenicity of AGN 192024 using a systemic anaphylaxis and a passive cutaneous anaphylaxis (PCA) assay in guinea pigs
Compound: AGN 192024, 0.2% (Lot#: 11461)
Vehicle: [redacted]
(+) Control: [redacted]
Animal: Male Hartley guinea pigs, 4-5 weeks old, 247-303 g for dose-range finding studies, 311-416 g for systemic anaphylaxis study and 249-389 g for PCA
Study site: [redacted]
GLP/QAU: Yes
Study Initiation Date: August 1999
Study Design:
Dose range finding phase: Dosing regimen is summarized in the table below. Animals were observed immediately after dosing, and 0.25, 0.5, 1, 4 and 24 hr after dosing.

Group	Dosage (µg/kg)	Dosing volume (ml/kg)	Route	N
1	7	1	sc	4
2	7	1	iv	4

Systemic anaphylaxis: Study design for systemic anaphylaxis is summarized in the table below. Animals were observed once daily for clinical signs. Body weights were measured weekly. Blood samples were collected on Day 34 and serum was separated for PCA assay. Animals were challenged on day 35 by iv administration of AGN 192024 or control compounds.

Group	Treatment	Dosage (µg/kg) qw x 4 weeks	N	Route	Complete Freund's adjuvant	Challenge dosage (µg/kg)
1	AGN 192024	0.7	10	iv	-	7
2	AGN 192024	7	10	iv	-	7
3	AGN 192024	0.7	10	sc	+	7
4	AGN 192024	7	10	sc	+	7
5	[redacted]	2000	10	sc	+	2 mg
6	PSS		10	sc	+	7

Evaluation of systemic anaphylaxis reaction:

Negative:	No signs
Slight:	Piloerection, scratching of nose, sneezing and tremors
Moderate:	Urination, defection, cyanosis, dyspnea, wheezing, labored respiration, staggered gait
Severe:	Convulsions, prostration or death

Positive: if one or more animals exhibited moderate or severe clinical signs, or if majority of the animals (> 5/10) exhibited slight clinical signs.

PCA reaction: PCA was assayed by intradermal injection of naïve guinea pigs with sensitized guinea pig serum. Six 5-fold serial dilutions were prepared from the serum samples of each sensitized animal. Six groups of 20 guinea pigs (2 animals per serum sample) were injected. Four hr after the injection, animals were challenged iv with AGN 192024 or [redacted] in 1% evans blue as shown in the table below. Approximately 30 min after challenge, the animals were examined and areas of skin bluing were measured.

Group	Antigen for challenge	Challenge dosage (µg/kg)	N
1	AGN 192024	7	20
2	AGN 192024	7	20
3	AGN 192024	7	20
4	AGN 192024	7	20
5	[redacted]	2 mg	20
6	AGN 192024	7	20

Evaluation of PCA reaction:
Positive: if the diameter of the bluing area was greater than 5 mm. The antibody titer was expressed as the highest dilution producing a positive reaction.

Results:

Dose-range finding phase: No abnormal findings were noted for 24 hr after dosing. Therefore, the doses of 0.7 and 7 µg/kg were selected for sensitization phase and 7 µg/kg for challenge phase.

Systemic anaphylaxis: All animals in the [redacted] positive control group showed signs of anaphylaxis, of which eight animals were rated moderate to severe. None of the AGN 192024 treated or vehicle treated animals showed any signs of an anaphylaxis reaction. Body weights were comparable among all groups.

PCA: When challenged with [redacted], positive reactions were only noted in the animals that received serum from the positive control [redacted] sensitized animals. The animals that received serum from animals sensitized with vehicle or AGN 192024 did not respond to a challenge with AGN 192024.

In conclusion, AGN 192024 was not antigenic as assessed by a systemic anaphylaxis assay and a PCA assay.

3. Passive cutaneous anaphylaxis (PCA) assay in rodents. Vol. 38, Page 061

Study N°: TX 99054 (0745XA08.001)
Study purpose: To evaluate the potential antigenicity of AGN 192024 using a passive cutaneous anaphylaxis (PCA) assay in rodents
Compound: AGN 192024, 0.2% (Lot#: 11461)
Vehicle: [redacted]
(+) Control: Ovalbumin (OVA)
Carrier Control: Bovine serum albumin (BSA)
Animal: Male BALB/cByJ mice (4 groups) and male C3H/HeJ mice (4 groups), 6/group, 7-8 weeks old, 20-30 g
Female Sprague Dawley rats, 9-11 weeks old, 189-246 g, 18 groups, 12/group
Study site: [redacted]
GLP/QAU: Yes
Study Initiation Date: August 1999
Study Design:

Sensitization: On Days 0 and 7 mice were dosed with AGN 192024, AGN 192024/OVA, or vehicle in combination with 2% aluminum hydroxide gel by the ip route of administration (see table below). Clinical signs were observed daily, and body weights were measured weekly. On Day 21, blood samples were collected and serum was separated.

Group	Mouse strain	Dosage (µg/kg) qw x 4 weeks	Dosage (µg/kg)	N	Route	Adjuvant (2% aluminum hydroxide gel)
1	BALB/cByJ	AGN 192024	0.7	6	ip	+
2	BALB/cByJ	AGN 192024	7	6	ip	+
3	BALB/cByJ	AGN 192024/OVA	7/400	6	ip	+
4	BALB/cByJ	vehicle		6	ip	+
5	C3H/HeJ	AGN 192024	0.7	6	ip	+
6	C3H/HeJ	AGN 192024	7	6	ip	+
7	C3H/HeJ	AGN 192024/OVA	7/400	6	ip	+
8	C3H/HeJ	vehicle		6	ip	+

PCA reaction: PCA was assayed by intradermal injection of naïve Sprague Dawley rats with sensitized mouse serum. The serum samples were diluted 1:5 with physiological saline and six 5-fold serial dilutions (1:25, 1:125, 1:625, 1:3125, 1:15625 and 1:78125) were prepared. Rats were injected (id) on the back with 50 µl of each dilution (2 rats/serum sample/challenge treatment).Each animal was also injected with 50 µl of saline as control. Eighteen to 24 hr later the animals were challenged iv with AGN 192024, 192024/BSA or OVA in 1% evans blue as shown in the table below. Approximately 30 min after challenge, the animals were examined and areas of skin bluing were measured.

Group	Serum from mouse group	Antigen for challenge	Challenge dose	Dosing volume (ml/kg)	N
A	1	AGN 192024	7 µg/kg	1	12
B	1	AGN 192024/BSA	7 µg/kg/1 mg	1	12
C	2	AGN 192024	7 µg/kg	1	12
D	2	AGN 192024/BSA	7 µg/kg/1 mg	1	12
E	3	AGN 192024	7 µg/kg	1	12
F	3	AGN 192024/BSA	7 µg/kg/1 mg	1	12
G	3	OVA	1 mg	1	12
H	4	AGN 192024	7 µg/kg	1	12
I	4	AGN 192024/BSA	7 µg/kg/1 mg	1	12
J	5	AGN 192024	7 µg/kg	1	12
K	5	AGN 192024/BSA	7 µg/kg/1 mg	1	12
L	6	AGN 192024	7 µg/kg	1	12
M	6	AGN 192024/BSA	7 µg/kg/1 mg	1	12
Group	**Serum from mouse group**	**Antigen for challenge**	**Challenge dose**	**Dosing volume (ml/kg)**	**N**
N	7	AGN 192024	7 µg/kg	1	12
O	7	AGN 192024/BSA	7 µg/kg/1 mg	1	12
P	7	OVA	1 mg	1	12
Q	8	AGN 192024	7 µg/kg	1	12
R	8	AGN 192024/BSA	7 µg/kg/1 mg	1	12

Evaluation of PCA reaction:
Positive: if the diameter of the bluing area was greater than 5 mm. The antibody titer was expressed as the highest dilution producing a positive reaction.

Results:

Mice: On Day 1 following the 1st dosing, all mice exhibited decreased activity. No other clinical signs were noted during this phase of the study. No differences in body weights were detected between the vehicle control groups and AGN 192024 treatment groups at any time point.

PCA: The rats that received serum from mice sensitized with vehicle, AGN 192024 or AGN 192024/OVA did not respond to challenges with AGN 192024 or AGN 192024/BSA. When challenged with OVA, positive reactions were noted in the animals that received serum from AGN 192024/OVA sensitized mice. Therefore, all sera from OVA sensitized mice were positive for antibody to OVA but no antibodies were produced as a result of exposure to AGN 192024.

In conclusion, AGN 192024 was not antigenic as assessed by a PCA assay.

LABELING REVIEW:

Original version:

Carcinogenesis, Mutagenesis, Impairment of fertility:
Bimatoprost was not mutagenic or clastogenic in the Ames test, in mouse lymphoma or in mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (approximately 103 times the recommended human exposure).

Pregnancy: Teratogenic effects: ***Pregnancy Category C:***
In embryo/fetal developmental studies in pregnant mice and rats, abortion [redacted] was observed at oral doses of bimatoprost which achieved at least 33 or 97 times, respectively, the intended human exposure [redacted]

[redacted] 41 times the intended human exposure [redacted]

There are no adequate and well-controlled studies of **LUMIGAN™** administration in pregnant women. Because animal reproductive studies are not always predictive of human response, **LUMIGAN™** should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers:
It is not known whether **LUMIGAN™** is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when **LUMIGAN™** is administered to a nursing woman.

Revised version:

Carcinogenesis, Mutagenesis, Impairment of fertility:
Carcinogenicity studies were not performed with bimatoprost.

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test [redacted] in the in vivo mouse micronucleus test.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (approximately 103 times the recommended human exposure based on the blood AUC levels).

Pregnancy: Teratogenic effects: ***Pregnancy Category C:***
In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost that achieved at least 33 or 97 times, respectively, the intended human exposure based on the blood AUC levels.

[redacted] 41 times the intended human exposure (based on the blood AUC levels [redacted]

There are no adequate and well-controlled studies of **LUMIGAN™** administration in pregnant women. Because animal reproductive studies are not always predictive of human response, **LUMIGAN™** should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers:
It is not known whether **LUMIGAN™** is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when **LUMIGAN™** is administered to a nursing woman.

SUMMARY:

Pharmacology:

AGN 192024 is a synthetic analog of prostaglandin $F_{2\alpha}$ where the C1 carboxylic acid group is replaced by an electrochemically neutral substituent, ethylamide. AGN 192024 exerted its effects by stimulating a receptor that was pharmacologically distinct from the FP or any other known prostanoid receptors. AGN 192024 did not produce typical FP receptor mediated effects such as contraction of human uterus and cell proliferation. AGN 192024 and $PGF_{2\alpha}$ 1-ethanolamide, a novel hormone, share the similar pharmacological activity.

AGN 192024 at the concentration $\geq$ 0.001% showed significant and well-maintained IOP reductions in beagle dogs and cynomolgus monkeys. AGN 192024 had no effect on outflow facility in the beagle dog eye, and no effect on aqueous inflow in the monkey eye. The hypotensive activity was probably due to improved aqueous humor drainage via the uveoscleral pathway, which was verified in a cynomolgus monkey study. The large and sustained IOP decrease to AGN 192024 did not involve a COX-dependent mechanism.

At very high doses (1 mg/kg, iv), AGN 192024 affected cardiovascular system in rats ($\uparrow$ mean aterial blood pressure, $\downarrow$ heart rate). In dogs, AGN 192024 (10 µg/kg, iv) produced a transient increase in mean arterial blood pressure. In mice and rats, AGN 192024 at the doses up to 1 mg/kg (iv) produced no CNS effect. AGN 192024 at 2×10^{-7} M and 2×10^{-6} M increased contractile force of uterus specimens in non-pregnant rabbits. Similar effects were not observed in the isolated rat, mouse and human uterus. In rat studies, AGN 192024 at 1 mg/kg (iv) inhibited small intestinal charcoal transit and increased urine volume and urinary excretion of electrolytes (Na^+ and Cl^-).

ADME:

AGN 192024 was rapidly absorbed into monkey and rabbit eyes and distributed in various ocular tissues. The drug concentrations in iris and ciliary body were significant. Systemic exposure was very low after ocular dosing. The metabolism of AGN 192024 in rabbit eyes was extensive but slow in monkeys. In systemic ADME examinations conducted in rats, mice and monkeys, AGN 192024 was rapidly eliminated from blood following iv administration. Variable bioavailability was noted after oral administrations. The blood concentrations of C1-acid metabolite (AGN 191522) were very low. Both liver and lung may play an important role in AGN 192024 metabolism. The metabolism included deamidation, hydroxylation, β-oxidation and glucuronidation. AGN 192024 was cleared from the body rapidly. AGN 192024 was modestly free in mouse, rat, rabbit and monkey plasma proteins (unbound: 28-37%) and slightly unbound to human plasma [redacted]. Both urinary and fecal routes were important in eliminating AGN 192024 and its metabolites, while urinary excretion was the primary pathway in monkeys. In studies conducted in pregnant rats or lactating rats with ^{3}H-AGN 192024, Radioactivity was found in amniotic fluid and fetal tissues, and in the milk of lactating rats.

Toxicology:

Systemic toxicity studies

Summary of acute and subacute toxicity studies

Species/ strain	Sex	N	Dosage	Observations
Mice/Swiss-Webster	♂ and ♀	3/sex/group	96 mg/kg, ip, single dose	No abnormal findings were noted. NOAEL = 96 mg/kg
Rats/Sprague Dawley	♀ and ♀	6/sex/group	0.03, 0.3 and 3.0 mg/kg, iv, single dose	No abnormal findings were noted. NOAEL = 3 mg/kg
Mice/Swiss-Webster	♂ and ♀	11/sex/group	10, 50 and 100 mg/kg/day x 2 wks, po	No abnormal findings were noted. NOAEL = 100 mg/kg/day
Mice/Swiss-Webster	♂ and ♀	3/sex/group	250 and 500 mg/kg/day x 2 wks, po	500 mg/kg, ♂: Transient ↑ in the number of abnormal germ cells in the epididymides (mostly caudal region) NOAEL = 250 mg/kg/day
Rats/Sprague Dawley	♀ and ♀	3/sex/group	10, 50 and 100 mg/kg/day x 2 wks, po	50 and 100 mg/kg/day: 1 ♂ in each group, minimal to mild degeneration in 1 testis with abnormal germ cells in epididymides. NOAEL = 10 mg/kg
Rats/Sprague Dawley	♀ and ♀	3/sex/group	250 and 500 mg/kg/day x 2 wks, po	All treated groups: ↓ body weight gain, ↑ WBC counts and serum BUN levels
Mice/Swiss-Webster	♂ and ♀	10/sex/group	4, 8 and 16 mg/kg/day x 4 wks, po	No abnormal findings were noted. NOAEL = 16 mg/kg/day
Rats/Sprague Dawley	♂ and ♀	8/sex/group	4, 8 and 16 mg/kg/day x 4 wks, po	♂: all treated groups: ↑ vacuolization of the cortical cells in the adrenal glands, 16 mg/kg/day: bilateral degeneration of the testis, ↑ abnormal germ cells in the epididymides NOAEL = 8 mg/kg/day

Summary of subchronic and chronic toxicity studies

Species/ strain	Sex	N	Dosage	Observations
Mice/CD-1	♂ and ♀	10/sex/group	4, 8 and 16 mg/kg/day x 3 months, po	♀: Medullary lymphoid proliferation of the thymus at ≥ 8 mg/kg, acute inflammatory cells in the superficial layers of the vagina at 16 mg/kg. These changes were reversible. NOAEL = 4 mg/kg
Rats/Crl:CD BR	♂ and ♀	15/sex/group	0.1, 0.3 and 1.0 mg/kg/day x 3 months, po	♀: 0.3 and 1.0 mg/kg/day: ↑vacuolated corpora lutea and ovary weights. These changes were reversible. NOAEL = 1.0 mg/kg/day for ♂ and 0.1 mg/kg/day for ♀

Rats/Crl:CD BR	♂ and ♀	15/sex/group	4, 8 and 16 mg/kg/day x 3 months, po	All doses: ↓ body weight gain ♂: all doses: ↑ ALT & AST activities ♀: all doses: ↑number of corpora lutea, ↑number of cellular vacuolated corpora lutea, ↑ ovary weights All these changes were reversible.
Rats/Crl:CD BR	♂ and ♀	20/sex/group	0.1, 0.3 and 2.0 mg/kg/day x 52 weeks, po	♀: 0.3 and 2.0 mg/kg/day: Cellular vacuolation in corpora lutea and ↓body weight gain. These changes were reversible. NOAEL = 2.0 mg/kg/day for ♂ and 0.1 mg/kg/day for ♀
Rats/Sprague Dawley	♂ and ♀	10/sex/group	0.03, 0.3 and 1.0 mg/kg/day x 2 weeks, iv	No local and systemic toxicity was noted. NOAEL = 1.0 mg/kg/day
Rats/Sprague Dawley	♂ and ♀	12/sex/group	0.1, 0.3 and 1.0 mg/kg/day x 1 month, iv	♀: 1 mg/kg/day: ↓regression of corpora lutea (minimal to mild ↑corpora lutea in the ovary) NOAEL = 1.0 mg/kg/day for ♂ and 0.3 mg/kg/day for ♀
Monkeys/ cynomolgus	♂ and ♀	3/sex/group	0.1, 0.3 and 1.0 mg/kg/day x 4 weeks, iv	No local and systemic toxicity was noted. NOAEL = 1.0 mg/kg/day for ♂ and 0.3 mg/kg/day for ♀
Monkeys/ cynomolgus	♂ and ♀	6/sex/group	0.01, 0.1 and 1.0 mg/kg/day x 17 weeks, iv	All treated groups: ↑ prominent sulci, ↑palpebral fissure These changes were considered pharmacological effects of the drug class

Ocular toxicity studies

The ocular toxicity studies with repeated application are summarized in the table below. According to the results, AGN 192024 showed no ocular and systemic toxic effects.

Summary of ocular toxicity studies with repeated application

Species/ strain	Sex	N	Concen-tration	Volume	Dose	Formulation	Observations
Rabbit/Dutch Belted	♀ and ♀	10 per sex	0.03%	35 µl	bid x 1 month, left eye	Clinical formulation	No ocular and systemic toxicities were observed.
Rabbit/New Zealand white	♂ and ♀	10 per sex	0.001%, 0.01% and 0.1%	35 µl	qid x 1 month, left eye	Similar to the clinical formulation	No ocular and systemic toxicities were observed.
Rabbit/Dutch Belted	♀ and ♀	15 per sex	0.03% and 0.1%	35 µl	Qd or bid x6 month, left eye	Clinical formulation	No ocular and systemic toxicities were observed.
Dog/ Beagle	♂ and ♀	3 per sex	0.001%, 0.01% and 0.1%	35 µl	qid x 1 month, left eye	Similar to the clinical formulation	No ocular and systemic toxicities were observed.
Monkey/ cynomolgus	♀ and ♀	6 per sex	0.03% and 0.1%	35 µl	Qd or bid x 1 year, right eye	Clinical formulation	AGN 192024-treated eyes: ↑iridal pigmentation, prominent sulcus, ↑palpebral fissure

Reproductive Toxicology

Species/strain	N/sex/group	Dose level	Regimen	Duration	Findings
Rat/Sprague Dawley	25	0, 0.1, 0.3 and 0.6 mg/kg/day	po, qd	♂: 10 wks prior to and through copulation; ♀: 2 wks prior to mating through gestation Day 7	No effects on fertility in rats. NOAEL = 0.6 mg/kg
Rat/Sprague Dawley	8♀	0, 0.1, 0.3, 1.0 and 3.0 mg/kg	po, qd	Gestation Days 7-17	1 and 3 mg/kg/day: abortions, ↓body wt gain 1 mg/kg/day: prematural delivery, ↓implantations, ↓litter size and live fetuses 3 mg/kg/day: ↓food consumption, total resorption, NOAEL = 0.3 mg/kg for dams and fetuses
Mice/CD-1(ICR)BR	8♀	0, 0.3, 1.0, 4.0 and 16 mg/kg	po, qd	Gestation Days 6-15	≥ 1.0 mg/kg: Abortion, ↓body wt gain 1 mg/kg: ↓ fetus body weights 4 and 16 mg/kg: total resorption NOAEL = 0.3/kg for dams fetuses

Species/strain	N/sex/group	Dose level	Regimen	Duration	Findings
Rat/Sprague Dawley	25♀	0, 0.1, 0.3 and 0.6 mg/kg	po, qd	Gestation Days 7-17	0.6 mg/kg/day: abortions and localized alopecia NOAEL = 0.3 mg/kg for dams and 0.6 mg/kg for fetuses
Mice/CD-1(ICR)BR	25♀	0, 0.1, 0.3 and 0.6 mg/kg	po, qd	Gestation Days 6-15	0.3 mg/kg: Abortion 0.6 mg/kg: Early deliveries and abortions NOAEL = 0.1/kg for dams and 0.6 mg/kg for fetuses
Rat/Sprague Dawley	25♀	0, 0.05, 0.1, 0.3 and 0.6 mg/kg/day	po, qd	Gestation Day 7-lactation Day 20	F_0: 0.6 mg/kg: ↓the number of dams delivering litters. 0.3 and 0.6 mg/kg: ↓gestation length, ↑peri- and postnatal mortality, ↓the number of liveborn/litter and ↑the number of stillborn/litter F_1: 0.3 and 0.6 mg/kg: ↓ pup survival during Days 1-4 of lactation, ↓pup body weights during preweaning period 0.3 mg/kg: slight ↑ the number of days in cohabitation and slight ↓ in fertility index F_2: not affected NOAEL = 0.1 mg/kg/day

Genotoxicity Studies: AGN 192024 was negative in Ames test, in vitro mouse lymphoma TK assay and in vivo mouse micronucleus assay.

EVALUATION:

AGN 192024 is a synthetic analog of prostaglandin $F_{2\alpha}$. The drug is different from prostaglandins in that it does not stimulate any previously described prostanoid receptors. Preclinical studies have indicated that AGN 192024 is a potent ocular hypotensive agent. The drug is under development by Allergan as an ophthalmic formulation for the treatment of glaucoma.

In several systemic toxicity studies conducted in rats, ovarian changes evidenced by an increase in the numbers of vacuolated corpora lutea and an increase in ovary weight were noted in females receiving ≥ 0.3 mg/kg/day of AGN 192024, which were reversible after a recovery period. The mechanism of these changes was not known, but it was possibly related to pharmacological effects of luteolysis by PGF2α in rats. Similar changes were not found in the studies conducted in other species (mice and monkeys), so the changes could be species-specific as the sponsor indicated. These findings are not likely relevant to humans since humans have a longer (14-16 days) luteal phase compared to rats (1-2 days) and corpora lutea in humans are less responsive to the luteolytic effects of PGF2α. In addition, ovarian changes were not noted at the dose of 0.1 mg/kg (0.6 mg/m^2), which is 60-fold the recommended human dose (0.01 mg/m^2). Therefore, these findings should not be a safety concern for AGN 192024.

In two systemic and ocular toxicity studies conducted in monkeys, a drug-related increase in the prominence of the periocular sulci which resulted in a widening of the palpebral fissure of eyes was noted. Increased iridal pigmentation was noted in AGN 192024-treated eyes in monkeys. These findings were also observed in monkeys treated with other PG analogues (including latanoprost) and were considered to be related to this pharmacological class. No functional or anatomic ocular abnormalities were noted macroscopically and histopathologically.

Another concern is the impurities. Three impurities were found in drug products:

pharmacological activities in different prostanoid receptors, and the levels of these compounds are within the qualification threshold recommended by ICH Q3 documents. In addition, the chronic ocular toxicity studies conducted in rabbits and monkeys using the clinical drug formulation revealed no ocular and systemic toxicity. Two residual solvents were noted in drug substance specification: ethyl acetate (0.2%) and heptanes (0.2%). Both compounds are listed as Class 3 solvents in ICH Q3C. These compounds at the levels less than 0.5% would be acceptable without justification. Several container/closure extractables known as surfactants used in the label adhesive formulations were observed. The sponsor indicated that the same label adhesive has been used in other approved ophthalmic drug products. In conclusion, the impurities and extractables are expected to have no impact on the safety of this drug product.

RECOMMENDATION:

This application is approvable from a nonclinical perspective with some minor modifications of labeling as revised in the Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy section.

APPEARS THIS WAY ON ORIGINAL

Zhou Chen, Ph.D.

Concurred by: Robert Osterberg, Ph.D.

cc:
NDA 21-275/Division File
NDA 21-275/Original NDA
HFD-550/CSO/Puglisi
HFD-550/MO/Boyd
HFD-550/TL Pharm/Osterberg
HFD-550/Pharm/ChenZ