DEC 0 9 2008

This report is required by law (7 USC 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 21

See attached form for additional information.

Interagency Report Control No.:

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

1. CERTIFICATE NUMBER: 14-R-0144
CUSTOMER NUMBER: 1799

FORM APPROVED
OMB NO. 0579-0036

ANNUAL REPORT OF RESEARCH FACILITY
(TYPE OR PRINT)

Charles River Laboratories, Inc.
251 Ballardvale St
Wilmington, MA 01887

Telephone: (508) -658-6000

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, or experimentation, or held for these purposes. Attach additional sheets if necessary)

FACILITY LOCATIONS (Sites) - See Atached Listing

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY **(Attach additional sheets if necessary or use APHIS Form 7023A)**

A. Animals Covered By The Animal Welfare Regulations	B. Number of animal being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not ye used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use o pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals an for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for wh the use of appropriate anesthetic, analgesic, or tranquiliz drugs would have adversely affected the procedures, res or interpretation of the teaching, research, experiments, surgery, or tests. (An explanation of the procedures producing pain or distress in these animals and the reas such drugs were not used must be attached to this report	F. TOTAL NUMBER OF ANIMALS (COLUMNS C + D + E)
4. Dogs	87	1993	1191	63	3247
5. Cats					
6. Guinea Pigs	7	1862	4350	50	6262
7. Hamsters		1198	558		1756
8. Rabbits	1144	4813	1117	429	6359
9. Non-human Primates	3820	4904	998	5	5907
10. Sheep					
11. Pigs	27	649	106	15	770
12. Other Farm Animals					
13. Other Animals					
Gerbils		18			18

ASSURANCE STATEMENTS

1) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anestetic, analgesic, and tranquilizing drugs, prior to, during, and following actual rese teaching, testing, surgery, or experimentation were followed by this research facility.

2) Each principal investigator has considered alternatives to painful procedures.

3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and ap Institutional Animal Care and Use Committee (IACUC). **A summary of all such exceptions is attached to this annual report.** In addition to identifying the IACUC-approved exceptions, this summary inc brief explanation of the exceptions, as well as the species and number of animals affected.

4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
(Chief Executive Officer or Legally Responsible Institutional Official)

(B)(6) (B)(7)(c)

DATE SIGNED
11/20/2008

(AUG 91)

NP

REVIEW OF CATETORY "E" STUDIES

The following studies have been listed in Category "E" based upon the guidelines stated in the preface at the beginning of this report. The study designs that resulted in certain animals being placed retrospectively into Category "E" were required by federal regulations and guidelines listed in the applicable regulations/guidelines section below. For the purpose of this report studies have been given a unique number that corresponds to the actual study number. For reasons of confidentiality, actual study numbers are not presented but are available to the USDA for on-site inspection or report follow-up. Category "E" explanations/details are listed separately for each study.

CHARLES RIVER LABS PRECLINICAL SERVICES– (Pennsylvania - Site #014)

Study: #1

Animals: 5 Rabbits

Type of Study: Intravenous Dosage-Range Development toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Five rabbits** from this dosage range finding developmental toxicity study conducted in September through October 2007 have been placed in category E due to pain/distress that may have been associated with the effects of the test article and/or study procedures. The rabbits were dosed intravenously via the ear vein once daily from gestation day 7 through 19. The dosage levels were 0, 25, 50, 75 and 100 mg/kg/day. The test article had not been given to rabbits before and had resulted in death in rats at 100 mg/kg/day. The study was approved with the knowledge that possible adverse signs including death could occur. A second water source and a supplemental food item were approved for use in animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, at one hour after dosage, at two hours after dosage and at the end of the day. Moribund condition, abortion and severe injury were the approved endpoints for animals experiencing pain/distress due to test article effects. Veterinary exams were performed on all animals at least weekly and a total of 26 exams were conducted.

#3168 (IV), #3171 (V), #3174 (V) and #3175 (V) experienced mild to moderate body weight loss (7-14% over 6-8 days) and moderate reduction in feed consumption during the dosage period. Adverse signs included reduced fecal output. #3171 was euthanized as scheduled at the end of the study and was normal at necropsy examination though all fetuses were resorbed. #3175 was found dead at the morning check on GD17. Stomach erosions were present at necropsy exam and all fetuses were dead. #3168 and #3174 were euthanized due to abortion on GD19 and GD23, respectively. At necropsy exam, all fetuses were resorbed and #3168 had a firm liver.

#3173 (V) was examined for moderate swelling at the base of one ear and in the area of the dewlap after dosage on GD19 through scheduled euthanasia on GD29. Cold compresses were applied to the ear base. The swelling was reduced to slight by the time of scheduled euthanasia. It is likely that some of the test article had accumulated extravascularly in these areas. No discomfort was noted with handling at anytime (12 exams were completed for this animal.) However the ear was held in a downward position and/or was unable to be held in an upright position which could be interpreted as a possible indication of pain/distress. There was no adverse effect to body weight gain or feed intake. At necropsy exam, there were 9 fetuses alive and two resorptions while the rabbit appeared normal.

Study: #2
Animals: 12 Rabbits
Type of Study: Intravenous Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Twelve rabbits** from this developmental toxicity study conducted in December 2007 through January 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article and/or study procedures. The rabbits were dosed intravenously via the ear vein once daily from gestation day 7 through 19. The dosage levels were 0 (saline), 25, 50 and 75 mg/kg/day. The test article is being developed for treatment of hemorrhagic shock and increases oxygen delivery to tissues. The study was approved with the knowledge that possible adverse signs including discoloration of the whole body (yellow), swelling at injection sites, reduced feed consumption and body weight loss could occur. A second water source and supplemental food items (timothy cubes and Rabbit Stix) were approved for use in animals with body weight loss or reduced feed consumption. Cold compresses were applied twice daily to swelling at the injection sites. Animals were observed at morning viabilities, at daily dosage, at one hour after dosage and at the end of the day. Moribund condition, abortion and severe injury were the approved endpoints for animals experiencing pain/distress due to test article effects. Veterinary exams were performed on all animals at least weekly. In addition, 49 individual animal exams were also performed.

#4582 (0 MKD), #4542 (50 MKD), #4562-4563 (75 MKD), #4565 (75 MKD), #4600 (75 MKD), #4574 (75 MKD), #4576-4577 (75 MKD), #4579 (75 MKD), #4590 (75 MKD) and #4592 (75 MKD) experienced mild to severe body weight loss (0-23% over 4-19 days) and moderate to severe reduction in feed consumption (60-100% over 4-19 days) beginning during the dosage period. Adverse clinical signs included discoloration of the whole body (yellow) and swelling at the injection site (#4574, #4577, #4579, #4590 and #4592.) #4582, #4542, #4562, #4563, #4600, #4574, #4576, #4577, #4579 and #4592 were euthanized as scheduled at the end of the study. #4565 was euthanized due to abortion on gestation day 21. All internal organs were discolored (yellow) and all fetuses were resorbed. #4590 was euthanized on gestation day 16 at the time of the 7th veterinary examination. Euthanasia was recommended because no viable fetuses were detected by palpation, 20% weight loss occurred and discomfort at the sites of injection had not resolved with cold compresses. All internal organs were discolored (yellow) and all fetuses were resorbed.

Study: #3
Animals: 10 Rabbits
Type of Study: An Oral (Stomach Tube) dosage-Range Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Ten rabbits** from this dose range-finding developmental toxicity study conducted in October 2007-November 2007 have been placed in category E due to body weight loss and reduced feed intake that may have been an indication of pain/distress from and test article toxicity. The rabbits were dosed by stomach tube once daily from gestation day 7 through 19. Potential adverse effects were not known. A supplemental food item (timothy cubes) were approved to be provided to rabbits with weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, hourly for four hours after dosage (first three days of dosage), one-two hours after dosage (days 4 through 13 of dosage) and at the end of the day. Moribund condition was the approved endpoint for animals experiencing pain/distress due to test article effects. Forty one veterinary exams were performed.
#3359-3360 (150 MKD), #3372 (150 MKD), #3361-3365 (500 MKD) and #3375-3376 (500 MKD) had moderate to

severely reduced feed intake and body weight loss (7-23%) for 4-10 days during the dosage period. Reduced fecal output was the only adverse clinical signs in the 150 MKD dosage level rabbits and these animals were euthanized as scheduled at the end of the study. Two rabbits at the 500 MKD dosage level were found dead after the period of reduced feed intake (4-7 days) and body weight loss (15%) and had no other adverse clinical signs Adverse clinical signs in the other five 500 MKD rabbits included reduced fecal output, lacrimation, pale extremities, ptosis and cold to touch. These rabbits were euthanized when their clinical condition declined following the period of reduced feed intake and weight loss (three rabbits) or were euthanized when the dosage level was terminated following the period of reduced feed intake and weight loss (two rabbits.)

Study: #4
Animals: 8 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits, Including a Toxicokinetic Evaluation
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Eight rabbits** from the high dosage group of this dosage range-finding developmental toxicity study conducted in October 2007 have been placed in category E due to adverse effects from the test article that may be considered as indication of pain/distress. The rabbits were dosed by stomach tube once daily from gestation day 7 through 19. Reduced feed intake and body weight loss were expected adverse effects. Two water sources and a supplemental food item (timothy cubes) were approved to be provided to rabbits with weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, at one hour after each dosage and at the end of the day. Moribund condition was the approved endpoint for animals experiencing pain/distress due to test article effects. Thirteen veterinary exams were performed and all rabbits on study were examined at least weekly.

These animals were assigned to the high dosage group (80 mg/kg/day.) They experienced mild to moderate body weight loss (4-8%) and moderate to severe reduction in feed consumption (50-100% lower as compared to Control animals) during the dosage period. Adverse clinical signs included reduced fecal output. These rabbits were euthanized as scheduled at the end of the study.

Study: #5
Animals: 2 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits, Including a Toxicokinetic Evaluation
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Two rabbits** from this developmental toxicity study conducted in January 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article. The test article acts on the central nervous system and is being developed as a treatment for pain. The rabbits were dosed by stomach tube once daily from gestation day 7 through 19. All rabbits experiencing reduced feed intake and weight loss were provided with two water sources and a supplemental food item (timothy cubes.) Animals were observed at morning viabilities, at daily dosage, 1-3 hours after daily dosage and at the end of the day. Moribund condition was the approved endpoint for animals experiencing pain/distress due to test article effects. All animals were examined by the veterinary staff at arrival and at least once weekly until the end of the study. In addition, 31 individual animal exams were performed.

#4628 (4 mg/kg/day) and #4631 (4 mg/kg/day) experienced body weight loss (13% and 5% respectively) and severe

reduction (70-100%) in feed consumption for 4-5 days during the dosage period. The only adverse sign for #4631 was reduced fecal output. #4628 was noted as having blue mucous membranes on gestation days 17-21. Both animals were euthanized as scheduled at the end of the study and appeared normal at necropsy exam.

Study: #6
Animals: 51 Rabbits
Type of Study: Developmental Toxicity Study of Subcutaneously Administered xxx in Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Fifty one rabbits** from this developmental toxicity study conducted in November 2007 have been placed in category E based on effects on feed intake and adverse skin signs indicating that the test article may have resulted in more than momentary pain or distress. The rabbits were dosed subcutaneously (0.25 ml/kg) on gestation days 7, 9, 11, 13, 15, 17 and 19. A separate site was used for each injection. The test article is an endogenous bile acid being investigated for use as a subcutaneous cosmetic treatment. A previous study in rabbits injected subcutaneously with the test article at the same dosage and concentration levels resulted in acute decreases in feed consumption and adverse skin effects that indicated that the test article may have caused more than momentary pain or distress. All animals were provided with timothy cubes daily. Approved supportive care for adverse signs at injection sites included cold pack compression and K-Y jelly. Any rabbit with signs of reaction to manipulation of the injection site/adverse skin signs or with multiple ulcerations greater than 4 cm in diameter was approved to be euthanized. Animals were observed by the study staff at morning viabilities, daily at clinical observations, at dosage (every other day), 1 to 2 hours after dosage and at the end of every day. Animals in the saline control group were examined at least weekly by the veterinary staff. All animals in the treated groups were examined by the veterinary staff a minimum of once daily. More than 1,000 veterinary exams were completed for animals during this study.

#4321 (10 MKD), 4323 (10 MKD), #4325-4330 (10 MKD), #4333-4336 (10 MKD), #4338-4340 (10 MKD), #4341-4346 (20 MKD), #4348-4350 (20 MKD), #4352-4354 (20 MKD), #4356-4360 (20 MKD), #4361-4363 (30 MKD) and #4366-4380 (30 MKD) were euthanized as scheduled at the end of the study. These rabbits had adverse signs at one or more dosage sites. These included scab(s) and ulceration(s) that did not meet the approved endpoint criteria for euthanasia. Sizes ranged from less than 0.5 cm diameter to 3.0 x 0.5 cm diameter. The duration from time of onset until scheduled euthanasia was two to fourteen days. The feed intake was reduced by at least 20% for three or more days during the dosage period. In some animals, discomfort was noted at one or more affected sites for at least one day but no more than 2 days.

#4322 (10 MKD) experienced reduced feed intake (a 50-80% reduction) beginning on gestation day 11 resulting in a 10.4 % body weight reduction. Injection site B was ulcerated (2.5 cm diameter) beginning on gestation day 9 and this site was scabbed beginning on gestation day 13. No discomfort was associated with handling of this site on gestation day 9 or 10 but discomfort was noted beginning on gestation day 11. The rabbit was also observed licking and chewing at the area on gestation day 11. The twice daily cold compresses and applications of KY jelly did not appear to reduce the level of discomfort and the rabbit was euthanized on gestation day 15.

Study: #7
Animals: 8 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits, Including a Toxicokinetic Evaluation
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Eight rabbits** from the main portion of this developmental toxicity conducted in September 2007 through October 2007 have been placed in category E due to pain/distress that may have been associated with the effects of the test article/and or study procedures. The test article target acts on the central nervous system and is being developed for the treatment of Alzheimer's disease. The rabbits were dosed by stomach tube once daily from gestation day 7 through 19. The study was approved with the knowledge that possible adverse signs including reduced feed intake, body weight loss, reduced fecal output, hyperpnea, convulsions, tremors, splayed limbs and decreased activity. A second water source, supplemental food items (timothy cubes, Rabbit Stix®) and grooming were approved for use in animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, 1-2 hours after dosage and at the end of the day. Moribund condition and/or injury were the approved endpoints for animals experiencing pain/distress due to test article effects. Veterinary exams were performed on all animals three times during acclimation and at least weekly thereafter. Eight exams were completed for all rabbits on this study.

#3211 (vehicle), #3219 (vehicle), #3229 (3 MKD), #3258 (10 MKD), #3261 (30 MKD), #3262 (30 MKD), #3265 (30 MKD) and #3273 (30 MKD) experienced moderate to severe reduction in feed consumption for 3 to 7 days during the dosage period and body weight loss of 3-8%. Adverse signs included reduced fecal output and ungroomed coat. These rabbits were euthanized as scheduled at the end of the study and appeared normal at necropsy examination.

Study: #8
Animals: 3 Rabbits
Type of Study: Intravenous Dosage-range Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Three rabbits** from Part A of this dosage range-finding developmental toxicity study conducted December 2007 have been placed in category E due to pain/distress that may have been associated with the effects of the test article. The test article acts on the PNP enzyme and is being investigated as a treatment for T-lymphocyte disorders. The rabbits were dosed intravenously via the maginal ear vein on study days 1-5 and euthanized on study day 6. The study was approved with the knowledge that adverse signs and even death could occur. All rabbits experiencing reduced feed intake and weight loss were provided with two water sources and a supplemental food item (timothy cubes.) Animals were observed at morning viabilities, at daily dosage, immediately after dosage, at 1, 2 3 and 4 hours after each dosage and at the end of the day. Moribund condition was the approved endpoint for animals experiencing pain/distress due to test article effects. All rabbits were examined five or more times by the veterinary staff.

#1597-#1599 (120 MKD) experienced acute body weight loss (4-8%) as a result of a 50-100% reduction in feed consumption during each day of the 5 day dosage period. The rabbits did not eat the supplemental food items. Adverse signs included transient, mild facial swelling (1-2 hours on 1 or 2 days) and reduced fecal output. These rabbits were euthanized as scheduled at the end of the study and were normal at necropsy

Study: #9
Animals: 17 Rabbits
Type of Study: An Embryo-Fetal Development and Toxicokinetic Study of XXX Administered Orally (Gavage) in New Zealand White Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Seventeen rabbits** from of this developmental toxicity study conducted in October 2007 have been placed in category E due to adverse effects from the test article and/or procedures that may be considered as indicators of pain/distress. The rabbits were dosed by stomach tube once daily from gestation day 7 through 19. Reduced feed intake and body weight loss were expected adverse effects. Two water sources and a supplemental food item (timothy cubes) were approved to be provided to rabbits with weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, at one hour after each dosage and at the end of the each day. Moribund condition was the approved endpoint for animals experiencing pain/distress due to test article effects. Twenty veterinary exams were performed and all rabbits on study were examined at least weekly.

#2488-2491, #3476, #3478, #3441, #3442, #3445, #3447, #3452-3456 and #3458 were assigned to the high dosage group (80 mg/kg/day.) They experienced mild to moderate body weight loss (3-11%) and moderate to severe reduction in feed consumption (50-100% lower compared to vehicle control animals) during the dosage period. Adverse clinical signs included reduced fecal output. **#2458** was assigned to the vehicle group (0 mg/kg/day). This rabbit lost 7.5% body weight and experienced a fair to moderate reduction in feed consumption (50-75% lower compared to other animals in the vehicle group) during the last four days of the dosage period. These rabbits were euthanized as scheduled at the end of the study.

Study: #10
Animals: 21 Rabbits
Type of Study: An Embryo-Fetal Development and Toxicokinetic Study of XXX Administered Orally (Gavage) in New Zealand White Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Twenty one rabbits** from this developmental toxicity study conducted in January 2008 have been placed in category E due to pain/distress that was associated with the effects of the test article and/or study procedures. The rabbits were dosed by stomach tube once daily from gestation day 7 through 19. The dosage levels were 0, 20, 50 and 150 mg/kg/day. The test article is an anti-coagulant. The study was approved with the knowledge that possible adverse signs were reduced feed consumption, body weight loss and blood loss. All animals had two water sources. Supplemental food items (timothy cubes and Rabbit Stix) were approved for use in animals with body weight loss or reduced feed consumption. Styptic powder was approved for use on animals with bleeding that could not be stopped by direct pressure. Animals were observed at morning viabilities, at daily dosage, at one hour after dosage, at 4 hours after daily dosage and at the end of the day. Moribund condition and prolonged, uncontrolled bleeding, abortion and severe injury were the approved endpoints for animals experiencing pain/distress due to test article effects. Veterinary exams were performed on all animals at least weekly. In addition, 44 individual animal exams were also performed.

#4754 (50 MKD) was found dead 42 minutes after dosage administration on gestation day 10. A perforated trachea was noted at necropsy examination. The rabbit was normal prior to this event. Lab management maintains a tracking system for monitoring accidental events in order to help identify the need for re-training of any laboratory staff member. While this animal appeared normal at the time of dosage, the timing and frequency of the post dosage observations was appropriate and there was no intent to withhold relief in the form of euthanasia, the nature of the injury suggests that there may have been

more than momentary pain or distress prior to death.

#4761 (150 MKD), #4763-4766 (150 MKD), #4768-4777 (150 MKD), #4779 (150 MKD) and #4793-4796 (150 MKD) experienced mild to severe body weight loss (5-18% over 4-14 days) and moderate to severe reduction in feed consumption (50-100% over 4-14 days) during the dosage period. #4761, #4763-4764, #4766, #4769-4770, #4772, #4774, #4776-4777, #4779, and #4793-4796 were euthanized as scheduled at the end of the study. The only adverse sign in these rabbits was reduced fecal output. #4765 was euthanized on gestation day 25 at the time of abortion. The only adverse sign in this rabbit was reduced fecal output. #4768, #4771, #4773 and #4775 were found dead at viability checks on gestation days 25, 21, 26 and 25, respectively. Scant feces and ungroomed fur were the only adverse signs present. At necropsy examination, all fetuses were dead or resorbed. #4771 had a pale heart, liver and kidneys and blood was present inside the uterus. #4773 had a pale heart and liver. #4775 had numerous erosions in the stomach.

Study: #11
Animals: 7 Rabbits
Type of Study: Dosage-Range Developmental Toxicity Study of XXX following Oral (Stomach tube) Administration in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Seven rabbits** from the extension of part A of this dosage range-finding developmental toxicity study conducted in January 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article. The purpose of this part of the study was to determine if the test article, a treatment for patients with urea cycle disorders, could be given to rabbits without extensive toxicity. The rabbits were dosed by stomach tube once daily for five days. All rabbits experiencing reduced feed intake and weight loss were provided with two water sources and a supplemental food item (timothy cubes.) Animals were observed at morning viabilities, at daily dosage, hourly for six hours after each dosage and at the end of the day. Moribund condition was the approved endpoint for animals experiencing pain/distress due to test article effects. During the six days of this study, all animals were examined 3 times and 12 additional individual animal exams were performed.

#4193 (0.5 g/kg/day), #4195-4196 (0.5 g/kg/day), and #4197-4200 (0.7 g/kg/day) experienced daily body weight loss during each day of study (5-19% cumulative loss) and moderate to severe reduction (70-100%) in daily feed consumption during each day of the study. #4200 was euthanized per veterinary recommendation at re-examination on the morning of study day 3 because the rabbit's condition had not improved. Adverse signs began on the late afternoon of study day 2 and included decreased body temperature, decreased activity level (remained bright and alert) and increased respiratory rate. The heart was pale at necropsy exam. #4193, #4195-4196 and #4197-4199 were euthanized as scheduled at the end of the study. The only adverse signs were reduced fecal output. These rabbits appeared normal at necropsy exam.

Study: #12
Animals: 8 Rabbits
Type of Study: Subcutaneous Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Eight rabbits** from the high dosage group of this developmental toxicity conducted in October 2007 have been placed in category E due to effects of the test article that may have been associated with pain/distress. The test article target is being developed for the treatment of type 2 diabetes. The rabbits were dosed subcutaneously once every other day from gestation day 7 through 19. There were four dosage sites on each animal. The injections were rotated so that no site was

used more than twice. The study was approved with the knowledge that possible adverse signs including reduced feed intake, body weight loss and reduced water intake could occur. A supplemental food item (timothy cubes, Rabbit Stix®) and grooming were approved for use in animals with body weight loss and reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, 1-2 hours after dosage and at the end of the day. Moribund condition and/or injury were the approved endpoints for animals experiencing pain/distress due to test article effects. Veterinary exams were performed on all animals at arrival and six times (at least weekly) thereafter. In additional ten exams were completed on individual animals during the study.

#3661-3665 and #3687-3689 were in the high dosage group (0.4 mg/kg) and experienced moderate to severe reduction in feed consumption and water intake for 3 to 7 days during the dosage period and body weight loss of 4-11%. Adverse clinical signs included reduced fecal output and ungroomed coat. These rabbits were euthanized as scheduled at the end of the study and appeared normal at necropsy examination.

Study: #13
Animals: 9 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Nine rabbits** from this dosage range-finding study conducted in November 2007 have been placed in category E due to body weight loss, reduced feed intake and adverse clinical signs that may have been an indication of pain/distress resulting from the test article. Rabbits were dosed by stomach tube once daily from gestation day 7 through 19. The test article is being developed as a treatment for epilepsy. Any rabbit experiencing weight loss and reduced feed intake was provided with a supplemental food item (timothy cubes.) Animals were observed at morning viabilities, at daily dosage, 1-2 hours after each dosage and at the end of the day. Moribund condition and respiratory distress were the approved endpoint for animals experiencing pain/distress due to test article effects. During this study, 21 veterinary exams were performed and all rabbits were examined eight or more times.

During the dosage period, **#3991-#3993 (100 MKD), #3395 (100 MKD), #3996-#4000 (300 MKD)** experienced severely reduced feed intake (range of duration of 10-12 days) with 8-22% body weight loss. Adverse clinical signs present for one or more days included reduced fecal output and decreased activity level. #3992 and #4000 were euthanized on the date of abortion. After the dosage period ended, #3391, #3393 and #3395 experienced improved feed intake with weight gain and were euthanized as scheduled at the end of the study #3396, #3397 and #3999 were euthanized on GD19, GD21 and GD21, respectively, at the time when their clinical condition declined. #3998 was euthanized on GD21 because it was the last rabbit remaining in the high dosage group.

Study: #14
Animals: 8 Rabbits
Type of Study: Intravenous Dosage-range Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Eight rabbits** from Part A of this dose range-finding developmental toxicity study have been placed in category E due to necrosis and pain at the injection site of the test article that was present at least one day prior to euthanasia. Part A of this study was to determine the feasibility of intravenous infusion into the ear vein without vascular access ports or indwelling catheters. The test article was an enzymatic debriding agent for treatment of full thickness skin burns. Injection of the test article was preceded by a saline flush and preceded by a saline flush to help minimize irritancy. Euthanasia due to adverse clinical signs was approved to be addressed on a case-by-case basis. Moribund condition was approved as an

endpoint for animals experiencing pain/distress due to test article effects. A supplemental food item (timothy cubes) were provided and cold compresses were applied to the affected ears. Animals were observed at morning viabilities, at daily dosage, hourly after daily dosage and at the end of the day. Twelve exams were performed during this study which was terminated on day 3 due to severe localized tissue reactions.

#3398-3400 (5 MKD) and #3393 (1 MKD) experienced swelling, bleeding, and localized ulceration of the injection site beginning a few hours after the first dosage administration on study day 1. Other adverse signs included vocalization when examined, aggressive behavior when approached, head tilt and positioning the ear downward. There was no improvement the next morning and these rabbits were euthanized at that time. An IACUC meeting was held acknowledging the termination of the 5 MKD dosage level animals.

On study day 2, the volume of the pre-dosage saline and the post-dosage saline flush was increased for the remaining animals to help minimize irritancy. **#3392 (1 MKD), #3394 (1 MKD), #3395 (3 MKD) and #3397 (3 MKD)** experienced discoloration, bleeding, scabbing and discoloration at the injection site beginning a few hours after the second dosage administration. Other adverse signs included vocalization when examined (#3392 only), severely decreased feed intake (#3392 only) and positioning the ear(s) downward. There was no improvement the next morning and these rabbits were euthanized at that time (study day 3.)

Study: #15
Animals: 2 Rabbits
Type of Study: Oral (Gavage) Dosage Range-Finding Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Two rabbits** from this dosage range-finding developmental toxicity conducted in October-November 2007 have been placed in category E due to effects of the test article that may have been associated with pain/distress. The test article is being developed for the treatment of HIV. The rabbits were dosed once daily by stomach tube from gestation day 7 through 19 at 0, 3, 10, 30 and 60 mg/kg/day. The study was approved with the knowledge that possible adverse signs including mortality could occur. A supplemental food item (timothy cubes) was approved for use in animals with body weight loss and reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, hourly for four hours after dosage (dosage began at approx. 1000 each day) and at the end of the day. Moribund condition and/or injury were the approved endpoints for animals experiencing pain/distress due to test article effects. Veterinary exams were performed on all animals at arrival and at weekly intervals until the end of the study. An additional 7 exams were completed on individual animals during the study.

#3187 (10 MKD) experienced a severe reduction in feed consumption for 4 days during the dosage period and body weight loss of 5%. The only adverse clinical sign was reduced fecal output. This rabbit was euthanized as scheduled at the end of the study and appeared normal at necropsy examination.

#3191 (30 MKD) experienced excess salivation of a slight degree for a transient period (duration of 1 to 2 hours) following dosage administration on gestation days 9 and 10. Feed intake remained good and weight loss was 2%. Following dosage administration on gestation day 11, excess salivation, tachypnea and body tremors occurred. An exam was performed 15 minutes following the onset of the signs and euthanasia was recommended at that time. The study director wanted to see if the signs would resolve over the next two hours. Animal was observed hourly. The signs did not resolve and the rabbit was euthanized 2-1/2 hours after the onset of the adverse signs. All tissues appeared normal at necropsy examination.

Study: #16
Animals: 5 Rabbits
Type of Study: Oral (Gavage) Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as

CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.

- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Five rabbits** from this developmental toxicity conducted in December 2007 have been placed in category E due to effects of the vehicle and/or test article that may have been associated with pain/distress. The test article is being developed for the treatment of HIV. The vehicle was carboxymethylcellulose. The rabbits were dosed once daily by stomach tube from gestation day 7 through 19. The study was approved with the knowledge that possible adverse signs including reduced feed intake and body weight loss could occur. A supplemental food item (timothy cubes) and grooming were approved for use in animals with body weight loss and reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, 1 hour after dosage and at the end of the day. Moribund condition and/or injury were the approved endpoints for animals experiencing pain/distress due to test article effects. Veterinary exams were performed on all animals at arrival and at weekly intervals until the end of the study. An additional 26 exams were completed on individual animals during the study.

#4201 (vehicle), #4228 (3 MKD), #4237 (3 MKD), #4247 (10 MKD) and #4279 (20 MKD) experienced a moderate to severe reduction in feed consumption for 5 to 12 days during the dosage period and body weight loss of 5-10%. Adverse clinical signs included reduced fecal output and ungroomed coat. These rabbits were euthanized as scheduled at the end of the study and appeared normal at necropsy examination.

Study: #17
Animals: 1 Rabbit
Type of Study: Subcutaneous Developmental Toxicity Study of XXX in Rabbits Including a Satellite Toxicokinetic Evaluation
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **One rabbit** from this developmental toxicity study conducted in November 2007-December 2007 has been placed in category E due to body weight loss and reduced feed intake that may have been an indication of pain/distress and that may have been caused by effects of the test article. All rabbits were dosed by subcutaneous injection once daily from gestation day 7 through 19. Four separate injection sites on the dorsal back were used and the site of injection was rotated daily. Any rabbit experiencing weight loss and reduced feed intake was provided with a supplemental food item (timothy cubes.) Animals were observed at morning viabilities, at daily dosage and 1-2 hours after each dosage and at the end of the day. Moribund condition was the approved endpoint for animals experiencing pain/distress due to test article effects. During this study, ten veterinary exams were performed.

#4485 (20 MKD) had severely reduced feed intake from gestation day 10 through 15 with 8.5% body weight loss during this same period. Adverse clinical signs included reduced fecal output, one day of mild dehydration and one day of mild bruising at one injection site. Examination of the injection site bruising caused no apparent pain or discomfort to the rabbit. Grooming was performed to minimize loose hair ingested by the rabbit during self-grooming and timothy cubes and Rabbit Stix were provided as supplemental food items. Feed intake improved to a good level on gestation day 16 through scheduled euthanasia on gestation day 20 and body weight increased daily during this time.

Study: #18
Animals: 11 Rabbits
Type of Study: Oral (Stomach tube) Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.

- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Eleven rabbits** from this developmental toxicity study conducted in January 2008 through February 2008 have been placed in category E due to pain/distress that was associated with the effects of the test article and/or study procedures. The rabbits were dosed by stomach tube once daily from gestation day 7 through 19. The test article acts on the central nervous system and is being developed as a treatment for epilepsy. The study was approved with the knowledge that possible adverse signs were reduced feed consumption, body weight loss decreased activity and tremors. Timothy cubes were approved for use in animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, at 4 hours after daily dosage and at the end of the day. Severe body weight loss, severe injury and moribund condition were the approved endpoints for animals experiencing pain/distress due to test article effects. Veterinary exams were performed on all animals at least weekly. In addition, 30 individual animal exams were also performed.

#4095 (vehicle Control) was found dead 7 minutes after dosage administration on gestation day 10. A perforated lung lobe was noted at necropsy examination. The rabbit was normal prior to this event. Lab management maintains a tracking system for monitoring accidental events in order to help identify the need for re-training of any laboratory staff member. While this animal appeared normal at the time of dosage and there was no intent to withhold relief in the form of euthanasia, the nature of the injury suggests that there may have been more than momentary pain or distress prior to death.

#4914 (vehicle Control), #4956 (30 MKD), #4970 (90 MKD), #4971 (90 MKD), #4973 (90 MKD), #4974 (90 MKD), #4976 (90 MKD), #4980 (90 MKD), #4994 (90 MKD) and #4998 (90 MKD) experienced mild to moderate body weight loss (4-16% over 4-13 days) and moderate to severe reduction in feed consumption (60-95% over 4-13 days) during the dosage period. #4914, #4956, #4970, #4974, #4976, #4980, #4994 and #4998 were euthanized as scheduled at the end of the study. The only adverse sign in these rabbits was reduced fecal output. #4971 and #4973 were euthanized on gestation day 20 and 23, respectively, at the time of abortion. The only adverse sign in these rabbits prior to abortion was reduced fecal output and both appeared normal at necropsy examine.

Study: #19
Animals: 5 Rabbits
Type of Study: Oral (Stomach tube) Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Five rabbits** from this developmental toxicity study conducted in January 2008 through February 2008 have been placed in category E due to pain/distress that was associated with the effects of the test article and/or study procedures. The rabbits were dosed by stomach tube once daily from gestation day 7 through 19. The test article is being developed as a treatment for obesity, diabetes and neurodegenerative disease. The study was approved with the knowledge that possible adverse effects on body weight and feed intake could occur. Timothy cubes and an additional water source were approved for use in animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, 1-2 hours after daily dosage and at the end of the day. Moribund condition was the approved endpoints for animals experiencing pain/distress due to test article effects. Veterinary exams were performed on all animals at least weekly. In addition, 15 individual animal exams were also performed.

#5228 (100 MKD), #5239 (100 MKD), #5256 (300 MKD), #5266 (300 MKD) and #5274 (300 MKD) experienced mild body weight loss (3-10% over 4-7 days) and moderate to severe reduction in feed consumption (60-95% over 4-7 days) during the dosage period. These rabbits were euthanized as scheduled at the end of the study. The only adverse sign in these rabbits was reduced fecal output and/or un-groomed fur.

Study: #20
Animals: 2 Rabbits
Type of Study: XXX Oral (Gavage) Fertility and General Reproduction Toxicity Study in Male Rabbits
Guidelines/Regulations:

- This study will be conducted in compliance with the Good Laboratory Practice (GLP) regulations of the U.S. Food and Drug Administration (U.S. Food and Drug Administration 21 C.F.R. 58), and the Organisation for

Economic Co-operation and Development {OECD Environment Directorate [C(97)186/Final] (1998)}. The bioanalysis and Toxicokinetic portions of this study will be conducted in a facility that is part of the UK GLP Compliance programme but will not be subject to specific monitoring by Preclinical Compliance.

- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.

Diagnosis: **Two male rabbits** from this fertility and reproductive toxicity study conducted in August 2007-January 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article. The test article is being developed as a treatment for disorders effecting gastroparesis. The rabbits were dosed by stomach tube once daily beginning 70 days prior to mating through mating. The study was approved with the knowledge that possible adverse signs included reduced feed intake and body weight loss for approximately one week until food intake would increase and body weights would stabilize. A second water source and a supplemental food item (timothy cubes, Rabbit Stix®) were approved for use in animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, 1-2 hours after dosage and at the end of the day. Moribund condition and/or body weight loss of more than 20% in association with prolonged diarrhea and sever dehydration were the approved endpoints for animals experiencing pain/distress due to test article effects. Veterinary exams were performed on all animals three times prior to the start of dosage and weekly thereafter until scheduled euthanasia. In addition, fifty eight exams were completed for individual animals.

#3758 (80 MKD) and #3769 (80 MKD) experienced mild to moderate body weight loss (6-16% over 10 days) and moderate to severe reduction in feed consumption (80-100% over 8-10 days) at the beginning of the dosage period. The only adverse sign in these rabbits was reduced fecal output. Following this period, feed intake returned to a good level in each rabbit and the body weight lost was re-gained. These rabbits were euthanized as scheduled at the end of the study and both appeared normal at necropsy examination.

Study: #21
Animals: 5 Rabbits
Type of Study: Intramuscular Reproductive and Developmental Toxicity Study of XXX in Rabbits, Including a Potential Evaluation
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Five rabbits** from this reproductive and developmental toxicity study conducted in October 2007- February 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article and/or study procedures. The test article was a vaccine for influenza and the only anticipated adverse effects were mild redness, edema or flaking at the injection site. The rabbits were dosed by intramuscular injection (0.5 ml) on study days 1, 15 and 29 and gestation days 7 and 20. The hind limb was clipped free of hair on the day prior to each injection and alternate hind limbs were used for each injection. Blood was collected from the marginal ear vein on study days 15 and 29 and on gestation days 7 and 20. The rabbits and their litters were euthanized at the end of the lactation period. Any rabbit experiencing reduced feed intake and weight loss was provided with supplemental food item (timothy cubes.) Moribund condition was the approved endpoint for animals experiencing pain/distress due to adverse test article effects. Animals were observed a minimum of three times daily by study staff and at least weekly by the veterinary staff. An additional seventy five veterinary exams were also performed during this study.

#3831 (15mcg), #3837 (15 mcg), #3840 (15 mcg), #3841 (15 mcg) and #3843 (15 mcg) experienced mild to severe body weight loss (7 to 21%) and severe reduction (90-100%) in feed consumption (7 to 20 days in duration) beginning in early to late gestation. Adverse signs included reduced fecal output, soft feces and ungroomed coat. #3840 and #3841 were euthanized due to the fact that none of the kits in the litter survived. #3831 and #3837 were found dead at the time of the daily morning viability check. #3843 was euthanized at the time of abortion on gestation day 28.

Study: #22
Animals: 5 Rabbits
Type of Study: XXX Oral (Stomach tube) Study on Effect on Embryo-Fetal Development in Rabbits XXX
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Five rabbits** from this developmental toxicity study conducted in February 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article and/or the dosage procedures. The rabbits were dosed by stomach tube once daily from gestation day 7 through 19. The study was approved with the knowledge that possible adverse signs included reduced fecal output, reduced feed intake, reduced body weight, rales, ataxia, decreased activity, loss of righting reflex, ptosis, splayed limbs, abnormal posture and increased respiratory rate. A second water source and a supplemental food item (timothy cube) were approved for use in animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, 1 hour after dosage and at the end of the day. Moribund condition, abortion and severe injury were the approved endpoints for animals experiencing pain/distress due to test article effects. Veterinary exams were performed on all animals at least weekly and an additional 31 animal exams were performed.

#5357 (60 MKD) and #5370 (90 MKD) were found dead after dosage (44 minutes and 5 minutes later, respectively) on gestation day 14 and 19, respectively. Both rabbits appeared normal prior to dosage. At necropsy exam of both rabbits, one lung was perforated. Lab management maintains a system to track and identify accidental injuries that may indicate the need for re-training and re-certification of a technical staff member.

#5349 (60 MKD), #5364 (90 MKD) and #5366 (90 MKD) experienced mild to moderate body weight loss (3-14% over 6 to 19 days) and moderate to severe reduction in feed consumption (75-95%) during the dosage period. The only adverse observation in these animals was reduced fecal output. All were euthanized as scheduled at the end of the study and were normal at necropsy examination.

Study: #23
Animals: 3 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Three rabbits** from Part A of this dosage range-finding developmental toxicity study conducted in March 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article. The test article is a treatment for chronic hepatitis C viral infection. The non-mated rabbits were dosed by stomach tube once daily for five days and euthanized on study day 6. Group IV (high dosage level) was dosed one day after the first dose in groups I-III. The study was approved with the knowledge that possible adverse signs could result in pain or distress. A supplemental food item (timothy cube) was approved for use in animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, hourly for the first four hours after dosage and at the end of the day. Moribund condition was the approved endpoint for animals experiencing pain/distress due to adverse test article effects. During this six day study, all animals were examined by the vet staff three times and an additional 10 exams were performed.

#5507 (III; 270 MKD) lost body weight daily (11.8% cumulative loss) and feed intake was severely reduced during this time. Liquid feces were noted for two days prior to scheduled euthanasia. This rabbit was euthanized as scheduled at the end of the study.

#5511 (IV; 800 MKD) and #5512 (IV; 800 MKD) had severely reduced feed intake, mild BW loss, liquid feces, ungroomed fur and a moderate reduction in activity level beginning approximately one hour after dosage on the morning of study day 2. These adverse signs were still present at the end of the day on study day 2. #5511 was found dead at morning viability checks on study day 3. Euthanasia of #5512 was recommended by the veterinary staff on study day 3 because its condition had declined. At necropsy examination, the livers of both rabbits were dark red and #5511 had cecal and stomach erosions.

Study: #24
Animals: 3 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Three rabbits** from the high dosage level of Part A of this dosage range-finding developmental toxicity study conducted in March 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article. The non-mated rabbits were dosed by stomach tube once daily for five days and euthanized on study day 6. The test article is a treatment for cystic fibrosis. The study was approved with the knowledge that possible adverse signs included decreased activity, reduced feed intake, reduced body weight and death. A second water source and a supplemental food item (timothy cubes) were approved for use in animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, hourly for the first four hours after dosage and at the end of the day. Moribund condition was the approved endpoint for animals experiencing pain/distress due to test article effects. All animals were examined on the day of arrival and at least two additional times by the vet staff during the six days of this study.

#5490 (600 MKD), #5491 (600 MKD) and #5492 (600 MKD) had fair to low feed intake during the dosage period and lost between 7 and 13% body weight over the same period. All animals remained bright, alert and active. Other adverse signs included scant and/or no fecal output. These rabbits were euthanized as scheduled on study day six.

Study: #25
Animals: 2 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Two rabbits** from the high dosage group of this dosage range-finding developmental toxicity study conducted in February-March 2008 have been placed in category E due to pain/distress that was associated with the effects of the test article and/or study procedures. The rabbits were dosed by stomach tube once daily from gestation day 7 through 19. The test article is a neuronal receptor. The study was approved with the knowledge that possible adverse effects were reduced feed consumption and body weight loss. Supplemental food items (timothy cubes) were approved for use in animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, at one to two hour after daily dosage and at the end of the day. Moribund condition was the approved endpoint for animals experiencing pain/distress due to test article effects. Veterinary exams were performed on all animals at least weekly. In addition, 30 individual animal exams were also performed.

#5823 (1500 MKD) and #5839 (1500 MKD) experienced mild body weight loss (8% over 9-12 days) and severe reduction in feed consumption (90% reduction for 9-12 days) during the dosage period. The only adverse clinical signs in these rabbits were reduced fecal output and discolored feces. Feed intake improved and body weight was gained daily after the end of the dosage period in both rabbits. Both rabbits were euthanized as scheduled at the end of the study.

Study: #26
Animals: 3 Rabbits
Type of Study: Intravenous Dosage-Range Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Three rabbits** from Part A of this dosage range-finding developmental toxicity study conducted in March 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article. The non-mated rabbits were dosed via jugular access port once daily on study days 1 through 14 and euthanized on study day 15. The test article is an appetite suppressant. The study was approved with the knowledge that possible adverse signs included decreased activity, reduced feed intake, reduced water intake, reduced body weight, ataxia and respiratory distress. A supplemental food item (timothy cubes) was approved for use in animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, hourly for the first four hours after dosage and at the end of the day. Moribund condition was the approved endpoints for animals experiencing pain/distress due to test article effects. All animals were examined by the veterinary staff at least three times during the dosage period and an additional 19 exams were performed during the 14 day dosage period.

#6011 (5 mg/kg/day) lost body weight daily for 10 days (22.1% cumulative loss) and feed intake was severely reduced during this time. Scant fecal output, ungroomed coat and mucoid feces were noted. This rabbit was examined by the vet staff 10 times prior to euthanasia as scheduled at the end of the study.

#6012 (5 mg/kg/day) lost body weight daily for 8 days (13.7% cumulative loss) and feed intake was severely reduced during this time. Scant fecal output and ungroomed coat were noted on study days 4-8. This rabbit was examined by the vet staff 6 times. At the time of the sixth exam, the rabbit was weak, ataxic and had a brief seizure. This rabbit was euthanized on study day 8 and appeared normal at necropsy examination.

#6010 (5 mg/kg/day) lost body weight daily for 9 days (12.2% cumulative loss) and feed intake was severely reduced during this time. Scant fecal output was noted on study days 4-8. This rabbit was examined by the vet staff 7 times. On study day 8 hyper-reactivity was present and a brief seizure occurred. Throughout the day, the rabbit improved and had a normal gait, normal posture and normal respiration. This rabbit was found dead at the morning check on study day 9 and appeared normal at necropsy examination.

Study: #27
Animals: 4 Rabbits
Type of Study: XXX Oral (Stomach Tube) Dosage-Range Embryo-Fetal Developmental Toxicity Study in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Four rabbits** in the highest dosage group from this dosage range-finding developmental toxicity study conducted in April 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article. The rabbits were dosed by stomach tube once daily from gestation day 7 through 19. The test article is being developed as a reliever of pain. The study was approved with the knowledge that the test article could cause effects that resulted in more than momentary pain or distress. The test article had not been given to rabbits before. A second water source and a supplemental food item (timothy cubes) were approved for use in animals with weight loss and reduced feed intake. Animals were observed at morning viabilities, at dosage, hourly for four hours after dosage and at the end of the day. The approved endpoint for animals experiencing pain/distress due to test article effects was moribund condition. All animals were examined at arrival and six additional times by the veterinary staff ; an additional 24 exams were performed during the

29 days of this study.

#5661 (2000 MKD) seizured and died on gestation day 10 during veterinary examination at the one hour post dosage check. This animal was examined by the vet staff four times between GD8 and death (GD8, GD9, before dosage on GD10 and after dosage on GD10.) Scant fecal output was the only adverse clinical sign present prior to death. Beginning with the start of dosage on GD7, feed intake was severely reduced and 9% body weight was lost. At necropsy examination, the lungs and the stomach mucosa appeared red.

#5662 (2000 MKD) was found dead on gestation day 13 at the four hour post dosage check. This animal was examined six times by the vet staff between GD8 and death (GD8, GD9, GD10, GD11, GD12 and before dosage on GD13.) Beginning with the start of dosage on GD7, feed intake was severely reduced and 11% body weight was lost Reduced activity level and reduced fecal output were present prior to dosage on GD13. At necropsy examination, stomach erosions and areas of tan liver were present.

#5619 (2000 MKD) and #5620 (2000 MKD) were euthanized due to the severity and duration of (1-3 hours) adverse signs present after dosage on gestation day 13 and 12, respectively. These animals were examined one or more times daily by the veterinary staff beginning on GD8. Scant fecal output was the only adverse clinical sign present prior to the onset of the ataxia, reduced activity level, ptosis and bradypnea. Beginning with the start of dosage on GD7, feed intake was severely reduced and 11% body weight was lost in both animals. Adverse necropsy observations included lungs mottled red and tan, stomach erosions and white areas on the gallbladder.

Study: #28
Animals: 6 Rabbits
Type of Study: Intravenous Dosage-Range Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Six rabbits** from Part B of this dosage range-finding developmental toxicity study conducted in March 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article and/or the jugular access catheter. The test article was an enzymatic debriding agent for treatment of full thickness skin burns. Injection of the test article was via a jugular access port once daily on gestation days 7-19. Moribund condition was approved as an endpoint for animals experiencing pain/distress due to test article effects. A supplemental food item (timothy cube) and a second water source were provided to animals with reduced feed intake. Animals were observed at morning viabilities, at daily dosage, one to two hours after daily dosage and at the end of the day. Forty four veterinary exams were performed on individual animals and all animals on study were evaluated at least weekly by the vet staff.

#7485 (II; 0.1 MKD), #7488 (III; 0.05 MKD), #7496 (V; 0.25 MKD), #7497 (V;0.25 MKD) and #7500 (V;0.25 MKD) experienced body weight loss (6-12% over 4-8 days) and moderate to severe reduction (70-100% over 4-5 days) in daily feed consumption beginning during the dosage period. There were no adverse clinical signs present #7485 prior to being found dead at the morning viability check on gestation day 12. The only adverse sign present in #7488, #7496, 37497 and #7500 was reduced fecal output and these rabbits were euthanized as scheduled at the end of the study.

#7493 (IV; 0.10 MKD) was euthanized by veterinary recommendation on gestation day 17 because the rabbit's condition had not improved during the course of the day. Adverse signs began after dosage in the mid-morning of gestation day 17. The rabbit was monitored by the vet staff throughout the afternoon until euthanasia approximately six hours later. Adverse signs included ataxia, decreased activity, dypsnea, paleness and mydiasis. At necropsy examination, the jugular catheter extended into the heart.

Study: #29
Animals: 12 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be

based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Twelve rabbits** from this Part B of this dosage range-finding developmental toxicity study conducted in April 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article. The test article is a treatment for chronic hepatitis C viral infection. The rabbits were dosed by stomach tube once daily from gestation day 7 through 19. The study was approved with the knowledge that possible adverse signs could result in pain or distress. A supplemental food item (timothy cube) was approved for use in animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, at 1, 3 and 6 hours after dosage and at end of the day viabilities. Moribund condition was the approved endpoint for animals experiencing pain/distress due to adverse effects from the test article. All animals were examined by the vet staff at arrival and a least weekly. An additional 37 exams were performed on animals with adverse signs and/or body weight loss and reduced feed intake.

During the dosage period, **#5561 (III; 125 MKD), #5562 (III; 125 MKD), #5564 (III;125 MKD), #5565 (III;125 MKD), #5579 (III;125 MKD), #5566-#5570 (IV; 200 MKD) and #5581-#5582 (IV; 200 IV MKD)** lost body weight (5-24% over 4 to 12 days) and feed intake was moderately to severely reduced. Liquid feces, reduced fecal output, ungroomed fur and rales were noted. Three of these rabbits were euthanized as scheduled at the end of the study, one rabbit was euthanized at the time of delivery on GD29, one rabbit was found dead at the morning viability check on GD12 and seven rabbits were euthanized on GD16 when the high dosage group was terminated.

Study: #30
Animals: 20 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Twenty rabbits** from this of this dosage range-finding developmental toxicity study conducted in April 2008 have been placed in category E due to pain/distress associated with the effects of the test article. Twenty nine rabbits were dosed by stomach tube once daily from gestation day 7 through 19. The test article is a treatment for cystic fibrosis. The study was approved with the knowledge that possible adverse signs included decreased activity, reduced feed intake, reduced body weight and death. A supplemental food item (timothy cube) was approved for use in animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, 1 to 2 hours after dosage and at the end of the day. Moribund condition was the approved endpoint for animals experiencing pain/distress due to adverse effects from the test article. All animals were examined on the day of arrival and at least weekly. An additional 89 exams were performed on animals experiencing adverse signs and or body weight loss.

During the dosage period, **#5706 (II; 100 MKD), #5708 (II; 100 MKD), #5710 (II; 100 MKD), #5721-#5722 (II; 100 MKD), #5712-#5715 (III; 300 MKD), #5724-#5726 (III; 300 MKD), #5716-5720 (IV; 500 MKD) and #5727-5729 (IV; 500 MKD)** lost body weight (5-28% over 5 to18 days) and feed intake was severely reduced. #5715, #5716, #5718 and #5720 were found dead at the morning viability check on gestation day 24, 18, 18 and 21, respectively. The only adverse observation prior to death was reduced fecal output and each rabbit was examined by the veterinary staff 7 to 13 times prior to being found dead. #5713 died en route to being euthanized according to veterinary recommendation due to moribund condition after dosage administration on gestation day 15. Prior to this time, reduced fecal output was the only adverse observation present. This rabbit was examined by the veterinary staff 8 times prior to death. #5714 and #5719 were euthanized at the time of abortion on gestation day 24 and 26, respectively. Prior to this time, reduced fecal output and mild dehydration were the only adverse observations present. These rabbits were examined by the veterinary staff 14 and 17 times, respectively, prior to euthanasia. #5712, #5717 and #5728 were euthanized according to veterinary recommendation when the approved endpoint was reached (moribund condition) on gestation day 25, 21 and 13, respectively. Prior to this time, reduced fecal output and mild dehydration were the only adverse observations present. These rabbits were examined by the veterinary staff 6 to 16 times prior to euthanasia. #5706, #5708, #5710, #5721, #5722, #5724-5727 and #5729 were euthanized as scheduled at the end of the study. These rabbits were examined 5 to 10 times by the veterinary staff prior to euthanasia.

Study: #31
Animals: 8 Rabbits
Type of Study: Dosage-Range Developmental Toxicity Study of XXX following Oral (Stomach Tube) Administration in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Eight rabbits** from part B of this dosage range-finding developmental toxicity study conducted in April 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article. The test article is intended for treatment of humans with urea cycle disorders. The rabbits were dosed by stomach tube once daily from gestation day 7 through 19. Body weight loss, reduced feed intake and possible mortality were expected. All rabbits experiencing reduced feed intake and weight loss were provided with two water sources and a supplemental food item (timothy cubes.) Animals were observed at morning viabilities, at daily dosage, hourly for six hours after each dosage and at the end of the day. Moribund condition was the approved endpoint for animals experiencing pain/distress due to test article effects. All animals were examined by the veterinary staff on the day of arrival and at least weekly until euthanasia. All animals at the high dosage level were examined a minimum of four times prior to death or unscheduled euthanasia. In addition, 59 exams were performed on animals experiencing adverse signs and or body weight loss.

#3061 (III; 0.4 g/kg/day), #3066-3070 (IV; 0.6 g/kg/day) and #3077-3078 (0.6 g/kg/day) experienced severe, acute body weight loss (14-30% over 3-11 days) and consumed no feed or feed supplements the same period. #3070 was found dead at the morning viability check on gestation day 14. Scant fecal out put and mild dehydration were present for 3 days prior to death. This animal was examined six times by the veterinary staff prior to death. Necropsy revealed a pale heart, pale kidneys, a large volume of blood in the thoracic cavity and a defect in the diaphragm through which a portion of one lung lobe protruded. #3061, #3066, #3067, #3068, #3069, #3077 and #3078 were euthanized per veterinary recommendation on gestation days 18, 21, 19, 10, 18, 19 and 17 because there was progression to grave or to moribund condition. Adverse clinical signs that were present included decreased activity, ataxia, cold to touch, paleness, dehydration, ptosis, dypsnea, scant fecal output, lacrimation and clear nasal discharge. Each rabbit was examined 5 to 11 times by the veterinary staff prior to reaching the approved endpoint for euthanasia. Adverse findings at necropsy exam included fetal resorptions, pale hearts and pale or discolored livers and kidneys.

Study: #32
Animals: 2 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Two rabbits** from this developmental toxicity study conducted in May 2008 have been placed in category E as described below. The test article was an undisclosed medicinal product. The rabbits were dosed once daily by stomach tube form gestation day 7 through 19. The study was approved with the knowledge that test article toxicity could result in more than momentary pain/distress and to allow animals to reach moribund condition prior to euthanasia. An additional water source and timothy cubes were approved for use for animals with weight loss or reduced feed intake. Animals were observed at morning viabilities, at daily dosage, two hours after each dosage and at the end of the day Veterinary exams were performed on all animals on the day of arrival and at least weekly thereafter until the end of the study. In addition, 34 exams were performed on animals with body weight loss, reduced feed intake and/or adverse clinical signs.

#5991 (IV; 2000 MKD) per veterinary recommendation after dosage on GD19 when condition declined to grave (animal

was not expected to survive the night.) This was the ninth veterinary exam performed on this animal. The animal began to loose body weight at the start of the dosage period and feed intake was severely reduced. There was a loss of 23% body weight over 13 days. Adverse clinical signs present for three or more days prior to euthanasia included rales, hyperpnea, dehydration, ungroomed fur and reduced fecal output. At necropsy exam, all lung lobes were spongy and mottled brown and one lung lobe was firm.

#5928 (II; 200 MKD) was found dead 4 minutes after dosage administration on gestation day 16. A perforated lung lobe was found at necropsy examination. The rabbit was normal prior to this event. Lab management maintains a tracking system for monitoring accidental events in order to help identify the need for re-training of any laboratory staff member. While this animal appeared normal at the time of dosage and there was no intent to withhold relief in the form of euthanasia, the nature of the injury suggests that there may have been more than momentary pain or distress prior to death.

Study: #33
Animals: 13 Rabbits
Type of Study: Intravenous Dosage-Range Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: Thirteen rabbits from Part B of this dosage range-finding developmental toxicity study conducted in May 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article. The mated rabbits were dosed via jugular access ports once daily from gestation day 7 through 19. The test article is an appetite suppressant. The study was approved with the knowledge that possible adverse signs included decreased activity, reduced feed intake, reduced water intake, reduced body weight, ataxia and respiratory distress. A supplemental food item (timothy cubes) was approved for use in animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, hourly for the first four hours after dosage and at the end of the day. Moribund condition was the approved endpoints for animals experiencing pain/distress due to test article effects. All animals were examined by the veterinary staff on the day of arrival, three times prior to the start of the dosage period and a least weekly until the end of the study. Many rabbits were examined daily during the dosage period to assess skin cuts and abrasions not related to test article administration. In addition, 97 exams were performed on animals with weight loss, reduced feed intake and adverse clinical signs during the 23 days from the start of dosage until the end of the study.

#5646 (V; 2.5 MKD) lost body weight from GD12 –GD18 (10.8% cumulative loss) and feed intake was severely reduced from GD14-16. Scant fecal output was noted on GD16. This rabbit was examined by the vet staff 6 times. On GD17, hyper reactivity and a seizure occurred when the rabbit was being handled. Throughout the day, the rabbit improved and had a normal gait, normal posture and normal respiration. This rabbit was euthanized by veterinary recommendation on GD18 when handling-induced seizures occurred and the rabbit's overall condition declined. At necropsy examination, a large volume of tan fluid was observed in the thoracic cavity.

#5664 (V; 2.5 MKD) lost body weight from GD13-GD20 (17.4 % cumulative loss) and feed intake was severely reduced during this same period. Scant feces and ungroomed fur were noted. On GD18 – GD20, hyper reactivity and brief seizures occurred when the rabbit was handled. This rabbit was euthanized on GD20 by veterinary recommendation when the rabbit's overall condition declined and prognosis for survival overnight was poor.. At necropsy examination, stomach erosions and one tan, firm lung lobe were observed.

#5639 (III; 0.5 MKD), #99 (IV; 1.0 MKD), #5643 (IV; 1.0 MKD), #5647-#5650 (V; 2.5 MKD), #5661-#5662 (IV; 1.0 MKD), #5663 (V; 2.5 MKD) and #5665 (V; 2.5 MKD) lost body weight (10-26% over 6 to 18 days) and feed intake was severely reduced. Reduced fecal output, ungroomed fur, hyper reactivity and in some rabbits, brief seizures when handled or approached were noted. Each of these rabbits was examined by the veterinary staff six to 13 times. #5663 was euthanized at the time of abortion on GD22. All other rabbits were euthanized as scheduled at the end of the study.

Study: #34
Animals: 19 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Nineteen rabbits** from this developmental toxicity study conducted in June 2008 have been placed in category E due to pain/distress that was associated with the effects of the test article and/or study procedures. The rabbits were dosed by stomach tube once daily from gestation day 7 through 19. The test article is a treatment for cystic fibrosis. The study was approved with the knowledge that possible adverse signs included decreased activity, reduced feed intake and reduced body weight. A supplemental food item (timothy cube) was approved for use in animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, 1 to 2 hours after dosage and at the end of the day. Moribund condition was the approved endpoint for animals experiencing pain/distress due to adverse effects from the test article. All animals were examined on the day of arrival and at least weekly. An additional 170 exams were performed on animals experiencing adverse signs, reduced feed intake and body weight loss.

During the dosage period, **#6312 (I; vehicle), #6327 (II; 50 MKD), #6333 (II; 50 MKD), #6345 (III; 100 MKD), #6350 (III; 100 MKD), #6353 (III; 100 MKD), #6359 (III; 100 MKD), #6362-6369 (IV; 200 MKD), #5657 (IV; 200 MKD), #6373 (IV; 200 MKD), #6376 (IV; 200 MKD) and #6378 (IV; 200 MKD)** lost body weight (6-26% over 5 to19 days) and feed intake was severely reduced. #6363 was found dead at the morning viability check on gestation day 24. Reduced fecal output was noted for ten days and the day before death, mild dehydration was present. This rabbit was examined by the veterinary staff 9 times prior to being found dead. At necropsy exam, the heart and kidneys were pale, the lungs were red and all fetuses had been resorbed. #6366, #6369 and #5676 were euthanized at the time of abortion on gestation day 27, 25 and 25, respectively. Prior to this time, reduced fecal output and mild dehydration were the only adverse observations present. These rabbits were examined by the veterinary staff 9, 10 and 10 times, respectively, prior to euthanasia. At necropsy exam, the hearts were pale, the lungs were spongy and all fetuses were dead or had been resorbed. #6362 and #6367 were euthanized according to veterinary recommendation when the approved endpoint was reached (moribund condition) on gestation day 26 and 23, respectively. Prior to this time, reduced fecal output and mild dehydration were the only adverse observations present. These rabbits were examined by the veterinary staff 13 and 11 times, respectively, prior to euthanasia. At necropsy exam, #6362 had a tan liver, red lungs and all fetuses had been resorbed. At necropsy exam, #6367 had a pale heart, spongy lungs and most of the fetuses had been resorbed. #6312, #6327, #6333, #6345, #6350, #6353, #6359, #6364-6365, #6368, #6373, #6376 and #6378 were euthanized as scheduled at the end of the study. These rabbits were examined 6 to 12 times by the veterinary staff prior to euthanasia.

Study: #35
Animals: 2 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX in Rabbits, Including a Satellite Toxicokinetic Evaluation
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Two rabbits** in the high dosage level group of this dosage range-finding developmental toxicity study conducted in June 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article. The test article is intended as treatment for rheumatoid arthritis and other inflammatory disorders. The test article was given by stomach tube once daily on gestation days 7-19. The study was approved with the knowledge that adverse effects (reduced feed intake, weight loss, stomach irritation) from the test article could result in more than momentary pain or

distress. Moribund condition was approved as an endpoint for animals experiencing pain/distress due to test article effects. A supplemental food item (timothy cube) and a second water source were provided to animals with reduced feed intake. Animals were observed at morning viabilities, at daily dosage, one to two hours after daily dosage and at the end of the day. Twenty veterinary exams were performed on individual animals and all animals on study were examined at arrival and evaluated at least weekly by the vet staff.

#2799 (6 MKD) and #5688 (6 MKD) experienced body weight loss (8-15% over 12-14 days) and moderate to severe reduction (90-100% over 12-14 days) in daily feed consumption beginning at the start of the dosage period. The only adverse sign present was reduced fecal output and these rabbits were euthanized as scheduled at the end of the study.

Study: #36
Animals: 9 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Nine rabbits** from this developmental toxicity study conducted in June 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article and/or study procedures. The rabbits were dosed by stomach tube once daily from gestation day 7 through 19. The dosage levels were 0, 30, 60 and 120 mg/kg/day. The test article is a treatment for hepatitis C infection. The study was approved with the knowledge that possible adverse signs were reduced feed consumption and body weight loss. Supplemental food item (timothy cube) and a second water source were approved for use in animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, 1 to 2 hours after dosage and at the end of the day. Moribund condition and severe injury were the approved endpoints. Veterinary exams were performed on all animals at arrival and at least weekly until the end of the study. In addition, 48 individual animal exams were performed.

#6601 (I; vehicle) was euthanized on gestation day 8 two hours after dosage. Immediately after dosage the rabbit had an increased respiratory rate. An exam was requested at 0920 and performed at 0920. The respiratory rate was increased but there were no other signs present that are the typical indicators of an injury during intubation- respiratory distress, blood on tube or from nose or mouth. At 1000, the study director approved euthanasia and at 1141, the rabbit was euthanized. A perforated lung lobe was apparent at necropsy examination. Lab management maintains a tracking system for monitoring accidental events in order to help identify the need for re-training of any laboratory staff member.

#6631 (II; 30 MKD), #6659 (III; 60 MKD), #6668 (IV; 120 MKD), #6669 (IV; 120 MKD), #6672 (IV; 120 MKD), #6674 (IV; 120 MKD), #6676 (IV; 120 MKD) and #6690 (IV; 120 MKD) experienced mild to moderate body weight loss (5-12% over 4 to 10 days) and moderate to severe reduction in feed consumption during the dosage period. Adverse signs included reduced fecal output and soft or liquid feces. #6674 was euthanized at the time of abortion on gestation day 24. At necropsy exam, the lungs were red and all fetuses were dead or resorbed. All other animals were euthanized as scheduled at the end of the study.

Study: #37
Animals: 2 Rabbits
Type of Study: XXX Oral Embryo-fetal Developmental Toxicity Study in Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Two rabbits** from this developmental toxicity study conducted in June 2008 have been placed in category E due

to pain/distress that may have been associated with the effects of the test article and/or study procedures. The rabbits were dosed by stomach tube once daily from gestation day 7 through 19. The dosage levels were 0, 100, 300 and 1000 mg/kg/day. The test article is for management of pain. The study was approved with the knowledge that possible adverse signs were reduced feed consumption, body weight loss, decreased activity level and possibly death. Supplemental food item (timothy cube) and a second water source were approved for use in animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, 2 hours after dosage and at the end of the day. Moribund condition and severe injury were the approved endpoints. Veterinary exams were performed on all animals at arrival and on all animals at least weekly until the end of the study. In addition, 42 individual animal exams were performed.

#6495 (IV; 1000 MKD) and **#6247 (IV; 1000 MKD)** experienced moderate body weight loss (9-11 %) and severe reduction in feed consumption for 4-6 days during the dosage period. The only adverse clinical sign was reduced fecal output. #6495 was examined fives prior to being found dead after dosage on gestation day 15. At necropsy exam, the rabbit appeared normal and all fetuses were dead. #6247 was examined seven times and was euthanized as scheduled at the end of the study.

Study: #38
Animals: 18 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Eighteen rabbits** from the high dosage group of this developmental toxicity study conducted in August 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article. The rabbits were dosed by stomach tube once daily from gestation day 6 through 15, 16, 17 or 18. Due to unexpected adverse effects and mortality, the daily dosage was divided into two portions administered 12 hours apart beginning on gestation day 16, 17, 18 or 19 through 28. The dosage levels were 0, 350, 700 and 1400 mg/kg/day. The test article is a food supplement or herbal product. The study was approved with the knowledge that any test article could potentially result in adverse effects but that no adverse effects were expected to be caused by this particular test article. Supplemental food items (dry timothy cube and rehydrated timothy cube), a second water source and grooming to decrease hair ingested while self-grooming were provided to animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at each of the twice daily dosage administrations, 1 hour after each of the twice daily dosage administrations, at daily feed consumption and at the end of the day. Moribund condition and severe injury were the approved endpoints. Veterinary exams were performed on all animals at arrival and on all animals at least weekly until the end of the study. In addition, 173 individual animal exams were performed during the four week duration of this study.

#6564, #6566, #6578 and #6579 experienced mild to moderate body weight loss and moderate to severe reduction in feed consumption during 4-5 days of the dosage period. Adverse signs were reduced fecal output. After the 4-5 days, the feed consumption improved to a good level and body weight was gained daily. Each of these rabbits was examined at least 6 times (range 6 to 8 times) by the veterinary staff. These rabbits were euthanized as scheduled at the end of the study.

#6561-6563, #6565, #6567-6573, #6575-6576 and #6580 experienced severe, acute body weight loss (19-32% over 6 to 12 days) and severe reduction in feed consumption during the dosage period. #6562 (6 vet exams) and #6571 (1 vet exam) had no adverse clinical signs prior to being found dead on gestation days 17 and 8, respectively. At necropsy exam, #6562 had stomach erosions and pale areas of cardiac muscle. #6571 had one stomach perforation in an area of stomach that appeared necrotic and areas of pale cardiac muscle. #6563 (7 vet exams) and #6565 (3 vet exams) had scant fecal output as the only adverse clinical sign prior to being found dead on gestation days 20 and 12, respectively. At necropsy exam, #6563 had areas of pale cardiac muscle and #6565 had stomach erosions. #6570 (7 vet exams) and #6580 (7 vet exams) were found dead after dosage on gestation day 17 and dehydration and reduced activity were present on gestation day 16. At necropsy exam, #6570 had all lung lobes mottled and all conceptuses were resorbed. At necropsy exam, #6580 had one lung that was perforated. (Laboratory management maintains a tracking system for accidental deaths and injuries to help identify patterns that could indicate a particular staff member's need for re-training.) #6569 (11 vet exams) was euthanized per veterinary recommendation when condition declined to moribund after dosage on gestation day 19. At necropsy exam, all conceptuses were resorbed and there were pale areas of cardiac muscle. #6572 (7 vet exams), #6575 (8 vet exams) and #6576 (9 vet exams) were euthanized on gestation days 18, 17 and 17, respectively, per veterinary recommendation at the end of the day when there was no improvement in their poor condition over the course of that day. At necropsy exam, none of these three rabbits had viable conceptuses and the gall bladders had numerous tan areas. #6561 (8 vet exams) and #6573 (7 vet exams)

were euthanized per veterinary recommendation when condition declined to poor after dosage on gestation days 19 and 18, respectively. At necropsy exam, all conceptuses were dead or resorbed and the lungs were mottled red to dark red. #6567 (7 vet exams) and #6568 (8 vet exams) were euthanized at the time of abortion on gestation days 16 and 20, respectively. At necropsy exam of #6567, all conceptuses were dead or resorbed, the stomach was eroded, the liver was congested and all other tissues were pale. At necropsy exam of #6568, the lungs were dark red and the gallbladder had numerous tan areas.

Study: #39
Animals: 2 Rabbits
Type of Study: Intravenous Dosage-Range Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Two rabbits** from Part B of this dosage range-finding developmental toxicity study conducted August 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article. The test article is an antibiotic intended for human use. The rabbits were dosed intravenously via the ear vein once daily from gestation day 7-19. The study was approved with the knowledge that reduced feed intake and body weight loss could occur.. All rabbits experiencing reduced feed intake and weight loss were provided with two water sources and a supplemental food item (timothy cubes.) Animals were observed at morning viabilities, at daily dosage, immediately after dosage, at 1, 2, 3 and 4 hours after each dosage and at the end of the day. Severe adverse signs and moribund condition was the approved endpoints for animals experiencing pain/distress due to test article effects. Veterinary exams were performed on all animals at arrival and on all animals at least weekly until the end of the study. In addition, 69 individual animal exams were performed during the four week duration of this study.

#6794 (37.5 MKG) and #6795 (37.5 MKD) experienced acute body weight loss (10-15%) as a result of a 90-95% reduction in feed consumption over 12-15 days. Soft and reduced feces were adverse clinical signs. These rabbits were examined 8 and 9 times, respectively, by the veterinary staff. These rabbits were euthanized as scheduled at the end of the study.

Study: #40
Animals: 5 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX in Rabbits, Including a Satellite Toxicokinetic Evaluation
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Five rabbits** from developmental toxicity study conducted in August 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article. The test article is intended as treatment for rheumatoid arthritis and other inflammatory disorders. The test article was given by stomach tube once daily on gestation days 7-19. The study was approved with the knowledge that adverse effects from the test article could result in more than momentary pain or distress. Moribund condition was approved as an endpoint for animals experiencing pain/distress due to test article effects. A supplemental food item (timothy cube) and a second water source were provided to animals with reduced feed intake and BW loss. Animals were observed at morning viabilities, at daily dosage, one to two hours after daily dosage and at the end of the day. Veterinary exams were performed on all animals at arrival and on all animals at least weekly until the end of the study. In addition, sixty one individual animal exams were performed during the four week duration of this study.

#6862 (3 MKD), #6873 (6 MKD), #6880 (6 MKD) and #6884 (6 MKD) experienced body weight loss (6-13% over 4 to 9 days) and moderate to severe reduction (90-100% over 5 to 9 days) in daily feed consumption during the dosage period. The

only adverse sign present was reduced fecal output. Each of these rabbits was examined 7 to 10 times prior to scheduled euthanasia at the end of the study.

#6886 (6 MKD) was found dead at the morning check on gestation day 22. This rabbit experienced 17% body weight loss and 5 days of severely reduced feed intake prior to death. This rabbit was examined 9 times and adverse signs present on the day before death included ptosis and tachypnea. Necropsy examination showed a perforation of one lung lobe. The dosage period ended 4 days prior to death. This fact combined with the clinical history, makes it likely that this accidental injury occurred on gestation day 16 or 17. Lab management maintains a system to track and identify accidental injuries that may indicate the need for re-training and re-certification of a technical staff member.

Study: #41
Animals: 1 Rabbit
Type of Study: Intravenous Pilot Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **One rabbit** from this Part B of this dosage range-finding developmental toxicity study conducted in August 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article or with dosage procedures. The test article is a treatment for cancer in humans. The rabbits were dosed by stomach tube once daily from gestation day 7 through 19. The study was approved with the knowledge that possible adverse signs including body weight loss and reduced feed intake could result in pain or distress. A supplemental food item (timothy cube) and a second water source were provided to animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at daily dosage, 1 to 2 hours after dosage and at the end of the day. Moribund condition was the approved endpoint for animals experiencing pain/distress due to adverse test article effects. Veterinary exams were performed on all animals at arrival and on all animals at least weekly until the end of the study. In addition, sixteen individual animal exams were performed during the four week duration of this study.

#6773 (IV; 200 MKD) was euthanized by veterinary recommendation on gestation day 27 when adverse signs including ptosis, decreased activity, hyperpnea did not improve over the course of the day. This rabbit experienced body weight loss of 27.6% from gestation day 13 to 27 and severe reduction (90-100%) in daily feed consumption during this same period. The only adverse signs present prior to the day of euthanasia were reduced fecal output, soft feces and ungroomed fur. At necropsy exam, all fetuses were alive, the large intestines were distended with gas and the gall bladder was adhered to the liver.

Study: #42
Animals: 2 Rabbits
Type of Study: Intravenous Pilot Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: **Two rabbits** from this developmental toxicity study conducted in August 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article and/or procedures. The rabbits were dosed intravenously via the ear vein once daily from gestation day 7 through 19. The test article is intended to be used for treatment for leukemia and non-Hodgkin's lymphomas. The study was approved with the knowledge that the test article could potentially result in adverse effects. Supplemental food items (dry timothy cube and re-hydrated timothy cube), a second water source and grooming to decrease hair ingested while self-grooming were provided to animals with body weight loss or reduced feed consumption. Animals were observed at morning viabilities, at dosage administration, 1 to 2 hours after

each dosage, at daily feed consumption and at the end of the day. Moribund condition and severe injury were the approved endpoints. Veterinary exams were performed on all animals at arrival and on all animals at least weekly until the end of the study. In addition, 30 individual animal exams were performed during the four week duration of this study.

#7471 (IV; 120 MKD) and #4840 (I; vehicle) experienced body weight loss (11 and 26%, respectively), over 10 to 18 days and severe reduction in daily feed intake (90-100% over 10 to 17 days) beginning in the dosage period. The only adverse signs present were reduced fecal output and mucoid feces. #7471 was examined 13 times prior to scheduled euthanasia at the end of the study. #4840 was examined 7 times prior to scheduled euthanasia at the end of the study.

Study: #43
Animals: 1 Rabbit
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX in Rabbits, Including a Toxicokinetic Evaluation
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: One rabbit from the high dosage group of this developmental toxicity study conducted in September 2008 has been placed in category E due to pain/distress that may have been associated with the effects of the test article. The test article acts on the central nervous system and is being investigated as a treatment for Alzheimer's and Huntington's disease. The rabbits were dosed by stomach tube once daily from gestation day 7 through 19. The study was approved with the knowledge that adverse effects including tachypnea, ptosis, decreased activity, seizures, body weight loss and reduced fee consumption could occur. All rabbits experiencing severely reduced feed intake and weight loss were provided with a supplemental food item (timothy cube.) Animals were observed at morning viabilities, at daily dosage, at 15 minutes, 1 hour and 4 hours after each dosage, at daily feeding and at the end of the day. Moribund condition was the approved endpoint for animals experiencing pain/distress due to test article effects. Veterinary exams were performed on all animals at arrival and on all animals at least weekly until the end of the study. In addition, 27 individual animal exams were performed during the four week duration of this study.

#7172 (150 MKD) experienced mild body weight loss (10%) and severely reduced feed consumption during the last five days of the dosage period. Adverse signs included reduced fecal output. This rabbit had a brief seizure on gestation day 17 and muscle rigidity when handled on gestation day 18. This rabbit was examined by the veterinary staff 10 times and was euthanized as scheduled at the end of the study.

Study: #44
Animals: 6 Rabbits
Type of Study: Intramuscular Fertility, Developmental and Perinatal/Postnatal Reproduction Toxicity Study of XXX in Female Rabbits, Including a Postnatal Evaluation
Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

Diagnosis: Six rabbits from this reproductive and developmental toxicity study conducted in May 2008-September 2008 have been placed in category E due to pain/distress that may have been associated with the effects of the test article and/or study procedures. The test article is a vaccine for bacterial meningitis and the only anticipated adverse effects were mild redness, edema or flaking at the injection site. The rabbits were dosed by intramuscular injection (0.5 ml) on study days 1, 15 and 29 and gestation days 7 and 20. The hind limb was clipped free of hair on the day prior to each injection and alternate hind limbs were used for each injection. Blood was collected from the marginal ear vein pre-study, on study days 15 and 29 and on gestation days 7 and 20. Some rabbits were euthanized on gestation day 29 and some rabbits were euthanized on day

34 of lactation along with the delivered kits. Any rabbit experiencing reduced feed intake and weight loss was provided with supplemental food item (timothy cubes.) Moribund condition was the approved endpoint for animals experiencing pain/distress due to adverse test article effects. Animals were observed a minimum of three times daily by study staff and at least weekly by the veterinary staff. An additional 142 veterinary exams were also performed during this study.

#6109 (0 mcg), #6164 (0 mcg), #6189 (50 mcg), #6190 (50 mcg) and #6202 (50 mcg) experienced mild to severe body weight loss (8 to 19%) and severe reduction (90-100%) in feed consumption (10 to 20 days in duration) during the dosage period. #6109 re-gained all body weight lost and feed intake returned to a normal. This rabbit was examined seven times during the period of body weight loss and was euthanized as scheduled at the end of the study. #6190 was examined six times during the period of body weight loss and was found dead on study day 15 at the time of the morning viability check. #6202 was examined nine times during the period of body weight loss and died on gestation day 30 during a brief seizure. #6164 was examined seven times during the period of body weight loss and was found dead following delivery of one kit. #6189 was examined eleven times during the period of body weight loss and was euthanized by veterinary recommendation when activity level declined.

#6152 (50 mcg) sustained an accidental cut to the skin when the hair was being clipped away from the intended injection site on the left rear leg using electric clippers. The cut was 3 cm in length. On the date that the cut occurred, discomfort was diagnosed when the area was examined. No pain or distress to manipulation of the affected area was apparent during the subsequent four veterinary exams. The cuts healed completely in 8 days. Feed intake and body weight were not affected and the rabbits were euthanized as scheduled at the end of the study.

Study: #45
Animals: 1 Rabbit
Type of Study: Intravenous Dosage-Range Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on Health effects test guidelines. Prenatal development toxicity study. OPPTS 870.3700; August, 1998; Prevention, Pesticides and Toxic Substances. U. S. Environmental Protection Agency. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **One rabbit** from this dosage-range finding developmental toxicity study conducted in August-September 2008 has been placed in category E due to pain or distress that may have been associated with effects of the test article. The test article is a fungicide for use on vegetables and other foods. The rabbits were dosed by stomach tube once daily from gestation day 6 through 28. The study was approved with the knowledge that reduced feed intake and body weight loss could occur. All rabbits experiencing reduced feed intake and weight loss were provided with two water sources and a supplemental food item (timothy cubes.) Animals were observed at morning viabilities, at daily dosage, approximately 1 hour after dosage, at daily feed consumption and at the end of the day. Moribund condition was the approved endpoints for animals experiencing pain/distress due to test article effects. Veterinary exams were performed on all animals at arrival and on all animals at least weekly until the end of the study. In addition, 5 individual animal exams were performed during the four week duration of this study.

#5769 (V; 1000 MKD) experienced acute body weight loss (16.5%) as a result of a 90-95% reduction in feed consumption over 3 days during the dosage period. Reduced fecal output and reduced respiratory rate were noted the day before death. On gestation day 12, this rabbit was found dead after the morning check but prior to dosage administration. This rabbit was examined 3 times by the veterinary staff and supportive care was provided. The rabbit appeared normal at necropsy examination. While there was no intent to withhold relief in the form of euthanasia (the approved endpoint had not yet been reached) and the rabbit was observed frequently and regularly, the bradypnea the day prior to death could be interpreted as premonitory of death. And the bradypnea along with the degree of acute body weight loss and severely reduced feed intake that were not relieved could be interpreted as more than momentary pain or distress.

Study: #46
Animals: 18 Rabbits
Type of Study: Intravenous Dosage-Range Developmental Toxicity Study of XXX in Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for

Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Eighteen rabbits** from this dose range-finding developmental toxicity study conducted in September-October 2008 have been placed in category E due to discomfort and/or pain at the dosage injection site that was present at least one day during the dosage period. The test article is a recombinant human growth and differentiation factor being investigated for enhancing healing in bone defects and bone grafts. The rabbits were dosed once daily by intravenous injection (ear vein) from gestation day 7 through 19. Injection of the test article and of the vehicle was preceded by a saline flush and followed by a saline flush to help minimize irritancy. Moribund condition was the approved endpoint for animals experiencing pain/distress due to test article effects. Cold compresses were applied to the affected ears one or more times daily. Animals are observed at morning viabilities, at daily dosage, at one hour after dosage, at daily feed weights and at the end of the day. Each animal on study was examined by the vet staff daily. In addition, 151 exams and follow-up exams were completed for affected animals.

#7201-7202 (vehicle), #7204-7205 (vehicle), #7207-7208 (1.0 MKD), #7210-7212 (1.0 MKD), #7213-7218 (3.0 MKD), #7219 (9.0 MKD) and #7223-7224 (9.0 MKD) were diagnosed by the veterinary staff with discomfort and/or pain at the dosage injection site for one or more days during the dosage period. Mild to moderate localized swelling and increased warmth and redness were also noted in one or both ears. The extent of the irritancy did not prevent continued daily dosage administration in these animals. Cold compresses were applied to the affected ear(s). The feed consumption levels were not affected and no body weight was lost. While the discomfort and/or pain did not persist in any animal throughout the entire dosage period, it cannot be presumed that the cold compression provided timely or complete relief and no analgesia was approved for use due to the objectives of this developmental toxicology study.

Study: #47
Animals: 3 Rabbits
Type of Study: Six-Month Intravenous Immunogenicity Study of XXX in Female Rabbits
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Three rabbits** from this immunogenicity study that is currently in progress (as of September 30, 2008) have been placed in category E due to pain/distress that may have been a result of the test article and/or procedures. The test article is a blood system to inactivate blood-borne pathogens in donated blood products intended for transfusion. The rabbits are dosed intravenously (ear vein) once every two weeks. Moribund condition is the approved endpoint for animals experiencing pain/distress due to test article effects. Animals are observed at morning viabilities, at dosage, at one hour after dosage, at daily feeding and at the end of each day. All animals were examined by the vet staff at arrival and at least weekly thereafter. **#4802 and #4806** lost 20% or more body weight and had severely reduced feed intake over more than a 2 week period. Reduced fecal output was the only adverse clinical sign. Each was examined by the vet staff more than 8 times during this period. #4802 was found dead and #4806 was euthanized by veterinary recommendation. Adverse necropsy findings in these rabbits included stomach erosions, pale liver and pale kidneys. **#4804** was found dead with no prior adverse clinical signs and mild body weight loss (6%.) Necropsy findings included pale heart, pale, lungs, large spleen, stomach erosions, friable abdominal fat and yellow mesentery. It is possible that these were associated with pain or distress prior to death.

CHARLES RIVER LABS PRECLINICAL SERVICES – (Nevada - Site #005)

Study: #48
Animals: 1 Nonhuman Primate
Type of Study: 4 week Toxicology Study of XXX in Cynomolgus Monkeys with a 4 week recovery period (4,8,12 and 20 weeks after last dose) and a Pharmacokinetic Arm
Guidelines/Regulations:

- ICH m3
- ICH53a
- ICHS6
- OECD Guideline 417

Diagnosis: One nonhuman primate - Animal had been losing weight (was receiving nutritional supplementation and fluid therapy) and had decreased activity. Physical exam revealed pale in mucus membranes and shallow breathing. A decision was made to euthanize the animal, however, because blood samples for diagnostic workup and additional study data was collected just prior to euthanasia, the animal was categorized as an E (vs. D).

Study: #49
Animals: 3 Nonhuman Primates
Type of Study: A Rising Dose Safety Pharmacology Study of XXX given by IV injections to Cynomologus Monkeys
Guidelines/Regulations:

- ICHM3
- OECD GUIDELINE 417
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; 312.23

Diagnosis: Three nonhuman primates - Four telemetry animals were given increasing doses of Test Article at 0, 2, and 8 mg/kg IV. Animals were staggered dosed. Since animals had telemetry implants they were being recorded continuously and these recordings were evaluated every 15 minutes minimally. The first dosed animal had no clinical signs at one hour post dosing at the 8mg/kg. The other three animals were dosed at 10 minute intervals. Animals 2 and 3 had decreased activity, hunched posture, and lying down in the cage at 40 minutes post dosing. Animal 4 immediately post dosing was very lethargic, had heavy breathing and was lying down in its cage. Animals were given fruit and enrichment to encourage normal activity. Animal 3 recovered and had no further abnormal clinical signs. Animals 2 and 4 did not and continued to be depressed and very lethargic. At 6 hours post dosing immediately following a scheduled blood collection the animals 2 and 4 were euthanized. Even though animal 3 recovered, it is possible that the clinical signs of hunched posture, decreased activity and lying down were consistent with more than momentary distress/pain, so all three animals were categorized as E.

Study: #50
Animals: 6 pigs
Type of Study: A comparative toxicopharmacokinetic study of two test articles administered once by IV infusion followed by a 7 day observation period.
Guidelines/Regulations:

- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: Six pigs, #3809, #3805, 33821, #3823, #3837 and #3844, had multiple clinical signs consistent with a chemotherapeutic test article. Supportive care consisted of nutritional supplementation, fluid/electrolyte supplementation, antibiotic, external heat source and analgesic (1 animal). Two of the animals died and the remaining 4 were euthanized at the end of the study. Although animals received various treatments at different times during the study, the treatments were not 100% effective in relieving clinical signs that could be consistent with more than momentary distress. Animals were not euthanized prior to the scheduled end as this would have interfered with achieving the goals of the study. Therefore, these animals were categorized as E.

Study: #51
Animals: 1 pig
Type of Study: A 28 day Dermal Study of XXX administered by topical application to minipigs
Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies. This dose range and tolerance study is being done to determine dosage selection for future studies that will be based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals. Without conduct of this study prior to the required full toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: One pig, #5288, had skin irritation that was red, warm and sensitive to touch. The animal was placed on a dosing holiday and monitored closely. The animal continued to be active, alert and eating normal through out the time. Once the skin condition resolved, the animal was placed back on dose administration. Even though the pig was bright, alert and active, it is possible that it experienced more than momentary distress from the skin condition and therefore was categorized as a E.

Study: #52
Animals: 6 rabbits
Type of Study: A six-week repeated dose toxicity study of an ophthalmic antibiotic formulation via ocular administration to NZW rabbits with a 28 day recovery period.
Guidelines/Regulations:

- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **Six rabbitss, #8027, #8034, #8035, #8057, #8020, and 38042,** had blepharospasm, which could be consistent with distress/pain. Treatment consisting of extra rinsing and washing the peri-ocular area post-dosing and the condition resolved.

Study: #53
Animals: 1 rabbit
Type of Study: 28 day local toxicity study with a 14 day recovery period
Guidelines/Regulations:

- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: One rabbit, #3958, was noted to have impaired right hind limb and decreased activity. The animal was to be euthanized but died prior to euthanasia. Necropsy findings of fractured right tibia and fibula. Even though the animal was to be euthanized, it is categorized as E because of the necropsy findings.

Study: #54
Animals: 1 rabbit
Type of Study: A toxicity study comparing vaccines after IM administration in NZW rabbits
Guidelines/Regulations:

- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: One rabbit, #3428, had an ear that was swollen, warm and sensitive to touch post-blood collection. Analgesics and anti-inflammatory drugs would interfere with goals of the study. Treatment consisted of applying ice BID. Sensitivity resolved after two days of treatment. Even though the animal responded to treatment, it is possible that the animal experienced more than momentary distress, therefore this animal was categorized as E.

CHARLES RIVER LABS PRECLINICAL SERVICES – (Massachusetts – Site #022)

IACUC-APPROVED EXCEPTIONS TO REGULATIONS AND STANDARDS

The IACUC must approve exemptions from non-human primate environmental enhancement plans and dog exercise activities. The animals were observed daily by the animal care and technical staff and the veterinary technician (or veterinarian). The following exceptions to standards/regulations were approved by the IACUC during this reporting period.

Species: Nonhuman Primate
Number: 210
All animals were on metabolism and pharmacokinetics studies and may have been used on more than one study. Pair housing, environmental enrichment devices inside the cage and/or dietary restrictions (no fruit peels or peanut shells) were withheld after dose administration for up to 15 days during sample collection. Environmental enrichment devices were allowed outside the cage. External stimuli such as radios, televisions, and conspecific visualization, olfactory and auditory stimulation were provided. There were no exemptions while being held on the colony between studies.

Species: Nonhuman Primate
Number: 625
Exemption: 233 nonhuman primates were exempted for up to 68 days; 52 were exempted for up to 141 days; 340 were exempted for 170-330 days.
All animals were on toxicology studies and were exempt from social housing. Environmental enrichment devices and external stimuli such as radios, televisions, and conspecific visualization, olfactory and auditory stimulation were provided.

Species: Nonhuman Primate
Number: 30
Animals were on surgical studies and were exempted from social housing for up to 85 days.

Species: Nonhuman Primate
Number: 47
Animals were on pharmacology studies and may have been used on more than one study. Social housing was exempted for up to 29 days during telemetry monitoring.

Species: Dog
Number: 236
All animals were on metabolism and pharmacokinetics studies and may have been used on more than one study. Pair housing and/or exercise was exempted after dose administration for up to 15 days during sample collection. The square footage of the caging met all requirements for housing the animals, however, it did not meet the additional space needs to eliminate the requirement for exercise outside of the cage. There were no exemptions while being held on the colony between studies.

Species: Dog
Number: 788
Exemption: 574 dogs were exempted for up to 57 days; 52 dogs were exempted for up to 134 days; 162 dogs were exempted for 302-428 days. All animals were on toxicology studies. The square footage of the caging met all requirements for housing the animals, however, it did not meet the additional space needs to eliminate the requirement for exercise outside of the cage.

Species: Dog
Number: 146
All animals were on surgical studies and were exempted from social housing for up to 31 days.

Species: Dog
Number: 57
Animals were on pharmacology studies and may have been used on more than one study. Pair housing and/or exercise was exempted after dose administration for up to 15 days during sample collection and telemetry monitoring. The square footage of the caging met all requirements for housing the animals, however, it did not meet the additional space needs to eliminate the requirement for exercise outside of the cage. There were no exemptions while being held on the colony between studies.

Study: # 55
Animals: 1 Dog
Type of Study: Toxicology – To determine the potential toxicity and toxicokinetics of the TA.
Guidelines/Regulations:

- U.S. Food and Drug Administration 21 CFR Part 312 Investigational New Drug application section ; 312.23 subpart B 5 (ii)
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **One dog** had been noted to be lethargic, decreased activity and vomiting. Dog was monitored by the veterinary staff a minimum of three times per day. The dog was found dead. Since it is possible that the dog experienced more than momentary distress/pain prior to being found dead, this animal was categorized as an E.

Study: #56
Animals: 1 Nonhuman Primate
Type of Study: Toxicology – Assess the toxicological potential of TA after daily dosing for 28 days
Guidelines/Regulations:

- U.S. Food and Drug Administration 21 CFR Part 312 Investigational New Drug application section ; 312.23 subpart B 5 (ii)
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: Five nonhuman primates – Animals were observed and evaluated 4 times a day. **Monkey # 4102** was found dead. Other animals in the same dose group later had clinical signs that were treated appropriately with fluids, anti-diarrheal, nutritional support and external heat source. Since it is possible that Monkey #4102 may have experienced more than momentary distress/pain prior to being found dead, this animal was categorized as an E.

Study: # 57
Animals: 50 Guinea Pigs
Type of Study: Dermal sensitization test
Guidelines/Regulations:

- FDA
- OECD

Diagnosis: Fifty guinea pigs – All animals were bright, alert and responsive. Dermal test article exposure had occurred 48 hour previously . Animals were observed to be head shaking, actively scratching and grooming the test sites and vocalizing. The animals on this study were markedly more active than other animals housed in the room at the same time. Many of these animals had significantly scarified their lesions. Some of the signs could be consistent with more than momentary distress. Treatment would interfered with the goals of the study. All animals were rechecked the next day and were found to be bright, alert and the vast majority of animals resting and appearing comfortable. The animals were not vocalizing, head shaking or actively scratching. Though of short duration, less than 24 hours, some animals exhibited signs that could be consistent with more than momentary distress, so all were categorized as E.

Study: #58
Animals: 8 Swine
Type of Study: Oral Toxicity
Guidelines/Regulations:

- FDA
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
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Diagnosis: Eight swine – Animals **#S5107717, S5107504, S5107555, S5107521 and S5107415, S5107270, S5107776 and S5107792.** Animals were exhibiting signs consistent with respiratory distress and were humanely euthanized. Necropsy findings were consistent with gavage error. Even though animals were euthanized when observed in distress, prior to euthanasia they may have experienced more than momentary distress/pain and were therefore categorized as E.

Animal **#, S5107270, S5107776 and S5107792.** While active and alert, all had weight loss (36%, 9% and 20%) and some decrease in feed consumption over approximately 1 week. Necropsy findings were consistent with gavage error at some point. Even though animals did not exhibit clinical signs of respiratory distress, it is possible that the decreased feed consumption/weight loss may be indicative of more than momentary distress so these animals were categorized as E.

Study: #59
Animals: 14 Rabbits
Type of Study: Oral Toxicity
Guidelines/Regulations:

- FDA
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: - Four rabbits, R1033, R1041, R1031 and R1063, either died or were euthanized with signs of respiratory distress consistent with gavage error. These animals may have experienced more than momentary distress, so are categorized as E. **Ten rabbits, R1032, R1051, R1014, R1015, R1043, R1027, R1064, R1075, R1087 and R1071,** had varying levels of inappetance and weight loss. Most were offered multiple nutritional supplements (Nutrical, yogurt, fresh vegetables) and an additional water source. Weight loss ranged from 9 – 36% with most between 15-20%. A few animals were found dead with the majority euthanized. While animals appeared bright, active and alert, it is possible that the inappetance and weight loss might be consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: # 60
Animals: 16 Rabbits
Type of Study: Oral Toxicity
Guidelines/Regulations:

- FDA
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: Sixteen rabbits –
All group 4 males and females (12 total) and # R1529/R1546/R1552/R1543 – Clinical signs observed were prolonged inappetence resulting in excessive, acute weight loss and death in some cases. Animals were monitored 3x/daily and body weights monitored every other day. Alternate food sources were offered (lettuce, Nutra Blocs, Nutrical as necessary) towels to rest and water bottles as extra hydration. Animal **#R1543** was a possible gavage error. While animals appeared bright, active and alert, it is possible that the inappetance and weight loss might be consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #61
Animals: 13 Rabbits
Type of Study: Dermal Toxicity
Guidelines/Regulations:

- OECD

Diagnosis: Thirteen rabbits – All group 1 males and females (ten animals total) and Animals **#R1578, R1580 and R1582**- Clinical signs observed were excessive, acute weight loss (5-17%), decreased activity, with or without labored breathing. Supportive care provided included towels, lettuce and water bottles. Four of the thirteen were euthanized prior to the end of the study. These animals exhibited salivation, decreased activity and responsiveness and shallow breathing. The remaining animals were euthanized as scheduled. While animals that remained on study appeared bright, active and alert, it is possible that the inappetance and weight loss might be consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #62
Animals: 6 rabbits
Type of Study: 14 day Oral Toxicity Test

Guidelines/Regulations:

- FDA
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: Six rabbits: Animal R1467 was found dead and necropsy results were consistent with gavage error, thus categorized as E. **Animals R1465, R1456, R1459, R1472, and R1473** had inappetance, abnormal feces and weight loss (ranging from 13-37% over a 14 day period). Supportive care included food supplementation and water bottles. While animals that remained on study appeared bright, active and alert, it is possible that the inappetance and weight loss might be consistent with more than momentary distress and therefore these rabbits were categorized as E.

Study: #63
Animals: 1 rabbit
Type of Study: Oral Toxicity, single oral dose.

Guidelines/Regulations:

- FDA
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis – One rabbit; R1420 was noted to be bleeding after dosing. Not clear if rabbit bit it's tongue or if it had a nose bleed (was holding it's nose in the air). The rabbit had rapid breathing and Auscultation revealed some pulmonary congestion but rabbit appeared to be recovering. The animal was monitored and appeared to recover. The animal was found dead the next day. There was frank blood around nose and mouth. It is possible that there was more than momentary distress associated with the death, therefore categorized as E.

Study: #64
Animals: 1 rabbit
Type of Study: Ocular toxicity

Guidelines/Regulations:

- EPA, OECD

Diagnosis: **One rabbit: R0981** had mild edema and erythema around the right eye and the eyelid was partially closed, approximately 2.5 hours post-dose. Although the animal did not appear to be in pain or distress, it is possible that the partially closed eyelid may indicate some level of distress that is more than momentary, so this animal was categorized as E.

Study: #65
Animals: 1 dog
Type of Study: oral toxicity

Guidelines/Regulations:

- FDA, OECD, MHLW

Diagnosis: **One dog, #D2266,** was found dead shortly after dosing. Mucus membranes and tongue appeared cyanotic. There was some vomitus in the cage pan. Necropsy revealed a capsule lodged in the larynx. It is assumed that there may have been more than momentary distress associated with the aspiration and subsequent death, so this was categorized as E.

Study: #66
Animals: 16 dogs
Type of Study: 28 day toxicity followed by 28 day recovery, ocular dosing route

Guidelines/Regulations:

- FDA
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **Sixteen dogs, D1921, D1922, D1933, D1934, D1924, D1935, D1920, D1923, D1943, D1944, D1949, D1955, D1954, D1952, D1953 and DD1941,** dose dependent distended abdomens, increased feed consumption and enlarged livers at necropsy. This was an expected test-article effect that could not be treated without interfering with the goals of the study. Some dogs had abdominal tenderness and occasional labored breathing. Animals were handled as carefully in order to avoid putting pressure on abdomen. It was assumed that these clinical signs may have been consistent with more than momentary distress and therefore, these animals were categorized as E.

Study: #67
Animals: 2 dogs
Type of Study: oral toxicity

Guidelines/Regulations:

- FDA
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **Two dogs, D1010 and D1004**. Necropsy results were consistent with gavage error. It is assumed that there was more than momentary distress/pain, therefore categorized as E.

Study: #68
Animals: 2 dogs
Type of Study: oral toxicity

Guidelines/Regulations:

- FDA
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: Two dogs, D2009 and D2033, had multiple of self-limiting seizure activity post-dosing. Treatment with anti-seizure medication would have interfered with goals of study. Seizures are considered to be painful by the USDA, therefore these animals were categorized as E.

Study: #69
Animals: 6 dogs
Type of Study: oral toxicity

Guidelines/Regulations:

- FDA
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **Six dogs, D2060, D2076, D2050, D2057, D2059, and D2063** had gastrointestinal disturbances that resulted in prolonged inappetance and acute weight loss. Supplemental nutrition was provided. . While animals appeared active and alert, it is possible that the inappetance and weight loss might be consistent with more than momentary distress and therefore these dogs were categorized as E.

Study: #70
Animals: 20 dogs
Type of Study: 28 day oral toxicity

Guidelines/Regulations:

- FDA
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **Twenty dogs, group 3 males and females (10) and group 4 males and females (10),** had prolonged gastrointestinal disturbances resulting in protracted inappetance in all and acute weight loss in most. Treatment consisted of dosing holidays, nutritional supplementation and subcutaneous fluids. Inappetance and weight loss may be consistent with more than momentary distress and therefore these dogs were categorized as E.

Study: #71

Animals: 14 dogs
Type of Study: oral toxicity

Guidelines/Regulations:

- FDA
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **Fourteen dogs,** had prolonged gastrointestinal disturbances including watery diarrhea, inappetance, dehydration and weight loss. Treatment consisted of fluids for dehydration and nutritional supplements. . Inappetance and weight loss may be consistent with more than momentary distress and therefore these dogs were categorized as E.

Study: #72
Animals: 1 dog
Type of Study: oral toxicity

Guidelines/Regulations:

- FDA
- US Dept of Health and Human Services, FDA, Federal Register, Vol. 62, November 25,1997. Maintenance of the ICH Guideline M3(R1)on Non-Clinical Safety Studies for Conduct of human Clinical Trials for Pharmaceuticals
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **One dog, D2577,** exhibited clinical signs consistent with gavage error approximately 1.5 hours post-dosing. Even though animal was euthanized shortly after observation of clinical signs, the animal was exposed to more than momentary distress, thus categorized as E..