kidney, gastrointestinal tract, pancreas, skin, skeletal muscle and salivary gland; atrophic changes in lymphohaemopoietic tissues and changes in some endocrine related tissues; namely the adrenal and the female reproductive tract.

240 mg/kg: 17/24 males and 12/24 females died or were killed in extremis within the first 7 days of dosing. The remaining animals were terminated during week 2. Clinical signs including salivation and paddling of the forelimbs, thinning fur, hair loss, sores/lesions, shedding/peeling skin, ocular discharge, thinness and being hunched. Body weight lost 10 - 20% during first week of dosing. Marked decrease in food consumption (45-57%). Histopathological findings including degenerative, inflammatory or proliferative changes in various epithelial tissues, namely the liver, kidney, gastrointestinal tract, pancreas, skin, skeletal muscle and salivary gland; atrophic changes in lymphohaemopoietic tissues and changes in some endocrine related tissues; namely the adrenal and the female reproductive tract.

160 mg/kg: 14/24 males and 9/24 females died or were killed in extremis within the first 7 days of dosing. 20/24 males and 15/24 females died or were killed in extremis at the end of 13 weeks of dosing. Clinical signs including salivation and paddling of the forelimbs, thinning fur, hair loss, sores/lesions, shedding/peeling skin, ocular discharge, thinness and being hunched. Body weight lost 10 - 20% during first week of dosing and then increased through the study. Moderate decrease in food consumption. Marked decrease in food consumption (17-35%). Significant increases of ALT, AST and ALP. Histopathological findings including degenerative, inflammatory or proliferative changes in various epithelial tissues, namely the liver, kidney, gastrointestinal tract, pancreas, skin, skeletal muscle and salivary gland; atrophic changes in lymphohaemopoietic tissues and changes in some endocrine related tissues; namely the adrenal and the female reproductive tract.

80 mg/kg: 2/24 males died or were killed in extremis between weeks 2 and 13 of dosing. One dead animal exhibited very thin and hunched, pale, uncoordinated before death. Body weight increased through the study. However, lower weight (80-90% of control) was noted. Slight decrease in food consumption (16%) during first 6 weeks of dosing. Significant increases of ALT, AST and ALP. Histopathological findings including inflammatory or proliferative changes in liver.

The systemic exposure generally increased in a greater than dose-proportional manner over the dose range studied (80 to 320 mg/kg/day). No apparent sex and time-related difference were noted. However, the systemic exposures at the same dose level of 80 mg/kg in the 13-week study were generally higher than that of the two-year study.

Based on the results of this 13-week dose range-finding study, the Reviewer feels that the 80 mg/kg was probably an acceptable high dose in the 2-year study primarily based on the mortality in this study. However, the generally lower system exposure compared to this 13-week study and lower incidence of tumor findings compared to other statins in the 2-year study suggests that the high dose of 80 mg/kg in the complete 2-year may be not adequate.

INTEGRATION OF CAC RECOMMENDATION

Both mouse and rat carcinogenicity studies are judged to be adequate. It was concluded that treatment of mice with rosuvastatin at 200 mg/kg/day was associated with an increased incidence of hepatocellular adenoma/carcinoma in both sexes, these findings are consistent with other statins. It was also concluded that treatment of rats with rosuvastatin at ≥60 mg/kg/day was associated with an increased incidence of uterine stromal polyps, including a single stromal sarcoma in a female given 80 mg/kg/day.

COMMUNICATION TO SPONSOR

Executive CAC meeting was held on January 29, 2002.

The Division agrees to the recommendations of the Executive CAC.

Attachments:
1. Minutes of Executive CAC meeting on January 29, 2002
2. Minutes of Executive CAC meeting on January 16, 2001
3. Minutes of Executive CAC meeting on August 8, 2000
4. Minutes of Executive CAC meeting on March 14, 2000
5. Minutes of Executive CAC meeting on January 18, 2000
6. Minutes of Executive CAC meeting on August 10, 1999
7. Minutes of Executive CAC meeting on January 26, 1999

Reviewer signature: /S/

John Zhaolong Gong, Ph.D. Date
Pharmacology/Toxicology Reviewer

Team leader signature [Concurrence/Non-concurrence]

/S/

Davis-Bruno, Karen, Ph.D. Date
Pharmacology Supervisor

cc: IND Arch
HFD510
HFD510/Koch/Gong/Davis-Bruno

Executive CAC 2002
Date of Meeting: January 29, 2001

Committee: Joseph Contrera, Ph.D., HFD-901, Acting Chair
John Leighton, Ph.D., HFD-150, Alternate Member
Abby Jacobs, Ph.D., HFD-540, Alternate Member
Karen Davis-Bruno, Ph.D., Team Leader
John Zhaolong Gong, Ph.D., Presenting Reviewer

Author of Minutes: John Zhaolong Gong, Ph.D.,

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA 21,366 / IND 56,385
Drug Name: CRESTOR
Sponsor: Astra-Zeneca Pharmaceuticals Inc.

Background:
Crestor (rosuvastatin) is an HMG CoA reductase inhibitor being developed as an oral tablet for the treatment of primary hypercholesterolemia and mixed dyslipidemias.

The Sponsor initiated the 2-year carcinogenicity studies in rats and mice in 1998. The Sponsor submitted the dose selection document 6 months after the studies were started. The Committee concurred with the doses used in the mouse study, but could not concur on the doses used in rats due to the fact that the MTD had not be established. Six eCAC meetings were held to discuss this issue. Two additional dose range finding studies were conducted trying to establish MTD. In the second 3-month study with doses of 80, 160, 240, and 320 mg/kg, significant numbers of animal deaths were observed at ≥ 160 mg/kg. In the 80 mg/kg group, 2/24 males died or were killed *in extremis*, indicating 80 mg/kg was above MTD, though the AUC values at 80 mg/kg group in the 3-month study were generally 2 times the value in the 2-year study, indicating these two studies are not fully comparable, i.e., at the same dose level of 80 mg/kg, rats in the 3 month study were exposed to higher levels of compound than rats in the 2-year study, leading to the severe toxicity observed in the 3-month study.

Mouse Carcinogenicity Study
A 107-week oral gavage carcinogenicity study was conducted with doses of 10, 60, 200, and 400 mg/kg. 400 mg/kg group was terminated in week 3 due to mortality and deteriorating condition. A statistically significant higher incidence of hepatocellular adenoma/carcinoma was observed in males than females. An increased incidence of hepatocellular adenoma plus carcinoma were noted at 200 mg/kg in both sexes. An increased incidence of hepatocellular carcinoma was only observed at 200 mg/kg in both sexes.

Rat Carcinogenicity Study
A 104-week oral gavage carcinogenicity study was conducted with doses of 2, 20, 60, and 80 mg/kg. No increase in neoplasia in the forestomach and liver was noted..

Executive CAC Recommendations and Conclusions:

Mouse study:
The Committee confirmed the validity of the study and dose selection. They concluded that treatment of mice with rosuvastatin at 200 mg/kg/day was associated with an increased incidence of hepatocellular adenoma/carcinoma in both sexes. It was noted that these findings are consistent with other statins.

Rat study:
The Committee confirmed the validity of the study and dose selection. They concluded that treatment of rats with rosuvastatin at ≥ 60 mg/kg/day was associated with an increased incidence of uterine stromal polyps, including a single stromal sarcoma in a female given 80 mg/kg/day.

Joseph Contrera, Ph.D.
Acting Chair, Executive CAC

cc:\
IND 56,385/Division File, HFD 510
NDA 21,366/Division File, HFD 510
Karen Davis-Bruno /Team leader, HFD-510
John Zhaolong Gong/Reviewer, HFD-510
Bill Koch/CSO/PM, HFD-510
ASeifried, HFD-024

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/s/

Joe Contrera
2/6/02 04:28:39 PM

Executive CAC
Date of Meeting: January 16, 2001

Rat Carcinogenicity Study Evaluation

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Dave Morse, Ph.D., HFD-150, Alternate Member
Jeri El-Hage, Ph.D., Team Leader
John Zhaolong Gong, Ph.D., Presenting Reviewer

Author of Minutes: John Zhaolong Gong

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

IND #: 56,385
Drug Name: ZD4522
Sponsor: ZENECA Pharmaceuticals Inc., Wilmington, DE 19850.

Background
The sponsor submitted dose selection documents for rat and mouse 2-year carcinogenicity studies on November 25, 1998 and June 21, 1999. Executive CAC meetings were held on January 26, 1999, August 10, 1999, January 18, 2000, February 14, 2000, March 14, 2000, and August 8, 2000. The Committee could not concur with the dose selection in rats due to the lack of evidence to establish a MTD for the 2-year study.

The results of the 91-day dose range finding study and the completed 2-year carcinogenicity study do not clearly establish that the 80 mg/kg is an adequate high dose.

Executive CAC Recommendations and Conclusions:

Based on available information from the Sponsor, the Committee was not able to conclude that the 2-year carcinogenicity study was an adequate assessment of the carcinogenic potential of ZD4522 as the high dose had not been established as the MTD.

The Committee felt that the early studies conducted in different facilities, using different animal sources and diets could not successfully establish the MTD, due to discrepancy of the results. In the 91-day dose ranging finding study conducted under the same conditions as the 2-year carcinogenicity study with a single dose level of 160 mg/kg,

ZD4522 induced toxicity characterized by marked weight loss in a few animals per sex, while producing little toxicity in the majority of the rats. From CDER's analysis of the available information, it appeared that the weight loss was observed only during the second week of dosing, primarily in animals that were group caged (eg #31, 32, 33 males, #65, 67, 70 females). This suggests that the weight loss may have been due to technical error rather than drug toxicity. A dose range finding study with three dose levels of 80, 160, and 240 mg/kg may have had identified an MTD. If 240 mg/kg was found to cause marked toxicity or animal death, 80 mg/kg could still be considered as an acceptable high dose for the 2-year carcinogenicity study.

The Committee recommended that the sponsor could present their data in a Full CAC meeting to make their case that the completed study evaluated adequate doses. If interested, they should focus on dose adequacy, toxicity findings in the same strain and source of animals, as well as on the carcinogenicity findings. Another option may be to conduct a dose finding study that clearly establishes the MTD for ZD4522 in the appropriate strain and source of rats.

/S/

/s/

Joseph DeGeorge
1/18/01 01:50:41 PM

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\
IND 56,385/Division File, HFD 510
Jeri El-Hage/Team Leader, HFD-510
John Zhaolong Gong/Reviewer, HFD-510
William Koch/Project Manager, HFD-510
ASeifried, HFD-024

Executive CAC
Date of Meeting: August 8, 2000
Rat Carcinogenicity Dose-Selection Evaluation

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Glenna Fitzgerald, Ph.D., HFD-120, Alternate Member
Jeri El-Hage, Ph.D., Team Leader
John Zhaolong Gong, Ph.D., Presenting Reviewer

Author of Minutes: John Zhaolong Gong

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review. The committee did not address the sponsor's proposed statistical evaluation for the 2-year carcinogenicity bioassays, as this does not affect the sponsor's ability to initiate the bioassays. The sponsor may seek guidance on the statistical evaluation of bioassay results from Agency staff separately.

IND #: 56,385
Drug Name: ZD4522
Sponsor: ZENECA Pharmaceuticals Inc., Wilmington, DE 19850.

Background
The sponsor submitted dose selection documents for rat and mouse 2-year carcinogenicity studies on November 25, 1998 and June 21, 1999. Executive CAC meetings were held on January 26, 1999, August 10, 1999, January 18, 2000, February 14, 2000, and March 14, 2000. The Committee could not concur with the dose selection in rats due to the lack of evidence to establish a MTD for the ongoing 2-year study.

The sponsor conducted a 91-day dose range finding study in rats with a single dose group of 160 mg/kg/day in order to determine MTD. In the initial 5 weeks, body weight loss was noted in 7/20 males
(-6% to -23%) and 3/20 females (-14% to -28%). These 10 animals were terminated early due to weight loss and poor overall condition. Histopathological findings in these animals included changes in stomach (squamous cell hyperplasia), liver (diffuse hepatocyte cytoplasmic basophilia, together with cytomegaly/karyomegaly, single cell necrosis, increased mitoses and Kupffer cell pigment), kidney (tubular cell degeneration/regeneration), duodenum (villous atrophy), and spleen (lymphoid atrophy). The rest of the animals appeared to be in good condition. Histopathological findings in terminal kill animals were similar to the early terminated animals.

The 2-year carcinogenicity study was completed in May 2000. Based on the summary from the sponsor, little evidence of toxicity was found in this study. Deaths occurred more frequently after 70 weeks in males and after 60 weeks in females, and the survival reached 50% in most groups (including control). Deaths do not appear to be treatment related.

Executive CAC Recommendations and Conclusions:

The Committee noted that in the 91-day study, it was unclear why the drug was very toxic in the premature decedents, while producing apparently little toxicity in the majority of the rats. The Committee could not determine the adequacy of the rat carcinogenicity study based on the available information, although data from the 91-day study with 160 mg/kg/day suggest an MTD .

The Committee recommends that the final report of the completed 2-year study be submitted to the Agency. The Committee will evaluate the adequacy of the 2-year rat carcinogenicity study based on the results of the 2-year study together with the 91-day study with regard to adequacy of dose selection.

/S/ 8/10/01

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\
IND 56,385/Division File, HFD 510
Jeri El-Hage/Team Leader, HFD-510
John Zhaolong Gong/Reviewer, HFD-510
William Koch/Project Manager, HFD-510
ASeifried, HFD-024

Executive CAC
Date of Meeting: March 14, 2000

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Nakissa Sadrieh, Ph.D., Alternate Member
Ronald Steigerwalt, Ph.D., Team Leader
John Zhaolong Gong, Ph.D., Presenting Reviewer

Author of Minutes: John Zhaolong Gong

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

IND #: 56,385
Drug Name: ZD4522
Sponsor: ZENECA Pharmaceuticals Inc., Wilmington, DE 19850.

Background
The Sponsor initiated the 2-year carcinogenicity study in rats at 2, 20, 60 and 80 mg/kg/day on May 5, 1998. Currently, the study has been ongoing for 98 weeks.

The sponsor submitted a dose selection document for rats and mice 2-year carcinogenicity studies on November 25, 1998 and June 21, 1999. Executive CAC meetings were held on January 26, 1999 and August 10, 1999. The Committee could not concur with the dose selection on rats due to the lack of evidence to establish a MTD for the ongoing 2-year study.

On February 28, 2000, the sponsor requested the Division's input regarding the criteria of early termination of the ongoing rat carcinogenicity study. The ongoing rat carcinogenicity study has reached the 94-week point. No significant drug-related toxicity has been noted in any treated group. However, deaths have been occurring more frequently in the last few months and the survival reached 50% in most groups (including control). Deaths do not appear to be treatment related with the lowest survival in one of the control groups..

Executive CAC Recommendations and Conclusions:
The Committee advised against termination of the study at this time. There is still adequate survival and many (most) of the animals are undergoing moribund sacrifice and tissues are thus being adequately preserved. It was noted that as there may be some question about adequacy of dose levels, it could serve to compound the issue if the study is prematurely terminated.

The sponsor should contact the Division when the test group number reach 20 animals per group in any additional groups prior to the scheduled study termination.

/S/ 3/20/00

Chair, Executive CAC

cc:\
IND 56,385/Division File, HFD 510
Ronald Steigerwalt/Team leader, HFD-510
John Zhaolong Gong/Reviewer, HFD-510
ASelfried, HFD-024

Executive CAC
Date of Meeting: January 18, 2000

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Alex Jordan, Ph.D., HFD-580, Alternate Member
Glenna Fitzgerald, Ph.D., Alternate Member
Ronald Steigerwalt, Ph.D., Team Leader
John Zhaolong Gong, Ph.D., Presenting Reviewer

Author of Draft Minutes: John Zhaolong Gong

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

IND #: 56,385
Drug Name: ZD4522
Sponsor: ZENECA Pharmaceuticals Inc., Wilmington, DE 19850.

Background

The sponsor submitted dose selection document for ongoing 2 year carcinogenicity studies in rats and mice on November 25, 1998 and June 21, 1999. Executive CAC meetings were held on January 26, 1999 and August 10, 1999. The Committee conditionally concurred with the dose selection on mice providing that the pathology report could rule out gavage accidents and drug sampling accidents as the cause of the deaths at 400 mg/kg. The Committee could not concur with the dose selection on rats and recommended that the sponsor conduct a short study to determine the MTD. After a few teleconferences with the Division and Dr. DeGeorge, and an eCAC meeting on August 10, 1999, the sponsor is currently conducting a 91-day ranging finding at a single dose of 160 mg/kg. If 160 mg/kg induces significant toxicity, then, the 80 mg/kg can be accepted as the high dose in the ongoing rat carcinogenicity study.

The sponsor sent a new submission on December 6, 1999. The sponsor claimed that the demise of male mice at 400 mg/kg (12/51) was not due to any accident during mis-dosing, but was treatment-related. Histopathological findings include hepatocyte vacuolation with single cell necrosis in the liver, squamous cell hyperplasia with/without hyperkeratosis and gastritis in the stomach and tubular degeneration in the kidney. Therefore, 200 mg/kg appears to be an appropriate high dose for males in the ongoing carcinogenicity study. However, the sponsor could not determine the cause the female death. Therefore, the sponsor is proposing a 91-day ranging-finding study in which female mice will be dosed at 400 mg/kg, and ask the Division to review the protocol. The protocol is similar to the protocol in the rat at a single dose of 160 mg/kg for 91-days.

Mouse Carcinogenicity Study or Mouse Dose Selection

Sponsor proposed a 80-weeks carcinogenicity study at 10, 60, 200 and 400 mg/kg/day. The study was started on June 10, 1998. No adverse effects were observed in 10, 60 and 200 mg/kg groups. However, animal death occurred within the first two weeks of 400 mg/kg treatment, thus all animals in this group (both males and females) were sacrificed on Day 18.

Executive CAC Recommendations and Conclusions:

The Committee felt that the additional mouse study being proposed by the sponsor is not necessary. The data as reported indicate that the high dose female mice that died in the previous study did not show signs of gavage accidents, such as trachea puncture or evidence of drug delivery into the lung. Together with information on drug related deaths in males, this supports the dose selection of the ongoing 2-year study in mice.

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

1/19/00

cc:\
IND 56,385/Division File, HFD 510
Ronald Steigerwalt/Team leader, HFD-510
John Zhaolong Gong/Reviewer, HFD-510
ASelfried, HFD-024

Executive CAC
Date of Meeting: January 26, 1999

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Albert DeFelice, Ph.D., Alternate Member
Ronald Steigerwalt, Ph.D., Team Leader
John Zhaolong Gong, Ph.D., Presenting Reviewer

Author of Draft Minutes: John Zhaolong Gong

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

IND #: 56,385
Drug Name: ZD4522
Sponsor: ZENECA Pharmaceuticals Inc., Wilmington, DE 19850.

Background
The sponsor is seeking agency concurrence on doses being used in ongoing carcinogenicity studies. ZD4522 was found to be negative in a battery of genotoxic tests. It is currently in Phase II clinical trials and an End of Phase II Meeting will be held on February 24, 1999.

Mouse Carcinogenicity Study and Dose Selection
Sponsor is conducting a carcinogenicity study at 10, 60, 200 and 400 mg/kg/day with a planned duration of 80 weeks. The study was started on June 10, 1998. No adverse effects were observed in 10, 60 and 200 mg/kg groups. However, several deaths occurred within the first two weeks of 400 mg/kg treatment, thus all animals in this group (both males and females) were sacrificed on Day 18.

Rat Carcinogenicity Study or Rat Dose Selection
Sponsor is conducting a 2-year carcinogenicity study at doses of 2, 20, 60 and 80 mg/kg/day. The study was initiated on May 5, 1998. No adverse effects were observed in any treated groups, except for a 6% reduction of body weight gain in the female 80 mg/kg group.

Executive CAC Recommendations and Conclusions:

Mouse study: The committee concurs with 200 mg/kg as the MTD (new high dose) provided that the pathology report can rule out gavage accidents and drug sampling accidents as the cause of the deaths at 400 mg/kg.

The committee noted that the standard acceptable duration for a mouse carcinogenicity study is 104 weeks. If excessive deaths occur, it is recommended that the division and CAC be consulted prior early termination of the study.

Rat study: The committee could not provide concurrence with the doses being evaluated based on the data provided.

The committee recommended that the sponsor conduct a short study at sufficiently high doses to determine the MTD and the proximity of the current doses to the MTD, using the same animal strain and the same diet and mode of administration as the study currently being conducted. This could provide information about the utility of the doses being evaluated in the ongoing study in the event there are no clear findings of toxicity in the carcinogenicity study upon completion. Alternatively, the carcinogenicity study could be determined as adequate if sufficient evidence of toxicity or carcinogenic potential were observed in the completed 2 year study.

/S/ 1/29/99

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\

IND 56,385/Division File, HFD 510
Ronald Steigerwalt/Team leader, HFD-510
John Zhaolong Gong/Reviewer, HFD-510
ASelfried, HFD-024

Executive CAC
Date of Meeting: August 10, 1999

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Mark Vogel, Ph.D., Alternate Member
Ronald Steigerwalt, Ph.D., Team Leader
John Zhaolong Gong, Ph.D., Presenting Reviewer

Author of Minutes: John Zhaolong Gong

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

IND #: 56,385
Drug Name: ZD4522
Sponsor: ZENECA Pharmaceuticals Inc., Wilmington, DE 19850.

Background
The sponsor submitted dose selection document for rats and mice 2-year carcinogenicity studies on November 25, 1998. An Executive CAC meeting was held on January 26, 1999 and the minutes were sent to the sponsor on February 1, 1999. The Committee could not concur with the dose selection on rats. In the teleconference meeting on February 4, 1999, the Division discussed three options with the Sponsor: 1. Sponsor conducts a short study to determine the MTD under the same conditions as the ongoing rat carcinogenicity study. 2. Sponsor analyzes data in the one-year interim report, and determines whether 80 mkd can be used as the high dose in the carcinogenicity study. 3. Sponsor awaits the result of the two-year study, and determines whether 80 mkd is a suitable high dose in the carcinogenicity study.

The sponsor sent a new submission on June 21, 1999 to seek concurrence from the Division and Executive CAC on the dose selection of the ongoing rat study. Two studies were submitted. The results indicate that rats fed with low or high calcium diet exhibited different toxicity when exposed to same dose of 150 mg/kg. These studies still can not explain the difference between the ongoing study and the 3-month study. In the 3-month study with the diet calcium concentration of 1.02%, high mortality occurred at the 100 mg/kg group. However, in the ongoing study, a lower calcium (0.66%) diet is being used, animals did not show any notable toxicity at 80 mg/kg after 15 months of exposure. Therefore, the Agency is not sure whether 80 mg/kg is an appropriate high dose for this carcinogenicity study.

Rat Carcinogenicity Study or Rat Dose Selection
Sponsor proposed a 2-year carcinogenicity study at 2, 20, 60 and 80 mg/kg/day. The study was initiated on May 5, 1998. No adverse effects have been observed in any treated groups at 15 months.

Executive CAC Recommendations and Conclusions:
The committee could not provide concurrence with the dose selection based on the data available to the Agency. The Committee did not find sufficient data relevant to the ongoing study to support the dose selection. If the sponsor would like to discuss the issues further, the sponsor is invited to arrange a teleconference with the Division and Dr. DeGeorge.

The Committee suggests that the Sponsor conduct a dose range finding study using the same rat strain and the same diet as used in the ongoing study. Recommended doses for the range finding study are 80, 160, and 240 mg/kg to determine if the ongoing study doses are sufficiently high. If sufficient toxicity and/or tumors are not seen at 160 or 240 mg/kg, then the ongoing study may not have appropriate doses. The sponsor might want to consider also using even higher doses in the range finding study so that they will establish the MTD now, in case the doses in the ongoing study are determined as inadequate.

/s/ 8/16/99

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\
IND 56,385/Division File, HFD 510
Ronald Steigerwalt/Team leader, HFD-510
John Zhaolong Gong/Reviewer, HFD-510
ASeifried, HFD-024

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/s/

John Gong
4/12/02 02:04:31 PM
PHARMACOLOGIST

Karen Davis-Bruno
4/12/02 03:11:20 PM
PHARMACOLOGIST

45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY

NDA 21,366 from AstraZeneca
CRESTOR™ (rosuvastatin calcium) Tablets

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	X		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X		
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA (genotox, reprotox, adequate duration of chronic tox, carcinogenicity)	X		Have electronic files of the carcinogenicity studies been submitted for statistical review? Yes, the electronic files of the carcinogenicity studies have been submitted for statistical review. These files can be retrieved from EDR. Currently, we have not formally accepted the high dose of 80 mg/kg in the 2-year rat study as the MTD. We will review the final report of the 13-week dose range finding study and schedule an eCAC meeting to make final decision. However, based on the draft report the 13-week study, it appears that the high dose of 80 mg/kg may be acceptable.

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?	X		
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	X		
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	X		
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	X		

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	X		
10) Reasons for refusal to file:			

Reviewing Pharmacologist

John Gong

Supervisory Pharmacologist

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/s/

Karen Davis-Bruno
8/17/01 03:06:12 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

NDA:	21-366
Name of drug:	CRESTOR™ (rosuvastatin calcium) Tablets
Applicant:	AstraZeneca Pharmaceuticals LP
Indication:	Dyslipidemia
Documents reviewed:	Zeneca ZD4522: 104 Week Oral (Gavage Administration) Oncogenicity Study in the Rat. —— Study Number 88/232. Sponsor Reference Number TCR/2852 \\CDSESUB1\N21366\N_000\2001-06-26\pharmtox\tox\tcr2852.pdf Zeneca ZD4522: 107 Week Oral (Gavage Administration) Oncogenicity Study in the Mouse. — Study Number 88/233. Sponsor Reference Number TCM/1088 \\CDSESUB1\N21366\N_000\2001-06-26\pharmtox\tox\tcm1088.pdf
Project manager:	Bill Koch, R.Ph. (HFD-510)
Pharmacological reviewer:	John Gong, Ph.D. (HDF-510)
Dates:	Received 6/26/01; user fee (10 months) 4/26/02
Statistical reviewer:	Cynthia Liu, MA (HFD-715)
Statistics team leader:	Todd Sahlroot, Ph.D. (HFD-715)
Carcinogenicity expert:	Karl Lin, Ph.D. (HFD-715)
Biometrics division director:	Ed Nevius, Ph.D. (HFD-715)

Keywords: NDA review, carcinogenicity studies, survival, neoplastic lesions

TABLE OF CONTENTS

Summary of Statistical Review

- Documents of two standard 2-year oncogenicity studies (rat and mouse) with two sexes each, submitted by the sponsor along with electronic data sets, were reviewed.

- Dose levels for the rat study were 0, 2, 20, 60, and 80 mg/kg/day; and 0, 10, 60, 200, and 400 mg/kg/day for the mouse study. The 400 mg/kg/day group was excluded from the statistical analyses because it was removed from the mouse study around Week 3 due to unexpectedly high toxicity (concurred by the ECAC/CAC committee). However, the committee had a concern in regard to whether the 80 mg/kg/day group is high enough to be MTD to cause tumor challenge in the rat study.

- There were at least 50% of male and female animals surviving in both studies at the beginning of Week 90, indicative of sufficient number of animals with adequate exposure to the treatment.

- In the rat study, there was no detrimental effect on survival due to the administration of treatment, ZD4522, in both sexes. There was a marginally significant positive trend in the incidences of pancreatic islet cell adenoma/carcinoma in the females. However, no significant group comparisons were associated with the significant positive trend.

- In the mouse study, there was no detrimental effect on survival due to the administration of treatment, ZD4522, in both sexes. Significant positive trends were observed in the incidences of hepatocellular adenomas and/or carcinomas in both sexes, which were apparently driven by the highly elevated incidences in the 200 mg/kg/day group. The 10 and 60 mg/kg/day groups did not exhibit a significant effect in these cases.

- There were no analyses of combining tumors, tissues, and/or related hyperplastic lesions required by the reviewing pharmacologist.

Introduction

The sponsor has submitted two oncogenicity studies (rat and mouse) conducted by —— —— for the new drug application (NDA 21-366) for CRESTOR™ (rosuvastatin calcium) Tablets. There were two sexes in each study. The purpose of these two oncogenicity studies was to determine any effects of the test article, ZD4522, on the incidence and morphology of tumors following oral (gavage) administration once daily to the rats and mice for at least 104 and 107 weeks, respectively.

This reviewer has performed her own independent statistical analyses on survival and neoplastic lesions, using the electronic data sets submitted by the sponsor. The FDA's Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (May 2001) was used as a reference. The study designs of the two studies are briefly described below, followed by this reviewer's analysis methods and discussion in regard to the differences between the sponsor and reviewer's results.

Study Design

The group designation, dose level, and number of animals per group for the rat and mouse studies are provided below. Note that the two control groups are identical.

Group Number	Group Description	Rat			Mouse		
		Dose Level mg/kg/day	Animals/group		Dose Level mg/kg/day	Animals/group	
			Male	Female		Male	Female
1	Control 1	0	50	50	0	51	51
2	Low	2	50	50	10	51	51
3	Intermediate I	20	50	50	60	51	51
4	Intermediate II	60	50	50	200	51	51
5	High	80	50	50	400	51	51
6	Control 2	0	50	50	0	51	51

The Sprague Dawley rats of the Crl:(IGS)CD strain were obtained from —— —— —— . The mice of the B6C3F1 strain were obtained from ——

As indicated in the sponsor's mouse study report (filename TCM1088.pdf), due to excessive toxicity occurring in Group 5 (400 mg/kg/day), the high-dose animals were removed from the study at the beginning of Week 3, and Group 4 (200 mg/kg/day) was then considered as the

high-dose group. This was concurred by the Pharm/Tox ECAC/CAC committee, as noted in the sponsor's communication log with FDA. Therefore, only data from Groups 1–4 and 6 for the mouse study were submitted by the sponsor and were analyzed by this reviewer.

Reviewer's Analyses

Survival. Evaluations of dose-response trend in mortality and group comparisons were conducted using Cox-Tarone binary regression (parametric) and Gehan-Breslow (nonparametric) tests. The former method is weighted more heavily toward late incidences and the latter method is weighted more heavily toward early incidences due to treatment. As a result, both are valuable tools for incidence data with onset times. Kaplan-Meier product limit survival curves were a supplementary tool to examine the survival distribution patterns among the study groups. One-sided tail probabilities for trend and group comparisons are evaluated at the 5% significance level.

Neoplastic Lesions. To minimize Type I (false positive) error rate, neoplastic lesions were chosen for statistical analyses if the incidence in at least one treated group was increased or decreased by at least two occurrences over that of either control group or the combined control group. For example, 1, 0, 1, 1, 1, and 0 corresponding to the incidences of Groups 1-6 would not be chosen for the analysis; while 0, 0, 0, 0, 2, and 0 for Groups 1-6, respectively, would be. In the cases where the study groups did not have complete histopathology examination, they were excluded from the statistical analyses.

The occult tumors (incidental and/or fatal) were analyzed by interval-based exact permutation test incorporating cause of death information. The cut-off points used for the intervals were Weeks 0-52, 53-78, 79-92, 93-before terminal sacrifice, and terminal sacrifice, which are based on the suggestions from National Toxicology Program (NTP). The palpable (superficial) tumors were also analyzed by interval-based exact permutation test as in the case of fatal tumors, using the first palpation time (provided in the sponsor's electronic data files) as the tumor onset time. SAS PROC MULTTEST (1999) was used to implement the interval-based exact permutation test. Comparisons of control versus treated groups were performed only if there was a significant trend in the incidence data.

The benign and malignant neoplastic lesions, which met the selection criterion for the analysis, were evaluated individually as well as combined. In the cases of multiple-organ findings (e.g., hemangioma, hemangiosarcoma, endometrial stromal polyp, and endometrial stromal sarcoma), the incidences were counted by animal as well as by tissue type. They were evaluated statistically if they met the selection criterion for the analysis. The statistical results for these cases may be biased because not all the animals were examined for every

tissue. This reviewer has selected combined tumor types and/or combined organ types, where appropriate, for the analyses based on the work of McConnell et al. (1986) and her past experience. There were some additional merged tissues analyzed by the sponsor. This reviewer has also done the analyses for those cases. There were no other combining cases required by the reviewing pharmacologist.

Since whether tumor incidence rates increase as doses increase is the main concern of the FDA/CDER pre-clinical review team regardless of the real direction indicated by the data, upper-tailed probabilities (p-values) were, therefore, always computed in testing for positive trend and group comparisons. The following table provides the criterion for determining the statistical significance according to the FDA's guidance (May 2001).

	Test for Positive Trend	Control-High Pairwise Comparisons
Standard 2-Year Studies with 2 Species and 2 Sexes	Common and rare tumors are tested at 0.005 and 0.025 significance levels, respectively.	Common and rare tumors are tested at 0.01 and 0.05 significance levels, respectively.

Common tumor is defined as a tumor type with background (control) rate >1% and rare tumor with background (control) rate ≤1%. Both the concurrent combined control and historical control (where applicable) data were taken into consideration in determining commonality of a tumor.

Based on this reviewer's visual inspection, there were no significant differences between the two controls in the mortality rates and tumor incidences. Therefore, this reviewer used combined control (Groups 1+6) in all the statistical analyses.

There are some minor differences between the sponsor and reviewer's analysis methods. For example, ordinal dose levels (e.g., 0, 1, 2, 3, etc.) were used in this reviewer's analyses as opposed to true dose levels in the sponsor's. The cut-off points used by the sponsor were Weeks 1-50, 51-80, 81-before terminal sacrifice, and terminal sacrifice, which are based on the suggestions from FDA. The sponsor did not analyze palpable tumors by life-table techniques or onset-rate methods. Whether the onset times were used in the sponsor's analyses is questionable. Interval-based methods were applied to both incidental (prevalence) and fatal (mortality) incidences in this reviewer's analyses, while only incidental tumors were analyzed using the interval-based methods in the sponsor's analyses. Nevertheless, those differences did not cause any major discrepancies in the results and conclusion.

Results and Discussion

The Rat Study

Survival. As indicated in Tables 1 (male) and 2 (female), there were no significant positive trends in mortality in either of the two sexes in the rat study. In fact, the female rats showed a significant negative trend in mortality associated with significantly decreased mortality rates in Groups 4 and 5 when compared to that of the combined control. There was a marginally significant increase ($p = 0.0409$) in the Group 5 mortality rate in the males over that of the combined control. This finding might not have any biological meaning because no significant positive trend was associated with it and no such finding was observed in the females.

The Kaplan-Meier product limit survival curves for the males and females are depicted in Figures 1 and 2, respectively, which show at least 58% of male animals and 54% of female animals still surviving in each group at the beginning of Week 90. This indicates that there was sufficient number of animals with adequate exposure to the treatment according to the FDA's guidance (May 2001).

This reviewer's results for the survival analysis of the rat study agree with the sponsor's.

Neoplastic Lesions. There was a marginally significant positive trend in the incidences of pleomorphic lymphoma in the males (Table 3, $p = 0.0217$, rare tumor), which may be due to chance variation since there was no tumor found except 2 occurrences in the 80 mg/kg/day group. In addition, malignant lymphoma (lymphoid tumor), which is a combined form of lymphocytic leukemia, lymphocytic lymphoma, and pleomorphic lymphoma, did not show any significance in the males.

In the females, a borderline significant positive trend was observed in the incidences of pancreatic islet cell adenoma/carcinoma (Table 4, $p = 0.0233$, rare tumor). The historical control background rate for islet cell adenoma, provided by the sponsor, is within 0-6.7%, and 0-1% for islet cell carcinoma. The concurrent combined control rates for the islet cell adenoma, carcinoma, and adenoma/carcinoma are 0/100 (0%), 1/100 (1%), and 1/100 (1%). Therefore, the female islet cell adenoma/carcinoma in this study was judged to be a rare tumor and evaluated at $p \leq 0.025$ level. The marginally significant positive trend in this combined case was driven by the increased incidences in the 60 and 80 mg/kg/day groups (3/50 in both groups) when compared to the combined control (1/100), even though the increases were not statistically significant. Also, the doubled sample size in the combined

control had some effect on producing the significant positive trend. No significant findings were observed when the islet cell adenoma and carcinoma were analyzed separately.

There were no other significant positive trends in the incidences of any common tumors at the 0.005 significance level and of any rare tumors at the 0.025 significance level in either of the two sexes of the rat study, as shown in Tables 3 (males) and 4 (females).

The following table summarizes the significant findings mentioned in the sponsor's rat report. Those significant cases were determined at $p < 0.05$. When the new decision rules of $p \leq 0.005$ for common and $p \leq 0.025$ for rare tumor types are applied, some of the cases are no longer significant. In addition, the significant negative trends are not of concern in this review.

Sex	Organ-Tumor Finding	Sponsor's p-value	Reviewer's Comment
M	HAEM/LYMPH/RETIC – Lymphocytic Leukemia	0.036 ↓	No Concern
M	Skin + Subcutis – Squamous Cell Carcinoma	0.037 ↑	NS
M	Glial Cell Tumor	0.025 ↓	No Concern
F	Mammary Gland – Fibroadenoma	0.036 ↓	No Concern
F	Mammary Gland – Adenocarcinoma	0.045 ↓	No Concern
F	Mammary Gland – Fibroadenoma/Adenocarcinoma/ Adenoma	0.018 ↓	No Concern
F	Pituitary – Adenoma	0.023 ↓	No Concern
F	Pituitary – Adenoma/Carcinoma	0.007 ↓	No Concern
F	Pancreas – Islet Cell Adenoma/Carcinoma	0.025 ↑	Rare Tumor, S
F	Uterus – Stromal Polyp	0.028 ↑	NS
F	Uterus – Stromal Polyp/Sarcoma	0.015 ↑	Common Tumor, NS

NS = Not significant; ↑ = Positive trend; ↓ = Negative trend.

The concurrent combined control rate for the stromal polyp/sarcoma of the uterus is 11/100 (11%). The historical control background rate for stromal polyp, provided by the sponsor, is within 3-13.3%, and 0-1% for stromal sarcoma. Therefore, the stromal polyp/sarcoma is considered not to have a significant positive trend at $p \leq 0.005$ for a common tumor type (sponsor's $p = 0.015$ and reviewer's $p = 0.0505$).

The Mouse Study

Survival. As indicated in Tables 5 (male) and 6 (female), there were no significant positive trends and group comparisons in mortality in either of the two sexes in the mouse study. The Kaplan-Meier product limit survival curves for the males and females are depicted in Figures 3 and 4, respectively, which show at least 78% of male and female animals in each group still

surviving at the beginning of Week 90, indicative of sufficient number of animals with adequate treatment exposure.

This reviewer's results for the survival analysis of the mouse study agree with the sponsor's.

Neoplastic Lesions. As indicated in Tables 7 (male) and 8 (female), there were significant positive trends in the incidences of hepatocullular adenoma and/or carcinoma in both sexes. The significant positive trends in these cases were mainly driven by the significantly increased incidences in the 200 mg/kg/day group. The hepatocellular tumor incidences in both sexes and their statistical results based on this reviewer's analyses are summarized below. The p-values under 0 mg/kg/day group are for positive trend and the p-values under the other treated groups are for the comparison of combined control versus that particular treatment group.

	Tumor Type	Dose Level (mg/kg/day)			
		0	10	60	200
Male, Liver – Hepatocellular Adenoma	Common	29/102	12/51	19/51	25/51
p-value		**0.0050**	0.8034	0.1525	**0.0095**
Male, Liver – Hepatocellular Carcinoma	Common	18/102	10/51	11/51	16/51
p-value		0.0315			
Male, Liver – Hepatocellular Adenoma/Carcinoma	Common	42/102	20/51	25/51	34/51
p-value		**0.0024**	0.7300	0.1854	**0.0039**
Female, Liver – Hepatocellular Adenoma	Common	6/102	3/51	6/51	9/51
p-value		0.0114			
Female, Liver – Hepatocellular Carcinoma	Common	0/102	1/51	0/51	4/51
p-value (see the note below)		0.0078			
Female, Liver – Hepatocellular Adenoma/Carcinoma	Common	6/102	4/51	6/51	12/51
p-value		**0.0012**	0.3780	0.1395	**0.0031**

According to Haseman et al. (1998), the historical control background rate for female hepatocellular carcinoma in B6C3F1 mice is within 0-20% range with mean 8.4%. If one used this criterion, the female hepatocellular carcinoma in this study would, therefore, be classified as common tumor type and no significance would be observed (p = 0.0078), even though there was no hepatocellular carcinoma found in the concurrent combined control.

There were no other significant positive trends in the incidences of any common tumors at the 0.005 significance level and of any rare tumors at the 0.025 significance level in either of the two sexes of the mouse study.

The following table summarizes the significant findings mentioned in the sponsor's mouse report. Those significant cases were determined at $p < 0.05$. When the new decision rules of $p \leq 0.005$ for common and $p \leq 0.025$ for rare tumor types are applied, some of the cases are no longer significant. In addition, the significant negative trends are not of concern in this review.

Sex	Organ-Tumor Finding	Sponsor's p-value	Reviewer's Comment
M	Liver – Hemangioma	0.015 ↓	No Concern
M	Liver – Hepatocellular Adenoma	0.002 ↑	Common Tumor, S
M	Liver – Hepatocellular Carcinoma	0.028 ↑	NS
M	Liver – Hepatocellular Adenoma/Carcinoma	< 0.001 ↑	Common Tumor, S
M	Lung – Bronchiolo-Alveolar Adenoma	0.025 ↑	Common Tumor, NS
M	Blood Vessel Tumor	0.019 ↓	No Concern
M	Histiocytic Sarcoma	0.031 ↑	NS
F	Liver – Hepatocellular Adenoma	0.010 ↑	Common Tumor, NS
F	Liver – Hepatocellular Carcinoma	0.004 ↑	Common Tumor, NS
F	Liver – Hepatocellular Adenoma/Carcinoma	< 0.001 ↑	Common Tumor, S

S = Significant; NS = Not significant; ↑ = Positive trend; ↓ = Negative trend.

In the case of female hepatocellular carcinoma, the sponsor's p-value is 0.004 which is significant at $p \leq 0.005$ for a common tumor type; however, this reviewer's p-value is 0.0078 which is judged to be not significant, i.e., no significant positive trend was observed. The difference between the sponsor and reviewer's results is due to the different scales of the dose levels (arithmetic vs. ordinal) used in the analyses. Either 0.004 or 0.0078 is borderline around $p \leq 0.005$ for a common tumor type. Therefore, special attention should be paid to the combined adenoma/carcinoma analysis.

Conclusion

There were no detrimental effects on survival in both rat and mouse studies due to the administration of treatment, ZD4522. In the rat study, a marginally significant positive trend was observed in the incidences of pancreatic islet cell adenoma/carcinoma in the females, where the higher dose incidences were increased, but not statistically significant, over that of the combined control. No significant findings were observed when the islet cell adenoma and carcinoma were analyzed alone. In the mouse study, it is evident that the incidences of

hepatocellular tumors (adenomas and/or carcinomas) in both sexes were in an increasing fashion, which were mainly driven by the highly elevated incidences in the 200 mg/kg/day group.

Based on the examinations of the validity of the study designs, both rat and mouse studies showed at least 50% of male and female animals still surviving at the beginning of Week 90, indicative of sufficient number of animals with adequate treatment exposure according to the FDA's guidance (May, 2001). However, the ECAC/CAC committee had a concern in regard to whether the 80 mg/kg/day group is high enough to be MTD to cause tumor challenge in the rat study.

Labeling Comments

In the proposed labeling, the sponsor indicates a significantly increased incidence of uterine polyps in the 80 mg/kg/day group in the rat study, which is no longer considered to be significant if the new decision rule of $p \leq 0.005$ for common tumor (FDA, May, 2001) is applied. On the other hand, in the mouse study, wherever it says "an increased incidence of hepatocellular tumors ...", this reviewer would recommend ——— ——— be used.

/S/

Cynthia Liu, MA Date
Statistical Reviewer

Concur: /S/

Todd Sahlroot, Ph.D. Date
Team Leader

/S/

Karl K. Lin, Ph.D. Date
Expert Mathematical Statistician
(Applications in Pharmacology and Toxicology)

CC: HFD-510/WKoch, KDavisbruno, JGong, MParks, WLubas
HFD-715/ENevius, KLin, TSahlroot, CLiu
HFD-700/Canello

Table 1

Results of Statistical Analyses of Mortality Data for Male Rats

Group	1	2	3	4	5	6
Dose	0	2	20	60	80	0
Number of Deaths						
Weeks 0-52	2 a	4 a	2	4	2	4 a
Weeks 53-78	7	3	5	10	8	9
Weeks 79-92	5	11	8	5	14 a	4
Weeks 93-104	9	7	9	2	6	3
Terminal Sacrifice Weeks	27	25	26	29	20	30
Unadjusted Mortality	22/50 (0.44)	24/50 (0.48)	24/50 (0.48)	21/50 (0.42)	29/50 (0.58)	19/50 (0.38)
Kaplan-Meier Estimate (Final)	0.449	0.489	0.480	0.420	0.586	0.387

	Cox-Tarone Test	Gehan-Breslow Test
Groups 1+6 vs. 2-5 Trend (one-sided p)	0.0650 +	0.0624 +
Departure from Trend (two-sided p)	0.6771	0.8188
Homogeneity (two-sided p)	0.4193	0.5114
Groups 1+6 vs. 2 (one-sided p)	0.3069 +	0.3266 +
Groups 1+6 vs. 3 (one-sided p)	0.3890 +	0.4361 +
Groups 1+6 vs. 4 (one-sided p)	0.4469 +	0.3077 +
Groups 1+6 vs. 5 (one-sided p)	0.0409 + *	0.0511 +

a = Including one accidental death.
+ = Effect in the positive (increasing) direction.
* = Significant at $p \leq 0.05$.

Table 2
Results of Statistical Analyses of Mortality Data for Female Rats

Group	1	2	3	4	5	6
Dose	0	2	20	60	80	0
Number of Deaths						
Weeks 0-52	0	2	2	1	0	0
Weeks 53-78	12	10	12	4	7	14
Weeks 79-92	10	11	10	11	12	15
Weeks 93-103	8	11	11	13	9	8
Terminal Sacrifice Weeks	20	16	15	21	22	13
Unadjusted Mortality	30/50 (0.60)	34/50 (0.68)	35/50 (0.70)	29/50 (0.58)	28/50 (0.56)	37/50 (0.74)
Kaplan-Meier Estimate (Final)	0.600	0.680	0.700	0.580	0.560	0.740

	Cox-Tarone Test	Gehan-Breslow Test
Groups 1+6 vs. 2-5 Trend (one-sided p)	0.0302 - *	0.0144 - *
Departure from Trend (two-sided p)	0.6048	0.5120
Homogeneity (two-sided p)	0.2427	0.1318
Groups 1+6 vs. 2 (one-sided p)	0.4698 +	0.4753 +
Groups 1+6 vs. 3 (one-sided p)	0.4187 +	0.3876 +
Groups 1+6 vs. 4 (one-sided p)	0.0728 -	0.0292 - *
Groups 1+6 vs. 5 (one-sided p)	0.0751 -	0.0384 - *

+ = Effect in the positive (increasing) direction.
- = Effect in the negative (decreasing) direction.
* = Significant at $p \leq 0.05$.

Table 3
Results of Statistical Analyses of Neoplastic Lesions for Male Rats

Group	1	2	3	4	5	6
Dose	0	2	20	60	80	0
Adrenal (AD) – Benign Pheochromocytoma, Benign (302)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	9	6	7	6	7	9
Total Incidence Rate	9/50	6/50	7/50	6/50	7/50	9/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.7578						
Adrenal (AD) – Malignant Pheochromocytoma, Malignant (492)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	0	2	2	0	0	1
Total Incidence Rate	0/50	2/50	2/50	0/50	0/50	1/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.7467						
Adrenal (AD) – Benign Pheochromocytoma/Malignant Pheochromocytoma (302/492)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	9	7	9	6	7	9
Total Incidence Rate	9/50	7/50	9/50	6/50	7/50	9/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.7394						
Brain (BR) – Malignant Astrocytoma, Malignant (229)						
Fatal Incidence	2	0	0	0	0	1
Incidental Incidence	0	1	1	0	0	0
Total Incidence Rate	2/50	1/50	1/50	0/50	0/50	1/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9612						
Mesenteric Lymph Node (MS) – Hemangioma, Benign (423)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	1	0	1	0	1	4
Total Incidence Rate	1/50	0/50	1/48	0/50	1/50	4/49
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9419						
Mesenteric Lymph Node (MS) – Hemangiosarcoma, Malignant (554)						
Total Incidence Rate	0/50	1/50	0/48	0/50	0/50	0/49
Note: Incidences across groups did not meet the selection criterion.						
Mesenteric Lymph Node (MS) – Hemangioma/Hemangiosarcoma (423/554)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	1	1	1	0	1	4
Total Incidence Rate	1/50	1/50	1/48	0/50	1/50	4/49
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9471						
Pancreas (PA) – Islet Cell Adenoma, Benign (332)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	2	1	4	2	4	2
Total Incidence Rate	2/50	1/50	4/49	2/50	4/49	2/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.0920						
Pancreas (PA) – Islet Cell Carcinoma, Benign (299)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	0	0	0	0	2	2
Total Incidence Rate	0/50	0/50	0/49	0/50	2/49	2/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.3900						

Table 3 (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Male Rats

Group	1	2	3	4	5	6
Dose	0	2	20	60	80	0
Pancreas (PA) – Islet Cell Adenoma/Carcinoma (332/299)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	2	1	4	2	6	4
Total Incidence Rate	2/50	1/50	4/49	2/50	6/49	4/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.0812						
Pancreas (PA) – Acinar-Islet Cell Adenoma, Benign (550)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	0	0	2	0	0	0
Total Incidence Rate	0/50	0/50	2/49	0/50	0/49	0/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.4197						
Pancreas (PA) – Islet Cell Adenoma/Carcinoma/Acinar-Islet Cell Adenoma (332/299/550)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	2	1	6	2	6	4
Total Incidence Rate	2/50	1/50	6/49	2/50	6/49	4/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.0699						
Pituitary (PI) – Adenoma, Benign (168)						
Fatal Incidence	7	7	8	6	4	3
Incidental Incidence	21	15	15	12	16	20
Total Incidence Rate	28/50	22/50	23/49	18/50	20/50	23/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9051						
Pituitary (PI) – Carcinoma, Malignant (271)						
Total Incidence Rate	0/50	0/50	1/49	0/50	0/50	0/50
Note: Incidences across groups did not meet the selection criterion.						
Pituitary (PI) – Adenoma/Carcinoma (168/271)						
Fatal Incidence	7	7	9	6	4	3
Incidental Incidence	21	15	15	12	16	20
Total Incidence Rate	28/50	22/50	24/49	18/50	20/50	23/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9003						
Skin + Subcutis (SK) – Benign Basal Cell Tumor, Benign (566)						
Total Incidence Rate	0/50	2/50	0/50	0/50	0/50	0/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.7533						
Skin + Subcutis (SK) – Fibroma, Benign (319)						
Total Incidence Rate	3/50	3/50	5/50	0/50	3/50	4/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.7559						
Skin + Subcutis (SK) – Fibrosarcoma, Malignant (277)						
Total Incidence Rate	4/50	1/50	0/50	2/50	2/50	2/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.7562						
Skin + Subcutis (SK) – Fibroma/Fibrosarcoma (319/277)						
Total Incidence Rate	7/50	4/50	5/50	2/50	5/50	6/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.8253						
Skin + Subcutis (SK) – Lipoma, Benign (384)						
Total Incidence Rate	0/50	1/50	1/50	3/50	1/50	0/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.0461						

Table 3 (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Male Rats

Group	1	2	3	4	5	6
Dose	0	2	20	60	80	0
Skin + Subcutis (SK) – Benign Hair Follicle Tumor, Benign (543)						
Total Incidence Rate	0/50	0/50	3/50	2/50	2/50	4/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.3115						
Skin + Subcutis (SK) – Squamous Cell Papilloma, Benign (448)						
Total Incidence Rate	1/50	0/50	0/50	0/50	0/50	1/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 1.0000						
Skin + Subcutis (SK) – Squamous Cell Carcinoma, Malignant (395)						
Total Incidence Rate	0/50	0/50	1/50	0/50	2/50	0/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.0388						
Skin + Subcutis (SK) – Squamous Cell Papilloma/Carcinoma (448/395)						
Total Incidence Rate	1/50	0/50	1/50	0/50	2/50	1/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.3279						
Skin + Subcutis (SK) – Dermal Fibroma, Benign (450)						
Total Incidence Rate	8/50	3/50	3/50	3/50	5/50	3/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.6126						
Skin + Subcutis (SK) – Sebaceous Cell Adenoma, Benign (514)						
Total Incidence Rate	1/50	2/50	0/50	0/50	0/50	1/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9538						
Skin + Subcutis (SK) – Sarcoma, Malignant (115)						
Total Incidence Rate	0/50	2/50	1/50	0/50	1/50	2/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.7172						
Testis (TE) – Benign Interstitial Cell Tumor, Benign (420)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	0	5	3	2	0	2
Total Incidence Rate	0/50	5/50	3/50	2/50	0/50	2/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.6995						
Thymus (TH) – Benign Thymoma, Benign (411)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	1	0	0	0	0	1
Total Incidence Rate	1/49	0/47	0/46	0/50	0/47	1/44
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 1.0000						
Thymus (TH) – Malignant Thymoma, Malignant (173)						
Total Incidence Rate	0/49	0/47	1/46	0/50	0/47	0/44
Note: Incidences across groups did not meet the selection criterion.						
Thymus (TH) – Benign Thymoma/Malignant Thymoma (411/173)						
Fatal Incidence	0	0	1	0	0	0
Incidental Incidence	1	0	0	0	0	1
Total Incidence Rate	1/49	0/47	1/46	0/50	0/47	1/44
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9023						

Table 3 (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Male Rats

Group	1	2	3	4	5	6
Dose	0	2	20	60	80	0
Thyroid (TY) – C-Cell Adenoma, Benign (210)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	9	10	11	11	6	5
Total Incidence Rate	9/50	10/50	11/48	11/48	6/48	5/48
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.3950						
Thyroid (TY) – C-Cell Carcinoma, Malignant (364)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	1	0	0	0	2	0
Total Incidence Rate	1/50	0/50	0/48	0/48	2/48	0/48
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.1699						
Thyroid (TY) – C-Cell Adenoma/Carcinoma (210/364)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	10	10	11	11	8	5
Total Incidence Rate	10/50	10/50	11/48	11/48	8/48	5/48
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.2833						
Thyroid (TY) – Follicular Cell Adenoma, Benign (383)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	1	0	1	2	0	0
Total Incidence Rate	1/50	0/50	1/48	2/48	0/48	0/48
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.3248						
Thyroid (TY) – Follicular Cell Carcinoma, Malignant (551)						
Total Incidence Rate	0/50	1/50	1/48	0/48	0/48	0/48
Note: Incidences across groups did not meet the selection criterion.						
Thyroid (TY) – Follicular Cell Adenoma/Carcinoma (383/551)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	1	1	2	2	0	0
Total Incidence Rate	1/50	1/50	2/48	2/48	0/48	0/48
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.3643						
Multiple Organs – Hemangioma, Benign (423/473)						
Fatal Incidence	0	0	0	0	1	0
Incidental Incidence	1	0	1	0	1	4
Total Incidence Rate	1/50	0/50	1/48	0/50	2/50	4/49
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.8030						
Multiple Organs – Hemangiosarcoma, Malignant (536/263/554)						
Fatal Incidence	0	0	0	0	0	1
Incidental Incidence	0	2	0	0	0	1
Total Incidence Rate	0/50	2/50	0/49	0/50	0/50	2/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9559						
Multiple Organs – Hemangioma/Hemangiosarcoma (423/473/536/263/554) [Blood Vessel Tumor]						
Fatal Incidence	0	0	0	0	1	1
Incidental Incidence	1	2	1	0	1	5
Total Incidence Rate	1/50	2/50	1/49	0/50	2/50	6/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9462						

Table 3 (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Male Rats

Group	1	2	3	4	5	6
Dose	0	2	20	60	80	0
Multiple Organs – Fibroma/Fibrosarcoma/Dermal Fibroma/Sarcoma (319/277/408/450/115) [Fibroblastic Tumor]						
Fatal Incidence	13	9	9	4	11	11
Incidental Incidence	0	1	0	0	0	0
Total Incidence Rate	13/50	10/50	9/50	4/50	11/50	11/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.8238						
Multiple Organs – Malignant Astrocytoma/Glioma/Oligodendroglioma (229/432/511) [Glial Cell Tumor]						
Fatal Incidence	2	1	0	0	0	1
Incidental Incidence	1	1	1	0	0	0
Total Incidence Rate	3/50	2/50	1/50	0/50	0/50	1/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9833						
Multiple Organs – Histiocytic Sarcoma (385/304) [Histiocytic Sarcoma]						
Fatal Incidence	1	1	1	1	1	0
Incidental Incidence	0	1	0	0	0	0
Total Incidence Rate	1/50	2/50	1/50	1/50	1/50	0/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.3977						
Multiple Organs – Squamous Cell Papilloma/Carcinoma/Benign Hair Follicle Tumor (448/456/547/395/543) [S/A Squamous Cell Tumor]						
Total Incidence Rate	1/50	0/50	5/50	2/50	5/50	7/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.2658						
HAEM/LYMPH/RETIC (HE) – Malignant Lymphoma - Pleomorphic, Malignant (260)						
Fatal Incidence	0	0	0	0	1	0
Incidental Incidence	0	0	0	0	1	0
Total Incidence Rate	0/50	0/50	0/50	0/50	2/50	0/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.0217 #						
Groups 1+6 vs. 5 One-sided (Upper-tailed) p = 0.0878						
HAEM/LYMPH/RETIC (HE) – Lymphocytic Leukemia, Malignant (99)						
Fatal Incidence	1	0	1	0	0	2
Incidental Incidence	1	1	0	0	0	0
Total Incidence Rate	2/50	1/50	1/50	0/50	0/50	2/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9815						
HAEM/LYMPH/RETIC (HE) – Malignant Lymphoma, Malignant (260/99) [Lymphoid Tumor]						
Fatal Incidence	1	0	1	0	1	2
Incidental Incidence	1	1	0	0	1	0
Total Incidence Rate	2/50	1/50	1/50	0/50	2/50	2/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.7008						

= Significant at $p \leq 0.025$ for trend for rare tumor type.

Table 4
Results of Statistical Analyses of Neoplastic Lesions for Female Rats

Group	1	2	3	4	5	6
Dose	0	2	20	60	80	0
Adrenal (AD) – Benign Pheochromocytoma, Benign (302)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	4	4	3	2	2	4
Total Incidence Rate	4/50	4/50	3/50	2/50	2/50	4/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9293						
Adrenal (AD) – Malignant Pheochromocytoma, Malignant (492)						
Total Incidence Rate	0/50	0/50	1/50	0/50	0/50	0/50
Note: Incidences across groups did not meet the selection criterion.						
Adrenal (AD) – Benign Pheochromocytoma/Malignant Pheochromocytoma (302/492)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	4	4	4	2	2	4
Total Incidence Rate	4/50	4/50	4/50	2/50	2/50	4/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9206						
Adrenal (AD) – Cortical Adenoma, Benign (524)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	0	0	2	1	0	0
Total Incidence Rate	0/50	0/50	2/50	1/50	0/50	0/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.3678						
Adrenal (AD) – Cortical Carcinoma, Malignant (498)						
Total Incidence Rate	0/50	0/50	0/50	1/50	0/50	0/50
Note: Incidences across groups did not meet the selection criterion.						
Adrenal (AD) – Cortical Adenoma/Carcinoma (524/498)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	0	0	2	2	0	0
Total Incidence Rate	0/50	0/50	2/50	2/50	0/50	0/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.2485						
Liver (LI) – Hepatocellular Adenoma, Benign (388)						
Total Incidence Rate	0/50	1/50	0/50	1/50	1/50	1/50
Note: Incidence across groups did not meet the selection criterion.						
Liver (LI) – Hepatocellular Carcinoma, Malignant (564)						
Total Incidence Rate	0/50	0/50	0/50	1/50	0/50	0/50
Note: Incidences across groups did not meet the selection criterion.						
Liver (LI) – Hepatocellular Adenoma/Carcinoma (388/564)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	0	1	0	2	1	1
Total Incidence Rate	0/50	1/50	0/50	2/50	1/50	1/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.2892						
Mammary Gland (MA) – Fibroadenoma, Benign (179)						
Total Incidence Rate	31/50	28/50	32/50	25/49	27/49	28/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9320						
Mammary Gland (MA) – Adenoma, Benign (276)						
Total Incidence Rate	6/50	1/50	3/50	2/49	4/49	3/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.7782						

Table 4 (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Female Rats

Group	1	2	3	4	5	6
Dose	0	2	20	60	80	0
Mammary Gland (MA) – Adenocarcinoma, Malignant (192)						
Total Incidence Rate	8/50	7/50	11/50	6/49	5/49	11/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9511						
Mammary Gland (MA) – Fibroadenoma/Adenoma, Benign (179/276)						
Total Incidence Rate	32/50	28/50	32/50	27/49	28/49	29/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9184						
Mammary Gland (MA) – Fibroadenoma/Adenoma/Adenocarcinoma (179/276/192)						
Total Incidence Rate	35/50	31/50	39/50	30/49	30/49	34/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9599						
Pancreas (PA) – Islet Cell Adenoma, Benign (332)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	0	0	1	2	1	0
Total Incidence Rate	0/50	0/49	1/50	2/50	1/50	0/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.0769						
Pancreas (PA) – Islet Cell Carcinoma, Malignant (299)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	1	0	1	1	2	0
Total Incidence Rate	1/50	0/49	1/50	1/50	2/50	0/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.1176						
Pancreas (PA) – Islet Cell Adenoma/Carcinoma (332/299)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	1	0	2	3	3	0
Total Incidence Rate	1/50	0/49	2/50	3/50	3/50	0/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.0233 #						
Groups 1+6 vs. 2 One-sided (Upper-tailed) p = 1.0000						
Groups 1+6 vs. 3 One-sided (Upper-tailed) p = 0.2603						
Groups 1+6 vs. 4 One-sided (Upper-tailed) p = 0.2111						
Groups 1+6 vs. 5 One-sided (Upper-tailed) p = 0.1145						
Pituitary (PI) – Adenoma, Benign (168)						
Fatal Incidence	12	12	8	9	11	14
Incidental Incidence	22	25	19	19	21	22
Total Incidence Rate	34/50	37/49	27/50	28/49	32/50	36/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9816						
Pituitary (PI) – Carcinoma, Malignant (271)						
Fatal Incidence	1	1	2	1	0	2
Incidental Incidence	1	0	0	0	0	0
Total Incidence Rate	2/50	1/49	2/50	1/49	0/50	2/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9429						
Pituitary (PI) – Adenoma/Carcinoma (168/271)						
Fatal Incidence	13	13	10	10	11	16
Incidental Incidence	23	25	19	19	21	22
Total Incidence Rate	36/50	38/49	29/50	29/49	32/50	38/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.9945						

= Significant at $p \leq 0.025$ for trend for rare tumor type.

Table 4 (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Female Rats

Group	1	2	3	4	5	6
Dose	0	2	20	60	80	0
Skin + Subcutis (SK) – Fibroma, Benign (319)						
Total Incidence Rate	0/50	4/50	1/50	4/50	1/50	1/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.3691						
Skin + Subcutis (SK) – Squamous Cell Papilloma, Benign (448)						
Total Incidence Rate	0/50	0/50	0/50	0/50	0/50	2/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 1.0000						
Skin + Subcutis (SK) – Histiocytic Sarcoma, Malignant (304)						
Total Incidence Rate	2/50	2/50	0/50	2/50	2/50	1/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.5332						
Thyroid (TY) – C-Cell Adenoma, Benign (210)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	8	6	7	5	4	1
Total Incidence Rate	8/50	6/49	7/48	5/50	4/49	1/49
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.6389						
Thyroid (TY) – C-Cell Carcinoma, Malignant (364)						
Total Incidence Rate	0/50	0/49	0/48	0/50	0/49	1/49
Note: Incidences across groups did not meet the selection criterion.						
Thyroid (TY) – C-Cell Adenoma/Carcinoma (210/364)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	8	6	7	5	4	2
Total Incidence Rate	8/50	6/49	7/48	5/50	4/49	2/49
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.7175						
Thyroid (TY) – Follicular Cell Adenoma, Benign (383)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	1	2	1	0	0	0
Total Incidence Rate	1/50	2/49	1/48	0/50	0/49	0/49
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.8790						
Uterus (UT) – Stromal Polyp, Benign (307)						
Fatal Incidence	0	0	0	0	2	0
Incidental Incidence	5	6	0	8	10	6
Total Incidence Rate	5/50	6/50	0/50	8/50	12/50	6/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.0815						
Uterus (UT) – Stromal Sarcoma, Malignant (462)						
Total Incidence Rate	0/50	0/50	0/50	0/50	1/50	0/50
Note: Incidences across groups did not meet the selection criterion.						
Uterus (UT) – Stromal Polyp/Sarcoma (307/462)						
Fatal Incidence	0	0	0	0	2	0
Incidental Incidence	5	6	0	8	11	6
Total Incidence Rate	5/50	6/50	0/50	8/50	13/50	6/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.0505						
Vagina (VA) – Stromal Sarcoma, Malignant (500)						
Total Incidence Rate	0/50	0/50	0/50	1/50	0/50	0/50
Note: Incidences across groups did not meet the selection criterion.						

Table 4 (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Female Rats

Group	1	2	3	4	5	6
Dose	0	2	20	60	80	0
Uterus/Vagina (UT/VA) – Stromal Polyp/Sarcoma (307/462/500)						
Fatal Incidence	0	0	0	0	2	0
Incidental Incidence	5	6	0	9	11	6
Total Incidence Rate	5/50	6/50	0/50	9/50	13/50	6/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.0389						
Uterus (UT) – Benign Granular Cell Tumor, Benign (479)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	2	1	1	1	1	0
Total Incidence Rate	2/50	1/50	1/50	1/50	1/50	0/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.6533						
Vagina (VA) – Benign Granular Cell Tumor, Benign (427)						
Total Incidence Rate	0/50	1/50	0/50	0/50	0/50	0/50
Note: Incidence across groups did not meet the selection criterion.						
Uterus/Vagina (UT/VA) – Benign Granular Cell Tumor, Benign (479/427)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	2	2	1	1	1	0
Total Incidence Rate	2/50	2/50	1/50	1/50	1/50	0/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.7184						
Uterus (UT) – Adenoma, Benign (486)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	0	0	0	2	0	0
Total Incidence Rate	0/50	0/50	0/50	2/50	0/50	0/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.2061						
Uterus (UT) – Adenocarcinoma, Malignant (593)						
Total Incidence Rate	0/50	0/50	0/50	0/50	1/50	0/50
Note: Incidences across groups did not meet the selection criterion.						
Uterus (UT) – Adenoma/Adenocarcinoma (486/593)						
Fatal Incidence	0	0	0	0	0	0
Incidental Incidence	0	0	0	2	1	0
Total Incidence Rate	0/50	0/50	0/50	2/50	1/50	0/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.0666						
Multiple Organs – Hemangioma, Benign (586/423)						
Total Incidence Rate	0/50	1/50	1/50	0/50	0/50	0/50
Note: Incidences across groups did not meet the selection criterion.						
Multiple Organs – Hemangiosarcoma, Malignant (189)						
Total Incidence Rate	0/50	0/50	1/50	0/50	0/50	0/50
Note: Incidences across groups did not meet the selection criterion.						
Multiple Organs – Hemangioma/Hemangiosarcoma (586/423/189) [Blood Vessel Tumor]						
Fatal Incidence	0	0	1	0	0	0
Incidental Incidence	0	1	1	0	0	0
Total Incidence Rate	0/50	1/50	2/50	0/50	0/50	0/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.6052						

Table 4 (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Female Rats

Group	1	2	3	4	5	6
Dose	0	2	20	60	80	0
Multiple Organs – Fibroma/Dermal Fibroma/Sarcoma (319/485/450/115) [Fibroblastic Tumor]						
Total Incidence Rate	1/50	4/50	1/50	7/50	1/50	1/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.2612						
HAEM/LYMPH/RETIC (HE) – Malignant Lymphoma - Lymphocytic, Malignant (613)						
Total Incidence Rate	0/50	0/50	0/50	0/50	1/50	0/50
Note: Incidences across groups did not meet the selection criterion.						
HAEM/LYMPH/RETIC (HE) – Lymphocytic Leukemia, Malignant (99)						
Fatal Incidence	0	0	1	0	0	0
Incidental Incidence	1	0	0	0	2	0
Total Incidence Rate	1/50	0/50	1/50	0/50	2/50	0/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.2303						
HAEM/LYMPH/RETIC – Malignant Lymphoma, Malignant (613/99) [Lymphoid Tumor]						
Fatal Incidence	0	0	1	0	0	0
Incidental Incidence	1	0	0	0	3	0
Total Incidence Rate	1/50	0/50	1/50	0/50	3/50	0/50
Groups 1+6 vs. 2-5 One-sided (Upper-tailed) Trend p = 0.0979						

Table 5
Results of Statistical Analyses of Mortality Data for Male Mice

Group	1	2	3	4	6
Dose	0	10	60	200	0
Number of Deaths					
Weeks 0-52	2	0	2 b	2 b	0
Weeks 53-78	1	0	0	3	0
Weeks 79-92	4	5	5	2	5
Weeks 93-107	3	4 a	6	4	9
Terminal Sacrifice Weeks	41	42	38	40	37
Unadjusted Mortality	10/51 (0.196)	8/51 (0.157)	11/51 (0.216)	9/51 (0.176)	14/51 (0.275)
Kaplan-Meier Estimate (Final)	0.196	0.157	0.224	0.184	0.275

	Cox-Tarone Test	Gehan-Breslow Test
Groups 1+6 vs. 2-4 Trend (one-sided p)	0.3099 -	0.3001 -
Departure from Trend (two-sided p)	0.5919	0.6280
Homogeneity (two-sided p)	0.7154	0.7517
Groups 1+6 vs. 2 (one-sided p)	0.1932 -	0.1637 -
Groups 1+6 vs. 3 (one-sided p)	0.4297 -	0.4209 -
Groups 1+6 vs. 4 (one-sided p)	0.3101 -	0.2611 -

a = Including one accidental death.
b = Including two accidental deaths.
- = Effect in the negative (decreasing) direction.

Table 6
Results of Statistical Analyses of Mortality Data for Female Mice

Group	1	2	3	4	6
Dose	0	10	60	200	0
Number of Deaths					
Weeks 0-52	1	3 a	3 c	2 a	2 a
Weeks 53-78	1	1	2 a	1	4
Weeks 79-92	4	2	2	2	8
Weeks 93-107	5	12	7	7	4
Terminal Sacrifice Weeks	40	33	37	39	33
Unadjusted Mortality	11/51 (0.216)	17/51 (0.333)	10/51 (0.196)	11/51 (0.216)	17/51 (0.333)
Kaplan-Meier Estimate (Final)	0.216	0.340	0.212	0.220	0.340

	Cox-Tarone Test	Gehan-Breslow Test
Groups 1+6 vs. 2-4 Trend (one-sided p)	0.1236 -	0.0839 -
Departure from Trend (two-sided p)	0.5124	0.5662
Homogeneity (two-sided p)	0.4232	0.3853
Groups 1+6 vs. 2 (one-sided p)	0.3530 +	0.3766 +
Groups 1+6 vs. 3 (one-sided p)	0.1995 -	0.1182 -
Groups 1+6 vs. 4 (one-sided p)	0.2354 -	0.1547 -

a = Including one accidental death.
c = Including three accidental deaths.
+ = Effect in the positive (increasing) direction.
- = Effect in the negative (decreasing) direction.

Table 7
Results of Statistical Analyses of Neoplastic Lesions for Male Mice

Group	1	2	3	4	6
Dose	0	10	60	200	0
Adrenal (AD) – Cortical Adenoma, Benign (224)					
Fatal Incidence	0	0	0	0	0
Incidental Incidence	5	2	1	1	0
Total Incidence Rate	5/51	2/51	1/51	1/50	0/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8760					
Harderian Gland (HG) – Adenoma, Benign (52)					
Fatal Incidence	1	3	1	0	2
Incidental Incidence	4	4	5	3	6
Total Incidence Rate	5/51	7/51	6/51	3/51	8/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9101					
Harderian Gland (HG) – Adenocarcinoma, Malignant (202)					
Fatal Incidence	0	0	0	1	0
Incidental Incidence	0	0	0	1	0
Total Incidence Rate	0/51	0/51	0/51	2/51	0/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.0397					
Harderian Gland (HG) – Adenoma/Adenocarcinoma (52/202)					
Fatal Incidence	1	3	1	1	2
Incidental Incidence	4	4	5	4	6
Total Incidence Rate	5/51	7/51	6/51	5/51	8/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7458					
Liver (LI) – Hemangioma, Benign (294)					
Fatal Incidence	1	0	0	0	0
Incidental Incidence	1	1	0	0	3
Total Incidence Rate	2/51	1/51	0/51	0/51	3/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9965					
Liver (LI) – Hemangiosarcoma, Malignant (289)					
Total Incidence Rate	1/51	0/51	0/51	0/51	0/51
Note: Incidences across groups did not meet the selection criterion.					
Liver (LI) – Hemangioma/Hemangiosarcoma (294/289)					
Fatal Incidence	1	0	0	0	0
Incidental Incidence	2	1	0	0	3
Total Incidence Rate	3/51	1/51	0/51	0/51	3/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9987					
Liver (LI) – Hepatocellular Adenoma, Benign (43)					
Fatal Incidence	1	1	1	0	0
Incidental Incidence	12	11	18	25	16
Total Incidence Rate	13/51	12/51	19/51	25/51	16/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.0050 *					
Groups 1+6 vs. 2 One-sided (Upper-tailed) p = 0.8034					
Groups 1+6 vs. 3 One-sided (Upper-tailed) p = 0.1525					
Groups 1+6 vs. 4 One-sided (Upper-tailed) p = 0.0095 *					
Liver (LI) – Hepatocellular Carcinoma, Malignant (53)					
Fatal Incidence	2	0	4	5	5
Incidental Incidence	6	10	7	11	5
Total Incidence Rate	8/51	10/51	11/51	16/51	10/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.0315					

* = Significant at $p \leq 0.005$ for trend or at $p \leq 0.01$ for group comparison for common tumor type.

Table 7 (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Male Mice

Group	1	2	3	4	6
Dose	0	10	60	200	0
Liver (LI) – Hepatocellular Adenoma/Carcinoma (43/53)					
Fatal Incidence	3	1	5	5	5
Incidental Incidence	16	19	20	29	18
Total Incidence Rate	19/51	20/51	25/51	34/51	23/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.0024 *					
Groups 1+6 vs. 2 One-sided (Upper-tailed) p = 0.7300					
Groups 1+6 vs. 3 One-sided (Upper-tailed) p = 0.1854					
Groups 1+6 vs. 4 One-sided (Upper-tailed) p = 0.0039 *					
Liver (LI) – Histiocytic Sarcoma, Malignant (196)					
Fatal Incidence	0	0	0	1	0
Incidental Incidence	0	0	0	1	0
Total Incidence Rate	0/51	0/51	0/51	2/51	0/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.0398					
Lung (LU) – Bronchiolo-Alveolar Adenoma, Benign (206)					
Fatal Incidence	0	0	0	0	0
Incidental Incidence	9	5	6	13	8
Total Incidence Rate	9/51	5/51	6/51	13/51	8/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.1492					
Lung (LU) – Bronchiolo-Alveolar Carcinoma, Malignant (225)					
Fatal Incidence	0	0	0	0	0
Incidental Incidence	0	4	1	1	2
Total Incidence Rate	0/51	4/51	1/51	1/51	2/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5719					
Lung (LU) – Bronchiolo-Alveolar Adenoma/Carcinoma (206/225)					
Fatal Incidence	0	0	0	0	0
Incidental Incidence	9	9	7	14	10
Total Incidence Rate	9/51	9/51	7/51	14/51	10/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.1710					
Spleen (SP) – Hemangioma, Benign (249)					
Fatal Incidence	0	0	0	0	0
Incidental Incidence	0	0	2	0	0
Total Incidence Rate	0/51	0/51	2/51	0/51	0/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.2401					
Spleen (SP) – Hemangiosarcoma, Malignant (267)					
Total Incidence Rate	0/51	0/51	0/51	0/51	1/51
Note: Incidences across groups did not meet the selection criterion.					
Spleen (SP) – Hemangioma/Hemangiosarcoma (249/267)					
Fatal Incidence	0	0	0	0	1
Incidental Incidence	0	0	2	0	0
Total Incidence Rate	0/51	0/51	2/51	0/51	1/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.4948					
Thyroid (TY) – Follicular Cell Adenoma, Benign (90)					
Total Incidence Rate	1/51	0/51	1/51	1/51	0/51
Note: Incidences across groups did not meet the selection criterion.					

* = Significant at $p \leq 0.005$ for trend or at $p \leq 0.01$ for group comparison for common tumor type.

Table 7 (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Male Mice

Group	1	2	3	4	6
Dose	0	10	60	200	0
Thyroid (TY) – Follicular Cell Carcinoma, Malignant (232)					
Total Incidence Rate	0/51	0/51	0/51	1/51	0/51
Note: Incidences across groups did not meet the selection criterion.					
Thyroid (TY) – Follicular Cell Adenoma/Carcinoma (90/232)					
Fatal Incidence	0	0	0	0	0
Incidental Incidence	1	0	1	2	0
Total Incidence Rate	1/51	0/51	1/51	2/51	0/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.1068					
Multiple Organs – Hemangioma, Benign (335/294/227/249)					
Fatal Incidence	1	0	0	0	0
Incidental Incidence	1	1	2	0	4
Total Incidence Rate	2/51	1/51	2/51	0/51	4/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9714					
Multiple Organs – Hemangiosarcoma, Malignant (289/267)					
Fatal Incidence	0	0	0	0	1
Incidental Incidence	1	0	0	0	0
Total Incidence Rate	1/51	0/51	0/51	0/51	1/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 1.0000					
Multiple Organs – Hemangioma/Hemangiosarcoma (335/294/227/249/289/267) [Blood Vessel Tumor]					
Fatal Incidence	1	0	0	0	1
Incidental Incidence	2	1	2	0	4
Total Incidence Rate	3/51	1/51	2/51	0/51	5/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9925					
Multiple Organs – Histiocytic Sarcoma (462/196) [Histiocytic Sarcoma]					
Fatal Incidence	0	0	0	1	0
Incidental Incidence	0	0	1	1	0
Total Incidence Rate	0/51	0/51	1/51	2/51	0/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.0311					

Table 8
Results of Statistical Analyses of Neoplastic Lesions for Female Mice

Group	1	2	3	4	6
Dose	0	10	60	200	0
Harderian Gland (HG) – Adenoma, Benign (52)					
Fatal Incidence	1	3	0	0	1
Incidental Incidence	3	2	0	3	3
Total Incidence Rate	4/51	5/51	0/51	3/51	4/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8953					
Harderian Gland (HG) – Adenocarcinoma, Malignant (202)					
Total Incidence Rate	1/51	1/51	1/51	1/51	0/51
Note: Incidences across groups did not meet the selection criterion.					
Harderian Gland (HG) – Adenoma/Adenocarcinoma (52/202)					
Fatal Incidence	1	3	1	1	1
Incidental Incidence	4	3	0	3	3
Total Incidence Rate	5/51	6/51	1/51	4/51	4/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8093					
Liver (LI) – Hepatocellular Adenoma, Benign (43)					
Fatal Incidence	0	0	0	0	0
Incidental Incidence	3	3	6	9	3
Total Incidence Rate	3/51	3/51	6/51	9/51	3/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.0114 @					
Liver (LI) – Hepatocellular Carcinoma, Malignant (53)					
Fatal Incidence	0	0	0	1	0
Incidental Incidence	0	1	0	3	0
Total Incidence Rate	0/51	1/51	0/51	4/51	0/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.0078 @					
Liver (LI) – Hepatocellular Adenoma/Carcinoma (43/53)					
Fatal Incidence	0	0	0	1	0
Incidental Incidence	3	4	6	11	3
Total Incidence Rate	3/51	4/51	6/51	12/51	3/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.0012 *					
Groups 1+6 vs. 2 One-sided (Upper-tailed) p = 0.3780					
Groups 1+6 vs. 3 One-sided (Upper-tailed) p = 0.1395					
Groups 1+6 vs. 4 One-sided (Upper-tailed) p = 0.0031 *					
Lung (LU) – Bronchiolo-Alveolar Adenoma, Benign (206)					
Fatal Incidence	0	0	0	0	0
Incidental Incidence	3	3	1	1	3
Total Incidence Rate	3/51	3/51	1/51	1/51	3/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9272					
Lung (LU) – Bronchiolo-Alveolar Carcinoma, Malignant (225)					
Total Incidence Rate	0/51	0/51	1/51	0/51	0/51
Note: Incidences across groups did not meet the selection criterion.					

@ = Not significant at $p \leq 0.005$ for trend for common tumor type.
* = Significant at $p \leq 0.005$ for trend or at $p \leq 0.01$ for group comparison for common tumor type.

Table 8 (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Female Mice

Group	1	2	3	4	6
Dose	0	10	60	200	0
Lung (LU) – Bronchiolo-Alveolar Adenoma/Carcinoma, Malignant (206/225)					
Fatal Incidence	0	0	0	0	0
Incidental Incidence	3	3	2	1	3
Total Incidence Rate	3/51	3/51	2/51	1/51	3/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8822					
Mammary Gland (MA) – Adenocarcinoma, Malignant (188)					
Total Incidence Rate	0/50	2/50	3/51	2/51	3/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.3719					
Pituitary (PI) – Adenoma, Benign (79)					
Fatal Incidence	0	1	0	2	1
Incidental Incidence	7	3	8	6	2
Total Incidence Rate	7/51	4/50	8/51	8/51	3/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.1416					
Skin + Subcutis (SK) – Fibrosarcoma, Malignant (83)					
Total Incidence Rate	1/51	2/51	1/51	0/51	1/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8299					
Spleen (SP) – Hemangiosarcoma, Malignant (267)					
Fatal Incidence	1	0	0	0	0
Incidental Incidence	1	0	0	0	0
Total Incidence Rate	2/51	0/51	0/51	0/51	0/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 1.0000					
Thyroid (TY) – Follicular Cell Adenoma, Benign (90)					
Fatal Incidence	0	0	0	0	0
Incidental Incidence	2	0	2	3	2
Total Incidence Rate	2/51	0/51	2/51	3/51	2/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.2647					
Uterus (UT) – Stromal Polyp, Benign (149)					
Fatal Incidence	1	0	0	0	0
Incidental Incidence	0	2	2	4	1
Total Incidence Rate	1/51	2/51	2/51	4/51	1/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.0649					
Uterus (UT) – Hemangioma, Benign (87)					
Fatal Incidence	0	1	0	0	0
Incidental Incidence	0	1	0	1	1
Total Incidence Rate	0/51	2/51	0/51	1/51	1/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.4971					
Uterus (UT) – Leiomyoma, Benign (397)					
Fatal Incidence	0	0	0	0	0
Incidental Incidence	1	1	0	0	1
Total Incidence Rate	1/51	1/51	0/51	0/51	1/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9371					
Uterus (UT) – Histiocytic Sarcoma, Malignant (189)					
Fatal Incidence	0	0	0	0	0
Incidental Incidence	0	0	1	2	1
Total Incidence Rate	0/51	0/51	1/51	2/51	1/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.0968					

Table 8 (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Female Mice

Group	1	2	3	4	6
Dose	0	10	60	200	0
Uterus (UT) – Adenoma, Benign (380)					
Total Incidence Rate	0/51	0/51	1/51	0/51	0/51
Note: Incidences across groups did not meet the selection criterion.					
Uterus (UT) – Adenocarcinoma, Malignant (406)					
Fatal Incidence	0	1	0	0	0
Incidental Incidence	0	1	0	0	0
Total Incidence Rate	0/51	2/51	0/51	0/51	0/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.6967					
Uterus (UT) – Adenoma/Adenocarcinoma (380/406)					
Fatal Incidence	0	1	0	0	0
Incidental Incidence	0	1	1	0	0
Total Incidence Rate	0/51	2/51	1/51	0/51	0/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5171					
Multiple Organs – Hemangioma, Benign (87/294/427/227/385)					
Fatal Incidence	0	1	0	0	0
Incidental Incidence	0	2	1	1	3
Total Incidence Rate	0/51	3/51	1/51	1/51	3/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7312					
Multiple Organs – Hemangiosarcoma, Malignant (267/359/289)					
Fatal Incidence	2	0	0	0	0
Incidental Incidence	1	0	0	1	0
Total Incidence Rate	3/51	0/51	0/51	1/51	0/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8443					
Multiple Organs – Hemangioma/Hemangiosarcoma (87/294/427/227/385/267/359/289) [Blood Vessel Tumor]					
Fatal Incidence	2	1	0	0	0
Incidental Incidence	1	2	1	2	3
Total Incidence Rate	3/51	3/51	1/51	2/51	3/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8421					
Skin – Fibrosarcoma/Malignant Fibrous Histiocytoma (83/456) [Fibroblastic Tumor]					
Total Incidence Rate	1/51	2/51	2/51	0/51	1/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7291					
Uterus – Stromal Polyp/Sarcoma-NOS (149/394) [Stromal Tumor]					
Fatal Incidence	1	0	0	0	0
Incidental Incidence	1	3	2	4	1
Total Incidence Rate	2/51	3/51	2/51	4/51	1/51
Groups 1+6 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.1509					

Figure 1
Kaplan-Meier Product Limit Survival Curves for Male Rats

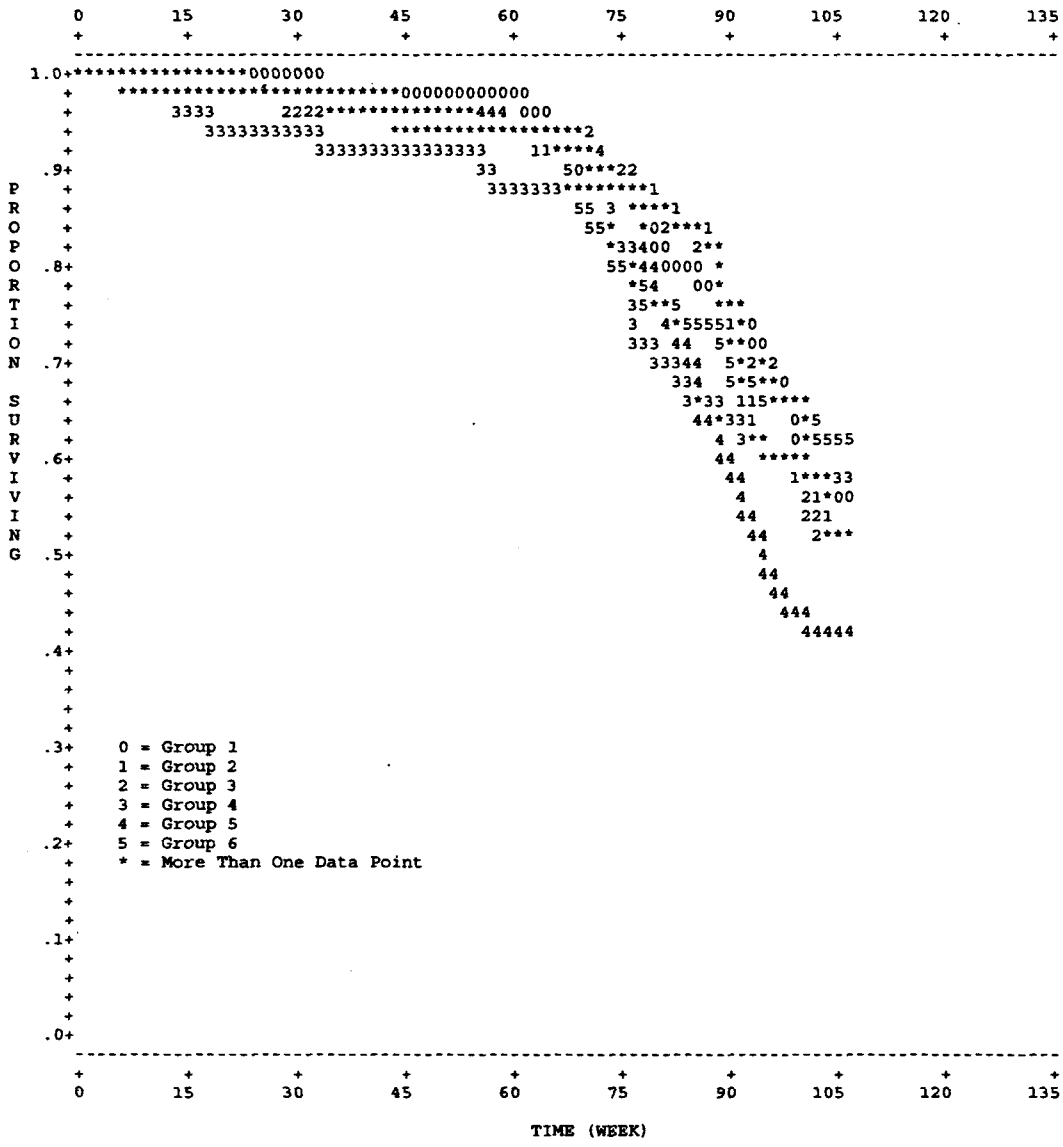


Figure 2
Kaplan-Meier Product Limit Survival Curves for Female Rats

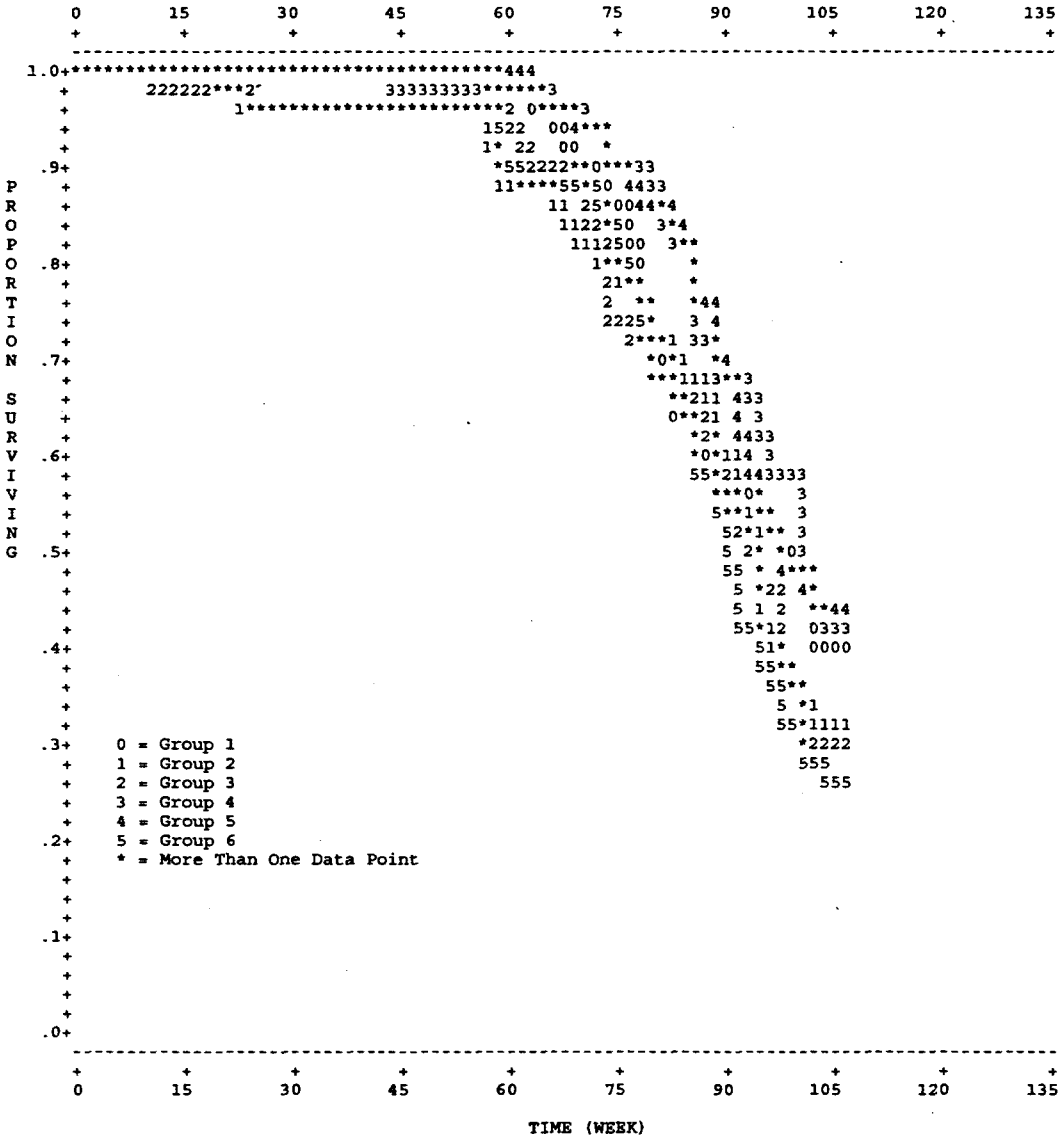


Figure 3
Kaplan-Meier Product Limit Survival Curves for Male Mice

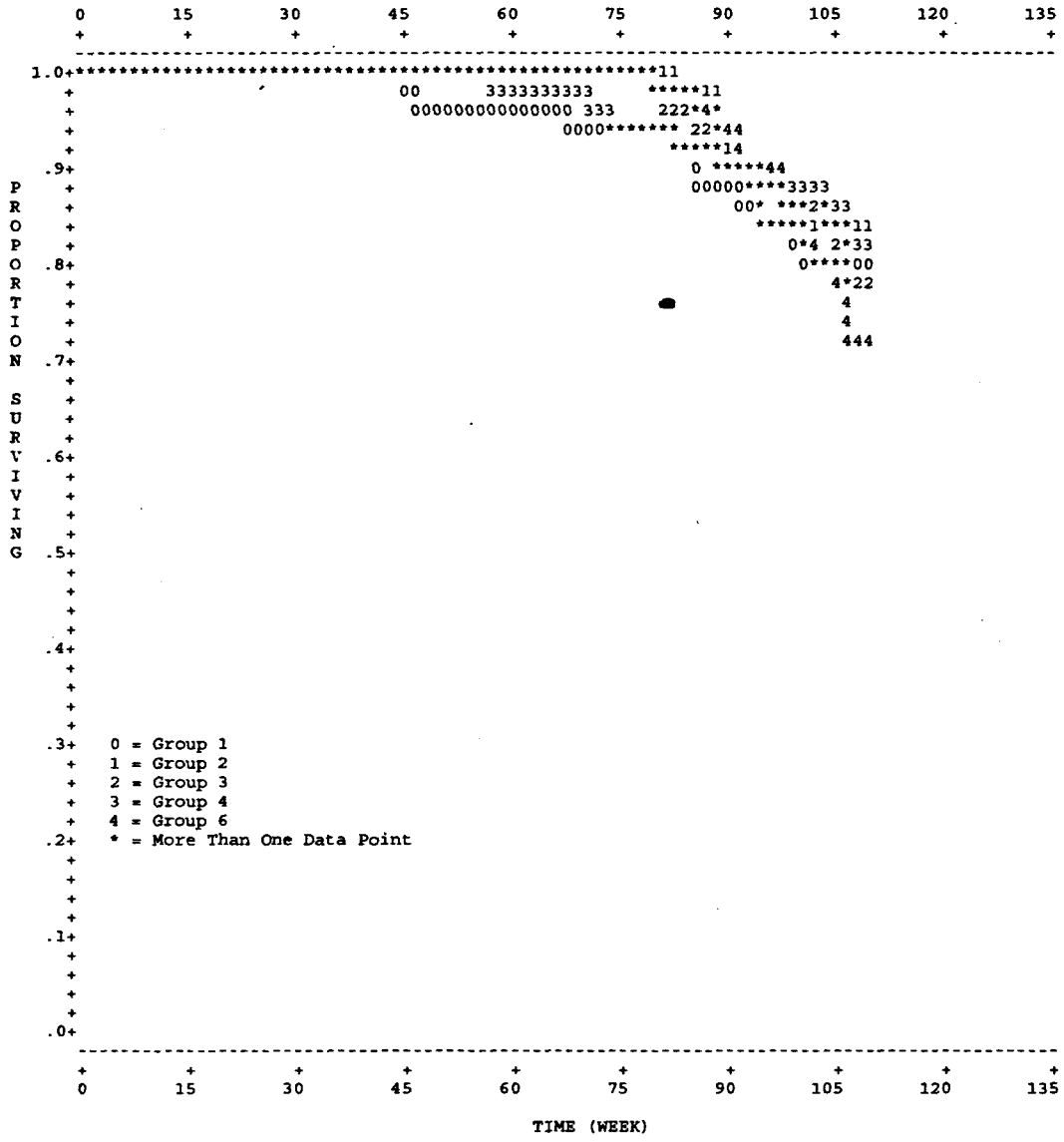
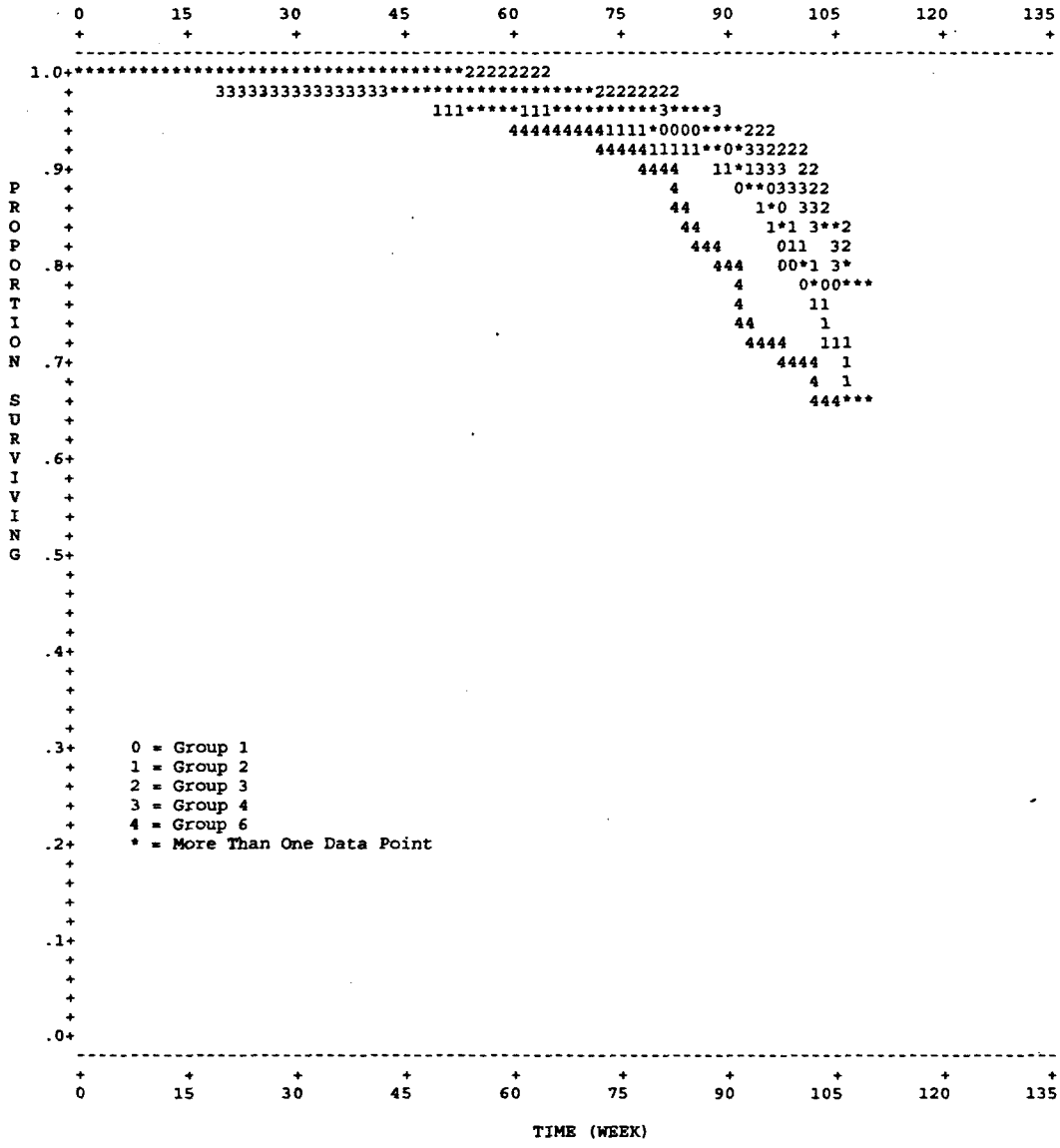


Figure 4
Kaplan-Meier Product Limit Survival Curves for Female Mice



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Todd Sahlroot
3/18/02 01:30:31 PM
BIOMETRICS

Karl Lin
3/21/02 07:45:39 AM
BIOMETRICS
Concur with review

9/6/02

Executive CAC
Date of Meeting: January 29, 2001

Committee: Joseph Contrera, Ph.D., HFD-901, Acting Chair
John Leighton, Ph.D., HFD-150, Alternate Member
Abby Jacobs, Ph.D., HFD-540, Alternate Member
Karen Davis-Bruno, Ph.D., Team Leader
John Zhaolong Gong, Ph.D., Presenting Reviewer

Author of Minutes: John Zhaolong Gong, Ph.D.,

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA 21,366 / IND 56,385
Drug Name: CRESTOR
Sponsor: Astra-Zeneca Pharmaceuticals Inc.

Background:
Crestor (rosuvastatin) is an HMG CoA reductase inhibitor being developed as an oral tablet for the treatment of primary hypercholesterolemia and mixed dyslipidemias.

The Sponsor initiated the 2-year carcinogenicity studies in rats and mice in 1998. The Sponsor submitted the dose selection document 6 months after the studies were started. The Committee concurred with the doses used in the mouse study, but could not concur on the doses used in rats due to the fact that the MTD had not be established. Six eCAC meetings were held to discuss this issue. Two additional dose range finding studies were conducted trying to establish MTD. In the second 3-month study with doses of 80, 160, 240, and 320 mg/kg, significant numbers of animal deaths were observed at ≥ 160 mg/kg. In the 80 mg/kg group, 2/24 males died or were killed *in extremis*, indicating 80 mg/kg was above MTD, though the AUC values at 80 mg/kg group in the 3-month study were generally 2 times the value in the 2-year study, indicating these two studies are not fully comparable, i.e., at the same dose level of 80 mg/kg, rats in the 3 month study were exposed to higher levels of compound than rats in the 2-year study, leading to the severe toxicity observed in the 3-month study.

Mouse Carcinogenicity Study
A 107-week oral gavage carcinogenicity study was conducted with doses of 10, 60, 200, and 400 mg/kg. 400 mg/kg group was terminated in week 3 due to mortality and deteriorating condition. A statistically significant higher incidence of hepatocellular adenoma/carcinoma was observed in males than females. An increased incidence of hepatocellular adenoma plus carcinoma were noted at 200 mg/kg in both sexes. An increased incidence of hepatocellular carcinoma was only observed at 200 mg/kg in both sexes.

Rat Carcinogenicity Study
A 104-week oral gavage carcinogenicity study was conducted with doses of 2, 20, 60, and 80 mg/kg. No increase in neoplasia in the forestomach and liver was noted..

Executive CAC Recommendations and Conclusions:

Mouse study:
The Committee confirmed the validity of the study and dose selection. They concluded that treatment of mice with rosuvastatin at 200 mg/kg/day was associated with an increased incidence of hepatocellular adenoma/carcinoma in both sexes. It was noted that these findings are consistent with other statins.

Rat study:
The Committee confirmed the validity of the study and dose selection. They concluded that treatment of rats with rosuvastatin at ≥ 60 mg/kg/day was associated with an increased incidence of uterine stromal polyps, including a single stromal sarcoma in a female given 80 mg/kg/day.

Joseph Contrera, Ph.D.
Acting Chair, Executive CAC

cc:\

IND 56,385/Division File, HFD 510
NDA 21,366/Division File, HFD 510
Karen Davis-Bruno /Team leader, HFD-510
John Zhaolong Gong/Reviewer, HFD-510
Bill Koch/CSO/PM, HFD-510
ASeifried, HFD-024

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/s/

Joe Contrera
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