CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-081

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA 21-081/Class 1-S
Drug name: Lantus (insuline glargine injection)
Applicant: Hoechst Marion Roussel, Inc.
Indication: Treatment of type 1 diabetes

Volumes reviewed: 1.1-2, 1.160-477 dated 23 April 1999
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Reviewer: Z. Jonathan Ma, Ph.D., HFD-725
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Project manager: Julie Rhee
Medical reviewer: Robert I. Misbin, M.D.

1.INTRODUCTION

Insulin glargine (HOE 901) is an analogue of human insulin produced by recombinant DNA technology. The NDA submission by Hoechst Marion Roussel, Inc. is intended for an approval of HOE 901 indicated for treatment for patients with type I or II diabetes.

The sponsor conducted five Phase 3 studies. Among them, Studies 3001, 3004 and 3005 were conducted in patients with type I diabetes and Studies 3002 and 3006 in patients with type II diabetes. As suggested by the medical reviewer, since type I diabetic patients will be more sensitive to an insulin regimen, this statistical review will focus on evaluating the efficacy results from the three studies on type I diabetic patients. Studies 3001 and 3004 were similarly designed evaluating the efficacy of 28-week treatment of HOE 901 and therefore will be discussed in greater detail together.

Section 2 of this review focuses on Studies 3001 and 3004, mainly discussing the study design, patient population, and the results of the primary and secondary efficacy analyses. Section 3 discusses Study 3005. Section 4 contains the discussions and comments on the overall results of the primary and secondary efficacy analyses of the three studies. Section 5 discusses the pediatric exclusivity study. Conclusions are drawn in Section 6.

An adverse event, hypoglycemia, was considered as one of the secondary efficacy endpoints. The sponsor has done a number of analyses on the variable and more discussion will be seen on this variable later in this review. The evaluation of the overall safety profiles of HOE 901 can be found in the medical reviewer's review.

2. STUDIES 3001 & 3004

2.1 Study Design

Studies 3001 and 3004 were similarly designed and titled: "28-week, multicenter, controlled, randomised, open clinical trial comparing HOE 901 with NPH human insulin in subjects with type I diabetes". Table 2.2.1 summarizes the study design and the primary efficacy results for the two studies.

Table 2.2.1. Summary of Phase III Studies:3001 and 3004

	3001	3004
Overall Design	Multi-center, Active-Controlled, Randomized, Open-label, Parallel-Group, Phase III	
Study Treatment	HOE 901 once daily, individually titrated, plus regular insulin injections.	
Control Treatment	NPH once or twice daily, individually titrated, plus regular insulin injections.	
Duration of Treatment	28 weeks	
Patient Population	Type 1 diabetic subjects: >1 yr insulin trt; C-peptide<0.5 nmol/L; GHb≤12%	
Primary Efficacy Endpoint	GHb: change from baseline to 28 weeks or study endpoint	
Secondary Efficacy Endpoints	Hypoglycemia; fasting glucose (FPG;SMBG); 24-hr blood glucose profile; variability of fasting glucose; insulin dose. (3001 had nocturnal blood glucose)	
Randomization Stratification	On center	On center and basal insulin regimen
Sample Size	585 (292 HOE 901, 293 NPH)	534 (264 HOE 901, 270 NPH)
No. of Centers	63 in 12 European countries	49 in US
Primary Efficacy Analysis		
ANCOVA model	Change in GHb at endpoint = treatment + (pooled) center + baseline GHb	
ITT population	557 (283 HOE 901, 274 NPH)	518 (256 HOE 901, 262 NPH)
GHb (%): adj mean chg from baseline at endpoint	0.21 (0.053) vs 0.10 (0.053)	-0.16 (0.05) vs –0.21 (0.049)
Difference in adj mean chg	0.11	0.05 (0.069)
95% Confidence Interval	(-0.03, 0.24)	(-0.08, 0.19)

The design was a multi-center, open-label, active-controlled, randomized, parallel-group study in patients with type I diabetes mellitus. The study consisted of up to a 4-week screening phase, followed by a 28-week treatment phase.

In each center, subjects were randomized to one of the two treatment groups, HOE 901 or NPH insulin. Due to the different appearance of the two insulins, the trial was designed as an open-label study. The randomization was stratified on center in both studies. In Study 3004, subjects were also stratified by their basal insulin regimen of a once or more than once daily injection on the day immediately preceding randomization. Patients were asked to visit study sites on the following time: screening (-1 to - 4 weeks), baseline (week 0), and treatment (weeks 1, 4, 8, 12, 20, and 28).

The primary objectives were to compare the effects and the safety of HOE 901 and NPH human insulin on GHb in subjects with type 1 diabetes mellitus. The secondary objectives were to compare HOE 901 and NPH human insulin in terms of blood glucose variability, other indicators of metabolic control, quality of life, and pharmacoeconomics in subjects with type 1 diabetes mellitus.

2.2 Inclusion and exclusion criteria

Inclusion criteria

- Men or women, 18 - 80 years of age;
- Women of childbearing potential were to be using adequate contraceptive protection;
- type 1 diabetes mellitus as shown by post-prandial C-peptide negative status, i.e. < 0.5 nmol/L
- (< 1.5 ng/mL) with concomitant capillary blood glucose value 100 mg/dL, measured at visit 1;
- More than 1 year of continuous insulin treatment;
- GHb < 12% (measured at visit 1 as levels of glycated hemoglobin A1c [HbA1c]);
- Ability and willingness to perform blood glucose profiles using a blood glucose meter at home, as evidenced by a complete 8-point blood glucose profile obtained over a single 24-hour period during the screening phase.

Exclusion criteria:

- Pregnancy (as determined by pregnancy blood test at visit 1) or breast feeding;
- Treatment with blood-glucose-lowering drugs other than insulin in the last 4 weeks before study entry;
- Diabetic retinopathy with surgical treatment (laser photocoagulation or vitrectomy) in the 3 months before study entry, or requiring treatment within 3 months of study entry;
- Likelihood of requiring treatment during the study period with drugs not permitted by the clinical study protocol (oral antidiabetic drugs or systemic corticosteroids;
- Night shift workers;
- Treatment with any investigational drug in the last 2 months before study entry;
- Pancreatectomised subjects;
- Clinically relevant cardiovascular, hepatic, neurologic, endocrine, or other major systemic disease, making implementation of the clinical study protocol or interpretation of the study results difficult;
- History of drug or alcohol abuse;
- Impaired hepatic function, as shown by but not limited to SGPT (ALAT) or SGOT (ASAT) greater than twice the normal upper limit measured at Visit 1;
- Impaired renal function, as shown by but not limited to serum creatinine >177 mmol/L (>2.0 mg/dL) measured at Visit 1;
- Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study;
- Evidence of an uncooperative attitude;
- Inability to attend follow-up visits.

2.3 Study Population

In Study 3001, a total of 655 subjects were screened and 602 were randomized from a total of 63 centers in 12 European countries. Among them, 585 subjects received study medication. Therefore, the intent-to-treat (ITT) population defined in the protocol consisted of 585 subjects. However, the sample sizes used in the efficacy analysis for each efficacy variable were in most cases slightly smaller than 585 because only those who had both baseline and post-baseline values were used. For example, the primary efficacy analysis on GHb change from baseline was performed on 557 subjects. This difference is acceptable and seems to be balanced between treatment groups.

Similarly, in Study 3004, a total of 677 subjects were screened 540 subjects were randomized. Among them, 534 subjects received study medication. The ITT population defined in the protocol consisted of 534 subjects and the primary efficacy analysis was performed on 518 subjects.

In both studies, the sponsor also performed a per-protocol analysis on the primary efficacy variable, GHb. The per-protocol population was defined as all ITT subjects with both a baseline and a post baseline value after 24 weeks of treatment (i.e. having a post-baseline value after day 168), but excluding major protocol violators. The results based on the per-protocol population were in general consistent with those based on the ITT population and, therefore, will not be discussed separately in this review.

Table 2.3.1. Study Populations

Study	3001			3004		
	Total	HOE 901	NPH	Total	HOE 901	NPH
ITT population	585	292	293	534	264	270
Evaluable for safety	585	292	293	534	264	270
Evaluable for primary efficacy variable (GHb)	557	283	274	518	256	262
Per-Protocol evaluable for primary efficacy Variable (GHb)	526	268	258	480	234	246

As summarized in Table 2.3.2, no significant differences were detected between the two treatment groups in baseline demographic characteristics, such as age, sex, body mass index, race or diabetic history. Metabolic control at baseline as defined by GHb, FPG, and FBG was also similar in both treatment groups.

Table 2.3.2. Baseline Demographics
ITT Populations in Studies 3001 and 3004

Study	3001			3004		
	Total N=585	HOE 901 N=292	NPH N=293	Total N=534	HOE 901 N=264	NPH N=270
Sex						
Men	326 (55.7%)	160 (54.8%)	166 (56.7%)	270 (50.6%)	141 (53.4%)	129 (47.8%)
Women	259 (44.3%)	132 (45.2%)	127 (43.3%)	264 (49.4%)	123 (46.6%)	141 (52.2%)
Age (years)						
Mean	39.2	39.4	39.0	38.5	38.2	38.9
SD	11.89	12.08	11.72	12.04	12.2	11.9
BMI (kg/m^2)						
Mean	24.87	24.62	25.12	25.78	25.63	25.93
SD	3.221	3.148	3.278	4.29	4.01	4.55
Ethnic group						
White	579 (99.0%)	291 (99.7%)	288 (98.3%)	509 (95.3%)	251 (95.1%)	258 (95.6%)
All Others	6 (1.0%)	1 (0.3%)	5 (1.7%)	25 (4.7%)	13 (4.9%)	12 (4.4%)

2.4 Primary Efficacy Analysis

The primary efficacy variable was

- Change in GHb (glycohemoglobin) from baseline to the study endpoint. Baseline GHb was defined as the last value available prior to start of treatment. Endpoint GHb was defined as the last post-baseline value collected during treatment or within 14 days following the last dose of study treatment.

An analysis of covariance (ANCOVA) was performed using the change from baseline to endpoint as the dependent variable, with treatment and (pooled) center as fixed effects adjusted for baseline GHb:

Change in GHb = treatment + (pooled) center + baseline GHb value

The difference in mean change from baseline between HOE 901 and NPH was estimated using adjusted means along with the associated standard error and 95% confidence interval from the ANCOVA model.

In Study 3001, centers were pooled both by country and their previous insulin regimens: once daily, twice daily or a mixture. Further pooling was done for centers with less than 6 evaluable subjects for the primary analysis of GHb from the ITT population. In Study 3004, pooling was done for centers with fewer than 8 subjects evaluable for the primary analysis of GHb from the ITT population.

The actual pooling procedures were slightly different from the ones described in the Protocols. In Protocol 3001 (3004), it said that centers with less than 6 (4) completed subjects per treatment group were to be pooled in all efficacy and safety analyses. It also said that such pooling was to be performed on the basis of medical, cultural or geographical considerations. The actual pooling procedures, however, seemed to be similar to the one suggested in Agency's Written Request for pediatric exclusivity.

As shown in Table 2.4.1, in Studies 3001 and 3004, the mean baseline GHb was comparable between the treatment groups (p values were 0.49 and 0.73, respectively). A slight increase in

mean GHb at endpoint compared to baseline was observed in the HOE 901 and NPH-treated groups (0.21% and 0.10%, respectively) in Study 3001, but a slight decrease was observed in Study 3004 (-0.16% and -0.21%, respectively). In both studies, the 95% confidence interval of the difference in adjusted mean GHb included 0, indicating that the difference was not statistically significant (p values were 0.13 and 0.44, respectively).

Both the self-reported and the confirmed (by a blood glucose value < 2.0 mmoL/L) incidence rates were listed in the Tables and graphically shown the Figures. The separated analysis of data on Month 1 was not planned in the original protocol, but seemed to be reasonable from a clinical point of view.

Table 2.4.1. GHb (%) Change from baseline at endpoint*
ITT populations for 3001 and 3004

Adjusted means**	HOE901	NPH	Difference (HOE901-NPH)	95% CI of the difference	P-value**
Study 3001 (N=557)	N=283	N=274			
Baseline value	7.98 ± 0.07	8.05 ± 0.07	-0.07 ± 0.10	(-0.25, 0.12)	0.49
Change from baseline value	**0.21 ± 0.05**	**0.10 ± 0.05**	**0.11 ± 0.07**	**(-0.03, 0.24)**	**0.13**
Study 3004 (N=518)	N=256	N=262			
Baseline value	7.73 ± 0.07	7.70 ± 0.07	0.03 ± 0.10	(-0.16, 0.23)	0.73
Change from baseline value	**-0.16 ± 0.05**	**-0.21 ± 0.05**	**0.05 ± 0.07**	**(-0.08, 0.19)**	**0.44**

*Endpoint is defined as the last available value collected on study treatment.
**P-values and adjusted means from ANCOVA model.

In both studies, treatment-by-baseline and treatment-by-center interactions were tested in the ANCOVA model. No significant findings were noted. The p values were 0.13 and 0.46 for treatment-by-baseline interaction and 0.63 and 0.76 for treatment-by-center interaction, in the two studies, respectively.

2.5 Secondary Efficacy Analysis

- GHb: change from baseline to each visit;

  In Study 3001, change from baseline in GHb was also analyzed by each time point, i.e., Weeks 8, 20, and 28, and Endpoint. As shown in Table 2.5.1, except for Week 20, the two treatments were not statistically significantly different from each other. A marginal significance (p=0.04) was detected at Week 20 where HOE 901 showed a higher increase of GHb from baseline than NPH.

Table 2.5.1. Change from Baseline in GHb by Timepoints (ITT) (Study 3001)							
Timepoint	N	HOE 901 Adj Mean±SE	N	NPH Adj Mean±SE	HOE901-NPH Adj Mean±SE	95 % CI	P value
Baseline	283	7.98 ± 0.07	274	8.05 ± 0.07	-0.07 ± 0.10	(-0.25, 0.12)	0.49
Change from baseline at							
Week 8	267	-0.12 ± 0.05	259	-0.18 ± 0.05	0.06 ± 0.05	(-0.04, 0.16)	0.26
Week 20	261	0.16 ± 0.05	250	0.03 ± 0.05	0.13 ± 0.07	(0, 0.26)	0.04
Week 28	264	0.19 ± 0.06	257	0.08 ± 0.06	0.11 ± 0.07	(-0.03, 0.25)	0.14
Endpoint	283	0.21 ± 0.05	274	0.10 ± 0.05	0.11 ± 0.07	(-0.03, 0.24)	0.13

In Study 3004, change from baseline in GHb was also analyzed by each time point, i.e., Weeks 8, 20, and 28, and Endpoint. There was no statistically significant difference between the effects of HOE 901 and NPH at any of these visits.

Table 2.5.2. Change from Baseline in GHb by Timepoints (ITT) (Study 3004)							
Timepoint	N	HOE 901 Adj Mean±SE	N	NPH Adj Mean±SE	HOE901-NPH Adj Mean±SE	95 % CI	P value
Baseline	256	7.73 ± 0.073	262	7.7 ± 0.07	0.03±0.1	(-0.16, 0.23)	0.73
Change from baseline at							
Week 8	234	-0.23 ± 0.04	241	-0.18 ± 0.04	-0.05 ± 0.06	(-0.16, 0.07)	0.43
Week 20	231	-0.09 ± 0.05	239	-0.13 ± 0.05	0.04 ± 0.07	(-0.09, 0.17)	0.52
Week 28	232	-0.17 ± 0.05	245	-0.21 ± 0.05	0.04 ± 0.07	(-0.10, 0.18)	0.58
Endpoint	256	-0.16 ± 0.05	262	-0.21 ± 0.05	0.05 ± 0.07	(-0.08, 0.19)	0.44

- Hypoglycemia

Symptomatic hypoglycemia was analyzed based on three categories: all symptomatic episodes, severe episodes, and nocturnal episodes. The percent of patients and the frequency of these episodes were calculated for three time periods: month 1 of treatment, month 2 to the end of treatment, and the entire treatment period. The frequency tables used to generate these figures can be found in the Appendix. Figures 2.5.1-6 illustrate the percentages of patients who experienced these episodes, comparing HOE 901 and NHP side by side. The incidence of asymptomatic hypoglycemia in the two studies is shown in Figure 2.5.7.

Figure 2.5.1. Percent of patients who had any symptomatic hypoglycemia
(Study 3001)

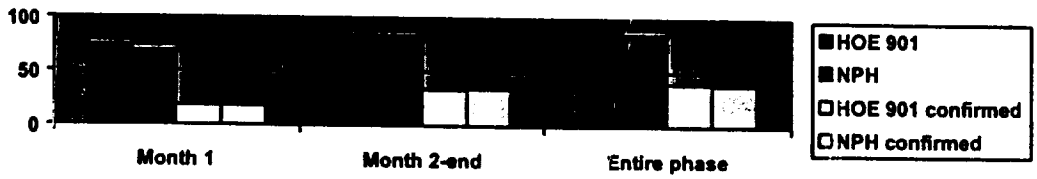


Figure 2.5.2. Percent of patients who had any symptomatic hypoglycemia
(Study 3004)

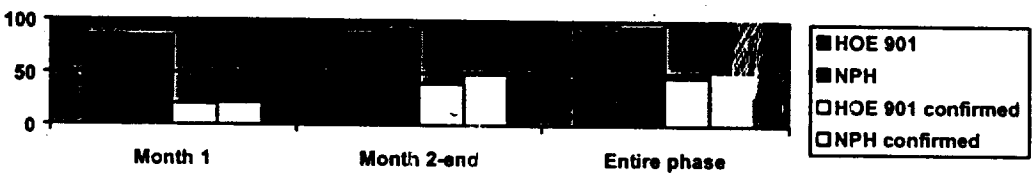


Figure 2.5.3. Percent of patients who had nocturnal hypoglycemia
(Study 3001)

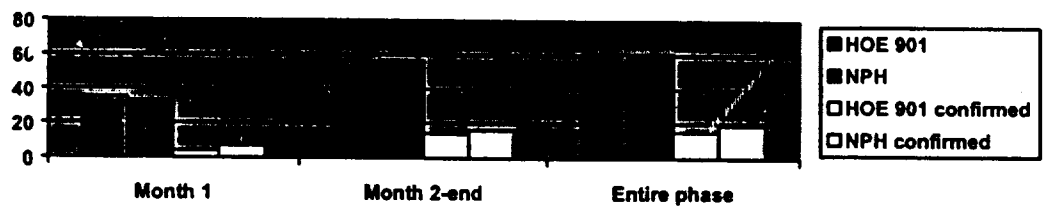


Figure 2.5.4. Percent of patients who had nocturnal hypoglycemia (Study 3004)

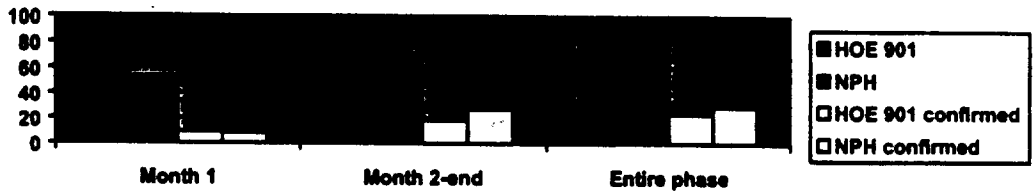


Figure 2.5.5. Percent of patients who had severe hypoglycemia (Study 3001)

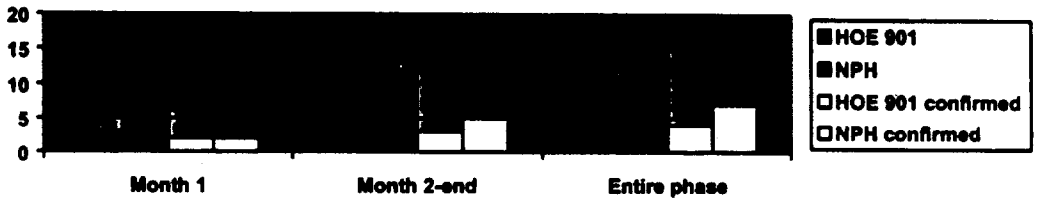


Figure 2.5.6. Percent of patients who had severe hypoglycemia (Study 3004)

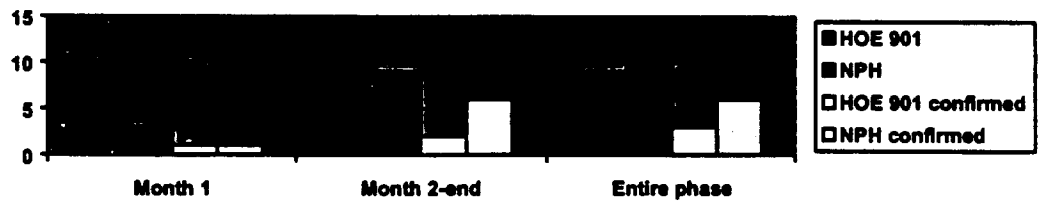
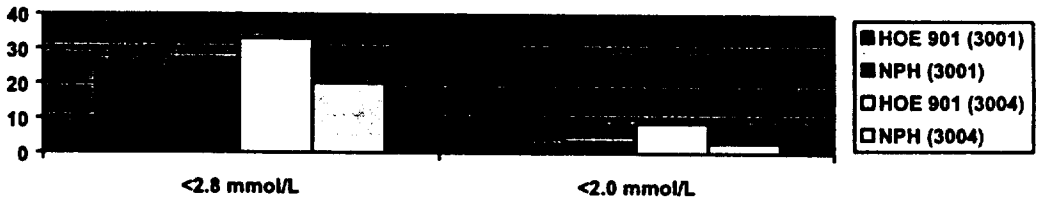


Figure 2.5.7. Percent of patients who had asymptomatic hypoglycemia (Studies 3001 and 3004)



- Glucose measurements: change from baseline to each visit and to study endpoint, including FPG, variability of FPG, FBG, variability of FBG, nocturnal blood glucose, etc.

  The main findings were:
  - There was a similar decrease of mean FPG in both treatment groups.
  - Statistically significant differences in the average self-monitored FBG decrease were reported at Weeks 8 and 28 for Study 3001, and at Weeks 8 and 20 for Study 3004, as shown in Tables 2.5.3 and 2.5.4.

Table 2.5.3. Change in Self-monitored FBG (mmol/L) Study 3001

Timepoint	HOE 901		NPH		HOE 901 - NPH	
	N	Adjusted mean± SE	N	Adjusted mean± SE	Adjusted mean± SE	p-value
Baseline	280	9.29 ± 0.17	274	9.20 ± 0.17	0.09 ± 0.22	0.68
Change from baseline to						
Week 8	269	-1.01 ± 0.16	263	-0.59 ± 0.16	-0.42 ± 0.18	0.02
Week 20	258	-0.98 ± 0.12	254	-0.94 ± 0.12	-0.05 ± 0.16	0.77
Week 28	260	-1.23 ± 0.13	251	-0.88 ± 0.13	-0.35 ± 0.17	0.04
Endpoint	280	-1.17 ± 0.12	274	-0.89 ± 0.12	-0.29 ± 0.16	0.07

Table 2.5.4. Change in Self-Monitroed FBG (mmol/L) Study 3004

Timepoint	HOE 901 Adjusted mean (N=244)	NPH all regimens Adjusted mean (N=258)	HOE 901- NPH Adjusted mean	P-value
Baseline	9.23	9.71	-0.49	0.06
Change from baseline to				
Week 8	-1.17	-0.37	-0.81	0.0001
Week 20	-1.20	-0.51	-0.69	0.0004
Week 28	-1.16	-1.07	-0.09	0.66
Endpoint	-1.12	-0.94	-0.18	0.35

- No significant difference in day-to-day variability in FBG or nocturnal glucose was seen between the two treatment groups.

APPEARS THIS WAY
ON ORIGINAL

3. STUDY 3005

Title: 16-Week Multicenter, Controlled, Randomized, Open-Label Clinical Trial Comparing HOE 901 Insulin and NPH Human Insulin in Subjects with Type I Diabetes Treated with Insulin Lispro. The study design is summarized in Table 3.1.

Primary objectives were to compare the effects of HOE 901 and NPH human insulin on glycohemoglobin (GHb) when used with insulin lispro and to compare the safety of HOE 901 and NPH human insulin when used with insulin lispro. Secondary objectives were to compare HOE 901 and NPH human insulin when used with insulin lispro in terms of fasting glucose, fasting glucose variability, hypoglycemia and pharmacoeconomics in subjects with type I diabetes.

Table 3.1. Summary of Study 3005

Overall Design	Multi-center, Active-Controlled, Randomized, Open-label, Parallel-Group, Phase III
Study Treatment	HOE 901 once daily, individually titrated, plus regular insulin injections.
Control Treatment	NPH once or twice daily, individually titrated, plus regular insulin injections.
Duration of Treatment	16 weeks
Patient Population	Type 1 diabetic subjects: >1 yr daily insulin and NPH and Lispro for 3 months; C-peptide<0.5 nmol/L; GHb≤12%
Primary Efficacy Endpoint	GHb: change from baseline
Secondary Efficacy Endpoints	Hypoglycemia; fasting glucose (FPG;SMBG); 24-hr blood glucose profile; variability of fasting glucose; insulin dose.
Sample Size	619 (310 HOE 901, 319 NPH)
No. of Centers	60 in US and Canada

The primary efficacy variable was the change in GHb from baseline to endpoint. The ITT analysis was performed using a total of 604 subjects, excluding 15 randomized and treated subjects (9 from the HOE 901 group and 6 from the NPH group) because of missing on-treatment or baseline GHb value.

As shown in Table 3.2, subjects entered the study with an average baseline GHb of 7.6% and no statistically significant difference (p=0.27) was observed in baseline GHb between the two groups. On average, small reductions in GHb were observed in both treatment groups. There was no statistically significant difference (p=0.84) in change of GHb from baseline to endpoint between the HOE 901 and NPH treatment groups.

Table 3.2. GHb (%) Change from baseline at endpoint* ITT population for 3005					
Adjusted means**	HOE901	NPH	Difference (HOE901-NPH)	95% CI of the difference	P-value**
Study 3005 (N=604)	N=301	N=303			
Baseline value	7.60 ± 0.07	7.71 ± 0.07	-0.11 ± 0.10	(-0.30 ; 0.09)	0.27
Change from baseline value	**-0.07 ± 0.04**	**-0.08 ± 0.04**	**0.01 ± 0.06**	**(-0.11 ; 0.13)**	**0.84**
*Endpoint is defined as the last available value collected on study treatment. **P-values and adjusted means from ANCOVA model.					

The main findings with the secondary efficacy endpoints were

- The two treatment groups were similar with respect to the frequency of symptomatic, nocturnal and severe hypoglycemia.
- Average decreases in fasting plasma and blood glucose were highly statistically significantly greater with HOE 901 compared to NPH throughout the study.

Table 3.3. Change in Mean FBG (mmol/L) Study 3005				
Timepoint	HOE 901 Adjusted mean (N=297)	NPH all regimens Adjusted mean (N=298)	HOE 901 – NPH Adjusted mean	P-value
Baseline	9.68	9.56	0.11	0.64
Change from baseline to				
Week 8	-1.42	-0.43	-0.99	0.0001
Week 16	-1.57	-0.70	-0.87	0.0001
Endpoint	-1.63	-0.66	-0.96	0.0001

In conclusion, once daily HOE 901 was equally effective as once or twice daily NPH in maintaining glycemic control in subjects with type 1 diabetes using insulin lispro. After the first month titration period, HOE 901 and NPH treatments were associated with similar frequencies of symptomatic hypoglycemia.

4. DISCUSSION

The primary efficacy analyses from the three studies (3001, 3004 and 3005) showed a consistent picture, that is, no statistically significant difference was observed in the GHb change post-baseline between the HOE 901 treatment group and the NPH treatment group. This conclusion seems to hold true over the entire treatment phase: weeks 8, 16, 20 and 28, regardless of prior basal regimen (once daily or more than once daily).

However, it should be noted that failure to detect a statistically significant difference between treatments does not necessarily imply absence of a difference. Instead, the sponsor needs to demonstrate that differences favoring the active control of a clinically meaningful magnitude can statistically be ruled out.

An non-inferiority trial typically requires the pre-specification of a non-inferiority margin Δ and the conclusion of non-inferiority can be drawn if the upper endpoint [favoring the control] of the 95% confidence interval for the treatment difference excludes Δ. One difficulty of designing such a trial is to find an appropriate Δ.

In this submission, without a pre-specified non-inferiority margin Δ, the sponsor performed a post hoc non-inferiority test. The 95% confidence intervals of the treatment differences in GHb change from baseline were calculated and presented in the Tables. As summarized in Table 4.1, from the primary efficacy analyses on Endpoint from the three trials, the smallest lower bound of the 95% confidence intervals was –0.11 and the highest upper bound was 0.24. Therefore, it seems reasonable to conclude that the true difference of the two treatments should fall in the interval of (-0.11, 0.24). If including the 95% confidence intervals from all other visits (weeks 8, 20 and 28), the interval becomes (-0.16, 0.25). Clinical judgement is required to determine if the statistical confidence limits are consistent with clinical non-inferiority. In addition, the clinicians need to have confidence that the active control clearly shows superiority to placebo.

Table 4.1. Summary for primary efficacy variable: GHb (%) Change from baseline at endpoint* ITT population for 3001, 3004 and 3005

Adjusted means**	HOE901	NPH	Difference (HOE901-NPH)	95% CI of the difference	P-value**
Study 3001 (N=557) Change from baseline value to Week 28 or Endpoint	N=283 0.21 ± 0.05	N=274 0.10 ± 0.05	0.11 ± 0.07	(-0.03, 0.24)	0.12
Study 3004 (N=518) Change from baseline value to Week 28 or Endpoint	N=256 -0.16 ± 0.05	N=262 -0.21 ± 0.05	0.05 ± 0.07	(-0.08, 0.19)	0.44
Study 3005 (N=604) Change from baseline value to Week 16 or Endpoint	N=301 -0.07 ± 0.04	N=303 -0.08 ± 0.04	0.01 ± 0.06	(-0.11, 0.13)	0.84

*Endpoint is defined as the last available value collected on study treatment.
**P-values and adjusted means are from ANCOVA model.

The sponsor performed a number of analyses comparing the incidence of hypoglycemia between the HOE 901 and NPH treatments. The comparisons were conducted within each of four categories of hypoglycemia: symptomatic hypoglycemia, nocturnal hypoglycemia, severe hypoglycemia and asymptomatic hypoglycemia. The incidence of hypoglycemia was also stratified based on prior basal insulin regimen (once daily or more than once daily).

In Study 3001, patients from both groups reported comparable incidence of hypoglycemia, across all categories, study phases and regardless of prior basal regimen. No p-values reported in the summary tables were less than 0.05.

However, Study 3004 told a somewhat difference story. Lower percentages of patients from HOE 901 experienced hypoglycemia (symptomatic, nocturnal and severe) than the NPH group during the study period from month 2 to the end. Some of the p values from Cochran-Mantel-Haenszel tests were lower than 0.05 (see Table 4.2). On the other hand, however, for

asymptomatic hypoglycemia, the HOE 901 group showed a statistically significant higher incidence than the NPH group (p=0.0005).

The increase in asymptomatic hypoglycemia and the decrease in symptomatic, nocturnal and severe hypoglycemia seemed to be similar in magnitude. For example, there was a 9% (=49%-40%) decrease in the confirmed symptomatic hypoglycemia, compared to a 6-13% (=33%-20%, 9%-3%) increase in the asymptomatic hypoglycemia. Therefore, the overall hypoglycemia incidence seemed to be even.

Table 4.2. Percentage of patients who experienced hypoglycemia in Study 3004 (Data are for Phase Month 2 – End, except for asymptomatic hypoglycemia)

	HOE 901	NPH	P value from CMH test
Symptomatic Hypoglycemia			
All events	224/258 (85%)	243/266 (91%)	0.07
Confirmed by blood glucose	103/258 (40%)	131/266 (49%)	0.02
Nocturnal Hypoglycemia			
All events	176/258 (68%)	189/266 (71%)	0.42
Confirmed by blood glucose	47/258 (18%)	72/266 (27%)	0.01
Severe Hypoglycemia			
All events	17/258 (7%)	23/266 (9%)	0.28
Confirmed by blood glucose	5/258 (2%)	15/266 (6%)	0.01
Asymptomatic Hypoglycemia			
Fasting glucose<2.8 mmol/L	88/264 (33%)	53/270 (20%)	0.0005
Fasting glucose<2.0 mmol/L	23/264 (9%)	8/270 (3%)	0.005

In Study 3005, the HOE 901 and NPH groups showed a comparable incidence of symptomatic, nocturnal and severe hypoglycemia, regardless of study phase and prior basal regimen. However, the HOE 901 group had a statistically significant higher rate of asymptomatic hypoglycemia than the NPH group with a p value of 0.02 (Table 4.3).

Table 4.3. Frequency of asymptomatic hypoglycemia during treatment phase (Study 3005)

	HOE 901 (N=310)	NPH (N=309)	
Fasting Glucose value	**# of subjects (%)**	**# of subjects (%)**	**P-value**
<2.8 mmol/L	60 (19%)	41 (13%)	0.02
<2.0 mmol/L	4 (1%)	0 (0%)	0.05

P-values from Cochran-Mantel-Haenszel test.

Overall, there was no consistent picture regarding whether patients on HOE 901 experienced less hypoglycemia than did patients on NPH. While Study 3004 gave some statistical evidence that patients on HOE 901 tended to have a lower incidence of symptomatic, nocturnal and severe hypoglycemia (especially after 1 month on treatment), both Studies 3001 and 3005 showed that the two treatments were comparable in these incidence rates. In both Studies 3004 and 3005, patients on HOE 901 even had a significant higher incidence of asymptomatic hypoglycemia than NPH.

The inconsistency makes it difficult to draw a favorable conclusion for HOE 901 regarding hypoglycemia, especially when these trials were all open-label.

On the other hand, the three studies did tell a consistent story, which is that a larger decrease in self-monitored fasting blood glucose (FBG) was reported by the patients from the HOE 901 group than from the NPH group. The difference between the two groups was statistically significant at most of the post-baseline time points. Again, whether the open-label nature of the trials could be partially responsible for this difference is not clear.

5. PEDIATRIC STUDY

Study 3003: 28-Week multicenter, controlled, randomized, open clinical trial comparing HOE 901 insulin with NPH human insulin in children with type 1 diabetes mellitus.

This was an open-label, NPH human insulin-controlled, randomized (1:1), parallel-group, multicenter (30 centers in 10 countries) study. The study population was children (6-15 years old) who had type 1 diabetes mellitus with more than 1 year of insulin treatment and with GHb $\leq$ 12.0%. The treatment phase was 28 weeks.

The primary efficacy endpoint was change in GHb from baseline to endpoint. The secondary endpoints included change in GHb from baseline to each visit; fasting blood glucose (FBG), nocturnal blood glucose, 24-hour blood glucose profile, variability of FBG, and hypoglycemia.

Of the 385 subjects who entered the screening phase, 349 were randomized and received study medication including 174 HOE 901 subjects and 175 NPH subjects (114 once daily NPH and 61 twice daily NPH). The baseline characteristics of the 349 patients are summarized in Table 5.1. No significant differences in age, sex, body mass index (BMI), race or puberty stage were detected between the two treatment groups at baseline. However, as shown in Table 5.2, the two groups were statistically significantly different in baseline GHb.

Table 5.1. Baseline characteristics (Randomized and treated population) Study 3003			
Variable	Total treated (N = 349)	HOE 901 (N = 174)	NPH (N = 175)
Sex			
Male	181 (52%)	97 (56%)	84 (48%)
Female	168 (48%)	77 (44%)	91 (52%)
Age (years)			
Mean	11.7	11.8	11.5
SD	2.4	2.5	2.4
BMI (kg/m^2)			
Mean	18.9	18.8	18.9
SD	2.8	2.8	2.9
Puberty stage			
Pre-adolescent	119 (34%)	57 (33%)	62 (35%)
Adolescent	230 (66%)	117 (67%)	113 (65%)

Primary Efficacy Analyses - change from baseline to endpoint in GHb (%)

A slight increase of mean GHb at the endpoint from baseline was observed in both treatment groups. Although the adjusted mean baseline GHb in the HOE 901 group was statistically significantly lower than in the NPH group (p=0.04), there was no difference in the effect of HOE 901 and NPH on change from baseline to endpoint in GHb (p=0.93).

Table 5.2. GHb (%) Change from baseline at endpoint* ITT population for 3003					
Adjusted means**	HOE901	NPH	Difference (HOE901-NPH)	95% CI of the difference	P-value**
Study 3003 (N=311)	N=155	N=156			
Baseline value	8.48 ± 0.114	8.81 ± 0.114	-0.33	(-0.64, -0.02)	0.04
Change from baseline value	0.28 ± 0.094	0.27 ± 0.093	0.01	(-0.24, 0.26)	0.93

*Endpoint is defined as the last available value collected on study treatment.
**P-values and adjusted means from ANCOVA model.

Secondary Efficacy Analyses

The two groups had a similar incidence rate in symptomatic hypoglycemia (all events), nocturnal hypoglycemia, severe symptomatic hypoglycemia and asymptomatic hypoglycemia.

However, on average, a larger decrease in self-monitored fasting blood glucose (FBG) was reported by the patients from the HOE 901 group than from the NPH group. The difference between the two groups was statistically significant at Weeks 4, 16 and at endpoint (p=0.007, p=0.001 and p=0.023, respectively, as shown in Table 5.3).

Table 5.3. Change in self-monitored fasting blood glucose (FBG) (mmol/L) Secondary Efficacy Analysis for Study 3003						
Timepoint	HOE 901		NPH		HOE 901 – NPH	
	N	Adjusted mean ± SE[a]	N	Adjusted mean ± SE[a]	Adjusted mean ± SE[a]	p-value[a]
Baseline	173	10.8 ± 0.25	172	10.6 ± 0.25	0.2 ± 0.35	0.66
Change from Baseline to:						
Week 4	170	-1.2 ± 0.21	166	-0.4 ± 0.22	-0.8 ± 0.30	0.007
Week 16	146	-1.5 ± 0.21	140	-0.5 ± 0.22	-1.0 ± 0.30	0.001
Week 28	167	-1.3 ± 0.19	159	-0.8 ± 0.20	-0.5 ± 0.26	0.077
Endpoint	173	-1.3 ± 0.19	172	-0.7 ± 0.20	-0.6 ± 0.27	0.023
Note: Endpoint defined as the last available value collected on study treatment. [a] p-values and adjusted means from ANCOVA model.						

In conclusion, the two groups appeared to be comparable in terms of change in GHb from baseline. The frequencies of hypoglycemic events were also comparable between the two groups. A significant reduction in FBG was observed in the HOE 901 group compared to the NPH group, however, there was no significant difference observed between the two groups in the variability in FBG, the nocturnal blood glucose and the 24-hour average blood glucose.

The Written Request (WR) and the analysis report (AR) are compared in the following from the statistical point of view:

1. WR: Treatment group comparisons for change from baseline in HbA1c will be made using an analysis of covariance model with baseline as the covariate. Small centers (<4 completed subjects per treatment group) will be pooled. Centers using twice-a-day dosing NPH will not be pooled with centers using once-a-day dosing NPH.

   AR: Centers with less than 12 subjects in the ITT population and who were evaluable for the primary analysis of GHb have been pooled. Pooling was done by country and by previous insulin regimens. Within a single country, there are three types of pools possible, corresponding to the previous NPH regimens: once daily, twice daily, or a mixture of once and twice daily.

   There were two pooled centers (one from Belgium and one from Finland) with mixed previous insulin regimens (once or twice daily). Center 3361 had 1 (out of 8) patients on NPH twice daily, Center 3387 had 2 (out of 5) on NPH twice daily, and Center 3388 had 1 (out of 10) on NPH twice daily. All other centers were pooled by either once or twice daily only.

   Therefore, it appeared that the method of pooling centers roughly followed the WR, though there were two pooled centers with mixed previous insulin regimens.

1	3301 (16)	Austria	NPH_2
2	3303+3304 (5+7=12)	Austria	NPH_2
3	3311+3312+3313+3317+ 3319+3341+3322 (3+1+6+2+10+8+5=35)	Germany + Netherlands	NPH_2
4	3318 (13)	Germany	NPH_2
5	3331 (12)	Great Britain	NPH_2
6	3342+3343 (7+11=18)	Netherlands	NPH_1
7	3361+3362 (8+12=20)	Belgium	NPH_b
8	3372+3374 (25+4=29)	South Africa	NPH_1
9	3373+3375 (40+7=47)	South Africa	NPH_2
10	3381 (17)	Czech Republic	NPH_1
11	3382+3383 (10+20=30)	Czech Republic	NPH_1
12	3386+3389 (8+11=19)	Finland	NPH_1
13	3387+3388 (5+11=16)	Finland	NPH_b
14	3391 (17)	Switzerland	NPH_1
15	3396 (29)	Croatia	NPH_1
16	3398 (28)	Czech Republic	NPH_1
17	3399 (27)	Czech Republic	NPH_1

* NPH_1 = NPH once treatment therapy; NPH_2 = NPH twice treatment therapy; NPH_b = both NPH regimen applied

2. WR: Analyses of data from both the intent-to-treat (ITT) population and the completers will be performed to ascertain if dropouts biased the ITT results. Additional analyses to assess the effect of missing data on the interpretation of the results will be performed.

   AR: both the ITT and per-protocol (PP) analyses were performed on the primary efficacy endpoint and yielded generally consistent results. No additional analysis was found.

   It should be noted that, since the ITT and PP analyses were generally consistent, although useful, any additional analysis on the missing data would be expected to be also consistent with the general results.

3. WR: The ITT population will include all patients randomized who have baseline data and any post-baseline data; not just patients with data after the Week 4 visit.

   AR: consistent with the WR.

In conclusion, the sponsor has generally followed the statistical plan of the Agency's pediatric Written Request issued on December 23, 1998 and amended on May 12, 1999. Only minor discrepancies were found.

6. CONCLUSIONS

No statistically significant difference in the effect of HOE 901 and NPH on GHb over the 28-week treatment phase was detected. With at least 95% confidence, the true difference in GHb change from baseline at Week 28 between the HOE901 and NPH treatment groups falls in the interval (-0.16, 0.25) with the upper endpoint indicating the maximum inferiority to NPH.

Study 3004 suggested that, while patients receiving HOE 901 reported less symptomatic, nocturnal and severe hypoglycemia after 2 months than patients receiving NPH insulin, patients on HOE 901 had a statistically significantly higher incidence of asymptomatic hypoglycemia. Hence, the overall incidence of hypoglycemia in Study 3004 seemed to be similar in the two treatment groups. In Study 3001, all hypoglycemia rates were very similar between treatment groups. In Study 3005, patients on HOE 901 again had a statistically significantly higher incidence of asymptomatic hypoglycemia than did those on NPH insulin. Overall, no consistent pattern emerged regarding the between group incidence of hypoglycemia in these trials.

Therefore, the claim of a possible benefit of experiencing less hypoglycemia for patients on HOE 901 than those on NPH insulin was not supported by statistical analyses of the data from these trials.

A statistically significantly larger decrease in self-monitored fasting blood glucose (FBG) was reported by the patients on HOE 901 compared to NPH in all trials. However, it is not clear how much the open-label nature of these trials might have accounted for this difference.

The pediatric study was analyzed generally following the statistical plan of the Agency's Written Request. Only minor discrepancies were found.

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Appendix: Tables for Hypoglycemia (from sponsor's submission)

Symptomatic hypoglycemia was evaluated using three primary subsets of hypoglycemic episodes: all symptomatic episodes, severe episodes, and nocturnal episodes. These episodes were evaluated during the following four time periods: screening phase, month 1 of treatment, month 2 to the end of treatment, and the entire treatment period.

1. Symptomatic hypoglycemia

Table A.1. Frequency of all symptomatic hypoglycemia Study 3001

Treatment phase	HOE 901 Number of subjects	(%)	Number of episodes	Number of subjects	NPH (%)	Number of episodes	p-value
Month 1	214/292	(73.3)	1155	198/293	(67.6)	983	0.0788
Month 2 to end	240/289	(83.0)	4012	233/282	(82.6)	4358	0.7310
Entire phase	260/292	(89.0)	5167	248/293	(84.6)	5341	0.0692
Confirmed by a blood glucose <2.0 mmol/L							
Month 1	53/292	(18.2)	92	52/293	(17.7)	71	0.8946
Month 2 to end	96/289	(33.2)	285	97/282	(34.4)	278	0.8136
Entire phase	114/292	(39.0)	377	112/293	(38.2)	349	0.7627

Note: Number (%) of subjects reporting at least one episode of symptomatic hypoglycemia.
[a] p-value from Cochran-Mantel-Haenszel test.

Table A.2. Frequency of symptomatic hypoglycemia Study 3004

	HOE 901			NPH all regimens			
Treatment phase	No. of subjects	(%)	No. of episodes	No. of subjects	(%)	No. of episodes	P-value[a]
All symptomatic events							
Month 1	224/264	(84.8)	1385	227/270	(84.1)	1347	0.5804
Month 2 – end	224/258	(86.8)	4847	243/266	(91.4)	5230	0.0659
Entire phase	251/264	(95.1)	6232	254/270	(94.1)	6577	0.5721
Confirmed by blood glucose <2.0 mmol/L							
Month 1	53/264	(20.1)	85	57/270	(21.1)	95	0.6927
Month 2 – end	103/258	(39.9)	228	131/266	(49.2)	413	0.0219
Entire phase	120/264	(45.5)	313	141/270	(52.2)	508	0.0826

Note: Number (%) of subjects reporting at least 1 episode of symptomatic hypoglycemia.
[a] P-values from Cochran-Mantel-Haenszel test.

Table A.3. Frequency of symptomatic hypoglycemia by prior basal insulin regimen Study 3004

	Prior once daily basal insulin				Prior more than once daily basal insulin			
	HOE 901		NPH once daily		HOE 901		NPH twice daily	
Treatment phase	No. of subjects	(%)	No. of subjects	(%)	No. of subjects	(%)	No. of subjects	(%)
All symptomatic events								
Month 1	56/69	(81.2)	60/71	(84.5)	168/195	(86.2)	167/199	(83.9)
Month 2 – end	59/67	(88.1)	64/69	(92.8)	165/191	(86.4)	179/197	(90.9)
Entire phase	66/69	(95.7)	67/71	(94.4)	185/195	(94.9)	187/199	(94.0)
Confirmed by blood glucose <2.0 mmol/L								
Month 1	16/69	(23.2)	19/71	(26.8)	37/195	(19.0)	38/199	(19.1)
Month 2 – end	33/67	(49.3)	40/69	(58.0)	70/191[a]	(36.6)	91/197[a]	(46.2)
Entire phase	38/69	(55.1)	42/71	(59.2)	82/195	(42.1)	99/199	(49.7)

Note: Number (%) of subjects reporting at least 1 episode of symptomatic hypoglycemia.
[a] Statistically significant difference at the 0.05 level.

2. Nocturnal hypoglycemia

A.4. Frequency of all nocturnal symptomatic hypoglycemia Study 3001

Treatment phase	HOE 901			NPH			p-value
	Number of subjects	(%)	Number of episodes	Number of subjects	(%)	Number of episodes	
Month 1	103/292	(35.3)	211	96/293	(32.8)	201	0.4276
Month 2 – end	154/289	(53.3)	761	161/282	(57.1)	939	0.4436
Entire phase	178/292	(61.0)	972	179/293	(61.1)	1140	0.8917
Confirmed by a blood glucose <2.0 mmol/L							
Month 1	12/292	(4.1)	24	20/293	(6.8)	26	0.1411
Month 2 – end	39/289	(13.5)	76	45/282	(16.0)	86	0.3924
Entire phase	45/292	(15.4)	100	56/293	(19.1)	112	0.2456

Note: Number (%) of subjects reporting at least one episode of symptomatic hypoglycemia.
[a] p-value from Cochran-Mantel-Haenszel test.

A.5. Frequency of nocturnal hypoglycemia Study 3004

Treatment phase	HOE 901			NPH all regimens			P-value[a]
	No. of subjects	(%)	No. of episodes	No. of subjects	(%)	No. of episodes	
All nocturnal events							
Month 1	136/264	(51.5)	342	142/270	(52.6)	347	0.8875
Month 2 – end	176/258	(68.2)	1105	189/266	(71.1)	1232	0.4210
Entire phase	204/264	(77.3)	1447	208/270	(77.0)	1579	0.8876
Confirmed by blood glucose <2.0 mmol/L							
Month 1	24/264	(9.1)	32	21/270	(7.8)	32	0.6931
Month 2 – end	47/258	(18.2)	74	72/266	(27.1)	121	0.0116
Entire phase	61/264	(23.1)	106	78/270	(28.9)	153	0.1172

Note: Number (%) of subjects reporting at least 1 episode of nocturnal hypoglycemia.
[a] P-values from Cochran-Mantel-Haenszel test.

A.6. Frequency of nocturnal symptomatic hypoglycemia based on prior basal regimen Study 3001

Treatment Phase	Prior once daily				Prior more than once daily			
	HOE 901		NPH once daily		HOE 901		NPH twice daily	
	No of subjects	(%)	No of subjects	(%)	No of subjects	(%)	No of subjects	(%)
Month 1	39/153	(25.5)	42/131	(32.1)	64/139	(46.0)	40/130	(30.8)
Month 2 – end	75/152	(49.3)	72/128	(56.3)	79/137	(57.7)	69/122	(56.6)
Entire phase	82/153	(53.6)	82/131	(62.6)	96/139	(69.1)	75/130	(57.7)
Confirmed by blood glucose <2.0 mmol/L								
Month 1	3/153	(2.0)	9/131	(6.9)	9/139	(6.5)	10/130	(7.7)
Month 2 – end	14/152	(9.2)	19/128	(14.8)	25/137	(18.2)	20/122	(16.4)
Entire phase	15/153	(9.8)	25/131	(19.1)	30/139	(21.6)	24/130	(18.5)

[a] p-value from Cochran-Mantel-Haenszel test stratified by pooled center.

A.7. Frequency of nocturnal hypoglycemia by prior basal insulin regimen Study 3004								
	Prior once daily basal insulin				Prior more than once daily basal insulin			
	HOE 901		NPH once daily		HOE 901		NPH twice daily	
Treatment phase	No. of subjects	(%)	No. of subjects	(%)	No. of subjects	(%)	No. of subjects	(%)
All nocturnal events								
Month 1	30/69	(43.5)	38/71	(53.5)	106/195	(54.4)	104/199	(52.3)
Month 2 – end	40/67[a]	(59.7)	52/69[a]	(75.4)	136/191	(71.2)	137/197	(69.5)
Entire phase	46/69	(66.7)	57/71	(80.3)	158/195	(81.0)	151/199	(75.9)
Confirmed by blood glucose <2.0 mmol/L								
Month 1	5/69	(7.2)	9/71	(12.7)	19/195	(9.7)	12/199	(6.0)
Month 2 – end	10/67[a]	(14.9)	23/69[a]	(33.3)	37/191	(19.4)	49/197	(24.9)
Entire phase	14/69[a]	(20.3)	26/71[a]	(36.6)	47/195	(24.1)	52/199	(26.1)
Note: Number (%) of subjects reporting at least 1 episode of nocturnal hypoglycemia. a Statistically significant difference at the 0.05 level.								

3. Severe hypoglycemia

A.8. Frequency of severe symptomatic hypoglycemia Study 3001							
Treatment phase	HOE 901			NPH			p-value
	Number of Subjects	(%)	Number of episodes	Number of subjects	(%)	Number of episodes	
Month 1	10/292	(3.4)	17	16/293	(5.5)	22	0.2817
Month 2 – end	28/289	(9.7)	68	35/282	(12.4)	87	0.3812
Entire phase	31/292	(10.6)	85	44/293	(15.0)	109	0.1465
Confirmed by blood glucose <2.0 mmol/L							
Month 1	5/292	(1.7)	6	7/293	(2.4)	7	0.5843
Month 2 – end	8/289	(2.8)	12	14/282	(5.0)	17	0.2008
Entire phase	11/292	(3.8)	18	20/293	(6.8)	24	0.1137
Note: Number (%) of subjects reporting at least one episode of symptomatic hypoglycemia. [a] p-value from Cochran-Mantel-Haenszel test.							

A.9. Frequency of severe symptomatic hypoglycemia Study 3004							
	HOE 901			NPH all regimens			
Treatment phase	No. of Subjects	(%)	No. of episodes	No. of subjects	(%)	No. of episodes	P-value
All severe events							
Month 1	7/264	(2.7)	9	7/270	(2.6)	10	0.9541
Month 2 – end	17/258	(6.6)	28	23/266	(8.6)	45	0.2785
Entire phase	23/264	(8.7)	37	28/270	(10.4)	55	0.4223
Confirmed by blood glucose <2.0 mmol/L							
Month 1	2/264	(0.8)	2	3/270	(1.1)	3	0.6045
Month 2 – end	5/258	(1.9)	9	15/266	(5.6)	20	0.0117
Entire phase	7/264	(2.7)	11	16/270	(5.9)	23	0.0307
Note: Number (%) of subjects reporting at least 1 episode of severe hypoglycemia. [a] P-values from Cochran-Mantel-Haenszel test.							

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4. Asymptomatic hypoglycemia

A.10. Frequency of asymptomatic hypoglycemia over the entire treatment phase Study 3001

Blood Glucose value	HOE 901 (N=292)			NPH (N=293)			p-value
	Number of Subjects	(%)	Number of episodes	Number of subjects	(%)	Number of episodes	
<2.8 mmol/L (50 mg/dL)	75	(25.7)	181	78	(26.6)	159	0.8172
<2.0 mmol/L (36 mg/dL)	7	(2.4)	10	10	(3.4)	13	0.5317

Note: Number (%) of subjects reporting with at least one fasting blood/plasma glucose value satisfying criteria for asymptomatic hypoglycemia.

[a] p-value from Cochran-Mantel-Haenszel test.

A.11. Frequency of asymptomatic hypoglycemia during treatment phase Study 3004

Fasting Glucose Value	HOE 901			NPH all regimens			
	No. of Subjects	(%)	No. of episodes	No. of subjects	(%)	No. of episodes	P-value[a]
<2.8 mmol/L (50 mg/dL)	88	(33.3)	198	53	(19.6)	90	0.0005
<2.0 mmol/L (36 mg/dL)	23	(8.7)	27	8	(3.0)	11	0.0049

Note: Number (%) of subjects reporting with at least 1 fasting blood or plasma glucose value satisfying criteria for asymptomatic hypoglycemia.

[a] P-values from Cochran-Mantel-Haenszel test.

A.12. Asymptomatic hypoglycemia by prior basal insulin regimen during entire treatment phase Study 3004

Fasting glucose Value	Prior once daily basal insulin		Prior more than once daily basal insulin			
	HOE 901 No. of subjects (%)	NPH once daily No. of subjects (%)	HOE 901 No. of subjects	(%)	NPH twice daily No. of subjects	(%)
<2.8 mmol/L	15 (21.7)	18 (25.4)	73[α]	(37.4)	35[α]	(17.6)
<2.0 mmol/L	3 (4.3)	3 (4.2)	20[α]	(10.3)	5[α]	(2.5)

Note: Number (%) of subjects reporting at least 1 fasting blood or plasma glucose value satisfying criteria for asymptomatic hypoglycemia.

α: Statistically significant difference at the 0.05 level.

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Archival: NDA 21-081
cc:
HFD-715/E. Nevius
HFD-510/J. Rhee
HFD-510/R. Misbin
HFD-510/S. Malozowski
HFD-510/J. Jenkins
HFD-715/T. Sahlroot
HFD-725/J. Ma
HFD-510/division file
HFD-715/division file

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STATISTICAL REVIEW AND EVALUATION
CARCINOGENICITY

Date:	DEC 2 2 1999
NDA No:	21,081
Applicant:	Hoechst Marion Roussel, Inc. Jabsas City, MO
Drug Name:	HOE 901 (I 90 1459)
Document Reviewed	Vol: 1.1, 1.16. 1.21, 1.23, 1.41
Data Source:	two diskettes - mice and rats
Pharmacologist:	Herman Rhee, Ph.D., ODE2, HFD-510
Statistical Reviewer:	Moh-Jee Ng, Div II, OEB, HFD-715
User Fee Date:	Feb. 23, 2000

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1. Introduction

This reviewer evaluated the studies of HOE 901 (I 90 1459) for the carcinogenic potential of giving dose of HOE 901 subcutaneously once daily to mice, and rats, conducted by Hoechst Marion Roussel, Inc. In this report, this reviewer presents to the reviewing pharmacologist, Dr. Herman Rhee her independent carcinogenicity analysis based on the sponsor's data.

2. Sponsor's Studies

The sponsor reported results of two experiments in male and female rats and mice. Table 1 summarizes the sponsor's studies.

Species	Mouse	Rat
Strain	Crl: NMRI BR	CD/Sprague-Dawley
Route of Administration	Subcutaneous injections	Subcutaneous injections
Dose Unit	Mg/kg/day	Mg/kg/day
Dose Level (saline control, placebo control, low, med, high) HOE 36H	0,0,0.073.0.182,0.455, 12.5 I.U./kg	0,0,0.073,0.182,0.455 5 I.U./kg/day
Number of Animals/per treatment group	50	50
Length of Study	105-106 weeks	105-106 weeks

In each of these experiments there were two control groups, three treated groups, and one group received HOE 36H. The animals in the control group 1 received saline solution and those in control group 2 received placebo. The treated groups (3, 4 and 5) received doses of 0.073, 0.182, and 0.455 mg/kg/day, corresponding approximately 2, 5, 12.5 IU/kg/day. HOE 36H (group 6) received doses approximately 12.5 IU/kg for mice and 5 IU/kg for rats.

3. Sponsor's Findings

The sponsor analyzed groups 2, 3, 4, 5 versus group 1, and group 6 versus group 1.

In survival analysis, the sponsor claimed that:

- Majority of deaths occurred in the 2nd year of the study. Especially, the high incidence of death in the high dose and HOE 36H groups.

In tumor data analysis, the sponsor claimed that:

- There was a statistically significant increase in malignant fibrous histiocytoma at the injection site in male mice and male rats when compared with the saline control. The sponsor's stated that malignant fibrous histocytomas is a common tumor in the subcutaneous for males than females.
- There was a statistically significant increase in pancreatic islet cell adenoma in female rats when compared with the saline control group

4. Reviewer's Evaluation

This reviewer performed independent analyses on the survival and tumor data submitted by the sponsor, using the programs developed by Dr. Ted Guo of Division of Biostatistics II. The primary statistical methods used were described in Peto *et al* (1980), and Lin and Ali (1994). These methods adjust differences in animal mortality and take contexts of observation of the tumors into consideration. The intervals used for the adjustment of mortality were 0-52, 53-78, 79-91 and 92-105 weeks and terminal sacrifice for animals.

The statistical analyses of carcinogenicity study data consist of two parts, namely, the survival data analysis and the tumor data analysis. The survival data analysis is: 1) to examine the differences in survival distributions among the treatment groups (homogeneity test); and 2) to determine if there is a positive linear trend in the proportion of deaths with respect to the dose levels (Linear trend test). Two statistical tests were used in the survival data analysis: the Cox test and the generalized Kruskal-Wallis test. The theoretical background of these tests was described in Lin and Ali (1994) and Thomas *et al* (1977).

The tumor data analysis is: 1) to determine if there is a positive linear trend in the proportions of a selected tumor type in a selected organ/tissue with respect to the dose levels. The tumors were classified as either fatal (lethal) or non-fatal (non-lethal), according to Peto *et al*(1980). The reviewer applied the death-rate method to fatal tumors and the prevalence method to non-fatal tumors. For tumors that caused death for some, but not for all, animals, a combined test was performed.

A rule for adjusting the effect of multiple tests proposed by Haseman (1983) can be used in control-high pairwise comparisons. Haseman's rule says that rare tumors should be tested at 0.05 level of significance and common tumors should be tested at 0.01 level of significance. A similar rule proposed by the Divisions of Biometrics, CDER/FDA for trend tests was used in this review for tests for postitive trend. The rule states that in order to keep the overall false-positive rate at the nominal level of approximately 0.1, rate tumor types should be tested at 0.025 significance level, otherwise (common tumors) at 0.005 significance level (Lin and Rahman, 1988). A tumor type with spontaneous rate of 1% or less is defined as rare, and as common, otherwise.

4.1 Evaluation of Carcinogenicity Study on Male Mice

This reviewer analyzed the sponsor's data, to evaluate the sponsor's carcinogenicity study on male mice. This reviewer's evaluation comprises the following:

- Survival data analysis
- Tumor data analysis

4.1.1 Survival Data Analysis

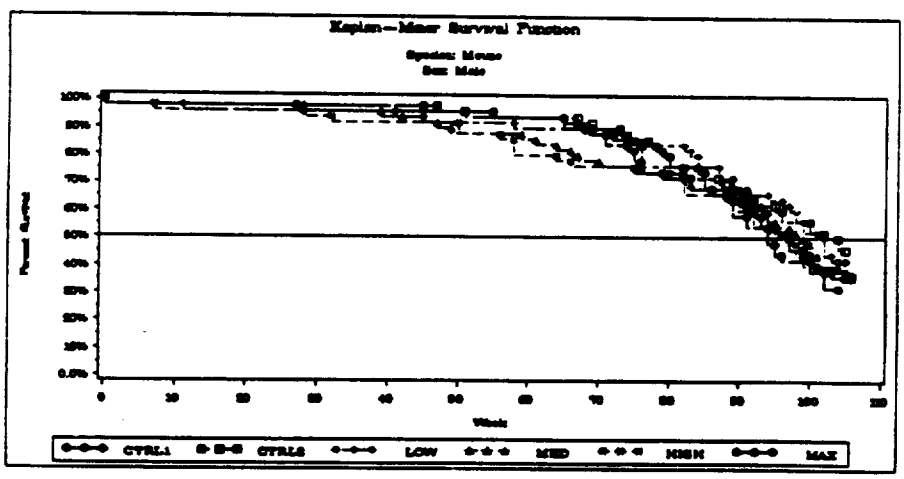
The survival data analysis determines whether the dose-mortality trend is statistically significant. A positive result indicates that more deaths are likely to occur as the dose level increases. Table 1 below describes, for the male mice, the number of deaths, the numbers at risk, and the cumulate percentages of deaths by treatment and age group. The time interval "107-107" represents the terminal-sacrifice week.

Table 1
Analysis of Mortality
Male Mice

	Saline control			Placebo Control			Low			Medium			High			HOE 36H		
Week	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead
0-52	1	50	2.0	2	50	4.0	3	50	6.0	5	50	10.0	4	50	8.0	2	50	4.0
53-78	7	49	16.0	6	48	16.0	4	47	14.0	7	45	24.0	8	46	24.0	9	48	22.0
79-91	11	42	38.0	9	42	34.0	9	43	32.0	5	38	34.0	6	38	36.0	10	39	42.0
92-106	31	50	62.0	25	33	84.0	29	34	90.0	29	33	92.0	30	32	96.0	26	29	94.0
107-107	0	0	0	8	50	16.0	5	50	10.0	4	50	8.0	2	50	4.0	3	50	6.0

Figure 1 presents plot of Kaplan-Meier estimates of the survival distributions of the treatment groups of male mice.

Figure 1: Kaplan-Meier Survival Functions for Male Mice



The test for dose-mortality trend (Table 2) shows no significant results based on the Cox test and the Kruskal-Wallis test.

Table 2: Dose-Mortality Trend in Male Mice

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Mouse
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.87	0.3500
	Depart from Trend	2.35	0.5706
	Homogeneity	3.23	0.6663
Kruskal-Wallis	Dose-Mortality Trend	1.48	0.2236
	Depart from Trend	1.87	0.7593
	Homogeneity	3.14	0.6780

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4.1.2 Tumor Data Analysis

The tumor data analysis determines whether the dose-tumor positive linear trend in tumor incidence is statistically significant. This reviewer tested this trend for data of every organ and tumor provided by the sponsor by analyzing the dose-tumor trend of two control groups and three treated groups 2, 3, and 4. The resulting p-values were compared against the p-value cutoff points set by the FDA procedures. There was no significant positive dose-response relationship in incidence rates in tumors tested in male mice.

4.1.3 Conclusions on Male Mice Study

The test for dose-mortality trend (Table 2) shows no significant results based on the Cox test and the Kruskal-Wallis test. However, survival data in Table 1, clearly show that survival rates of the male mice in all groups dropped tremendously during weeks 92-106.

Dr. Rhee, the pharmacologist reviewer was concerned with high mortality in the male mice study, as show in Table 3 below.

Table 3: The survival percentages of male mice

	End of 52 weeks	End of 90 weeks	End of study weeks
Saline Control	98%	62%	0 %
Placebo Control	96%	66%	16%
Low	94%	68%	10%
Medium	90%	66%	8%
HOE 901	92%	64%	4%
HOE 36H	96%	68%	6%

Haseman (1985) considered 21 two–year studies of 50 mice or rats per group conducted at [redacted] using B6C3F mice and Fischer 344 rats. In those studies, there were 50% survivals at end of the two-year study period. Because CD mice and CD rats have shorter life span, Haseman suggested that a survival rate of 50% of 50 animals in the high dose group, between weeks 80-90, would be considered as a sufficient number of animals to be at risk for late developing tumors. From the data in Table 3, it appears that the sponsor's study satisfies Haseman's criteria. However, it is worth investigating why so many male mice died in the last 13 weeks of the study.

In the 2-year male mice study, there was no statistically significant positive-dose relationship trend in tumor analysis.

In addition to the above evaluation of survival data, in a negative study, the appropriateness of the high doses used should also be evaluated to see if the tested animals received sufficient tumor challenge. The appropriateness of dose selection can be evaluated by looking at the body weight data, mortality data, and clinical signs or severe histogpathologic toxic effects that was attributed to the chemical in the dosed animals.

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4.2 Evaluation of Carcinogenicity Study on Female Mice

This reviewer analyzed the sponsor's data, to evaluate the sponsor's carcinogenicity study on female mice, This reviewer's evaluation comprises the following:

- Survival data analysis
- Tumor data analysis

4.2.1. Survival Data Analysis

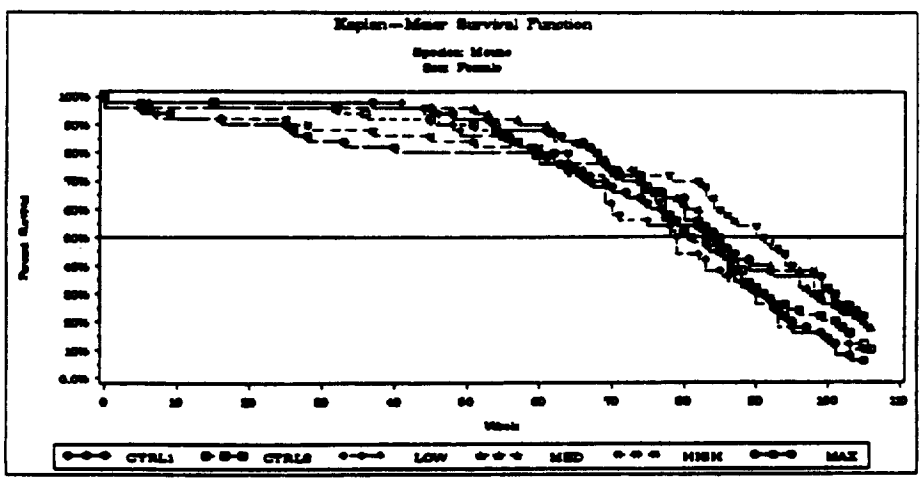
The survival data analysis determines whether the dose-mortality trend is statistically significant. A positive result indicates that more deaths are likely to occur as the dose level increases. Table 4 below describes, for the female mice, the number of deaths, the numbers at risk, and the cumulate percentages of deaths by treatment and age group. The time interval "106-106" represents the terminal-sacrifice week.

Table 4
Analysis of Mortality
Female Mice

	Saline control			Placebo Control			Low			Medium			High			HOE 36H		
Week	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead
0-52	3	50	6.0	5	50	10.0	6	50	12.0	2	50	4.0	8	50	16.0	9	50	18.0
53-78	14	47	34.0	16	45	42.0	17	44	46.0	15	48	34.0	6	42	28.0	11	41	40.0
79-91	18	33	70.0	14	29	70.0	12	27	70.0	12	33	58.0	11	36	50.0	9	30	58 0
92-105	12	15	94.0	9	15	86.0	10	15	90.0	11	21	80.0	14	25	78.0	10	21	78.0
106-106	3	50	6.0	6	50	12.0	5	50	10.0	10	50	20.0	11	50	22.0	11	50	22.0

Figure 2 presents plot of Kaplan-Meier estimates of the survival distributions of the treatment groups of female mice.

Figure 2: Kaplan-Meier Survival Functions for Female Mice



The test for dose-mortality trend (Table 5) shows significant on the Cox test (p= 0.0124) but not signigicant on the Kruskal-Wallis test.

Table 5: Dose-Mortality Trend in Female Mice

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Mouse
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	6.25	0.0124
	Depart from Trend	2.13	0.7118
	Homogeneity	8.38	0.1386
Kruskal-Wallis	Dose-Mortality Trend	2.47	0.1161
	Depart from Trend	3.13	0.6388
	Homogeneity	5.60	0.3475

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4.2.2 Tumor Data Analysis

The tumor data analysis determines whether the dose-tumor positive linear trend in tumor incidence is statistically significant. This reviewer tested this trend for data of every organ and tumor provided by the sponsor by analyzing the dose-tumor trend of two control groups and three treated groups 2, 3, and 4. The resulting p-values were compared against the p-value cutoff points set by the FDA procedures. There was no significant positive dose-response relationship in incidence rates in tumors tested in male mice (see appendix Table 14).

4.2.3 Conclusions on Female Mice Study

The test for dose-mortality trend (Table 5) show no significant on the Cox test but not significnat on the Kruskal-Wallis test. However, survival data in Table 4, clearly shows that survival rates of the male mice in all groups dropped tremendously from weeks 79-91 to 92-106.

Dr. Rhee, the pharmacologist reviewer was concerned with high mortality in the male mice study, as show in Table 6 below.

Table 6: The survival percentages of female mice

	End of 52 weeks	End of 91 weeks	End of study weeks
Saline Control	94%	30%	6%
Placebo Control	90%	30%	12%
Low	88%	30%	10%
Medium	96%	42%	20%
HOE 901	84%	50%	22%
HOE 36H	82%	42%	22%

Haseman (1985) considered 21 two–year studies of 50 mice or rats per group conducted at —, using B6C3F mice and Fischer 344 rats. In those studies, there were 50% survivals at end of the two-year study period. Because CD mice and CD rats have shorter life span, Haseman suggested that a survival rate of 50% of 50 animals in the high dose group, between weeks 80-90, would be considered as a sufficient number of animals to be at risk for late developing tumors. From the data in Table 6, it appears that the sponsor's study satisfies Haseman's criteria. However, it is worth investigating why so many male mice died in the last 13 weeks of the study.

In the 2-year female mice study, there was no significant positive-dose relationship in tumor analysis.

In addition to the above evaluation of survival data, in a negative study, the appropriateness of the high doses used should also be evaluated to see if the tested animals received sufficient tumor challenge. The appropriateness of dose selection can be evaluated by looking at the body weight data, mortality data, and clinical signs or severe histogpathologic toxic effects that was attributed to the chemical in the dosed animals.

4.3 Evaluation of Carcinogenicity Study on Male Rats

4.3 Evaluation of Carcinogenicity Study on Male Rats

This reviewer analyzed the sponsor's data, to evaluation the sponsor's carcinogenicity study on male rats. This reviewer's evaluation comprises the following:

- Survival data analysis
- Tumor data analysis

4.3.1 Survival Data Analysis

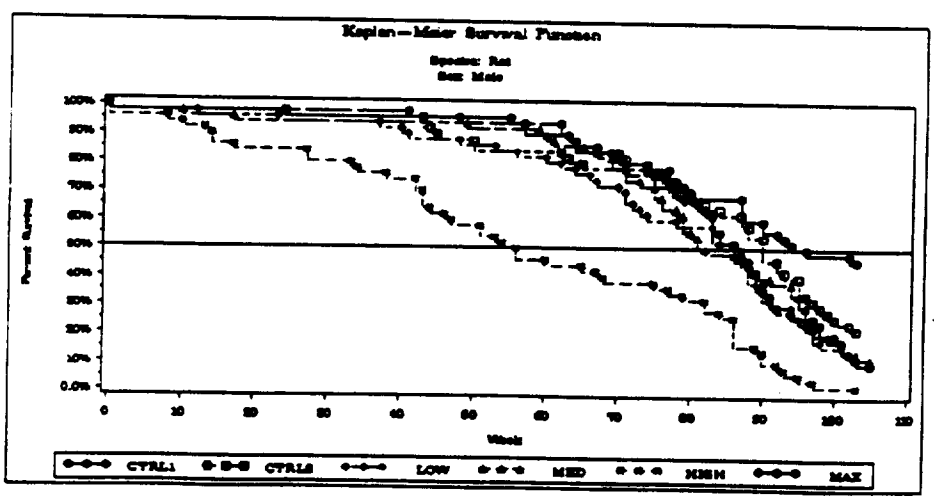
The survival data analysis determines whether the dose-mortality trend is statistically significant. A positive result indicates the more deaths are likely to occur as the dose level increases. The Table 7 below describes, for the male rats, the number of deaths, the numbers at risk, and the cumulate percentages of deaths by treatment and age group. The time interval "106-106" represents the terminal-sacrifice week.

Table 7
Analysis of Mortality
Male Rats

	Saline control			Placebo Control			Low			Medium			High			HOE 36H		
Week	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead
0-52	1	50	2.0	6	50	12.0	6	50	12.0	3	50	6.0	21	50	42.0	2	50	4.0
53-78	12	49	26.0	9	44	30.0	14	44	40.0	15	47	36.0	11	29	64.0	12	48	28.0
79-91	7	37	40.0	8	35	46.0	14	30	68.0	12	32	60.0	11	18	86.0	19	35	66.0
92-105	7	30	54.0	16	27	78.0	10	16	88.0	14	20	88.0	6	7	98.0	12	17	90.0
106-106	23	50	46.0	11	50	22.0	6	50	12.0	6	50	12.0	1	50	2.0	5	50	10.0

Figure 3 presents plot of kaplan-Meier estimates of the survival distributions of the treatment groups of male rats. The animal in the high dose (HOE 901) group had a lower survival rate than those in other groups.

Figure 3: Kaplan-Meier Survival Functions for Male Rats



The test for dose-mortality trend shows significant results on the Cox test ($p<0.0001$) and kruskal-Wallis test ($p<0.0001$). Results of the dose-mortality trend test in Table 8 below.

Table 8: Dose-Mortality Trend in Male Rats

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	p Value
Cox	Dose-Mortality Trend	27.81	0.0000
	Depart from Trend	32.85	0.0000
	Homogeneity	60.46	0.0000
Kruskal-Wallis	Dose-Mortality Trend	28.37	0.0000
	Depart from Trend	27.72	0.0000
	Homogeneity	61.10	0.0000

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This reviewer's survival data analysis concluded that there was a positive trend in mortality in male rats. Therefore, the age-adjusted trend test detailed in the following section (Tumor Data Analysis) is justified.

4.3.2 Tumor Data Analysis

The tumor data analysis determines whether the dose-tumor positive linear trend in tumor incidence is statistically significant. This reviewer tested this trend for data of every organ and tumor provided by the sponsor by analyzing the dose-tumor trend of two control groups and three treated groups 2, 3, and 4. The resulting p-values were compared against the p-value cutoff points set by the FDA procedures. The test showed significance for only 1 tumor type in an organ. The result is summarized in Table 9.

Table 9: Significant Trend Test for Male Rats

Organ	Tumor	Tumor-Bearing Animal	P-value
Skin/Injection Site (7600)	Histiocytomal fibrous (760010)	0,9,13,12,6 (versus 2 control groups)	=0.005 *
Skin/Injection Site (7600)	Histiocytomal fibrous (760010)	0,13,12,6 (versus saline control group)	=0.007
Skin/Injection Site (7600)	Histiocytomal fibrous (760010)	9,13,12,6 (versus placebo control group)	=0.145

* Indicate statistically significant of level 0.005

The positive dose-response relationship in histiocytomal fibrous in skin injection site is statistically significant when two control groups were combined, and when saline control alone was used.

4.3.3 Conclusions on Male Rats Study

In the 2-year male rat study, there was a statistically significant positive linear trend in mortality in the survival analysis. There was a statistically positive-dose relationships in histiocytomal in skin injection site in the tumor analysis.

4.4 Evaluation of Carcinogenicity Study on Female Rats

This reviewer analyzed the sponsor's data, to evaluate the sponsor's carcinogenicity study on female rats,. This reviewer's evaluation comprises the following:

- Survival data analysis
- Tumor data analysis

4.4.1 Survival Data Analysis

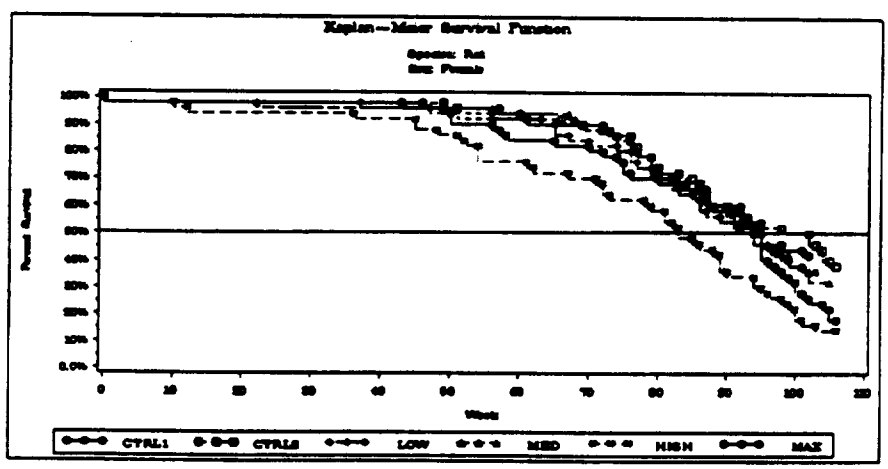
The survival data analysis determines whether the dose-mortality trend is statistically significant. A positive result indicates that the more deaths are likely to occur as the dose level increases. Table 10 below describes, for the female rats, the number of deaths, the numbers at risk, and the cumulate percentages of deaths by treatment and age group. The time interval "106-106" represents the terminal-sacrifice week.

Table 10
Analysis of Mortality
Female Rats

	Saline control			Placebo Control			Low			Medium			High			HOE 36H		
Week	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead	# of Dead	# of Risk	Cum u % Dead
0-52	1	50	2.0	2	50	4.0	2	50	4.0	1	50	2.0	8	50	16.0	3	50	6.0
53-78	9	49	20.0	7	48	18.0	10	48	24.0	9	49	20.0	11	42	38.0	11	47	28.0
79-91	10	40	40.0	11	41	40.0	10	38	44.0	11	40	42.0	13	31	64.0	3	36	34.0
92-105	9	30	58.0	10	30	60.0	10	28	64.0	13	29	68.0	10	18	84.0	22	33	78.0
106-106	21	50	42.0	20	50	40.0	18	50	36.0	16	50	32.0	8	50	16.0	11	50	22.0

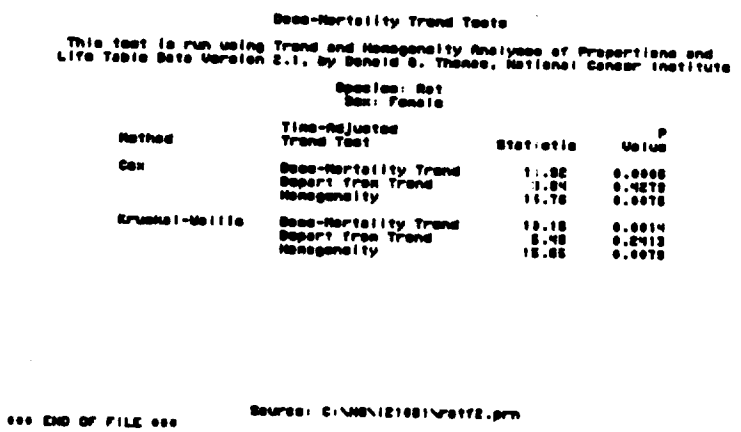
Figure 4 presents plot of Kaplan-Meier estiamtes of the survival distributions of the treatment groups of female rats. The animal in the high dose (HOE 901) group had a lower survival rate than those in other groups.

Figure 4: The Kaplan-Meier survival functions for female rats



The test for dose-mortality trend shows significant results on the Cox test (p=0.00061) and kruskal-Wallis test (p=0.0014). Results of the dose-mortality trend test in Table 11 below.

Table 11: Dose-Mortality Trend in Female Rats



Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald A. Thomas, National Cancer Institute

Species: Rat
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	11.82	0.0006
	Depart from Trend	1.84	0.4278
	Homogeneity	10.78	0.0078
Kruskal-Wallis	Dose-Mortality Trend	10.18	0.0014
	Depart from Trend	5.48	0.2413
	Homogeneity	15.65	0.0078

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This reviewer's survival data analysis concluded that there was a positive trend in mortality in female rats. Therefore, the age-adjusted trend test detailed in the following section (Tumor Data Analysis) is justified.

4.4.2 Tumor Data Analysis

The tumor data analysis determines whether the dose-tumor positive linear trend in tumor incidence is statistically significant. This reviewer tested this trend for data of every organ and tumor provided by the sponsor by analyzing the dose-tumor trend of two control groups and three treated group 2, 3, and 4. The resulting p-values were compared against the p-value cutoff points set by the FDA procedures. The result is summarized in Table 12 below.

Table 12: Significant Trend Test for Female Rats

Organ	Tumor	Tumor-Bearing Animal	P-value
Pancreas (2000)	Adenoma\islet cell (200002)	3, 1, 2, 3, 7 (3 treated groups versus 2 controls)	<0.001
Pancreas (2000)	Adenoma\islet cell (200002)	3, 2, 3, 7 (versus saline control group)	=0.002
Pancreas (2000)	Adenoma\islet cell (200002)	1, 2, 3, 7 (versus placebo control group)	<0.001
Urinary Bladder (2300)	Papilloma \transitional (230019)	0, 0, 0, 2, 0 (2 treated groups versus 2 controls)	=0.025

Statistically positive dose-response relationships incidence rate of pancreas in adenoma\islet cell ($p<0.001$) and in urinary bladder in papilloma\ transitional ($p=0.025$) were detected.

4.4.3 Conclusions on Female Rats Study

In the 2-year female rat study, there was a statistically significant positive linear trend in mortality in the survival analysis. There were statistically positive-dose relationships in incidence rate of pancreas in adenoma\islet cell ($p<0.005$) and in urinary bladder in papilloma\ transitional ($p=0.025$).

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/S/ 12/22/99

Moh-Jee Ng
Mathematical Statistician

Concur: /S/ 12/22/99

Karl Lin, Ph.D.
Expert Mathematical Statistician
(Applications in Pharmacology & Toxicology)

cc: Original NDA 21,081
HFD-510/Division File
HFD-510/Dr. Rhee
HFD-510/Division File, Chron
HFD-715/ENevius, TSahlroot, KLin, MNg

Table 13

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Study No.
Run Date & Time: December 20, 1999 (9:11)
Source: C:\NG\mice_n.prn

Note: Dose Levels Included: CTRL1 CTRL2 LOW MED HIGH (0 0 2 5 12.5)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES					EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT .GE. OBSERVED)
NOSE	(0600)	IN	53-78	1	0	0	0	0	1	0.258	0.056	0.068
Osteoma	(060008)	IN	53-78	2	7	6	4	6	7			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	0	1			
TRACHEA	(0800)	IN	92-106	1	0	0	0	1	0	0.409	0.417	0.459
Papilloma	(080006)	IN	92-106	2	31	25	29	28	30			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1	0			
LUNGS	(0900)	IN	53-78	1	1	0	1	2	1	0.935	0.931	0.934
Adenoma bronchiolo-alveol	(090025)	IN	53-78	2	6	6	3	4	7			
		IN	79-91	1	3	1	3	1	0			
		IN	79-91	2	8	8	6	4	6			
		IN	92-106	1	5	8	7	7	2			
		IN	92-106	2	26	17	22	22	28			
		IN	107-107	1	0	1	0	1	1			
		IN	107-107	2	0	7	5	3	1			
		FA	67	1	0	0	0	1	0			
		FA	67	2	47	48	46	40	39			
Spontaneous tumor pct: 19% in ctrl. - Total				-	9	10	11	12	4			
LUNGS	(0900)	IN	0-52	1	0	0	0	0	1	0.572	0.578	0.585
Carcinoma bronchiolo-alve	(090026)	IN	0-52	2	1	2	2	5	3			
		IN	79-91	1	0	1	1	0	0			
		IN	79-91	2	10	7	7	5	5			
		IN	92-106	1	4	3	2	7	4			
		IN	92-106	2	26	20	25	20	26			
		IN	107-107	1	0	2	1	0	0			
		IN	107-107	2	0	6	4	4	2			
		FA	45	1	0	0	1	0	0			
		FA	45	2	49	50	47	47	47			
		FA	69	1	1	0	0	0	0			
		FA	69	2	46	47	46	40	39			
		FA	75	1	0	0	0	0	1			
		FA	75	2	44	44	44	39	38			
		FA	84	1	0	0	1	0	0			
		FA	84	2	40	38	40	35	36			
		FA	87	1	0	1	0	0	0			
		FA	87	2	34	37	40	35	36			
		FA	88	1	1	0	0	0	1			

		FA 88	2	33	36	38	35	35		
		FA 99	1	0	0	1	1	0		
		FA 99	2	26	30	29	25	24		
		FA 100	1	0	1	0	0	0		
		FA 100	2	23	29	28	25	22		
		FA 101	1	0	0	0	1	0		
		FA 101	2	22	28	28	23	22		
		FA 102	1	1	0	0	0	0		
		FA 102	2	21	28	26	22	20		
		FA 104	1	0	1	1	0	0		
		FA 104	2	19	25	21	22	19		
Spontaneous tumor pct: 16% in ctrl. - Total			-	7	9	8	9	7		
STOMACH, GLANDULAR	(1502)	FA 80	1	1	0	0	0	0	1.000	0.789 0.819
Adenoma	(150207)	FA 80	2	40	42	43	38	37		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	0	0		
LIVER	(1800)	IN 79-91	1	0	1	0	0	0	0.993	0.980 0.981
Haemangioma	(180025)	IN 79-91	2	11	8	9	5	6		
		IN 92-106	1	1	1	0	0	0		
		IN 92-106	2	28	22	28	28	30		
		IN 107-107	1	0	0	1	0	0		
		IN 107-107	2	0	8	4	4	2		
		FA 76	1	0	1	0	0	0		
		FA 76	2	44	42	43	39	38		
		FA 92	1	0	1	0	0	0		
		FA 92	2	31	32	34	33	32		
		FA 97	1	0	0	0	1	0		
		FA 97	2	27	30	32	27	26		
		FA 99	1	1	0	0	0	0		
		FA 99	2	25	30	30	26	24		
		FA 100	1	0	1	0	0	0		
		FA 100	2	23	29	28	25	22		
		FA 102	1	1	0	1	0	0		
		FA 102	2	21	28	25	22	20		
Spontaneous tumor pct: 8% in ctrl. - Total			-	3	5	2	1	0		
LIVER	(1800)	IN 79-91	1	0	1	1	0	0	0.831	0.830 0.837
Adenoma hepatocellular	(180026)	IN 79-91	2	11	8	8	5	6		
		IN 92-106	1	0	4	4	5	1		
		IN 92-106	2	31	21	25	24	29		
		IN 107-107	1	0	1	0	0	0		
		IN 107-107	2	0	7	5	4	2		
Spontaneous tumor pct: 6% in ctrl. - Total			-	0	6	5	5	1		
LIVER	(1800)	IN 79-91	1	0	0	0	1	0	0.989	0.982 0.983
Carcinoma hepatocellular	(180027)	IN 79-91	2	11	8	8	4	6		
		IN 92-106	1	4	2	1	2	1		
		IN 92-106	2	25	21	27	27	29		
		IN 107-107	1	0	2	0	0	0		
		IN 107-107	2	0	6	5	4	2		
		FA 82	1	0	1	0	0	0		
		FA 82	2	40	41	43	38	37		
		FA 89	1	0	0	1	0	0		
		FA 89	2	33	35	37	35	33		
		FA 95	1	0	1	0	0	0		
		FA 95	2	29	31	33	30	27		

		FA 101	1	0	0	1	0	0		
		FA 101	2	22	28	27	24	22		
		FA 102	1	1	1	0	0	0		
		FA 102	2	21	27	26	22	20		
		FA 104	1	1	0	0	0	0		
		FA 104	2	18	26	22	22	19		
Spontaneous tumor pct: 13% in ctrl. - Total			-	6	7	3	3	1		
LIVER	(1800)	IN 92-106	1	1	0	0	0	0	0.092	0.042 0.048
Haemangiosarcoma	(180028)	IN 92-106	2	30	25	29	29	28		
		FA 96	1	0	0	0	0	1		
		FA 96	2	27	31	33	28	26		
		FA 97	1	0	0	0	0	1		
		FA 97	2	27	30	32	28	25		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	0	2	(Asymptotic P<0.050)	
LIVER	(1800)	FA 98	1	0	0	0	1	0	0.374	0.383 0.426
Histiocytoma fibrous mali	(180045)	FA 98	2	26	30	31	26	25		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1	0		
PANCREAS	(2000)	IN 92-106	1	0	0	0	1	0	0.409	0.417 0.459
Adenoma acinar cell	(200024)	IN 92-106	2	31	25	29	28	30		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1	0		
PANCREAS	(2000)	FA 100	1	1	0	0	0	0	1.000	0.787 0.818
Carcinoma islet cell	(200026)	FA 100	2	22	30	28	25	22		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	0	0		
URINARY BLADDER	(2300)	IN 92-106	1	2	1	0	0	0	1.000	0.928 0.936
Papilloma transitional ce	(230010)	IN 92-106	2	29	24	26	29	28		
Spontaneous tumor pct: 3% in ctrl. - Total			-	2	1	0	0	0		
URINARY BLADDER	(2300)	IN 53-78	1	0	0	0	1	0	0.414	0.432 0.445
Submucosal mesenchymal tu	(230011)	IN 53-78	2	7	6	3	6	8		
		IN 79-91	1	2	1	0	1	0		
		IN 79-91	2	9	8	9	4	6		
		IN 92-106	1	0	1	0	4	1		
		IN 92-106	2	31	24	26	25	27		
Spontaneous tumor pct: 4% in ctrl. - Total			-	2	2	0	6	1		
URINARY BLADDER	(2300)	IN 92-106	1	0	0	1	0	0	0.645	0.680 0.709
Carcinoma transitional ce	(230014)	IN 92-106	2	31	25	25	29	28		
		IN 107-107	1	0	0	1	0	0		
		IN 107-107	2	0	8	4	4	2		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	2	0	0		
SEMINAL VESICLES	(2800)	IN 92-106	1	1	0	0	1	0	0.656	0.676 0.703
Tumour granular cell beni	(280009)	IN 92-106	2	30	25	28	28	30		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	1	0		
SEMINAL VESICLES	(2800)	IN 92-106	1	0	0	0	1	0	0.412	0.418 0.460
Haemangioma	(280013)	IN 92-106	2	31	25	28	28	30		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1	0		
ADRENAL CORTEX	(4401)	IN 92-106	1	1	0	0	0	0	1.000	0.802 0.830
Adenoma subcapsular cell	(440113)	IN 92-106	2	30	25	29	29	30		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	0	0		

ADRENAL CORTEX	(4401)	IN	79-91	1	0	0	1	0	0	0.500	0.586	0.631
Adenoma subcapsular cell	(440114)	IN	79-91	2	11	9	8	5	6			
Spontaneous tumor pct: <= 1% in ctrl. -		Total		-	0	0	1	0	0			
ADRENAL CORTEX	(4401)	IN	53-78	1	1	1	0	1	0	0.597	0.609	0.619
Adenoma subcapsular cell	(440115)	IN	53-78	2	6	5	4	6	8			
		IN	79-91	1	1	0	0	0	0			
		IN	79-91	2	10	9	9	5	6			
		IN	92-106	1	3	1	1	2	3			
		IN	92-106	2	28	24	28	27	27			
		IN	107-107	1	0	1	0	0	0			
		IN	107-107	2	0	7	5	4	2			
Spontaneous tumor pct: 8% in ctrl. -		Total		-	5	3	1	3	3			
HAEMOLYMPHORET. SYS.	(4500)	IN	53-78	1	1	0	0	0	0	0.314	0.316	0.321
Lymphoma malignant	(450001)	IN	53-78	2	4	4	3	7	7			
		IN	79-91	1	0	1	1	0	0			
		IN	79-91	2	9	5	6	5	4			
		IN	92-106	1	2	5	6	6	6			
		IN	92-106	2	25	19	22	20	20			
		IN	107-107	1	0	0	1	1	0			
		IN	107-107	2	0	8	4	3	2			
		FA	28	1	0	0	0	1	0			
		FA	28	2	49	50	49	49	49			
		FA	47	1	0	1	0	0	0			
		FA	47	2	49	49	47	47	47			
		FA	58	1	0	0	0	0	1			
		FA	58	2	48	48	47	45	43			
		FA	69	1	0	1	0	0	0			
		FA	69	2	47	46	46	40	39			
		FA	73	1	0	1	0	0	0			
		FA	73	2	44	45	46	39	39			
		FA	74	1	0	0	1	0	0			
		FA	74	2	44	45	44	39	39			
		FA	77	1	1	0	0	0	0			
		FA	77	2	43	42	43	38	38			
		FA	78	1	1	0	0	0	0			
		FA	78	2	42	42	43	38	38			
		FA	79	1	1	0	0	0	0			
		FA	79	2	41	42	43	38	38			
		FA	82	1	0	2	1	0	1			
		FA	82	2	40	40	42	38	36			
		FA	83	1	0	0	1	0	0			
		FA	83	2	40	38	41	37	36			
		FA	86	1	1	0	0	0	0			
		FA	86	2	36	38	40	35	36			
		FA	88	1	0	0	0	0	1			
		FA	88	2	34	36	38	35	35			
		FA	89	1	0	1	0	0	0			
		FA	89	2	33	34	38	35	33			
		FA	94	1	0	0	0	1	1			
		FA	94	2	29	32	34	30	29			
		FA	97	1	1	0	1	0	0			
		FA	97	2	26	30	31	28	26			
		FA	99	1	2	0	0	0	0			
		FA	99	2	24	30	30	26	24			

		FA 101	1	0	0	0	0	2			
		FA 101	2	22	28	28	24	20			
		FA 104	1	1	0	0	2	0			
		FA 104	2	18	26	22	20	19			
		FA 105	1	0	1	0	0	0			
		FA 105	2	16	24	21	20	19			
		FA 106	1	0	0	0	0	1			
		FA 106	2	12	19	17	16	14			
Spontaneous tumor pct: 24% in ctrl. - Total			-	11	13	12	11	13			
HAEMOLYMPHORET. SYS.	(4500)	IN 92-106	1	0	0	1	0	0	0.836	0.791	0.814
Tumour mast cell malignan	(450002)	IN 92-106	2	31	25	28	29	30			
		IN 107-107	1	0	1	0	0	0			
		IN 107-107	2	0	7	5	4	2			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	1	0	0			
HAEMOLYMPHORET. SYS.	(4500)	FA 56	1	0	0	0	0	1	0.471	0.435	0.460
Histiocytic sarcoma	(450003)	FA 56	2	48	48	47	45	45			
		FA 65	1	1	0	0	0	0			
		FA 65	2	47	48	46	42	40			
		FA 90	1	1	0	0	0	0			
		FA 90	2	32	34	36	35	32			
Spontaneous tumor pct: 2% in ctrl. - Total			-	2	0	0	0	1			
SPLEEN	(4600)	FA 105	1	0	0	0	1	0	0.386	0.393	0.435
Haemangiosarcoma	(460015)	FA 105	2	16	25	21	19	19			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1	0			
THYMUS	(5000)	IN 79-91	1	0	0	1	0	0	0.500	0.586	0.631
Thymoma benign	(500009)	IN 79-91	2	11	9	8	5	6			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0	0			
SKIN/SUBCUTAN.TISSUE	(5700)	IN 92-106	1	0	0	1	0	0	0.605	0.666	0.703
Schwannoma malignant	(570011)	IN 92-106	2	31	25	26	29	30			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0	0			
SKIN/SUBCUTAN.TISSUE	(5700)	FA 58	1	0	0	1	0	0	0.803	0.807	0.822
Histiocytoma fibrous mali	(570022)	FA 58	2	48	48	44	45	44			
		FA 82	1	0	0	0	1	0			
		FA 82	2	40	42	41	37	37			
		FA 85	1	1	0	0	0	0			
		FA 85	2	37	38	38	35	36			
		FA 105	1	0	1	0	0	0			
		FA 105	2	16	24	21	20	19			
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	1	1	1	0			
SKIN/SUBCUTAN.TISSUE	(5700)	FA 103	1	0	0	1	0	0	0.594	0.638	0.680
Haemangiosarcoma	(570023)	FA 103	2	19	26	24	22	19			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0	0			
SKELETAL MUSCLE	(5800)	IN 92-106	1	0	0	0	0	1	0.208	0.036	0.045
Sarcoma NOS	(580011)	IN 92-106	2	31	25	29	29	29			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	0	1			
BODY CAVITIES	(6800)	IN 79-91	1	0	1	0	0	0	1.000	0.752	0.787
Histiocytoma fibrous mali	(680009)	IN 79-91	2	11	8	9	5	6			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	0	0			

STERNUM	(7200)	IN 79-91	1	0	0	0	0	1	0.150	0.013	0.018
Chondroma	(720004)	IN 79-91	2	11	9	9	5	5			
Spontaneous tumor pct: <= 1% in ctrl. -		Total	-	0	0	0	0	1			
INJECTION SITE	(7600)	IN 79-91	1	0	0	0	0	1	0.150	0.013	0.018
Lipoma	(760013)	IN 79-91	2	11	9	9	5	5			
Spontaneous tumor pct: <= 1% in ctrl. -		Total	-	0	0	0	0	1			
INJECTION SITE	(7600)	IN 92-106	1	0	1	1	0	1	0.614	0.626	0.636
Histiocytoma fibrous mali	(760018)	IN 92-106	2	31	24	26	28	28			
		IN 107-107	1	0	2	0	1	0			
		IN 107-107	2	0	6	5	3	2			
		FA 73	1	0	0	1	0	0			
		FA 73	2	44	46	45	39	39			
		FA 82	1	0	1	0	0	0			
		FA 82	2	40	41	43	38	37			
		FA 87	1	0	0	2	0	0			
		FA 87	2	34	38	38	35	36			
		FA 91	1	0	0	2	1	0			
		FA 91	2	32	34	34	33	32			
		FA 95	1	0	0	0	1	0			
		FA 95	2	29	32	33	29	27			
		FA 96	1	0	0	1	0	0			
		FA 96	2	27	31	32	28	27			
		FA 99	1	0	0	0	0	1			
		FA 99	2	26	30	30	26	23			
		FA 106	1	0	0	1	0	0			
		FA 106	2	12	19	16	16	15			
Spontaneous tumor pct: 4%		in ctrl. -	Total	-	0	4	8	3	2		

APPEARS THIS WAY
ON ORIGINAL

Table 14

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Study No.
Run Date & Time: December 20, 1999 (10:03)
Source: C:\NG\micef_n.prn

Note: Dose Levels Included: CTRL1 CTRL2 LOW MED HIGH (0 0 2 5 12.5)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT .GE. OBSERVED)	ASYMP PROB	ASYMP PROC /CONT CORR
LUNGS	(0900)	IN	53-78	1	0 3 2 2 0	0.874	0.870	0.875
Adenoma bronchiolo-alveol	(090025)	IN	53-78	2	14 13 15 13 6			
		IN	79-91	1	0 2 1 2 1			
		IN	79-91	2	18 12 11 10 10			
		IN	92-105	1	3 0 2 1 0			
		IN	92-105	2	9 9 8 10 14			
		IN	106-106	1	0 2 0 1 1			
		IN	106-106	2	3 4 5 9 10			
Spontaneous tumor pct: 10%	in ctrl. -	Total		-	3 7 5 6 2			
LUNGS	(0900)	IN	53-78	1	1 1 0 1 0	0.105	0.099	0.104
Carcinoma bronchiolo-alve	(090026)	IN	53-78	2	13 15 17 14 6			
		IN	79-91	1	1 1 0 2 1			
		IN	79-91	2	16 13 12 9 10			
		IN	92-105	1	0 0 1 1 1			
		IN	92-105	2	11 9 9 10 9			
		IN	106-106	1	0 0 1 1 0			
		IN	106-106	2	3 6 4 9 11			
		FA	89	1	1 0 0 1 0			
		FA	89	2	18 19 17 23 28			
		FA	93	1	0 0 0 0 1			
		FA	93	2	14 14 15 20 23			
		FA	95	1	0 0 0 0 1			
		FA	95	2	11 13 13 20 21			
		FA	99	1	1 0 0 0 2			
		FA	99	2	8 12 9 15 17			
Spontaneous tumor pct: 6%	in ctrl. -	Total		-	4 2 2 6 6			
FORESTOMACH	(1501)	IN	53-78	1	0 1 0 0 0	0.374	0.250	0.276
Papilloma squamous cell	(150105)	IN	53-78	2	14 15 17 15 6			
		IN	106-106	1	0 0 0 0 1			
		IN	106-106	2	3 6 5 10 10			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	0 1 0 0 1			
STOMACH, GLANDULAR	(1502)	IN	106-106	1	0 1 1 0 0	0.939	0.908	0.920
Adenoma	(150207)	IN	106-106	2	3 5 4 10 11			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	0 1 1 0 0			
CECUM	(1701)	IN	79-91	1	0 1 0 0 0	1.000	0.770	0.803
Schwannoma benign	(170106)	IN	79-91	2	18 13 12 12 11			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	0 1 0 0 0			

CECUM	(1701)	IN	53-78	1	0	1	0	0	0	1.000	0.773	0.813
Sarcoma not otherwise spe	(170107)	IN	53-78	2	14	15	17	15	6			
Spontaneous tumor pct: <= 1% in ctrl. -		Total		-	0	1	0	0	0			
COLON	(1702)	IN	53-78	1	0	0	1	0	0	0.558	0.577	0.631
Haemangioma	(170203)	IN	53-78	2	14	16	16	15	6			
Spontaneous tumor pct: <= 1% in ctrl. -		Total		-	0	0	1	0	0			
LIVER	(1800)	IN	92-105	1	0	0	1	0	0	0.861	0.850	0.864
Carcinoma hepatocellular	(180027)	IN	92-105	2	12	9	9	11	14			
		FA	49	1	0	0	1	0	0			
		FA	49	2	47	46	44	49	43			
		FA	87	1	0	1	0	0	0			
		FA	87	2	23	21	18	24	29			
Spontaneous tumor pct: <= 1% in ctrl. -		Total		-	0	1	2	0	0			
URINARY BLADDER	(2300)	IN	106-106	1	1	0	0	0	0	1.000	0.870	0.890
Papilloma transitional ce	(230010)	IN	106-106	2	2	6	5	10	11			
Spontaneous tumor pct: <= 1% in ctrl. -		Total		-	1	0	0	0	0			
URINARY BLADDER	(2300)	IN	79-91	1	0	0	0	0	1	0.051	0.008	0.010
Submucosal mesenchymal tu	(230011)	IN	79-91	2	18	14	12	12	10			
		IN	106-106	1	0	0	0	0	1			
		IN	106-106	2	3	6	5	10	10			
Spontaneous tumor pct: <= 1% in ctrl. -		Total		-	0	0	0	0	2			
OVARIES	(3200)	IN	106-106	1	0	0	1	0	0	0.742	0.767	0.796
Tumour sex cord stromal m	(320011)	IN	106-106	2	3	6	4	10	11			
Spontaneous tumor pct: <= 1% in ctrl. -		Total		-	0	0	1	0	0			
OVARIES	(3200)	IN	79-91	1	0	2	0	0	0	1.000	0.854	0.871
Tumour granulosa cell ben	(320012)	IN	79-91	2	18	12	12	12	11			
Spontaneous tumor pct: 2% in ctrl. -		Total		-	0	2	0	0	0			
OVARIES	(3200)	IN	79-91	1	0	0	0	1	0	0.478	0.437	0.467
Cystadenoma	(320014)	IN	79-91	2	18	14	12	11	11			
		IN	106-106	1	0	0	0	1	0			
		IN	106-106	2	3	6	5	9	11			
Spontaneous tumor pct: <= 1% in ctrl. -		Total		-	0	0	0	2	0			
OVARIES	(3200)	IN	0-52	1	0	0	1	0	0	0.666	0.715	0.745
Haemangioma	(320015)	IN	0-52	2	3	5	5	2	8			
Spontaneous tumor pct: <= 1% in ctrl. -		Total		-	0	0	1	0	0			
OVARIES	(3200)	IN	92-105	1	0	0	1	0	2	0.391	0.378	0.394
Adenoma tubulostromal	(320017)	IN	92-105	2	12	9	9	11	12			
		IN	106-106	1	1	0	1	1	0			
		IN	106-106	2	2	6	4	9	11			
Spontaneous tumor pct: <= 1% in ctrl. -		Total		-	1	0	2	1	2			
OVARIES	(3200)	IN	92-105	1	0	1	0	0	0	1.000	0.815	0.840
Tumour sertoli cell benig	(320024)	IN	92-105	2	12	8	10	11	14			
Spontaneous tumor pct: <= 1% in ctrl. -		Total		-	0	1	0	0	0			
UTERUS	(3400)	IN	53-78	1	1	0	0	0	0	0.997	0.990	0.991
Polyp stromal	(340013)	IN	53-78	2	13	16	17	15	6			
		IN	79-91	1	0	1	1	0	0			

		IN 79-91	2	18	13	11	12	11		
		IN 92-105	1	2	1	0	0	0		
		IN 92-105	2	10	8	10	11	14		
		IN 106-106	1	0	2	0	1	0		
		IN 106-106	2	3	4	5	9	11		
Spontaneous tumor pct: 7%	in ctrl. -	Total	-	3	4	1	1	0		
UTERUS	(3400)	IN 79-91	1	0	0	1	0	0	0.522	0.615 0.657
Polyp glandular	(340014)	IN 79-91	2	18	14	11	12	11		
Spontaneous tumor pct: <= 1%	in ctrl. -	Total	-	0	0	1	0	0		
UTERUS	(3400)	FA 77	1	0	1	0	0	0	0.885	0.861 0.874
Schwannoma malignant	(340021)	FA 77	2	36	32	28	35	37		
		FA 96	1	0	0	0	1	0		
		FA 96	2	10	13	9	19	20		
		FA 102	1	0	1	0	0	0		
		FA 102	2	6	9	7	13	14		
Spontaneous tumor pct: 2%	in ctrl. -	Total	-	0	2	0	1	0		
UTERUS	(3400)	IN 79-91	1	2	0	0	1	0	0.408	0.391 0.412
Tumour granular cell beni	(340025)	IN 79-91	2	16	14	12	11	11		
		FA 95	1	0	0	0	0	1		
		FA 95	2	11	13	13	20	21		
Spontaneous tumor pct: 2%	in ctrl. -	Total	-	2	0	0	1	1		
UTERUS	(3400)	IN 79-91	1	0	0	0	1	0	0.737	0.722 0.746
Sarcoma endometrial strom	(340028)	IN 79-91	2	18	14	12	11	11		
		IN 106-106	1	0	1	0	0	0		
		IN 106-106	2	3	5	5	10	11		
Spontaneous tumor pct: <= 1%	in ctrl. -	Total	-	0	1	0	1	0		
UTERUS	(3400)	FA 103	1	0	0	0	0	1	0.276	0.067 0.081
Leiomyosarcoma	(340030)	FA 103	2	6	9	7	12	12		
Spontaneous tumor pct: <= 1%	in ctrl. -	Total	-	0	0	0	0	1		
UTERUS	(3400)	IN 79-91	1	0	1	0	0	0	1.000	0.770 0.803
Histiocytoma fibrous mali	(340031)	IN 79-91	2	18	13	12	12	11		
Spontaneous tumor pct: <= 1%	in ctrl. -	Total	-	0	1	0	0	0		
PITUITARY GLAND	(4100)	IN 53-78	1	0	0	0	0	1	0.896	0.891 0.895
Adenoma pars distalis	(410005)	IN 53-78	2	14	16	17	15	5		
		IN 79-91	1	1	2	1	0	0		
		IN 79-91	2	17	10	10	12	11		
		IN 92-105	1	2	1	1	1	0		
		IN 92-105	2	10	8	8	10	14		
		IN 106-106	1	1	0	0	2	2		
		IN 106-106	2	2	6	5	8	9		
		FA 80	1	0	1	0	0	0		
		FA 80	2	33	28	25	32	36		
		FA 85	1	0	0	1	0	0		
		FA 85	2	26	23	20	26	32		
		FA 89	1	0	1	0	0	0		
		FA 89	2	19	18	17	24	28		
		FA 103	1	0	0	1	0	0		
		FA 103	2	6	9	6	12	13		
Spontaneous tumor pct: 9%	in ctrl. -	Total	-	4	5	4	3	3		

PITUITARY GLAND	(4100)	IN	79-91	1	1	0	0	0	0	0.938	0.932	0.939
Adenoma pars intermedia	(410010)	IN	79-91	2	17	14	12	12	11			
		IN	106-106	1	0	0	3	0	0			
		IN	106-106	2	3	6	2	10	11			
Spontaneous tumor pct: <= 1% in ctrl.		-	Total	-	1	0	3	0	0			
HAEMOLYMPHORET. SYS.	(4500)	IN	0-52	1	0	1	0	0	0	0.999	0.999	0.999
Lymphoma malignant	(450001)	IN	0-52	2	2	2	5	2	8			
		IN	53-78	1	1	2	1	0	0			
		IN	53-78	2	3	5	3	6	3			
		IN	79-91	1	0	1	0	1	0			
		IN	79-91	2	6	5	4	3	5			
		IN	92-105	1	3	0	2	2	0			
		IN	92-105	2	4	3	2	2	8			
		IN	106-106	1	1	4	3	3	8			
		IN	106-106	2	2	1	2	6	3			
		FA	15	1	0	1	0	0	0			
		FA	15	2	50	49	50	49	47			
		FA	45	1	1	1	0	0	0			
		FA	45	2	48	46	48	49	44			
		FA	48	1	0	0	1	0	0			
		FA	48	2	48	46	46	49	43			
		FA	53	1	1	0	0	0	0			
		FA	53	2	46	45	44	48	42			
		FA	54	1	0	1	0	0	0			
		FA	54	2	46	44	44	47	42			
		FA	55	1	0	1	0	0	0			
		FA	55	2	45	43	44	47	42			
		FA	56	1	0	0	1	0	0			
		FA	56	2	45	43	43	47	42			
		FA	59	1	0	0	2	0	0			
		FA	59	2	45	42	41	46	42			
		FA	60	1	0	0	0	0	1			
		FA	60	2	45	41	41	46	41			
		FA	61	1	1	0	2	0	0			
		FA	61	2	44	41	39	46	41			
		FA	62	1	0	1	0	0	0			
		FA	62	2	44	40	39	45	41			
		FA	63	1	1	0	0	0	0			
		FA	63	2	43	40	39	44	41			
		FA	66	1	1	0	1	0	0			
		FA	66	2	42	37	37	42	40			
		FA	67	1	0	0	1	1	0			
		FA	67	2	42	37	36	41	40			
		FA	68	1	1	0	0	1	0			
		FA	68	2	40	37	36	40	40			
		FA	69	1	1	0	1	1	2			
		FA	69	2	39	37	35	39	38			
		FA	70	1	1	0	1	0	0			
		FA	70	2	37	37	34	39	38			
		FA	71	1	0	1	2	2	0			
		FA	71	2	37	36	29	37	38			
		FA	74	1	1	1	0	1	0			
		FA	74	2	36	35	29	36	37			
		FA	75	1	0	0	1	0	0			
		FA	75	2	36	35	28	35	37			
		FA	76	1	0	1	0	0	0			

FA 76	2	36	33	28	35	37
FA 77	1	2	1	0	1	0
FA 77	2	34	32	28	34	37
FA 78	1	0	2	1	0	0
FA 78	2	33	29	27	33	37
FA 79	1	0	0	2	1	0
FA 79	2	33	29	25	32	36
FA 80	1	1	1	0	0	0
FA 80	2	32	28	25	32	36
FA 82	1	3	0	2	1	0
FA 82	2	29	25	23	30	36
FA 83	1	0	1	1	3	1
FA 83	2	28	24	21	27	34
FA 84	1	1	1	0	0	1
FA 84	2	26	23	21	27	33
FA 85	1	1	0	0	2	2
FA 85	2	25	23	21	24	30
FA 86	1	2	1	1	0	1
FA 86	2	23	22	18	24	29
FA 87	1	3	1	0	0	0
FA 87	2	20	21	18	24	29
FA 88	1	0	1	1	0	0
FA 88	2	19	19	17	24	28
FA 89	1	0	1	0	1	0
FA 89	2	19	18	17	23	28
FA 90	1	1	0	1	0	1
FA 90	2	16	17	15	21	27
FA 91	1	0	1	0	0	0
FA 91	2	16	16	15	21	27
FA 92	1	0	0	0	1	1
FA 92	2	15	15	15	20	24
FA 93	1	1	0	2	0	0
FA 93	2	13	14	13	20	24
FA 94	1	1	0	0	0	1
FA 94	2	11	14	13	20	22
FA 95	1	0	0	1	0	0
FA 95	2	11	13	12	20	22
FA 96	1	0	1	0	0	0
FA 96	2	10	12	9	20	20
FA 97	1	1	0	0	1	0
FA 97	2	9	12	9	18	20
FA 98	1	0	0	0	1	1
FA 98	2	9	12	9	15	19
FA 99	1	0	1	1	1	1
FA 99	2	9	11	8	14	18
FA 100	1	0	0	1	0	0
FA 100	2	8	11	7	14	15
FA 101	1	1	1	0	1	1
FA 101	2	6	10	7	13	14
FA 103	1	1	1	0	0	0
FA 103	2	5	8	7	12	13
FA 104	1	0	0	0	1	0
FA 104	2	4	8	6	11	12
FA 105	1	0	2	1	1	1
FA 105	2	4	6	5	10	11
FA 106	1	0	1	0	1	0
FA 106	2	3	5	5	9	11

Spontaneous tumor pct: 67% in ctrl. - Total				-	33	34	34	29	23			
HAEMOLYMPHORET. SYS.	(4500)	FA	102	1	0	0	0	1	0	0.540	0.506	0.546
Histiocytic sarcoma	(450003)	FA	102	2	6	10	7	12	14			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1	0			
SPLEEN	(4600)	IN	79-91	1	1	0	0	0	0	1.000	0.770	0.803
Haemangioma	(460014)	IN	79-91	2	17	14	12	12	11			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0	0			
BONE MARROW	(4700)	IN	53-78	1	1	0	0	0	0	1.000	0.773	0.813
Haemangioma	(470009)	IN	53-78	2	13	16	17	15	6			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0	0			
THYMUS	(5000)	IN	53-78	1	0	1	0	0	0	1.000	0.773	0.813
Thymoma benign	(500009)	IN	53-78	2	14	15	17	15	6			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	0	0	0			
MAMMARY GLAND	(5600)	IN	92-105	1	0	0	0	0	1	0.268	0.240	0.256
Adenocarcinoma	(560005)	IN	92-105	2	11	9	10	11	13			
		FA	73	1	0	0	0	0	1			
		FA	73	2	37	36	29	37	37			
		FA	87	1	1	0	0	0	0			
		FA	87	2	22	22	18	24	29			
		FA	93	1	1	0	0	0	0			
		FA	93	2	13	14	15	20	24			
Spontaneous tumor pct: 2% in ctrl. - Total				-	2	0	0	0	2			
SKIN/SUBCUTAN.TISSUE	(5700)	IN	106-106	1	0	1	0	0	0	1.000	0.921	0.931
Carcinoma basal cell	(570013)	IN	106-106	2	3	5	5	10	11			
		FA	80	1	0	1	0	0	0			
		FA	80	2	33	28	25	32	36			
Spontaneous tumor pct: 2% in ctrl. - Total				-	0	2	0	0	0			
SKIN/SUBCUTAN.TISSUE	(5700)	IN	53-78	1	1	0	0	0	0	1.000	0.773	0.813
Carcinoma sebaceous	(570017)	IN	53-78	2	13	16	17	15	6			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0	0			
SKIN/SUBCUTAN.TISSUE	(5700)	IN	92-105	1	0	0	1	0	0	0.848	0.824	0.843
Keratoacanthoma	(570021)	IN	92-105	2	12	9	9	11	14			
		FA	63	1	0	1	0	0	0			
		FA	63	2	44	39	39	44	41			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	1	0	0			
SKIN/SUBCUTAN.TISSUE	(5700)	IN	92-105	1	0	0	1	0	0	0.625	0.689	0.724
Histiocytoma fibrous mali	(570022)	IN	92-105	2	12	9	9	11	14			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	0			
INJECTION SITE	(7600)	IN	79-91	1	0	0	1	0	0	0.721	0.744	0.767
Histiocytoma fibrous mali	(760018)	IN	79-91	2	18	14	11	12	11			
		FA	95	1	0	0	1	0	0			
		FA	95	2	11	13	12	20	22			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	2	0	0			
INJECTION SITE	(7600)	IN	79-91	1	0	0	0	1	0	0.343	0.352	0.394
Tumour granular cell beni	(760028)	IN	79-91	2	18	14	12	11	11			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1	0			

Table 15

Analysis of Carcinogenic Potential in Male
Test of Dose-Response (Tumor) Positive Linear Study No
Run Date & Time: November 12, 1999
(Source: C:\NG\I21081\ratm0_4.dat

Note: Dose Levels Included: CTRL1 CTRL2 LOW MED HIGH (0 0 2 5 12.5)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES					EXACT PROB =P(STAT .GE. OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
BRAIN	(0100)	IN	106-106	1	0	1	0	0	0	0.322	0.268	0.315
Astrocytoma \ malignant	(010001)	IN	106-106	2	23	10	6	6	1			
		FA	103	1	0	0	0	1	0			
		FA	103	2	24	12	7	8	2			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	0	1	0			
CEREBRUM	(0101)	IN	106-106	1	1	0	0	0	0	1.000	0.686	0.756
Reticulosis \ malignant	(010113)	IN	106-106	2	22	11	6	6	1			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0	0			
CEREBRUM	(0101)	IN	53-78	1	1	0	1	0	0	0.917	0.854	0.871
Oligodendroglioma \ benig	(010114)	IN	53-78	2	11	9	13	15	11			
		IN	106-106	1	1	0	0	0	0			
		IN	106-106	2	22	11	6	6	1			
Spontaneous tumor pct: 2% in ctrl. - Total				-	2	0	1	0	0			
HEART	(0400)	IN	106-106	1	1	0	0	0	0	1.000	0.686	0.756
Mesothelioma \ atriocaval	(040021)	IN	106-106	2	22	11	6	6	1			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0	0			
NOSE	(0600)	FA	93	1	1	0	0	0	0	1.000	0.742	0.789
Carcinoma \ squamous cell	(060001)	FA	93	2	26	23	14	19	5			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0	0			
FORESTOMACH	(1570)	IN	92-105	1	0	0	0	0	1	0.113	0.008	0.011
Carcinoma \ squamous cell	(157016)	IN	92-105	2	7	16	10	14	5			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	0	1			
GLANDULAR STOMACH	(1580)	IN	79-91	1	0	1	0	0	0	1.000	0.832	0.859
Tumor \ neuroendocrine ce	(158017)	IN	79-91	2	5	7	14	12	10			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	0	0	0			
DUODENUM	(1601)	FA	94	1	1	0	0	0	0	1.000	0.723	0.790
Adenocarcinoma	(160108)	FA	94	2	25	16	11	11	1			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0	0			
JEJUNUM	(1602)	FA	42	1	0	0	0	0	1	0.033	0.000	0.000
Adenocarcinoma	(160205)	FA	42	2	35	25	10	17	2			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	0	1	(Exact		P<0.050)
LIVER	(1800)	IN	53-78	1	0	0	0	1	0	0.351	0.356	0.373
Carcinoma \ hepatocellula	(180001)	IN	53-78	2	12	9	14	14	11			
		IN	79-91	1	0	0	1	0	1			
		IN	79-91	2	7	8	13	12	10			

		IN	92-105	1	1	1	0	1	0		
		IN	92-105	2	6	15	10	13	6		
		IN	106-106	1	2	0	0	1	0		
		IN	106-106	2	21	11	6	5	1		
Spontaneous tumor pct: 4% in ctrl. - Total				-	3	1	1	3	1		
LIVER	(1800)	IN	53-78	1	1	0	0	0	0	0.307	0.293 0.313
Adenoma \ hepatocellular	(180003)	IN	53-78	2	11	9	14	15	11		
		IN	79-91	1	0	0	1	0	0		
		IN	79-91	2	7	8	13	12	11		
		IN	92-105	1	0	0	0	0	1		
		IN	92-105	2	7	16	10	14	5		
		IN	106-106	1	1	1	0	1	0		
		IN	106-106	2	22	10	6	5	1		
PANCREAS	(2000)	IN	79-91	1	0	1	1	1	0	0.868	0.866 0.873
Adenoma \ islet cell	(200002)	IN	79-91	2	7	7	13	11	11		
		IN	92-105	1	3	1	0	2	0		
		IN	92-105	2	4	15	10	12	6		
		IN	106-106	1	6	1	0	2	0		
		IN	106-106	2	17	10	6	4	1		
Spontaneous tumor pct: 12% in ctrl. - Total				-	9	3	1	5	0		
PANCREAS	(2000)	IN	106-106	1	1	0	0	0	0	0.379	0.323 0.370
Adenoma \ acinar cell	(200027)	IN	106-106	2	22	11	6	6	1		
		FA	95	1	0	0	0	1	0		
		FA	95	2	26	21	15	18	4		
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	1	0		
EPIDIDYMIDES	(2600)	IN	92-105	1	0	1	0	0	0	1.000	0.786 0.821
Mesothelioma \ benign	(260020)	IN	92-105	2	7	15	10	14	6		
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	0	0	0		
PROSTATE	(2700)	IN	79-91	1	0	0	0	1	0	0.442	0.442 0.485
Adenoma	(270010)	IN	79-91	2	7	8	14	11	11		
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1	0		
PROSTATE	(2700)	FA	91	1	0	0	1	0	0	0.451	0.525 0.584
Adenocarcinoma	(270011)	FA	91	2	30	27	18	21	7		
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	0		
PREPUTIAL GLANDS	(2900)	IN	106-106	1	0	0	1	0	0	0.276	0.362 0.443
Adenocarcinoma	(290002)	IN	106-106	2	23	11	5	6	1		
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	0		
PITUITARY GLAND	(4100)	IN	0-52	1	0	0	0	0	2	0.615	0.617 0.622
Adenoma \ pars distalis	(410001)	IN	0-52	2	1	6	6	3	19		
		IN	53-78	1	2	2	1	7	1		
		IN	53-78	2	6	1	5	2	7		
		IN	79-91	1	2	1	3	3	6		
		IN	79-91	2	1	3	8	3	5		
		IN	92-105	1	3	4	3	10	2		
		IN	92-105	2	3	5	0	1	4		
		IN	106-106	1	19	7	3	4	0		
		IN	106-106	2	4	4	3	2	1		
		FA	53	1	0	0	0	0	1		
		FA	53	2	49	44	44	47	28		

FA	56	1	0	0	1	0	0
FA	56	2	48	44	42	47	26
FA	57	1	1	0	0	0	0
FA	57	2	47	44	42	47	25
FA	60	1	0	0	1	0	1
FA	60	2	47	44	41	46	24
FA	62	1	0	1	0	0	0
FA	62	2	47	43	41	44	23
FA	63	1	1	1	0	0	0
FA	63	2	46	41	40	44	23
FA	64	1	1	0	0	0	0
FA	64	2	44	41	40	44	23
FA	65	1	0	1	0	1	0
FA	65	2	44	40	39	43	23
FA	67	1	0	0	1	0	0
FA	67	2	44	40	37	43	22
FA	69	1	0	0	0	1	0
FA	69	2	43	40	37	41	20
FA	70	1	0	0	1	0	0
FA	70	2	43	40	36	41	20
FA	71	1	0	0	1	1	0
FA	71	2	42	40	35	40	20
FA	72	1	0	0	1	0	0
FA	72	2	41	40	34	39	20
FA	73	1	0	0	1	0	0
FA	73	2	41	40	32	39	20
FA	74	1	1	1	0	0	0
FA	74	2	40	39	32	37	20
FA	75	1	0	0	0	0	1
FA	75	2	40	39	31	37	19
FA	76	1	0	1	0	2	0
FA	76	2	40	38	31	34	19
FA	77	1	0	1	0	0	0
FA	77	2	40	37	31	34	19
FA	78	1	0	0	1	1	0
FA	78	2	39	37	30	33	18
FA	79	1	1	0	0	1	0
FA	79	2	36	35	30	31	18
FA	80	1	0	0	0	1	0
FA	80	2	36	35	30	30	17
FA	81	1	0	0	0	1	0
FA	81	2	35	34	30	27	17
FA	82	1	0	1	0	1	0
FA	82	2	35	33	30	26	17
FA	84	1	0	1	1	0	0
FA	84	2	35	32	28	25	16
FA	87	1	0	1	0	0	0
FA	87	2	35	31	26	24	13
FA	88	1	0	1	0	0	0
FA	88	2	34	30	25	24	13
FA	89	1	0	0	0	1	0
FA	89	2	34	29	22	22	13
FA	90	1	3	0	0	0	0
FA	90	2	31	29	22	21	8
FA	91	1	0	0	2	1	0
FA	91	2	30	27	17	20	7
FA	92	1	0	2	0	0	0

		FA 92	2	30	25	16	20	7			
		FA 94	1	0	0	1	0	0			
		FA 94	2	27	21	15	20	4			
		FA 95	1	0	0	2	0	0			
		FA 95	2	26	21	13	19	4			
		FA 96	1	1	3	0	1	0			
		FA 96	2	25	17	13	6	3			
		FA 97	1	0	1	0	0	0			
		FA 97	2	25	16	12	15	3			
		FA 98	1	0	0	2	0	0			
		FA 98	2	25	16	9	12	2			
		FA 101	1	0	0	1	1	0			
		FA 101	2	25	13	8	9	2			
		FA 102	1	0	1	1	0	0			
		FA 102	2	25	12	7	9	2			
		FA 105	1	0	0	0	1	0			
		FA 105	2	23	11	6	6	1			
Spontaneous tumor pct: 66%	in ctrl. - Total		-	35	31	28	39	14			
THYROID GLAND	(4200)	IN 92-105	1	0	1	0	0	0	1.000	0.782	0.817
Adenoma \ C-cell	(420003)	IN 92-105	2	7	15	10	13	6			
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	0	1	0	0	0			
ADRENAL MEDULLA	(4402)	IN 92-105	1	0	1	0	1	0	0.616	0.588	0.623
Tumor \	(440201)	IN 92-105	2	7	15	10	13	6			
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	0	1	0	1	0			
HEMOLYMPHORET. SYS.	(4500)	IN 106-106	1	0	3	1	1	0	0.219	0.221	0.234
Lymphoma \ malignant	(450001)	IN 106-106	2	23	8	5	5	1			
		FA 50	1	0	1	0	0	0			
		FA 50	2	49	44	44	47	30			
		FA 60	1	0	0	0	0	1			
		FA 60	2	47	44	42	46	24			
		FA 62	1	0	1	0	0	0			
		FA 62	2	47	43	41	44	23			
		FA 73	1	0	0	0	2	0			
		FA 73	2	41	40	33	37	20			
		FA 86	1	0	0	0	1	0			
		FA 86	2	35	32	26	24	14			
		FA 95	1	0	1	0	0	0			
		FA 95	2	26	20	15	19	4			
Spontaneous tumor pct: 6%	in ctrl. - Total		-	0	6	1	4	1			
HEMOLYMPHORET. SYS.	(4500)	FA 43	1	0	0	0	0	1	0.384	0.388	0.407
Leukemia \ granulocytic	(450002)	FA 43	2	49	49	45	48	36			
		FA 49	1	0	0	0	1	0			
		FA 49	2	49	45	44	47	30			
		FA 53	1	0	0	1	0	0			
		FA 53	2	49	44	43	47	29			
		FA 67	1	1	0	0	0	0			
		FA 67	2	43	40	38	43	22			
		FA 77	1	1	0	0	0	0			
		FA 77	2	39	38	31	34	19			
		FA 83	1	0	0	1	0	0			
		FA 83	2	35	33	29	25	16			
Spontaneous tumor pct: 2%	in ctrl. - Total		-	2	0	2	1	1			

HEMOLYMPHORET. SYS.	(4500)	IN	106-106	1	1	0	0	0	0	0.391	0.407	0.428
Sarcoma \ histiocytic	(450003)	IN	106-106	2	22	11	6	6	1			
		FA	55	1	1	0	0	0	0			
		FA	55	2	48	44	43	47	26			
		FA	87	1	1	0	0	0	0			
		FA	87	2	34	32	26	24	13			
		FA	88	1	0	0	1	0	0			
		FA	88	2	34	31	24	24	13			
		FA	90	1	1	0	0	0	0			
		FA	90	2	33	29	22	21	8			
		FA	92	1	0	0	0	0	1			
		FA	92	2	30	27	16	20	6			
		FA	97	1	0	0	0	1	0			
		FA	97	2	25	17	12	14	3			
		FA	103	1	1	0	0	0	0			
		FA	103	2	23	12	7	9	2			
Spontaneous tumor pct: 5% in ctrl. - Total				-	5	0	1	1	1			
SPLEEN	(4600)	IN	92-105	1	0	1	0	0	0	1.000	0.786	0.821
Hemangioma	(460029)	IN	92-105	2	7	15	10	14	6			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	0	0	0			
MESENT. LYMPH NODE	(5104)	IN	92-105	1	0	2	0	1	0	0.811	0.781	0.802
Hemangioma	(510402)	IN	92-105	2	7	14	10	13	6			
		IN	106-106	1	0	1	0	0	0			
		IN	106-106	2	23	10	6	6	1			
Spontaneous tumor pct: 3% in ctrl. - Total				-	0	3	0	1	0			
ILIAC LYMPH NODE	(5106)	IN	106-106	1	0	0	0	1	0	0.148	0.053	0.080
Lymphangioma	(510619)	IN	106-106	2	23	11	6	5	1			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1	0			
MESENTERY	(5311)	IN	53-78	1	0	0	0	1	0	0.426	0.405	0.450
Hemangiosarcoma	(531117)	IN	53-78	2	12	9	14	14	11			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1	0			
MAMMARY GLAND	(5600)	IN	92-105	1	0	0	1	0	1	0.115	0.065	0.078
Adenocarcinoma	(560001)	IN	92-105	2	7	16	9	14	5			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	1			
MAMMARY GLAND	(5600)	IN	53-78	1	0	1	0	0	0	0.469	0.476	0.499
Fibroadenoma	(560004)	IN	53-78	2	12	8	13	15	11			
		IN	92-105	1	1	0	0	0	1			
		IN	92-105	2	6	16	9	14	5			
		IN	106-106	1	0	1	0	0	0			
		IN	106-106	2	23	10	6	6	1			
		FA	66	1	0	0	1	0	0			
		FA	66	2	44	40	38	43	22			
		FA	103	1	0	0	1	0	0			
		FA	103	2	24	12	6	9	2			
Spontaneous tumor pct: 3% in ctrl. - Total				-	1	2	2	0	1			
	(5700)	IN	79-91	1	0	0	1	0	0	0.460	0.518	0.551
Carcinoma \ squamous cell	(570001)	IN	79-91	2	7	8	13	12	11			
		FA	71	1	0	0	0	1	0			
		FA	71	2	42	40	36	40	20			

Spontaneous tumor pct: <= 1% in ctrl. - Total		-		0	0	1	1	0			
	(5700)	IN 79-91	1	0	0	1	0	0	0.925	0.898	0.906
Fibroma	(570005)	IN 79-91	2	6	8	13	12	11			
		IN 92-105	1	2	1	0	1	0			
		IN 92-105	2	5	15	10	13	6			
		IN 106-106	1	1	0	1	0	0			
		IN 106-106	2	22	11	5	6	1			
		FA 80	1	1	0	0	0	0			
		FA 80	2	35	35	30	31	17			
Spontaneous tumor pct: 5% in ctrl. - Total		-		4	1	2	1	0			
	(5700)	IN 92-105	1	0	0	0	0	1	0.113	0.008	0.011
Lipoma	(570007)	IN 92-105	2	7	16	10	14	5			
Spontaneous tumor pct: <= 1% in ctrl. - Total		-		0	0	0	0	1			
	(5700)	IN 92-105	1	0	0	0	1	0	0.899	0.875	0.884
Histiocytoma \ fibrous \	(570008)	IN 92-105	2	7	16	10	13	6			
		IN 106-106	1	1	1	1	0	0			
		IN 106-106	2	22	10	5	6	1			
		FA 24	1	0	1	0	0	0			
		FA 24	2	50	49	48	48	43			
		FA 43	1	0	1	0	0	0			
		FA 43	2	49	48	45	48	37			
		FA 63	1	1	0	0	0	0			
		FA 63	2	46	42	40	44	23			
		FA 90	1	0	1	1	0	0			
		FA 90	2	34	28	21	21	8			
Spontaneous tumor pct: 6% in ctrl. - Total		-		2	4	2	1	0			
	(5700)	IN 92-105	1	0	0	1	0	0	0.566	0.611	0.659
Keratoacanthoma	(570020)	IN 92-105	2	7	16	9	14	6			
Spontaneous tumor pct: <= 1% in ctrl. - Total		-		0	0	1	0	0			
SKIN/INJECTION SITE	(7600)	IN 53-78	1	0	0	1	0	0	0.005	0.003	0.003
Histiocytoma \ fibrous \	(760010)	IN 53-78	2	12	9	13	13	10			
		IN 79-91	1	0	0	3	0	0			
		IN 79-91	2	7	7	7	9	9			
		IN 92-105	1	0	2	2	3	0			
		IN 92-105	2	7	11	7	9	5			
		IN 106-106	1	0	3	2	2	1			
		IN 106-106	2	23	8	4	4	0			
		FA 38	1	0	0	0	0	1			
		FA 38	2	49	49	47	48	38			
		FA 61	1	0	0	0	1	0			
		FA 61	2	47	44	41	44	23			
		FA 65	1	0	0	0	0	1			
		FA 65	2	44	41	39	44	22			
		FA 67	1	0	0	0	1	0			
		FA 67	2	44	40	38	42	22			
		FA 80	1	0	0	0	1	0			
		FA 80	2	36	35	30	30	17			
		FA 84	1	0	0	2	0	0			
		FA 84	2	35	33	27	25	16			
		FA 86	1	0	0	0	0	1			
		FA 86	2	35	32	26	25	13			
		FA 87	1	0	0	1	0	0			
		FA 87	2	35	32	25	24	13			

		FA 88	1	0	0	0	1	0
		FA 88	2	34	31	25	23	13
		FA 89	1	0	0	0	1	1
		FA 89	2	34	29	22	22	12
		FA 90	1	0	1	1	0	0
		FA 90	2	34	28	21	21	8
		FA 92	1	0	1	0	0	1
		FA 92	2	30	26	16	20	6
		FA 93	1	0	2	0	0	0
		FA 93	2	28	21	16	20	5
		FA 95	1	0	0	0	1	0
		FA 95	2	26	21	15	18	4
		FA 96	1	0	0	1	1	0
		FA 96	2	26	20	12	16	3
Spontaneous tumor pct: 9%	in ctrl.	- Total	-	0	9	13	12	6

(Asymptotic P<0.010)

SKIN/INJECTION SITE	(7600)	IN 106-106	1	0	0	0	1	0	0.148 0.053 0.080
Fibroma	(760012)	IN 106-106	2	23	11	6	5	1	
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	0	0	0	1	0	

APPEARS THIS WAY
ON ORIGINAL

Table 16

Analysis of Carcinogenic Potential in Female Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Study No.
Run Date & Time: November 12, 1999 (15:42)
Source: C:\NG\I21081\ratf0_4.dat

Note: Dose Levels Included: CTRL1 CTRL2 LOW MED HIGH (0 0 2 5 12.5)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT .GE. OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
BRAIN	(0100)	IN	92-106	1	0 1 0 0 0	1.000	0.800	0.830
Astrocytoma \ malignant	(010001)	IN	92-106	2	19 19 20 23 18			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 1 0 0 0			
CEREBRUM	(0101)	IN	92-106	1	1 0 0 0 0	1.000	0.800	0.830
Tumor \ granular cell \ b	(010102)	IN	92-106	2	18 20 20 23 18			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0 0 0 0			
CEREBRUM	(0101)	IN	92-106	1	0 0 0 0 1	0.180	0.026	0.034
Oligodendroglioma \ benig	(010114)	IN	92-106	2	19 20 20 23 17			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 0 0 0 1			
CEREBRUM	(0101)	IN	92-106	1	0 0 1 0 0	0.610	0.655	0.695
Astrocytoma \ benign	(010116)	IN	92-106	2	19 20 19 23 18			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 0 1 0 0			
NOSE	(0600)	IN	0-52	1	0 0 0 0 1	0.538	0.183	0.207
Carcinoma \ squamous cell	(060001)	IN	0-52	2	1 2 2 1 6			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 0 0 0 1			
LUNGS	(0900)	IN	107-107	1	0 0 0 1 0	0.171	0.024	0.043
Leiomyosarcoma	(090035)	IN	107-107	2	10 11 8 5 0			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 0 0 1 0			
LIVER	(1800)	IN	92-106	1	1 1 0 0 0	0.784	0.777	0.798
Carcinoma \ hepatocellula	(180001)	IN	92-106	2	18 19 20 23 18			
		IN	107-107	1	1 0 0 1 0			
		IN	107-107	2	9 11 8 5 0			
Spontanecus tumor pct: 3% in ctrl. - Total				-	2 1 0 1 0			
LIVER	(1800)	IN	107-107	1	0 0 0 1 0	0.171	0.024	0.043
Cholangiocarcinoma	(180002)	IN	107-107	2	10 11 8 5 0			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 0 0 1 0			
LIVER	(1800)	IN	92-106	1	0 0 1 0 0	0.306	0.349	0.388
Adenoma \ hepatocellular	(180003)	IN	92-106	2	19 20 19 23 18			
		IN	107-107	1	0 0 0 1 0			
		IN	107-107	2	10 11 8 5 0			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 0 1 1 0			
PANCREAS	(2000)	IN	79-91	1	0 0 0 0 2	0.000	0.000	0.000
Adenoma \ islet cell	(200002)	IN	79-91	2	10 11 10 11 11			
		IN	92-106	1	1 1 0 1 5			
		IN	92-106	2	18 19 20 22 13			
		IN	107-107	1	2 0 2 2 0			

		IN	107-107	2	8	11	6	4	0		
Spontaneous tumor pct: 4% in ctrl. - Total				-	3	1	2	3	7	(Exact	P<0.010)
PANCREAS	(2000)	IN	92-106	1	0	1	0	0	0	1.000	0.800 0.830
Adenoma \ acinar-islet ce	(200028)	IN	92-106	2	19	19	20	23	18		
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	0	0	0		
URINARY BLADDER	(2300)	IN	53-78	1	0	0	1	0	0	0.652	0.689 0.724
Papilloma \ transitional	(230001)	IN	53-78	2	9	7	9	9	11		
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	0		
URINARY BLADDER	(2300)	IN	107-107	1	0	0	0	2	0	0.025	0.002 0.004
Papilloma \ transitonal c	(230019)	IN	107-107	2	10	11	8	4	0		
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	2	0	(Exact	P<0.050)
UTERUS	(3400)	IN	92-106	1	0	0	1	0	0	0.610	0.655 0.695
Adenocarcinoma	(340001)	IN	92-106	2	19	20	19	23	18		
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	0		
UTERUS	(3400)	IN	92-106	1	0	1	0	0	0	1.000	0.800 0.830
Adenoma	(340006)	IN	92-106	2	19	19	20	23	18		
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	0	0	0		
UTERUS	(3400)	IN	79-91	1	0	1	0	0	0	0.228	0.240 0.254
Polyp \ endometrial strom	(340008)	IN	79-91	2	10	10	10	11	13		
		IN	92-106	1	0	1	0	3	1		
		IN	92-106	2	19	19	20	20	17		
		IN	107-107	1	0	0	0	1	0		
		IN	107-107	2	10	11	8	5	0		
Spontaneous tumor pct: 2% in ctrl. - Total				-	0	2	0	4	1		
UTERUS	(3400)	IN	53-78	1	0	0	0	0	1	0.211	0.211 0.222
Tumor \ granular cell \ b	(340011)	IN	53-78	2	9	7	10	9	10		
		IN	79-91	1	0	0	0	0	1		
		IN	79-91	2	10	11	10	11	12		
		IN	92-106	1	4	0	0	2	1		
		IN	92-106	2	15	20	20	21	17		
		IN	107-107	1	0	1	0	0	0		
		IN	107-107	2	10	10	8	6	0		
Spontaneous tumor pct: 5% in ctrl. - Total				-	4	1	0	2	3		
UTERUS	(3400)	FA	78	1	0	0	0	0	1	0.167	0.021 0.028
Schwannoma \ malignant	(340026)	FA	78	2	39	42	38	40	31		
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	0	1		
VAGINA	(3500)	IN	79-91	1	0	0	0	0	1	0.033	0.011 0.014
Tumor \ granular cell	(350004)	IN	79-91	2	10	11	10	11	12		
		IN	92-106	1	0	0	0	1	1		
		IN	92-106	2	19	20	20	22	17		
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1	2	(Exact	P<0.050)
VAGINA	(3500)	IN	92-106	1	0	0	1	0	0	0.610	0.655 0.695
Papilloma \ squamous cell	(350005)	IN	92-106	2	19	20	19	23	18		
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	0		
VAGINA	(3500)	FA	101	1	0	0	1	0	0	0.514	0.581 0.630
Hemangiosarcoma	(350006)	FA	101	2	22	27	19	21	11		
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	0		

VAGINA	(3500)	IN	92-106	1	0	1	0	0	0	1.000	0.800	0.830
Carcinoma \ squamous cell	(350007)	IN	92-106	2	19	19	20	23	18			
Spontaneous tumor pct: <= 1% in ctrl.		-	Total	-	0	1	0	0	0			
PITUITARY GLAND	(4100)	IN	0-52	1	0	0	0	0	1	0.330	0.332	0.335
Adenoma \ pars distalis	(410001)	IN	0-52	2	0	2	2	1	7			
		IN	53-78	1	1	0	0	1	5			
		IN	53-78	2	4	0	1	1	2			
		IN	79-91	1	2	2	2	1	5			
		IN	79-91	2	3	3	1	1	4			
		IN	92-106	1	12	7	12	12	11			
		IN	92-106	2	2	4	2	4	4			
		IN	107-107	1	5	11	6	6	0			
		IN	107-107	2	5	0	2	0	0			
		FA	46	1	1	0	0	0	0			
		FA	46	2	48	51	49	49	46			
		FA	61	1	0	0	0	0	1			
		FA	61	2	46	49	47	48	40			
		FA	62	1	0	0	0	0	1			
		FA	62	2	45	49	47	48	37			
		FA	63	1	0	0	1	0	0			
		FA	63	2	45	49	46	48	37			
		FA	65	1	0	0	1	0	0			
		FA	65	2	45	49	45	48	37			
		FA	66	1	0	2	0	0	0			
		FA	66	2	45	47	45	48	37			
		FA	67	1	0	0	2	1	1			
		FA	67	2	45	47	43	47	36			
		FA	68	1	0	0	0	1	0			
		FA	68	2	45	47	43	46	36			
		FA	69	1	0	1	0	0	0			
		FA	69	2	45	46	43	46	36			
		FA	70	1	0	0	1	0	0			
		FA	70	2	45	46	42	46	36			
		FA	72	1	1	1	0	1	1			
		FA	72	2	44	45	42	45	34			
		FA	73	1	1	0	0	0	0			
		FA	73	2	43	45	42	45	34			
		FA	74	1	1	0	1	1	0			
		FA	74	2	42	45	41	43	32			
		FA	76	1	0	1	1	1	0			
		FA	76	2	42	44	40	42	32			
		FA	77	1	1	2	2	2	0			
		FA	77	2	41	42	38	40	32			
		FA	79	1	1	0	1	1	0			
		FA	79	2	38	42	37	39	31			
		FA	80	1	2	2	1	2	0			
		FA	80	2	36	38	36	37	30			
		FA	83	1	1	1	1	1	0			
		FA	83	2	33	37	34	36	27			
		FA	84	1	0	0	0	1	0			
		FA	84	2	33	37	33	35	26			
		FA	85	1	0	1	1	0	1			
		FA	85	2	33	36	32	34	25			
		FA	86	1	1	1	1	1	0			
		FA	86	2	32	35	31	33	24			

		FA 87	1	0	1	1	0	0		
		FA 87	2	32	34	30	33	23		
		FA 88	1	0	0	0	2	1		
		FA 88	2	30	33	29	31	22		
		FA 89	1	0	0	1	0	1		
		FA 89	2	29	33	28	30	21		
		FA 90	1	0	0	0	0	1		
		FA 90	2	29	33	28	30	20		
		FA 91	1	0	0	0	1	0		
		FA 91	2	29	31	28	29	18		
		FA 92	1	1	0	0	2	0		
		FA 92	2	28	31	28	27	18		
		FA 93	1	2	2	0	0	0		
		FA 93	2	26	29	27	26	18		
		FA 94	1	0	0	0	1	0		
		FA 94	2	26	29	27	25	18		
		FA 95	1	0	0	0	0	1		
		FA 95	2	25	29	27	25	16		
		FA 96	1	0	0	3	1	1		
		FA 96	2	24	29	23	24	14		
		FA 98	1	1	2	0	0	0		
		FA 98	2	23	27	23	22	14		
		FA 99	1	0	0	2	1	0		
		FA 99	2	22	27	20	21	13		
		FA 101	1	1	0	0	2	0		
		FA 101	2	21	27	20	19	11		
		FA 102	1	0	1	0	0	0		
		FA 102	2	21	26	19	19	9		
		FA 103	1	0	1	1	0	0		
		FA 103	2	20	25	18	18	9		
		FA 104	1	0	1	0	0	0		
		FA 104	2	20	23	18	18	8		
		FA 105	1	0	2	0	0	0		
		FA 105	2	20	21	18	18	8		
		FA 106	1	0	0	0	0	1		
		FA 106	2	20	21	18	16	7		
Spontaneous tumor pct: 77%	in ctrl.	-	Total	-	35	42	42	43	33	
THYROID GLAND	(4200)	IN 92-106	1	0	0	0	0	1	0.181	0.026 0.034
Adenoma \ C-cell	(420003)	IN 92-106	2	19	20	20	22	17		
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total	-	0	0	0	0	1	
THYROID GLAND	(4200)	IN 92-106	1	0	0	1	0	0	0.606	0.653 0.693
Carcinoma \ C-cell	(420014)	IN 92-106	2	19	20	19	22	18		
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total	-	0	0	1	0	0	
ADRENAL CORTEX	(4401)	IN 79-91	1	0	0	1	0	0	0.618	0.681 0.717
Adenoma \ cortical	(440101)	IN 79-91	2	10	11	9	11	13		
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total	-	0	0	1	0	0	
ADRENAL MEDULLA	(4402)	IN 92-106	1	0	0	0	1	0	0.514	0.512 0.553
Tumor \	(440201)	IN 92-106	2	18	20	20	22	18		
		IN 107-107	1	0	1	0	0	0		
		IN 107-107	2	10	10	8	6	0		
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total	-	0	1	0	1	0	
HEMOLYMPHORET. SYS.	(4500)	IN 92-106	1	0	2	2	0	0	0.901	0.884 0.892

Lymphoma \ malignant	(450001)	IN	92-106	2	18	18	18	23	18		
		FA	73	1	0	0	0	1	0		
		FA	73	2	44	45	42	44	34		
		FA	84	1	0	0	0	1	0		
		FA	84	2	33	37	33	35	26		
		FA	90	1	0	1	0	0	0		
		FA	90	2	29	32	28	30	21		
		FA	95	1	1	0	0	0	0		
		FA	95	2	24	29	27	25	17		
Spontaneous tumor pct: 4% in ctrl.		- Total		-	1	3	2	2	0		
HEMOLYMPHORET. SYS.	(4500)	FA	77	1	1	0	0	0	0	1.000	0.784 0.816
Leukemia \ granulocytic	(450002)	FA	77	2	41	44	40	42	32		
Spontaneous tumor pct: <= 1% in ctrl.		- Total		-	1	0	0	0	0		
HEMOLYMPHORET. SYS.	(4500)	IN	92-106	1	0	0	0	1	0	0.560	0.560 0.583
Sarcoma \ histiocytic	(450003)	IN	92-106	2	19	20	20	21	18		
		FA	82	1	0	0	1	0	0		
		FA	82	2	34	38	35	37	29		
		FA	87	1	1	0	0	0	0		
		FA	87	2	31	35	31	33	23		
		FA	105	1	0	0	0	1	0		
		FA	105	2	20	23	18	17	8		
Spontaneous tumor pct: <= 1% in ctrl.		- Total		-	1	0	1	2	0		
THYMUS	(5000)	IN	79-91	1	0	1	0	1	0	0.691	0.710 0.729
Thymoma \ malignant	(500001)	IN	79-91	2	10	10	10	10	13		
		IN	92-106	1	1	0	0	0	0		
		IN	92-106	2	18	20	20	22	18		
		FA	102	1	0	0	0	1	0		
		FA	102	2	21	27	19	18	9		
Spontaneous tumor pct: 2% in ctrl.		- Total		-	1	1	0	2	0		
THYMUS	(5000)	IN	53-78	1	0	1	0	0	2	0.229	0.212 0.225
Thymoma \ benign	(500002)	IN	53-78	2	9	6	10	9	9		
		IN	92-106	1	0	0	1	1	0		
		IN	92-106	2	19	20	19	22	18		
		IN	107-107	1	0	2	0	0	0		
		IN	107-107	2	10	9	8	6	0		
Spontaneous tumor pct: 3% in ctrl.		- Total		-	0	3	1	1	2		
MESENT. LYMPH NODE	(5104)	IN	92-106	1	0	0	1	0	0	0.610	0.655 0.695
Lymphangioma	(510401)	IN	92-106	2	19	20	19	23	18		
Spontaneous tumor pct: <= 1% in ctrl.		- Total		-	0	0	1	0	0		
MESENT. LYMPH NODE	(5104)	IN	53-78	1	0	0	0	1	0	0.666	0.685 0.711
Hemangioma	(510402)	IN	53-78	2	9	7	10	8	11		
		IN	92-106	1	0	1	0	0	0		
		IN	92-106	2	19	19	20	23	18		
Spontaneous tumor pct: <= 1% in ctrl.		- Total		-	0	1	0	1	0		
ILIAC LYMPH NODE	(5106)	IN	92-106	1	0	0	1	0	0	0.610	0.655 0.695
Hemangioma	(510618)	IN	92-106	2	19	20	19	23	18		
Spontaneous tumor pct: <= 1% in ctrl.		- Total		-	0	0	1	0	0		
MAMMARY GLAND	(5600)	IN	0-52	1	0	1	0	0	2	0.698	0.700 0.707
Adenocarcinoma	(560001)	IN	0-52	2	1	1	2	1	6		

		IN	53-78	1	1	0	0	0	1	
		IN	53-78	2	6	7	10	8	9	
		IN	79-91	1	0	1	0	2	1	
		IN	79-91	2	9	9	10	9	11	
		IN	92-106	1	4	6	4	4	1	
		IN	92-106	2	15	14	15	19	17	
		IN	107-107	1	1	0	2	1	0	
		IN	107-107	2	9	11	6	5	0	
		FA	56	1	0	0	0	1	0	
		FA	56	2	48	49	48	48	41	
		FA	60	1	1	0	0	0	0	
		FA	60	2	46	49	47	48	41	
		FA	61	1	1	0	0	0	0	
		FA	61	2	45	49	47	48	41	
		FA	73	1	0	0	0	0	1	
		FA	73	2	44	45	42	45	33	
		FA	79	1	0	1	0	0	0	
		FA	79	2	39	41	38	40	31	
		FA	82	1	0	0	0	0	1	
		FA	82	2	34	38	36	37	28	
		FA	88	1	1	0	0	0	0	
		FA	88	2	29	33	29	33	23	
		FA	92	1	0	0	1	0	0	
		FA	92	2	29	31	27	29	18	
Spontaneous tumor pct: 18% in ctrl. -		Total		-	9	9	7	8	7	
MAMMARY GLAND	(5600)	IN	92-106	1	0	2	1	1	1	0.394 0.410 0.426
Carcinoma arising in Fibr	(560002)	IN	92-106	2	17	18	19	22	16	
		IN	107-107	1	1	0	0	0	0	
		IN	107-107	2	9	11	8	6	0	
		FA	94	1	1	0	0	0	0	
		FA	94	2	25	29	27	26	18	
		FA	98	1	1	0	0	0	0	
		FA	98	2	23	29	23	22	14	
		FA	101	1	0	0	0	0	1	
		FA	101	2	22	27	20	21	10	
Spontaneous tumor pct: 5% in ctrl. -		Total		-	3	2	1	1	2	
MAMMARY GLAND	(5600)	IN	79-91	1	0	0	1	0	0	0.847 0.856 0.868
Adenoma	(560003)	IN	79-91	2	10	11	9	11	13	
		IN	92-106	1	0	1	2	0	0	
		IN	92-106	2	19	19	18	23	18	
Spontaneous tumor pct: <= 1% in ctrl. -		Total		-	0	1	3	0	0	
MAMMARY GLAND	(5600)	IN	0-52	1	0	0	0	0	2	0.815 0.814 0.818
Fibroadenoma	(560004)	IN	0-52	2	1	2	2	1	6	
		IN	53-78	1	2	1	2	2	4	
		IN	53-78	2	5	6	7	7	7	
		IN	79-91	1	3	3	2	4	3	
		IN	79-91	2	5	8	7	6	10	
		IN	92-106	1	9	8	13	8	6	
		IN	92-106	2	9	11	5	12	12	
		IN	107-107	1	7	8	5	4	0	
		IN	107-107	2	3	3	3	2	0	
		FA	56	1	0	0	1	0	0	
		FA	56	2	48	49	47	49	41	
		FA	57	1	1	0	0	0	0	

		FA 57	2	47	49	47	48	41			
		FA 77	1	1	0	0	0	0			
		FA 77	2	41	44	40	42	32			
		FA 80	1	2	0	0	0	0			
		FA 80	2	36	40	37	39	30			
		FA 83	1	0	0	1	0	0			
		FA 83	2	34	38	34	37	27			
		FA 88	1	0	0	0	1	0			
		FA 88	2	30	33	29	32	23			
		FA 92	1	0	0	0	1	0			
		FA 92	2	29	31	28	28	18			
		FA 95	1	0	0	1	0	0			
		FA 95	2	25	29	26	25	17			
		FA 96	1	0	0	0	1	0			
		FA 96	2	24	29	26	24	15			
		FA 98	1	0	0	1	0	0			
		FA 98	2	24	29	22	22	14			
		FA 102	1	1	0	0	0	0			
		FA 102	2	20	27	19	19	9			
		FA 103	1	0	1	0	0	0			
		FA 103	2	20	25	19	18	9			
		FA 105	1	0	0	0	1	0			
		FA 105	2	20	23	18	17	8			
Spontaneous tumor pct: 47% in ctrl.		- Total	-	26	21	26	22	15			
MAMMARY GLAND	(5600)	FA 49	1	0	1	0	0	0	1.000	0.872	0.888
Tumor \ mixed \ malignant	(560012)	FA 49	2	48	50	48	49	44			
		FA 79	1	0	1	0	0	0			
		FA 79	2	39	41	38	40	31			
Spontaneous tumor pct: 2%	in ctrl.	- Total	-	0	2	0	0	0			
	(5700)	IN 53-78	1	1	0	0	0	0	0.864	0.849	0.863
Carcinoma \ squamous cell	(570001)	IN 53-78	2	8	7	10	9	11			
		IN 79-91	1	0	0	1	0	0			
		IN 79-91	2	10	11	9	11	13			
		IN 92-106	1	0	0	1	0	0			
		IN 92-106	2	19	20	19	23	18			
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	1	0	2	0	0			
	(5700)	IN 79-91	1	0	0	0	0	1	0.094	0.045	0.055
Schwannoma \ malignant	(570002)	IN 79-91	2	10	11	10	11	12			
		IN 107-107	1	0	0	1	0	0			
		IN 107-107	2	10	11	7	6	0			
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	0	0	1	0	1			
	(5700)	IN 0-52	1	0	0	0	0	1	0.176	0.150	0.163
Fibroma	(570005)	IN 0-52	2	1	2	2	1	7			
		IN 92-106	1	1	0	1	0	1			
		IN 92-106	2	18	20	19	23	17			
		IN 107-107	1	0	1	0	1	0			
		IN 107-107	2	10	10	8	5	0			
Spontaneous tumor pct: 2%	in ctrl.	- Total	-	1	1	1	1	2			
	(5700)	IN 92-106	1	0	1	0	0	0	1.000	0.800	0.830
Papilloma	(570006)	IN 92-106	2	19	19	20	23	18			
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	0	1	0	0	0			

	(5700)	IN	79-91	1	0	0	0	0	2	0.052	0.017	0.020
Lipoma	(570007)	IN	79-91	2	10	11	10	11	11			
		IN	107-107	1	0	1	0	0	0			
		IN	107-107	2	10	10	8	6	0			
Spontaneous tumor pct: <= 1% in ctrl.		-	Total	-	0	1	0	0	2			
	(5700)	IN	79-91	1	1	0	0	0	0	0.812	0.806	0.823
Histiocytoma \ fibrous \	(570008)	IN	79-91	2	9	11	10	11	13			
		IN	92-106	1	1	0	0	1	0			
		IN	92-106	2	18	20	20	22	18			
Spontaneous tumor pct: 2% in ctrl.		-	Total	-	2	0	0	1	0			
BONE	(5900)	IN	79-91	1	1	0	0	0	0	1.000	0.810	0.837
Osteosarcoma	(590001)	IN	79-91	2	9	11	10	11	13			
Spontaneous tumor pct: <= 1% in ctrl.		-	Total	-	1	0	0	0	0			
BODY CAVITIES	(6800)	IN	92-106	1	1	0	0	0	0	1.000	0.800	0.830
Lipoma	(680003)	IN	92-106	2	18	20	20	23	18			
Spontaneous tumor pct: <= 1% in ctrl.		-	Total	-	1	0	0	0	0			
SKIN/INJECTION SITE	(7600)	IN	92-106	1	0	1	1	1	0	0.654	0.680	0.702
Histiocytoma \ fibrous \	(760010)	IN	92-106	2	19	19	19	22	18			
		IN	107-107	1	0	0	1	0	0			
		IN	107-107	2	10	11	7	6	0			
Spontaneous tumor pct: <= 1% in ctrl.		-	Total	-	0	1	2	1	0			

APPEARS THIS WAY
ON ORIGINAL