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RESEARCH**

***APPLICATION NUMBER:***

**22-341**

**STATISTICAL REVIEW(S)**

**STATISTICAL REVIEW AND EVALUATION**  
**CLINICAL STUDIES**

**NDA/Serial Number:** 022341/0  
**Drug Name:** Victoza™ (liraglutide) injection  
**Indication(s):** Treatment of type 2 diabetes mellitus  
**Applicant:** Novo Nordisk Inc  
**Date(s):** Submission date: July 8, 2009  
Review date: September 8, 2009  
**Review Priority:** Standard  
**Biometrics Division:** Division of Biometrics 2  
**Statistical Reviewer:** Janice Derr, Ph.D.  
**Statistics Team Leader:** J. Todd Sahlroot, Ph.D.  
**Medical Reviewer:** Karen M. Mahoney, M.D.  
**Medical Team Leader:** Hylton Joffe, M.D.  
**Project Manager:** John Bishai, Ph.D.

This memorandum is the statistical review of the protocol of Study 3748, which is proposed to evaluate the long-term effect of liraglutide on cardiovascular and other clinically important outcomes. A brief description of the statistical aspects of the design and proposed analysis is included at the end of this memo.

**Statistical review comments, to be transmitted to the sponsor:**

1. We agree with the calculations of the number of subjects needed in the study, subject to clinical input on the appropriateness of the assumption of a 1.8% event rate per year in this clinical population. Our understanding is that the study is designed to accumulate a total of approximately 611 adjudicated primary outcome events across the two study arms. Please confirm or clarify this total.
2. We have the following requests concerning the proposed interim assessment of efficacy:
  - (a) The protocol should specify the number of events associated with the two proposed interim assessments. We assume that 50% of the expected number of events is approximately 306 and 75% is approximately 458. Please confirm or clarify this assumption.
  - (b) The protocol should specify which efficacy outcome variable(s) will be assessed for superiority, using the modified Haybittle-Peto stopping boundary. If more than one outcome variable will be assessed, the protocol should provide more information about the protection of Type I error for the primary cardiovascular outcome variable.

(c) The protocol should specify how the interim analysis of efficacy and futility will be conducted, in order to maintain the appropriate study blind.

3. The statistical methods for the analysis of primary and supportive outcome data that are generally described in this protocol are acceptable. In addition, we request that you submit the more detailed statistical analysis plan with sufficient lead time prior to your analysis of data so that we may review the plan and send you our review comments.

4. Study 3748 presents an opportunity to gain further information concerning the comparison between liraglutide and placebo in longitudinal changes in serum calcitonin in this study population. We recommend that the study protocol include a detailed analysis plan for evaluating this relationship. This analysis plan should include a pre-specified statistical analysis model, along with additional supportive analyses and descriptive summaries.

**APPEARS THIS WAY  
ON ORIGINAL**

**Summary of the study design (not to be transmitted to the sponsor):**

**Title of Study:** EX221-3748, "Liraglutide Effect and Action in Diabetes; Evaluation of cardiovascular outcome Results; A five-year, multi-centre, international, randomized, double-blind, placebo-controlled trial to determine liraglutide effects on cardiovascular events" (LEADER).

**Purpose:** The primary purpose of this study is to determine the long-term effect of liraglutide on cardiovascular and other clinically important outcomes.

**Trial design:** Subjects with type 2 diabetes treated with 0, 1 or 2 oral anti-diabetes drugs (OAD) will, after a single-blind run-in period of a minimum of two weeks, be randomized (1:1) to receive liraglutide 1.8 mg once daily or equivalent placebo as an add-on to their standard of care treatment. The study will enroll approximately 9000 patients among type 2 diabetic subjects who are at high risk for cardiovascular events. The recruitment period is planned for 18 months, and intended maximum trial duration will be 60 months. The minimum duration of observation after randomization will be 42 months.

**Number of subjects in the study:** The number of subjects to be randomized in the study was estimated based on a time to first outcome using a log rank test on an intention-to-treat analysis and the following assumptions: a) a conservative range of primary outcome event rate of 1.8% per year; b) a 1 sided alpha of 0.025; c) uniform enrolment over 1.5 years with a maximum follow-up of 5 years (including the accrual period) ; d) a non-inferiority margin versus placebo of 1.3 for the upper limit of the 2-sided 95% confidence interval; e) a non-adherence rate of 10% by the second year in trial and uniform thereafter; and f) 90% power to reject the null hypothesis that the hazard ratio is  $> 1.3$ .

Under the above assumptions, 8900 subjects need to be randomized to clearly evaluate the cardiovascular effects of liraglutide with high power.

*Statistical review comment:* I was able to recreate this calculation (approximately) using the statistical software East<sup>TM</sup>5.2. The study is designed to accumulate a total of 611 adjudicated primary outcome events in both study arms combined.

**Outcomes:** The primary outcome is the first occurrence of either cardiovascular (CV) death, nonfatal myocardial infarction (MI) or nonfatal stroke. Secondary outcomes include an expanded composite of CV events, a composite microvascular outcome, and all-cause mortality. Among the other endpoints are serious adverse events and other medical events of special interest such as pancreatitis, neoplasms, thyroid disease and adverse events leading to treatment discontinuation. HbA1c and laboratory endpoints such as calcitonin are also included as other endpoints.

**Assessment:** Pre-treatment clinical visits are planned for screening, the start of run-in, and randomization (baseline). Visits during the treatment period are planned for week 2, then months 1, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60. Assessments include composite cardiovascular and microvascular outcomes, all-cause mortality, individual components of the composite cardiovascular and microvascular outcomes, weight and waist-to-hip ratio, sustained normoglycaemia without severe hypoglycaemia, cognitive function, serious adverse events and

other medical adverse events of special interest (pancreatitis, neoplasm, thyroid-related events, adverse events leading to treatment discontinuation), blood pressure and heart rate, as well as selected laboratory parameters: blood lipids, HbA1c and selected safety parameters (including calcitonin, amylase and lipase).

**Data Monitoring Committee (DMC):** An independent external DMC will be constituted for the trial to perform ongoing safety surveillance at pre-defined time points, and to provide advice to the sponsor during the conduct of the trial as whether to continue, modify or terminate the trial as necessary. The DMC will evaluate all relevant safety information un-blinded. Clear evidence of net harm with respect to total mortality, cancer, hospitalizations or other variables identified by the DMC based on emerging data from this or other studies, that is consistent over time and across subgroups would justify a recommendation to stop the trial early.

**Event Adjudication Committee (EAC):** An external EAC will be constituted for the trial to perform ongoing adjudication, standardization and assessment of pertinent events in an independent and blinded manner, including cardiovascular death, acute coronary syndrome, stroke, cardiac insufficiency requiring acute hospitalization, pancreatitis, and all neoplasms.

**Evaluability of subjects for analysis:** The sponsor describes their intention to maximize adherence to the study protocol, and to follow up with subjects who prematurely discontinue their assigned treatment.

**Statistical considerations:** The sponsor plans to prepare a more detailed statistical analysis plan, which will be finalized before the database is released. No analyses of unmasked or between-group data is planned before the database is closed or released, except for confidential analyses performed to support the deliberations of the independent Data Monitoring Committee.

**Interim analysis of efficacy data:** The sponsor plans two interim analyses of efficacy data, after 50% and 75% of the expected number of primary cardiovascular outcome events have occurred. They plan to use a modified Haybittle-Peto stopping boundary such that if the difference in event rates between groups is greater than 4 standard deviations for the first interim analysis, and 3 standard deviations for the second and this difference is confirmed by a second analysis 3 months later, the trial may be terminated early. The sponsor notes that alpha spending associated with these criteria is very small; and for this reason they plan to evaluate the final primary analysis will be done at a 1 sided  $\alpha=0.025$ .

The sponsor also notes that the trial may also be stopped early if there is clear evidence of futility with respect to demonstrating non-inferiority. At the time of the two formal interim analyses, there will be an interim futility calculation of the conditional power to demonstrate non-inferiority of liraglutide versus placebo on the primary outcome at the end of this trial. If in the judgment of the DMC this conditional power is unreasonably low (e.g. < 10%), they may recommend early stopping.

Statistical review comments:

- Based on a total of 611 events, the interim analyses of efficacy will take place after 50% (approximately 306) and 75% (approximately 458) events have occurred.
- "Efficacy endpoints" in this study include the primary and secondary cardiovascular, microvascular and all-cause mortality endpoints, and individual components of the

*outcomes, as well as HbA1c, blood lipids, and other efficacy endpoints. We would like the sponsor to clarify that which endpoints the Haybittle-Peto stopping boundary refers to.*

- The sponsor also plans to evaluate the efficacy endpoints for futility after 50% and 75% of events have occurred. We would like the sponsor to clarify which endpoints will be evaluated for futility.*
- We also request clarification as to how this interim analysis will be conducted, in order to maintain the appropriate study blind.*

**Statistical methods:** The primary analysis will be a Cox regression including only treatment group as a covariate. Clinically relevant variables will be considered as covariates for further analyses that will be exploratory in nature. Major outcomes to be analyzed will be those that are confirmed by the Event Adjudication Committee (who will not have access to the treatment allocation at the time of adjudication) where applicable. All outcome analyses will be based on the time from randomization to the first occurrence of the outcome. Subjects who complete the study without having an outcome will be censored on the last day of their follow-up for the relevant analyses. After verifying the proportional hazards assumptions visually, Cox models will be used to estimate the hazard ratios and 2-sided 95% confidence intervals and to calculate the P value. Non-inferiority of liraglutide vs. placebo will be assessed from the upper bound of the 2-sided 95% confidence interval, and by testing that the hazard ratio is significant less than 1.3. If non-inferiority is established for the primary outcome, the data will then be tested for evidence of a significantly lower outcome hazard versus placebo. Additional exploratory analyses are also planned, as well as separate subgroup analyses based on gender, age group, body mass index, A1C, duration of diabetes, geographic region, and a history of a previous cardiovascular event.

*Statistical review comment: The proposed statistical methods are acceptable.*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22341	ORIG-1	NOVO NORDISK INC	VICTOZA (LIRAGLUTIDE)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/

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JANICE A DERR  
09/22/2009

JON T SAHLROOT  
09/22/2009



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

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**Drug Name:** Victoza™ (liraglutide) injection

**Indication(s):** Treatment of type 2 diabetes mellitus

**Applicant:** Novo Nordisk Inc

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## 1. EXECUTIVE SUMMARY

### 1.1 Conclusions and Recommendations

**Efficacy Conclusions:** Based on an evaluation of five key Phase 3 studies, I conclude that the efficacy of liraglutide 1.2 mg and 1.8 mg is supported by the comparisons to placebo and to active control comparators in a range of background antidiabetic therapies. The efficacy of liraglutide 0.6 mg is less well supported. The 0.6 mg dose is proposed for dose initiation, after which the dose levels of 1.2 mg or 1.8 mg may be selected, based on clinical response (see the draft patient insert under “Dosage and Administration.”)

*Monotherapy:* Liraglutide monotherapy resulted in a net average reduction in HbA1c at week 52 of 0.33 for the 1.2 mg dose and 0.62 for the 1.8 mg dose compared to the active comparator glimepiride 8 mg monotherapy. These comparisons were statistically significant in the direction of superiority of liraglutide monotherapy to the active control monotherapy.

*Add-on therapy:* Liraglutide as an add-on therapy resulted in net average reductions in HbA1c at week 26 that ranged from 0.78 to 1.36 compared to placebo, with a range of background antidiabetic therapies, for the 1.2 mg dose and the 1.8 mg dose. These reductions were statistically significant in the direction of superiority to liraglutide add-on therapy. The background therapies were metformin 2 g, glimepiride 4 mg, metformin 2 g + rosiglitazone 8 mg (*4 mg BID*), and glimepiride 4 mg + metformin 2 g.

With these same background therapies, liraglutide compared to an active control resulted in either a non-inferior HbA1c response or superior HbA1c response, as summarized below:

- Liraglutide was non-inferior to glimepiride 4 mg for both the 1.2 mg dose and the 1.8 mg dose (metformin 2 g background therapy).
- Liraglutide was superior to rosiglitazone 4 mg, for both the 1.2 mg dose and the 1.8 mg dose (glimepiride 4 mg background therapy). Caveat: by trial design, the active comparator dose of rosiglitazone was one half the maximal FDA approved dose of 8 mg.
- Liraglutide 1.8 mg was superior to insulin glargine (glimepiride 4 mg + metformin 2 g background therapy); this statistical review does not address the adequacy of the glargine titration.

The efficacy of liraglutide 0.6 mg is less well supported. Liraglutide 0.6 mg was non-inferior to rosiglitazone 0.4 mg (glimepiride background therapy). However, liraglutide 0.6 mg did not meet the criteria for non-inferiority to glimepiride 4 mg (metformin background therapy).

Although the studies were not powered for a comparison between liraglutide dose arms, and these comparisons were not included in the pre-specified sequential testing protocol, it can be noted that the 95% confidence intervals of the average HbA1c change from baseline for the 1.2 mg and 1.8 mg dose arms overlapped to a great extent in three of the four studies in which both doses were evaluated. In the other study, the 95% confidence interval of the 1.8 mg dose arms overlapped less with the 95% CI of the 1.2 mg dose, in the direction of a greater average reduction in HbA1c with the larger dose.

Results for fasting plasma glucose supported the efficacy of liraglutide as monotherapy and as an add-on to background therapy with the other anti-diabetic drugs used in these studies.

The average HbA1c response in the younger and older age groups (< 65 and  $\geq$  65 years) and in males and females were relatively similar. Most subjects were Caucasian in each of the five key studies. In the two studies with subjects from the U.S., the numbers of subjects in the other identified race categories were small and did not support an evaluation of potential race-related difference in HbA1c reduction. These two studies had reasonable representation in the Hispanic/Latino ethnicity subgroup, and the average HbA1c response was relatively similar in this subgroup compared to the non-Hispanic/Latino subgroup.

The results from the phase 3 studies support the conclusion that liraglutide is associated with an average net loss in weight at 26 weeks and 52 weeks compared to several of the background diabetic therapies used in the studies. This may be a clinically relevant finding, considering that a range of 43% to 74% of subjects in the five phase 3 studies were classified as obese at baseline with a BMI  $\geq$  30 kg/m<sup>2</sup>. Approximately half of the subjects (ranging from 40% to 62%) in the liraglutide arms lost from 0% to 5% of their baseline body weight at the study endpoint.

**Safety Conclusions:** Conclusions regarding the safety of liraglutide are addressed in the clinical review by Dr. Karen M. Mahoney and in the briefing document, "A Joint Clinical/Statistical Review of Cardiovascular Events and Thyroid Tumors," by Dr. Mahoney and this reviewer, for the April 2, 2009, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee.

**Recommendations:** General recommendations for labeling are included in part 5.3 of this review.

## 1.2 Brief Overview of Clinical Studies

The clinical development of liraglutide included efficacy studies of liraglutide monotherapy and add-on combination therapy with other common oral anti-diabetic drugs (glimepiride, metformin, rosiglitazone or insulin). Two general populations of subjects with type 2 diabetes mellitus were examined. A monotherapy phase 3 study was performed in subjects who had never received pharmacologic therapy or had received only minimal therapy. Add-on combination therapy studies were conducted in subjects who were inadequately controlled by

their existing therapy. The design of the five Phase 3 studies shared some common features and also had some differences. All studies were randomized, controlled and double-blind. The monotherapy study had an active control comparator arm, and the primary efficacy endpoint was evaluated after 52 weeks of treatment. The four add-on studies were evaluated after 26 weeks of treatment. Three of the add-on studies included both a placebo comparator arm and an active control comparator arm. One of the add-on studies had a placebo control arm but not an active control arm. Three dose levels of liraglutide, 0.6 mg, 1.2 mg and 1.8 mg were evaluated in the Phase 3 program, but not all three arms were included in each study.

The primary efficacy criterion in all major studies was the change from baseline to study endpoint (week 26 or 52) in glycated hemoglobin (HbA1c). Change in body weight was a key secondary efficacy endpoint. A total of 3992 subjects were randomized in five Phase 3 clinical studies. These five key studies are the focus of this statistical review.

### 1.3 Statistical Issues and Findings

Based on an evaluation of the five key Phase 3 studies, I conclude that the efficacy of liraglutide 1.2 mg and 1.8 mg is supported by the comparisons to placebo and to active control comparators in a range of background antidiabetic therapies. The efficacy of liraglutide 0.6 mg is less well supported. The estimated effects of liraglutide on HbA1c change from baseline at week 26 and week 52 in the different target populations and background antidiabetic therapies are summarized in TABLE 8. The sponsor proposes to market all three doses; however, based on the "Indications and Use" section of the draft patient insert, the 0.6 mg dose level may be used for dose initiation, followed by an increase after at least one week at 0.6 mg to the 1.2 mg dose level. The 1.8 mg dose may be used after at least one week on the 1.2 mg dose, " \_\_\_\_\_ " (draft patient insert).

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Support for the efficacy of liraglutide compared to a placebo control and compared to an active control also comes from a consistent pattern of early withdrawals due to ineffective therapy, when observed across the five studies. In the four studies that had a placebo add-on arm, subjects in this arm were more likely to withdraw early due to ineffective therapy than subjects in the liraglutide arms. In the four studies that had an active comparator arm, subjects in this arm were about equally likely to withdraw early due to ineffective therapy as subjects in the liraglutide arms.

A potential concern for the statistical analysis of the primary endpoint arose for the monotherapy study, because of the occurrence of a substantial percentage of subjects with HbA1c  $\leq 7.0$  at baseline. In the monotherapy study, conducted with an active control comparator, 11.7% of subjects had baseline HbA1c levels  $\leq 7.0$ , and another 18.1% of subjects had baseline HbA1c between 7.0 and 7.5. This relatively high proportion of subjects who were in reasonable diabetic control at baseline raised the concern that both the active control comparator and the liraglutide arms would tend to have a small average change from baseline HbA1c at the study endpoint. This assumption comes from a general finding across clinical studies of anti-diabetic drugs that

subjects with lower levels of HbA1c at baseline tend to experience smaller decreases in HbA1c at the study endpoint compared to subjects with higher levels at baseline. In this situation, the assay sensitivity of the comparison may not have supported a non-inferiority margin of 0.4. However, the two liraglutide arms were superior to the active control arm for the primary endpoint, with statistically significant differences for both comparisons. For this reason, the proportion of subjects in reasonable diabetic control at baseline was not a review issue. However, this topic is an important consideration for future active-controlled studies.

The inclusion of both an active control arm and a placebo control arm in three of the studies presented an opportunity to estimate the placebo-adjusted effect of the active control comparator within the study. In all three studies, the placebo-adjusted effect was statistically significantly different from 0. The net effect of glimepiride was similar to the results from the three historical placebo-controlled studies of glimepiride that were used to support the non-inferiority margin of 0.4.

## 2. INTRODUCTION

### 2.1 Overview

Type 2 diabetes mellitus (diabetes) is a complex metabolic disorder characterized by abnormal glucose metabolism. The pathogenesis is not fully understood but is heterogeneous, involving environmental, lifestyle, and genetic factors. This leads to chronic hyperglycemia caused by abnormal beta-cell function, peripheral tissue insulin resistance, and abnormal glucose metabolism in the liver. Diet and exercise are important and effective measures for maintaining glycemic control in individuals with insulin resistance, impaired glucose tolerance, and overt diabetes, and are particularly effective in the early stages of disease progression. In cases where diet and exercise alone fail to adequately maintain glycemic control, oral anti-diabetic drugs can be used. Major classes of oral antidiabetic drugs that are currently available are biguanides, sulfonylureas,  $\alpha$ -glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, and meglitinides<sup>1</sup>.

Victoza™ (liraglutide) is a member of an additional class of antidiabetic drug intended for the treatment of diabetes. Liraglutide is an analogue to human glucagon-like peptide-1 (GLP-1), classified as a GLP-1 receptor agonist. GLP-1 has been shown to reduce hyperglycemia in subjects with type 2 diabetes, perhaps by compensating for an impaired incretin effect. Studies with native GLP-1 have shown that the primary mechanisms of action are to stimulate insulin secretion and decrease glucagon secretion, to delay gastric emptying and to reduce appetite. Already approved drugs with GLP-1 mediated mode of action include the GLP-1 receptor agonist exenatide (Byetta™) and the DPP-IV inhibitor sitagliptin (Januvia™). Exenatide is

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<sup>1</sup> The sources of this paragraph (paraphrased) are part 1 (Product Development Rationale) in the clinical overview of this submission, and Harrison's Principles of Internal Medicine, 16<sup>th</sup> Ed, Part Fourteen: Endocrinology and Metabolism; Section 1; Endocrinology; Diabetes Mellitus (2005; from online.statref.com).

administered by twice daily subcutaneous injections in relation to meals, and sitagliptin is administered orally once daily<sup>2</sup>.

### **Scope of Statistical Review: Pivotal Efficacy and Safety Studies**

The statistical review covers five key Phase 3 studies that were designed to assess the efficacy and safety of liraglutide 0.6, 1.2 and 1.8 mg (by subcutaneous injection once a day) for the treatment of diabetes, either as monotherapy adjunct to diet and exercise, or as add-on therapy to other antidiabetic medications. Liraglutide was given once daily as monotherapy (Trial 1573), added to one oral antidiabetic drug (OAD; Trials 1572 and 1436) or to two OADs (Trial 1574 and 1697). Three different dose levels of liraglutide (0.6, 1.2 and 1.8 mg) were evaluated in the five key trials, but not all dose levels were evaluated in every trial. The duration of treatment in four of the five trials was 26 weeks. The duration of treatment in Trial 1573 was 52 weeks. An overview of the treatment regimens is given in TABLE 1. All studies were randomized, controlled and double-blind.

Depending on the trial, treatment with liraglutide was compared with placebo and/or a specific active comparator drug. One trial evaluated liraglutide monotherapy (1.2 and 1.8 mg) compared with glimepiride during 52 weeks of treatment (Trial 1573). The other four trials evaluated 26 weeks of treatment with liraglutide in combination with one or two OADs compared with placebo and/or an additional OAD active comparator (Trials 1572, 1436, 1574 and 1697).

Two of the therapeutic confirmatory trials were extended by open-labeled treatment periods. Trial 1573 was extended to a total of 5 years and Trial 1572 was extended to a total of 2 years.

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<sup>2</sup> The source of this paragraph (paraphrased) is part I (Product Development Rationale) in the clinical overview of this submission.

TABLE 1 Overview of treatment regimens in the five therapeutic confirmatory trials

Trial	Liraglutide 0.6 mg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	Placebo	Active Comparator
1573	N/A	Liraglutide 1.2 mg + placebo (glimepiride)	Liraglutide 1.8 mg + placebo (glimepiride)	N/A	Glimepiride 8 mg + placebo (liraglutide)
1572	Liraglutide 0.6 mg + placebo (glimepiride) + metformin 2 g	Liraglutide 1.2 mg + placebo (glimepiride) + metformin 2 g	Liraglutide 1.8 mg + placebo (glimepiride) + metformin 2 g	Placebo (liraglutide) + placebo (glimepiride) + metformin 2 g	Glimepiride 4 mg + placebo (liraglutide) + metformin 2 g
1436	Liraglutide 0.6 mg + placebo (rosiglitazone) + glimepiride 4 mg	Liraglutide 1.2 mg + placebo (rosiglitazone) + glimepiride 4 mg	Liraglutide 1.8 mg + placebo (rosiglitazone) + glimepiride 4 mg	Placebo (liraglutide) + placebo (rosiglitazone) + glimepiride 4 mg	Rosiglitazone 4 mg + placebo (liraglutide) + glimepiride 4 mg
1574	N/A	Liraglutide 1.2 mg + metformin 2 g + rosiglitazone 8 mg	Liraglutide 1.8 mg + metformin 2 g + rosiglitazone 8 mg	Placebo (liraglutide) + metformin 2 g + rosiglitazone 8 mg	N/A
1697	N/A	N/A	Liraglutide 1.8 mg + glimepiride 4 mg + metformin 2 g	Placebo (liraglutide) + glimepiride 4 mg + metformin 2 g	Insulin glargine + glimepiride 4 mg + metformin 2 g

Doses of metformin and glimepiride could be adjusted in Trial 1572 (metformin 1.5–2 g), Trial 1436 (glimepiride 2–4 mg) and Trial 1697 (glimepiride 2–4 mg).

N/A: not assessed

Source: CTD 2.7.3 Summary of Clinical Efficacy, Table 1-1

The five key studies involved 3992 randomized subjects, of whom 982 (24.6%) were enrolled at sites in the U.S. (TABLE 2). Only two studies, Trial 1573 and Trial 1574, enrolled subjects in the U.S. The numbers of randomized subjects, centers and countries for each study are summarized in TABLE 2.

TABLE 2 Number of randomized subjects and sites by country for each of the five Phase 3 studies

Region	Trial 1436		Trial 1572		Trial 1573		Trial 1574		Trial 1697	
	# sites	# pts.	# sites	# pts.	# sites	# pts.	# sites	# pts.	# sites	# pts.
<b>US</b>		<b>0</b>		<b>0</b>	<i>126</i>	<i>575</i>	<i>71</i>	<i>407</i>		<b>0</b>
<b>Rest of the Americas</b>		<b>81</b>		<b>51</b>		<b>171</b>		<b>126</b>		<b>52</b>
Argentina	<i>7</i>	81	<i>4</i>	51					<i>5</i>	52
Canada							<i>17</i>	126		
Mexico					<i>12</i>	171				
<b>Western Europe</b>		<b>153</b>		<b>526</b>		<b>0</b>		<b>0</b>		<b>241</b>
Austria									<i>7</i>	35
Belgium			<i>6</i>	36						
Denmark			<i>9</i>	54					<i>7</i>	35
Finland	<i>10</i>	72							<i>5</i>	12
France	<i>8</i>	35							<i>9</i>	28
Germany			<i>33</i>	200						
Ireland			<i>4</i>	22						
Italy	<i>5</i>	13	<i>10</i>	29					<i>8</i>	27
The Netherlands			<i>5</i>	20					<i>8</i>	22
Norway			<i>8</i>	51					<i>5</i>	12
Spain			<i>14</i>	48					<i>9</i>	44
Sweden			<i>8</i>	57						
Switzerland	<i>5</i>	33								
United Kingdom			<i>11</i>	9					<i>12</i>	26
<b>Eastern Europe</b>		<b>336</b>		<b>240</b>		<b>0</b>		<b>0</b>		<b>177</b>
Bulgaria	<i>6</i>	69	<i>1</i>	26						
Croatia	<i>3</i>	36	<i>2</i>	20						
Czech Republic	<i>7</i>	40								
Hungary			<i>5</i>	58						
Poland	<i>15</i>	126							<i>5</i>	48
Romania	<i>5</i>	65	<i>3</i>	31						
Russia			<i>6</i>	51					<i>4</i>	30
Serbia and Montenegro									<i>4</i>	63
Slovakia			<i>7</i>	54					<i>6</i>	36
<b>Asia / India</b>		<b>311</b>		<b>77</b>		<b>0</b>		<b>0</b>		<b>84</b>
Hong Kong	<i>1</i>	23								
India	<i>4</i>	66	<i>5</i>	77					<i>5</i>	65
Korea	<i>3</i>	33								
Malaysia	<i>3</i>	93								
Philippines	<i>4</i>	42							<i>4</i>	19
Taiwan	<i>4</i>	37								
Thailand	<i>3</i>	17								
<b>Africa / Middle East</b>		<b>118</b>		<b>65</b>		<b>0</b>		<b>0</b>		<b>27</b>
Israel	<i>3</i>	34								
South Africa	<i>5</i>	56	<i>7</i>	65					<i>4</i>	27
Turkey	<i>6</i>	28								
<b>Australia / New Zealand</b>		<b>42</b>		<b>132</b>		<b>0</b>		<b>0</b>		<b>0</b>
Australia	<i>9</i>	42	<i>19</i>	126						
New Zealand			<i>3</i>	6						
<b>Totals</b>	<b><i>116</i></b>	<b>1041</b>	<b><i>170</i></b>	<b>1091</b>	<b><i>138</i></b>	<b>746</b>	<b><i>88</i></b>	<b>533</b>	<b><i>107</i></b>	<b>581</b>

Sources: DEMOG.xpt files for Trials 1436, 1572, 1573, 1574 and 1697

**Study populations:** All subjects entering into these studies were required to have type 2 diabetes with inadequate glycemic control prior to randomization. Key inclusion criteria specific to each study are summarized below:

- Trial 1573 included subjects treated with diet/exercise or one OAD for at least two months. If treated with an OAD (sulphonylureas, meglitinides, amino acid derivatives, biguanides, alpha-glucosidase inhibitors or thiazolidinediones), the dose was to be no more than half maximal dose, except subjects previously treated with metformin ( $\leq 1500$  mg) or pioglitazone ( $\leq 30$  mg) were eligible for the trial. HbA1c at screening was to be in the range 7.0-11.0% for subjects on diet/exercise treatment and 7.0-10.0% for subjects on OAD therapy.
- Trials 1572 and 1436 included subjects treated with OAD(s) for at least 3 months. HbA1c at screening was to be in the range 7.0-11.0% for subjects on OAD monotherapy and 7.0-10.0% for subjects on OAD combination therapy.
- Trial 1574 included subjects treated with OAD(s) and/or exenatide for at least 3 months. HbA1c at screening was to be in the range 7.0-10.0% for subjects on combination therapy including OADs and/or exenatide.
- Trial 1697 included subjects treated with OAD(s) for at least 3 months. HbA1c at screening was to be in the range 7.5-10.0% for subjects on OAD monotherapy and 7.0-10.0% for subjects on OAD combination therapy.

**Stratification:** In all trials, subjects were stratified with respect to previous diabetes treatment (diet/exercise treated versus OAD monotherapy in Trial 1573 and OAD monotherapy versus OAD combination therapy in Trials 1572, 1436, 1574 and 1697).

**Maintaining the blind:** All trials made use of placebo pills and placebo injections to maintain the blind.

**Pre-randomization and post-randomization titration schedules:** Each trial had a pre-specified protocol regarding the OAD and liraglutide therapy associated with the trial. All trials used the following titration schedule for liraglutide in the two-week period following randomization: After randomization, subjects randomized to receive liraglutide started on 0.6 mg for the first week. For subjects randomized to receive 1.2 mg or 1.8 mg, the dose was increased to 1.2 mg for the second week. Subjects randomized to receive 1.8 mg of liraglutide started on this dose at the third week.

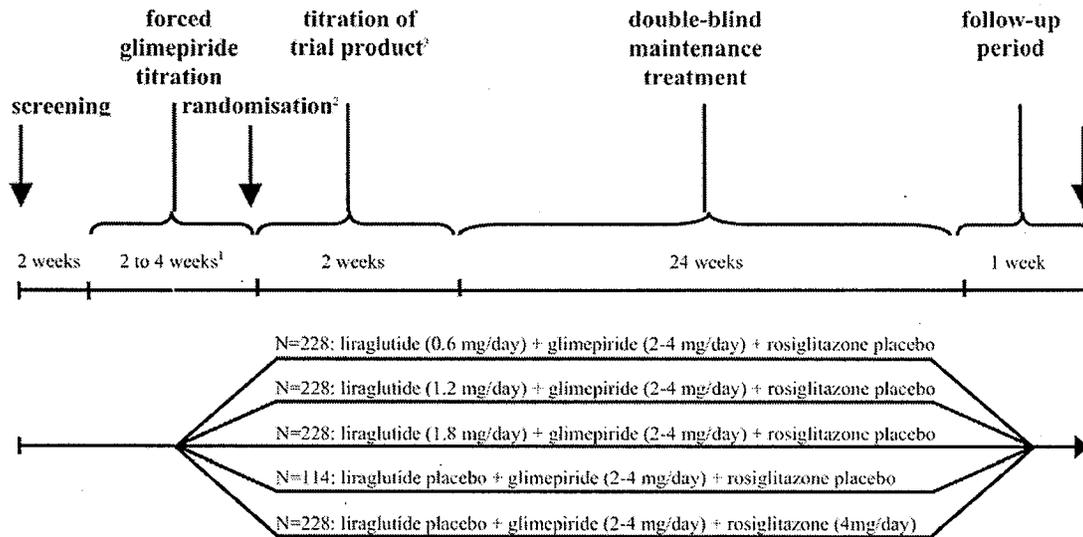
The protocol for OAD therapy associated with each trial is described below:

**Trial 1436:** Subjects who were identified as eligible at the screening visit were to discontinue their usual OAD(s) and start an open 2-week run-in period with forced titration of glimepiride therapy increasing to 4 mg/day followed by a 2-week maintenance period (FIGURE 1). Subjects on current glimepiride therapy could go through a modified titration period or advance directly to the 2-week maintenance period at the discretion of the investigator.

- **Glimepiride:** After randomization, the dose level of glimepiride could, at the discretion of the investigator, be decreased to a minimum of 2 mg/day in case of unacceptable hypoglycemia or other adverse events. The glimepiride dose could also be increased again to 4 mg/day, also at the discretion of the investigator. If a dose level less than 2 mg/day or more than 4 mg/day was required, the subject was to be withdrawn from the trial.
- **Rosiglitazone:** Rosiglitazone was to be kept at 4 mg/day. There was no titration schedule for rosiglitazone.
- **Liraglutide:** Liraglutide was up-titrated as described for all of the trials:

Clinic visits from randomization on took place at day 0 (randomization), weeks 1, 2, 4, 8, 12, 18, 26 and 27. The double-blind portion of the trial took place from May 29, 2006 to May 7, 2007.

FIGURE 1 Design of Trial 1436



<sup>1</sup> Depending on glimepiride dose level at entry into the titration phase.  
<sup>2</sup> Only if FPG is between 7.0 and 12.8 mmol/L (126-230 mg/dL) (both inclusive).  
<sup>3</sup> Up-titration of liraglutide (blinded) and glimepiride (open-label).

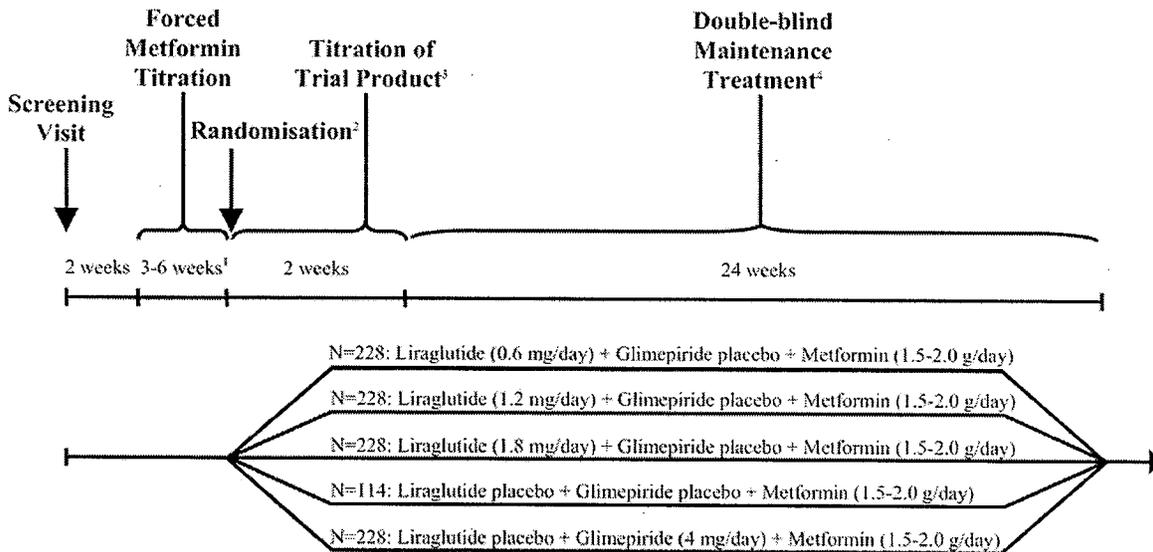
Source: Trial 1436 clinical report, Figure 9-1

**Trial 1572:** Subjects who were identified as eligible at screening discontinued their usual OAD(s) and started an open 3-week run-in period with forced titration of metformin therapy increasing to 2000 mg/day followed by a 3-week maintenance period. Subjects on current metformin therapy could go through a modified titration period or advance directly to the 3-week maintenance period at the discretion of the investigator.

After randomization, subjects assigned to glimepiride were started at 2 mg for the first two weeks, increased to 4 mg for the third week and to 4 mg for week 4 and beyond. Liraglutide was up-titrated as described for all of the trials (FIGURE 2). Clinic visits from randomization to the end of the double-blind period took place at day 0 (randomization), weeks 1, 2, 4, 8, 12, 18, 26 and 27. The double-blind portion of the trial took place from May 30, 2006 to May 4, 2007.

*Extension to Trial 1572:* At visit 10 at 26 weeks after randomization, all subjects were asked to confirm their continued participation in an 18-month open-label treatment extension period. Subjects who continued into the extension period were unblinded to treatment assignment at their first visit at the site after database release and continued the treatment regimen they had been randomized to in the blinded part of the trial.

FIGURE 2 Design of Trial 1572



<sup>1</sup> Depending on metformin dose level at entry into the titration phase.  
<sup>2</sup> Only if FPG is between 7.0 and 12.8 mmol/L (126-230 mg/dL) (both incl.).  
<sup>3</sup> Double-blind up-titration of liraglutide and glimepiride (active and/or placebo) (see section 9.4.1).  
<sup>4</sup> Subjects not participating in the open-label extension had a follow-up visit 1 week after termination of the double-blind maintenance treatment period.

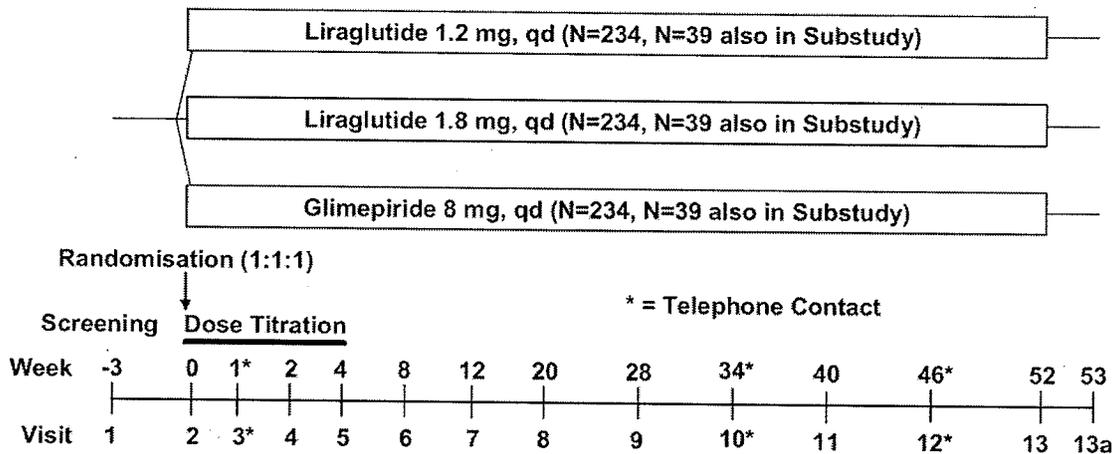
Source: Trial 1572 clinical report, Figure 9-1

**Trial 1573:** The protocol for Trial 1573 did not specify a pre-treatment period. A dose titration period for liraglutide or glimepiride followed randomization. Glimepiride was started at 2 mg for the first two weeks, increased to 4 mg for the third week and to 8 mg for week 4 and beyond (FIGURE 3). Liraglutide was up-titrated as described for all of the trials.

Clinic visits from randomization to the end of the double-blind period took place at day 0 (randomization), weeks 1, 2, 4, 8, 12, 20, 28, 40, 52 and 53. The double-blind portion of the trial took place from February 7, 2006 to November 2, 2007.

*Extension to Trial 1573:* This trial had a 52-week double-blind treatment period followed by a 52-week open-label extension period. Subjects who continued into the extension period were unblinded to treatment assignment at their first visit at the site after database release and continued the treatment regimen they had been randomized to in the blinded part of the trial.

FIGURE 3 Design of Trial 1573



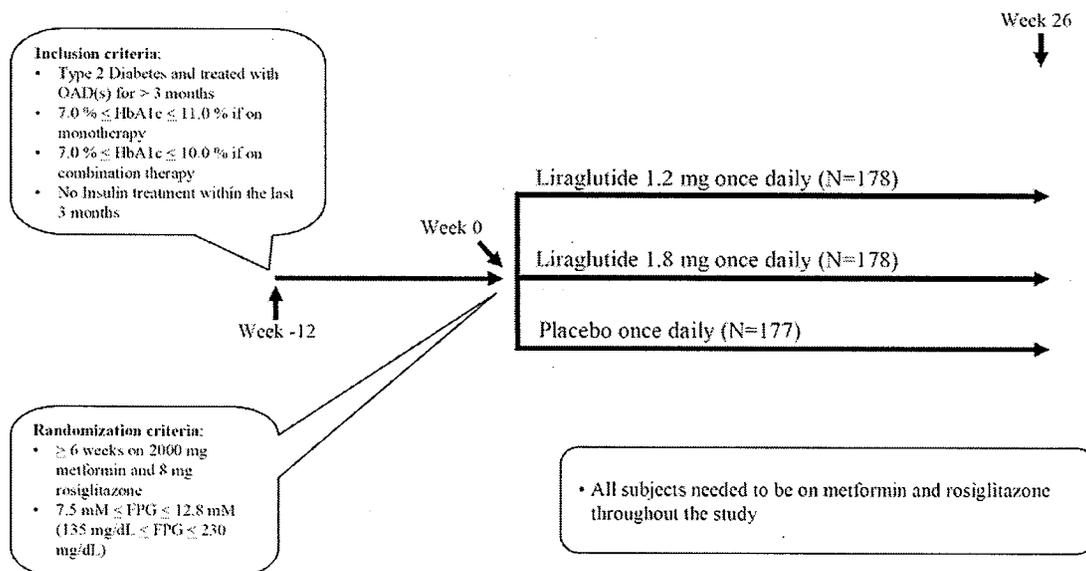
Source: Trial 1573 study report, Figure 9-1

**Trial 1574:** At randomization, all subjects had been titrated (as needed) and maintained on rosiglitazone 8 mg/day and metformin 2000 mg/day for at least six weeks (FIGURE 4). These doses were achieved as follows:

- **Rosiglitazone:** Before randomization, rosiglitazone was initiated at 4 mg once daily and was increased after 2 weeks to 8 mg/day (4 mg BID). Subjects who entered the trial on rosiglitazone therapy could start titration at the dose that they were currently taking or go directly to the maintenance dose of 8 mg at the discretion of the investigator. All subjects had a six-week maintenance period with 8 mg rosiglitazone prior to randomization at week 0.
- **Metformin:** Before randomization, subjects who were not currently treated with metformin underwent an open-label forced titration, initiated at 500 mg with weekly increments of 500 mg to a final dose of 2000 mg/day. Subjects on current metformin therapy could start at the dose they were currently treated with or go directly to the maintenance metformin dose of 2000 mg at the discretion of the investigator. All subjects had a six-week maintenance period with 2000 mg prior to randomization.

Clinic visits from randomization to the end of the double-blind period took place at day 0 (randomization), weeks 1, 2, 4, 8, 12, 19, 26 and 27. The double-blind portion of the trial took place from May 30, 2006 to August 14, 2007.

FIGURE 4 Design of Trial 1574

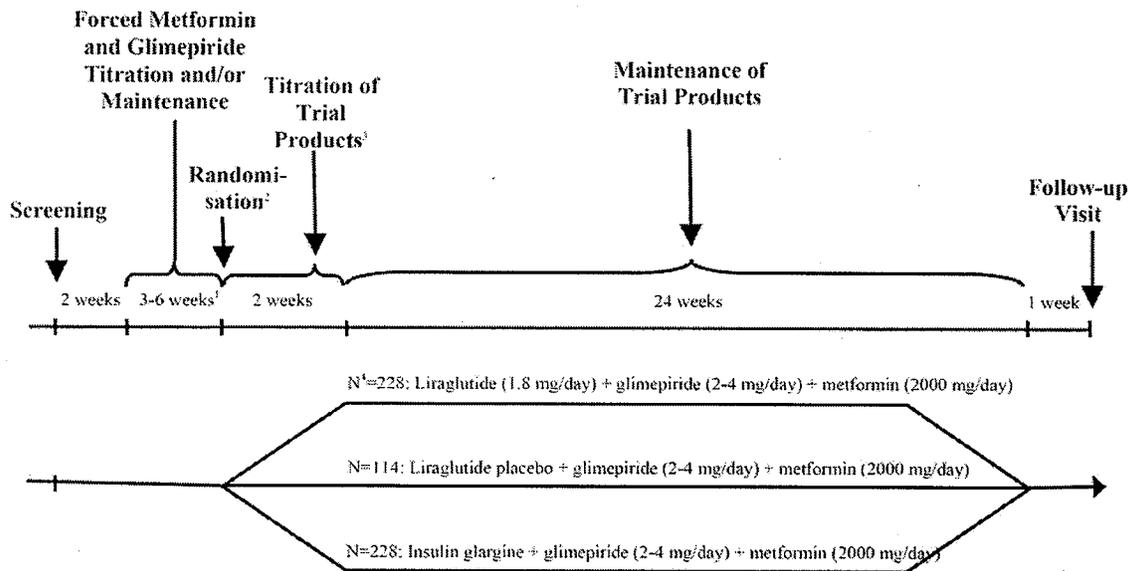


Source: Trial 1574 clinical report, Figure 9-1

**Trial 1697:** Subjects who were identified as eligible at screening discontinued their usual OADs at visit 2 and initiated an open 3-week period with forced titration of glimepiride and metformin therapy. The glimepiride and metformin therapy increased to 4 mg/day and 2000 mg/day, respectively, and the titration period was followed by a mandatory 3-week maintenance period. Subjects on current glimepiride and metformin combination therapy could go through a modified titration period or advance directly to the 3-week maintenance period at the discretion of the investigator (FIGURE 5).

Clinic visits from randomization to the end of the double-blind period took place at day 0 (randomization), weeks 1, 2, 4, 8, 12, 18, 26 and 27. The double-blind portion of the trial took place from May 30, 2006 to April 20, 2007.

FIGURE 5 Design of Trial 1697



<sup>1</sup> Depending on metformin and/or glimepiride dose level at entry into the titration phase.

<sup>2</sup> Only if FPG is between 7.5 and 12.8 mmol/L (135-230 mg/dL) (both inclusive).

<sup>3</sup> Up-titration of liraglutide (active and/or placebo) through doses of 0.6 mg and 1.2 mg liraglutide and titration of insulin glargine according to guideline (Sections 9.4.1 and 9.4.5).

Source: Trial 1697 clinical report, Figure 9-1

**Number of subjects in each trial:** The following assumptions were used for all five trials for the HbA1c endpoint (expressed as a change from baseline at week 26 for Trials 1436, 1572, 1574 and 1697, and at week 52 for Trial 1573):

- A margin of 0.4% for non-inferiority comparisons
- A net effect of liraglutide of 0.5% for superiority comparisons
- Desired statistical power of at least 85%
- A two-tailed  $\alpha$  of 0.05 for superiority comparisons
- A one-tailed  $\alpha$  of 0.025 for non-inferiority comparisons

Trial 1436: With a 2:2:2:2:1 allocation ratio to the liraglutide 0.6 mg + glimepiride : liraglutide 1.2 mg + glimepiride : liraglutide 1.8 mg + glimepiride : rosiglitazone + glimepiride : glimepiride arms, an estimated standard deviation of 1.2%, and a drop out rate of 25%, the applicant determined that the total number of subjects to be randomized was 1026, allocated as 228:228:228:228:114. In the study, 1041 subjects were randomized, allocated as 233:228:234:232:114.

Trial 1572: With a 2:2:2:2:1 allocation ratio to the liraglutide 0.6 mg + metformin : liraglutide 1.2 mg + metformin : liraglutide 1.8 mg + metformin : glimepiride + metformin : metformin arms, an estimated standard deviation of 1.2%, and a drop out rate of 25%, the applicant determined that the total number of subjects to be randomized was 1026, allocated as 228:228:228:228:114. In the study, 1091 subjects were randomized, allocated as 242:241:242:244:122.

Trial 1573: With a 1:1:1 allocation ratio to the liraglutide 1.2 mg : liraglutide 1.8 mg : glimepiride arms, an estimated standard deviation of 1.2%, and a drop out rate of 30%, the applicant determined that the total number of subjects to be randomized was 702, allocated as 234:234:234. In the study, 746 subjects were randomized, allocated as 246:251:248.

Trial 1574: With a 1:1:1 allocation ratio to the liraglutide 1.2 mg + metformin + rosiglitazone : liraglutide 1.8 mg + metformin + rosiglitazone : metformin + rosiglitazone arms, an estimated standard deviation of 1.3%, and a drop out rate of 25%, the applicant determined that the total number of subjects to be randomized was 492, allocated as 164:164:164. In the study, 533 subjects were randomized, allocated as 178:178:177.

Trial 1697: With a 2:2:1 allocation ratio to the liraglutide 1.8 mg + glimepiride + metformin : glargine + glimepiride + metformin : glimepiride + metformin arms, an estimated standard deviation of 1.2%, and a drop out rate of 25%, the applicant determined that the total number of subjects to be randomized was 570, allocated as 228:228:114. In the study, 581 subjects were randomized, in the ratio 232:234:115.

**Non-inferiority margin:** The selection of a non-inferiority margin for comparison of liraglutide with glimepiride (Amaryl™) in subjects who had not achieved adequate glycemic control on diet and exercise alone was based in part on an analysis of the effect of glimepiride monotherapy in three placebo-controlled studies. The estimated effect, combined across studies with a random effects meta-analysis, was -1.6%, with an upper 95% confidence bound of -1.3%, for HbA1c change from baseline after 14 weeks of therapy. Because the sponsor's proposed margin, 0.4%, is less than half of the upper bound, in the direction of inferiority of liraglutide compared to glimepiride, the proposed margin is acceptable from the statistical review perspective. A more detailed description of the methodology used to combine results across studies is in the statistical review of protocol 1573, submitted to IND 061040 on January 10, 2006 (amendment 060).

However, as noted in the statistical review of protocol 1573, the margin of difference of 0.4% is subject to the condition that the effect of glimepiride does not decline appreciably between 14 weeks and 52 weeks of therapy. Results from long-term extension studies that are described briefly in the Amaryl® label suggest that it may be reasonable to extend the 14-week results in HbA1c out to 52 weeks of therapy.

The non-inferiority margin 0.4% was used for several active control comparators and background therapies in the range of target populations of the Phase 3 studies. For this reason, I conducted a post-hoc evaluation of the non-inferiority margin from the results of the three studies that included both an active control arm and a placebo control arm.

## 2.2 Data Sources

The applicant submitted this NDA including the data to the FDA CDER Electronic Document Room (EDR). The submission is recorded in the EDR with the link shown in TABLE 3. Individual study reports were submitted for each study.

TABLE 3 Data sources for studies

Document: NDA 022341.0
CDER EDR link: \\CDSESUB1\N022341\
Company: Novo Nordisk
Drug: Liraglutide
Submission date: May 23, 2008

### 3. STATISTICAL EVALUATION

#### 3.1 Evaluation of Efficacy

##### 3.1.1. Subject disposition

Ineffective therapy: Subjects who were withdrawn early from the liraglutide studies due to hyperglycemia were classified as having “ineffective therapy.” The criteria for ineffective therapy were based on fasting plasma glucose (FPG). The FPG criteria were relatively similar across studies, but there were some differences (TABLE 4). In each study, subjects who met the criteria for being classified as having ineffective therapy had a final clinical visit, and then were withdrawn from the study. The last observation of HbA1c and other efficacy endpoints was carried forward to represent this subject’s endpoint response to therapy.

TABLE 4 Fasting Plasma Glucose criteria for the “ineffective therapy” classification

<b>Trial</b>	<b>Criteria for “ineffective therapy” classification</b>
1436	From weeks 8 to 26: FPG > 239 mg/dL
1572	Double-blind period: <ul style="list-style-type: none"> <li>• From weeks 8 to 26: FPG &gt; 239 mg/dL</li> </ul> Open-label extension period: <ul style="list-style-type: none"> <li>• From weeks 26 to 52: FPG &gt; 220 mg/dL</li> <li>• From weeks 52 to 105: FPG &gt; 200 mg/dL</li> </ul>
1573	Double-blind period: <ul style="list-style-type: none"> <li>• From weeks 8 to 28: FPG &gt; 240 mg/dL</li> <li>• From week 28 to 52: FPG &gt; 220 mg/dL</li> </ul> Open-label extension period: <ul style="list-style-type: none"> <li>• From week 52 to 104: FPG &gt; 220 mg/dL</li> </ul>
1574	From weeks 8 to 26: FPG > 240 mg/dL
1697	From weeks 8 to 26: FPG > 239 mg/dL
<i>Notes:</i>	
<ul style="list-style-type: none"> <li>• Subjects who met the criteria for ineffective therapy were removed from the study.</li> <li>• “Weeks” refer to the weeks post randomization</li> </ul>	
<i>Sources:</i> Section 9.3.3 (“Removal of patients from therapy and assessment”) in the report of each study	

Patterns of disposition across studies: Support for the efficacy of liraglutide compared to a placebo control and compared to an active control comes from a consistent pattern of early withdrawals due to ineffective therapy, when observed across the five studies. In the four studies that had a placebo add-on arm, subjects in this arm were more likely to withdraw early due to

ineffective therapy than subjects in the liraglutide arms (see Trials 1436, 1572, 1574 and 1697; TABLE 5). In the four studies that had an active comparator arm, subjects in this arm were about equally likely to withdraw early due to ineffective therapy as subjects in the liraglutide arms (see Trials 1436, 1572, 1697 and 1573; TABLE 5).

The possibility that the two larger doses of liraglutide may result in withdrawal due to adverse events when given in combination with metformin is suggested by the pattern of disposition in three of the studies that had metformin as background therapy (metformin in Trial 1572, metformin + rosiglitazone in Trial 1574, and metformin + glimepiride in Trial 1697). A greater percentage of subjects withdrew early due to adverse events in the liraglutide 1.2 mg + metformin and liraglutide 1.8 mg + metformin arms than in the metformin comparator arm within each of these studies (TABLE 5). This pattern was not observed in Trial 1436 which had glimepiride as background therapy rather than metformin. This pattern may suggest an increase in adverse events when liraglutide at the two higher dosages is combined with metformin. This finding is supported by the greater percentage of gastrointestinal adverse events (such as nausea, diarrhea, and vomiting) reported for liraglutide + metformin and liraglutide + metformin + glimepiride arms compared to liraglutide + glimepiride arms (summary not shown).

#### Patterns of disposition within studies:

- In Trial 1436 (glimepiride background therapy), the percentage of subjects who did not complete the study in the liraglutide arms ranged from 9% to 14%, of which the contribution due to ineffective therapy and adverse events was relatively similar and ranged from 2% to 5% (TABLE 5; FIGURE 6). In contrast, 27% of subjects in the placebo arm did not complete the study, of whom 18% (absolute) withdrew due to ineffective therapy. The disposition pattern in the rosiglitazone arm was similar to the pattern in the liraglutide arms.
- In Trial 1572 (metformin background therapy), the percentage of subjects who did not complete the study in the liraglutide arms ranged from 14% to 21% (TABLE 5; FIGURE 6). The largest contributor to this percentage was ineffective therapy in the liraglutide 0.6 mg arm (7.9%), and adverse events in the liraglutide 1.2 mg and liraglutide 1.8 mg arms (9.5% and 12.0% respectively). The placebo arm had the greatest percentage of subjects withdrawing from the study, 39%, compared to the other arms, with the majority of these early withdrawals, 24%, classified as “ineffective therapy.” The percentage of early withdrawals in the glimepiride arm was 14%, which was relatively evenly distributed across the four different reasons for withdrawal.
- Trial 1573 (monotherapy) was a 52-week study, and the percentage of subjects who withdrew early was evaluated at week 52. All three arms of Trial 1573 had relatively large percentages of subjects who withdrew before week 52, ranging from 30% to 39% (TABLE 5). By week 26, the percentage of subjects who had withdrawn from the study was approximately 20%, which is broadly similar to the disposition pattern of the 26-week studies (FIGURE 6). The most frequently cited reason for early withdrawal in each arm was “other,”

ranging from 15% to 21%. The two most common text entries accompanying the “other” classification were “withdrew consent” (44/125) and “lost to follow-up” (37/125).

- In Trial 1574 (metformin + rosiglitazone background therapy), 25% of subjects withdrew from the liraglutide 1.2 mg arm, of which the most frequently cited reason (15%; absolute) was adverse events (TABLE 5; FIGURE 6). A smaller percentage, 14%, withdrew from the liraglutide 1.8 mg arm; adverse events was also the most frequently cited reason (6%). The placebo arm had the greatest percentage of withdrawals (32%) of all three arms, and ineffective therapy was the most frequently cited reason (16%).
- Trial 1697 (glimepiride + metformin background therapy) had the smallest percentage of subjects withdraw from the study compared to the other four studies, ranging from 6% to 11% (TABLE 5; FIGURE 6). The most frequently cited reason for withdrawal was adverse events (5%) and other (5%) in the liraglutide 1.8 mg arm, ineffective therapy (11%) in the placebo arm, and adverse events (2%) and non-compliance with the protocol (2%) in the insulin arm.

TABLE 5 Subject disposition in each study

Trial 1436 (26 weeks) add-on to glimepiride 4 mg	liraglutide 0.6 mg		liraglutide 1.2 mg		liraglutide 1.8 mg		placebo	rosiglitazone 4 mg	Total
	n	(%)	n	(%)	n	(%)			
Randomized	233		228		234		114	232	1041
Exposed	233		228		234		114	231	1040
Completed	208 (89.3%)		196 (86.0%)		213 (91.0%)		83 (72.8%)	194 (83.6%)	894 (85.9%)
Withdrawn:	25 (10.7%)		32 (14.0%)		21 (9.0%)		31 (27.2%)	38 (16.4%)	147 (14.1%)
Ineffective therapy	12 (5.2%)		8 (3.5%)		7 (3.0%)		20 (17.5%)	16 (6.9%)	63 (6.1%)
Adverse events	5 (2.1%)		11 (4.8%)		9 (3.8%)		6 (5.3%)	7 (3.0%)	38 (3.7%)
Non-compliance with protocol	3 (1.3%)		5 (2.2%)		3 (1.3%)		2 (1.8%)	6 (2.6%)	19 (1.8%)
Other	5 (2.1%)		8 (3.5%)		2 (0.9%)		3 (2.6%)	9 (3.9%)	27 (2.6%)

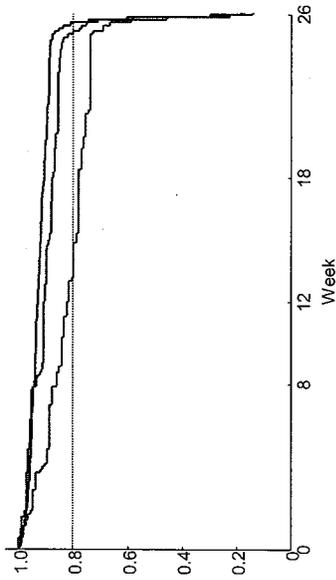
  

Trial 1572 (26 weeks) add-on to metformin 2 g	liraglutide 0.6 mg		liraglutide 1.2 mg		liraglutide 1.8 mg		placebo	glimepiride 4 mg	Total
	n	(%)	n	(%)	n	(%)			
Randomized	242		241		242		122	244	1091
Exposed	242		240		242		121	242	1087
Completed	208 (86.0%)		197 (81.7%)		191 (78.9%)		74 (60.7%)	210 (86.1%)	880 (80.7%)
Withdrawn:	34 (14.0%)		44 (18.3%)		51 (21.1%)		48 (39.3%)	34 (13.9%)	211 (19.3%)
Ineffective therapy	19 (7.9%)		8 (3.3%)		13 (5.4%)		29 (23.8%)	9 (3.7%)	78 (7.1%)
Adverse events	11 (4.5%)		23 (9.5%)		29 (12.0%)		2 (1.6%)	8 (3.3%)	73 (6.7%)
Non-compliance with protocol	2 (0.8%)		4 (1.7%)		4 (1.7%)		4 (3.3%)	5 (2.0%)	19 (1.7%)
Other	2 (0.8%)		9 (3.7%)		5 (2.1%)		13 (10.7%)	12 (4.9%)	41 (3.8%)

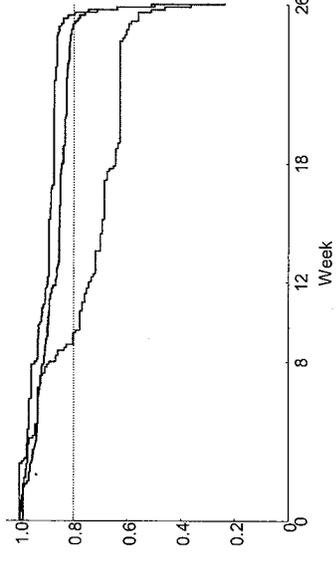
Trial 1573 (52 weeks) monotherapy	liraglutide		liraglutide		glimepiride		Total
	1.2 mg	1.8 mg	1.8 mg	8 mg	8 mg	8 mg	
Randomized	247	251	251	248	248	746	
Exposed	246	251	251	248	248	745	
Completed	173 (70.0%)	162 (64.5%)	162 (64.5%)	152 (61.3%)	152 (61.3%)	487 (65.3%)	
Withdrawn:	74 (30.0%)	89 (35.5%)	89 (35.5%)	96 (38.7%)	96 (38.7%)	259 (34.7%)	
Ineffective therapy	9 (3.6%)	15 (6.0%)	15 (6.0%)	25 (10.1%)	25 (10.1%)	49 (6.6%)	
Adverse events	18 (7.3%)	25 (10.0%)	25 (10.0%)	15 (6.0%)	15 (6.0%)	58 (7.8%)	
Non-compliance with protocol	11 (4.5%)	11 (4.4%)	11 (4.4%)	5 (2.0%)	5 (2.0%)	27 (3.6%)	
Other	36 (14.6%)	38 (15.1%)	38 (15.1%)	51 (20.6%)	51 (20.6%)	125 (16.8%)	
<b>Trial 1574 (26 weeks)</b>							
add-on to metformin 2 g + rosiglitazone 8 mg (4 mg BID)	liraglutide		liraglutide		placebo		Total
	1.2 mg	1.8 mg					
Randomized	178	178	178	177	177	533	
Exposed	178	177	177	175	175	530	
Completed	133 (74.7%)	153 (86.0%)	153 (86.0%)	121 (68.4%)	121 (68.4%)	407 (76.4%)	
Withdrawn:	45 (25.3%)	25 (14.0%)	25 (14.0%)	56 (31.6%)	56 (31.6%)	126 (23.6%)	
Ineffective therapy	3 (1.7%)	3 (1.7%)	3 (1.7%)	29 (16.4%)	29 (16.4%)	35 (6.6%)	
Adverse events	27 (15.2%)	11 (6.2%)	11 (6.2%)	6 (3.4%)	6 (3.4%)	44 (8.3%)	
Non-compliance with protocol	4 (2.2%)	4 (2.2%)	4 (2.2%)	5 (2.8%)	5 (2.8%)	13 (2.4%)	
Other	11 (6.2%)	7 (3.9%)	7 (3.9%)	16 (9.0%)	16 (9.0%)	34 (6.4%)	

Trial 1697 (26 weeks) add-on to glimepiride 4 mg + metformin 2 g	liraglutide 1.8 mg	placebo	insulin glargine	Total
Randomized	232	115	234	581
Exposed	230	114	232	576
Completed	207 (89.2%)	96 (83.5%)	219 (93.6%)	522 (89.8%)
Withdrawn:	25 (10.8%)	19 (16.5%)	15 (6.4%)	59 (10.2%)
<i>Ineffective therapy</i>	2 (0.9%)	13 (11.3%)	1 (0.4%)	16 (2.8%)
<i>Adverse events</i>	11 (4.7%)	1 (0.9%)	5 (2.1%)	17 (2.9%)
<i>Non-compliance with protocol</i>	1 (0.4%)	1 (0.9%)	5 (2.1%)	7 (1.2%)
<i>Other</i>	11 (4.7%)	4 (3.5%)	4 (1.7%)	19 (3.3%)
<i>Sources:</i>				
Trial 1436 clinical report, Table 10-1	Trial 1574 clinical report, Table 10-1			
Trial 1572 clinical report, Table 10-1	Trial 1697 clinical report, Table 10-1			
Trial 1573 clinical report, Table 10-1				

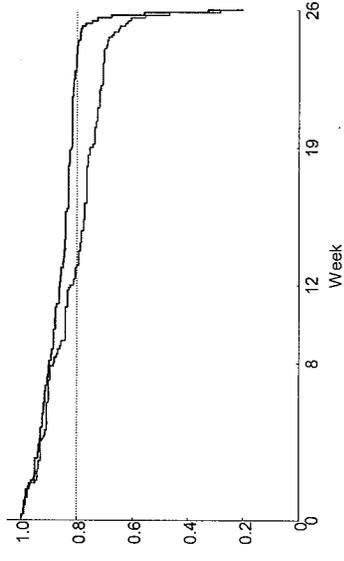
FIGURE 6 Disposition by week on study; Kaplan-Meier plots (horizontal axis shows the clinic visits where HbA1c was determined)  
Trial 1436 Trial 1572 Trial 1574



— Glimepiride + Liraglutide  
— Glimepiride + Rosiglitazone  
— Glimepiride

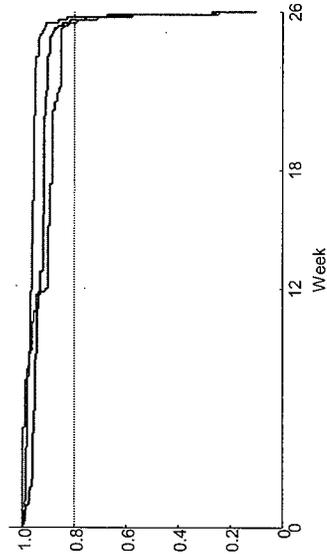


— Metformin + Liraglutide  
— Metformin + Glimepiride  
— Metformin



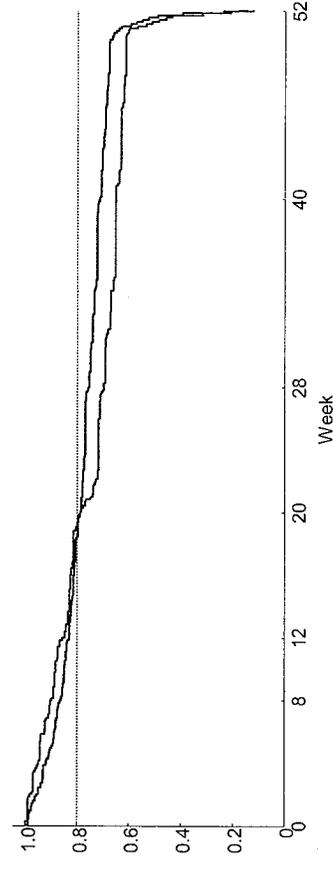
— Metformin + Rosiglitazone + Liraglutide  
— Metformin + Rosiglitazone

Trial 1697



— Metformin + Glimepiride + Liraglutide  
— Metformin + Glimepiride + Insulin Glargine  
— Metformin + Glimepiride

Trial 1573



— Liraglutide  
— Glimepiride

### 3.1.2. Subject demographic and baseline characteristics

Certain subject demographic and baseline characteristics were relatively similar among studies (TABLE 6). Each study had approximately equal numbers of males and females. The average age was relatively similar among studies, ranging from 53 to 58 years. The majority of subjects in each study were Caucasian, ranging from 64% to 87%. The majority of subjects in each study were younger than 65 years, ranging from 78% to 85% (TABLE 6). Within each study, the distribution of demographic and baseline characteristics was relatively similar among the randomized arms (not shown in the table).

Differences among studies reflect differences among the target populations with respect to the progression of diabetes. The shortest median duration of diabetes, 3.8 years, was observed in the monotherapy study, Trial 1573 (TABLE 6). This study was also the only study that used the “diet/exercise” category of “previous antidiabetic treatment,” with 37% of subjects reporting this category. The two longest median durations of diabetes, 7.9 and 8.4 years, were observed in the two studies with liraglutide added on to two OADs, Trial 1574 and Trial 1697 respectively. These two studies also had the largest percentages of subjects reporting “combination therapy” for “previous antidiabetic treatment” (83% and 94% respectively; TABLE 6).

A potential concern for the statistical analysis of the primary endpoint arises in certain studies because of the occurrence of subjects with  $HbA1c \leq 7.0$  at baseline. Within each study, the distribution of baseline  $HbA1c$  levels was relatively broad, including values less than 7.0 and values greater than 10.0 (TABLE 7, FIGURE 7). While the general screening range for  $HbA1c$  for the five studies was 7.0-10.0 (with some exceptions, see Part 2.1), four of the studies included a pre-randomization titration schedule of several weeks’ duration. During this period of time, most subjects experienced changes in their background OAD therapy (see Part 2.1). These changes may account for the occurrence of baseline  $HbA1c$  levels less than 7.0 or greater than 10.0 in some subjects. The percentage of subjects with baseline  $HbA1c$  levels less than 7.0 ranged from 5.4% to 11.7% across the five studies (FIGURE 7). Trial 1573 did not have a pre-randomization titration schedule.

Subjects with  $HbA1c \leq 7.0$  at baseline represent a potential concern for Trial 1573, which had an active comparator arm but not a placebo add-on arm. This concern is based on the assumption that subjects in an active therapy arm who are already at a reasonable level of diabetic control at baseline are not likely to change much from their baseline levels over the course of the study. This assumption comes from a general finding across clinical studies of anti-diabetic drugs that subjects with lower levels of  $HbA1c$  at baseline tend to experience smaller decreases in  $HbA1c$  at the study endpoint compared to subjects with higher levels at baseline. In Trial 1573, 11.7% of subjects had baseline  $HbA1c$  levels  $\leq 7.0$ , and another 18.1% of subjects had baseline  $HbA1c$  levels between 7.0 and 7.5, for a total of 28.8% at these lower baseline levels of  $HbA1c$  (FIGURE 7). With a relatively high proportion of subjects who are in reasonable diabetic control at baseline, both the liraglutide and the active comparator arms may tend to have a small average change from baseline  $HbA1c$  at the study endpoint. In this situation, the assay sensitivity of the comparison may not support a non-inferiority margin of 0.4. I evaluated this issue further in my analysis of the  $HbA1c$  endpoint in Trial 1573.

Subjects with HbA1c  $\leq 7.0$  at baseline represent less of a potential concern for studies that had both an active comparator arm and a placebo add-on arm. This design, used in Trials 1436, 1572 and 1697, permits an internal comparison of the active comparator to the placebo. The non-inferiority margin of 0.4 can be compared to the placebo-adjusted effect of the active comparator in each study.

Subjects with HbA1c  $\leq 7.0$  at baseline do not represent a particular concern for superiority comparisons of the liraglutide arm with a placebo add-on arm. Trials 1436, 1572, 1574 and 1697 include superiority comparisons.

TABLE 6 Subject demographic and baseline characteristics in the randomized subjects in each of the five key studies

	Trial 1436 n=1041	Trial 1572 n=1091	Trial 1573 n=746	Trial 1574 n=533	Trial 1697 n=581
Age (years)					
Mean $\pm$ SD	56.1 $\pm$ 9.8	56.8 $\pm$ 9.5	53.0 $\pm$ 10.9	55.1 $\pm$ 10.2	57.5 $\pm$ 9.9
Median	56.0	57.0	53.0	55.0	58.0
Range	24 to 80	25 to 79	19 to 79	23 to 80	24 to 80
$\geq 65$ years (n, %)	212 (20.4%)	243 (22.3%)	108 (14.5%)	93 (17.4%)	146 (17.4%)
Sex					
Male (n, %)	514 (49.4%)	635 (58.2%)	371 (49.7%)	298 (55.9)	328 (56.5%)
Female (n, %)	527 (50.6%)	456 (41.8%)	375 (50.3%)	235 (44.1)	253 (43.5%)
Race <sup>1</sup>					
Caucasian	670 (64.4%)	950 (87.1%)	578 (77.5%)	441 (82.7%)	436 (75.0%)
Black	29 (2.8%)	26 (2.4%)	94 (12.6%)	63 (11.8%)	21 (3.6%)
Asian/Pacific Islander	337 (32.4%)	98 (9.0%)	---	---	91 (15.7%)
Native Hawaiian / Pacific Islander	---	---	2 (0.3%)	0 (0.0%)	---
Asian	---	---	26 (3.5%)	10 (1.9%)	---
American Indian / Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.8%)	0 (0.0%)
Unknown	0 (0.0%)	0 (0.0%)	---	---	28 (4.8%)
Other	5 (0.5%)	17 (1.6%)	46 (6.2%)	15 (2.8%)	5 (0.9%)
Ethnicity <sup>2</sup>					
Hispanic/Latino	---	---	261 (35.0%)	81 (15.2%)	---
Not Hispanic/Latino	---	---	485 (65.0%)	452 (84.8%)	---
Diabetes duration (yr)					
Mean $\pm$ SD	7.9 $\pm$ 5.4	7.4 $\pm$ 5.2	5.4 $\pm$ 5.3	9.0 $\pm$ 5.6	9.4 $\pm$ 6.2
Median	6.6	6.5	3.8	7.9	8.4
Range	0.1 to 32.6	0.3 to 40.6	0.2 to 40.3	0.3 to 36.7	0.4 to 43.5
Previous anti-diabetic treatment					
Diet / Exercise <sup>3</sup>	---	---	272 (36.5%)	---	---
Monotherapy	315 (30.3%)	385 (35.3%)	474 (63.5%)	90 (16.9%)	33 (5.7%)
Combination therapy	726 (69.7%)	706 (64.7%)	---	443 (83.1%)	548 (94.3%)

	<b>Trial 1436 n=1041</b>	<b>Trial 1572 n=1091</b>	<b>Trial 1573 n=746</b>	<b>Trial 1574 n=533</b>	<b>Trial 1697 n=581</b>
<b>Weight (kg)</b>					
Mean ± SD	81.6 ± 17.4	88.6 ± 17.3	92.6 ± 19.6	97.0 ± 18.9	85.4 ± 18.3
Median	80.3	88.5	90.7	95.0	84.0
Range	40.3 to 138.1	42.0 to 151.0	46.7 to 163.3	54.0 to 165.1	45.6 to 150.0
<b>BMI (kg/m<sup>2</sup>)</b>					
Mean ± SD	29.9 ± 5.1	31.0 ± 4.7	33.1 ± 5.8	33.5 ± 5.2	30.5 ± 5.3
Median	29.3	30.8	32.3	33.2	30.0
Range	17.5 to 45.5	17.0 to 41.4	20.8 to 47.1	20.5 to 46.0	17.0 to 45.2
<i>Notes:</i>					
<sup>1</sup> In Trials 1573 and 1574 (with sites in the U.S.), racial groups were categorized differently than they were in Trials 1436, 1572 and 1697 (with no sites in the U.S.).					
<sup>2</sup> In Trials 1573 and 1574 (with sites in the U.S.), Hispanic/Latino status was coded in an ethnicity category separately from the race category. In Trials 1436, 1572 and 1697 (with no sites in the U.S.), this ethnicity category was not recorded.					
<sup>3</sup> In Trial 1573 (monotherapy) previous antidiabetic treatment was classified as “diet/exercise” and “monotherapy”, and in Trials 1436, 1572, 1574 and 1697 (combination therapies), previous antidiabetic treatment was classified as “monotherapy and “combination therapy.”					
Baseline characteristics and demographics were recorded at screening and/or at randomization. If an item was recorded in both visits, and if not otherwise specified, the value from the randomization visit was used when summarizing the study population.					
<i>Sources:</i>					
Clinical reports from Trial 1436 (Table 11-2), Trial 1572 (Table 11-1), Trial 1573 (Table 11-1), Trial 1574 (Table 14.1-1), Trial 1697 (Table 11-2), and additional analysis by this reviewer					

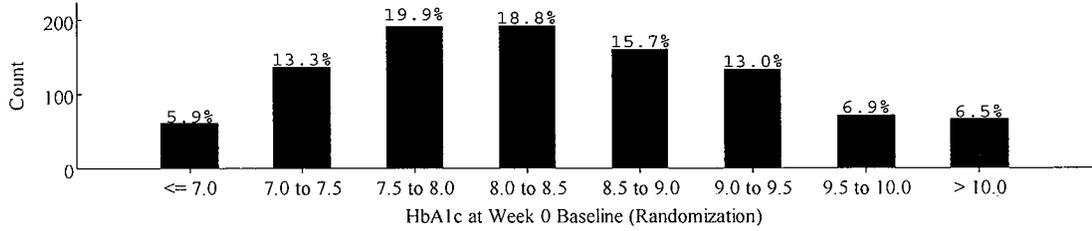
TABLE 7 Baseline levels of HbA1c in randomized subjects in each of the five key studies (by arm)

<b>Trial 1436 add-on to glimepiride 4 mg</b>	<b>liraglutide 0.6 mg</b>	<b>liraglutide 1.2 mg</b>	<b>liraglutide 1.8 mg</b>	<b>placebo</b>	<b>rosiglitazone 4 mg</b>
n	227	228	229	111	229
Mean ± SD	8.4 ± 1.0	8.5 ± 1.1	8.5 ± 0.9	8.4 ± 1.0	8.4 ± 1.0
Median	8.2	8.4	8.5	8.4	8.3
Range					
<b>Trial 1572 add-on to metformin 2 g</b>	<b>liraglutide 0.6 mg</b>	<b>liraglutide 1.2 mg</b>	<b>liraglutide 1.8 mg</b>	<b>placebo</b>	<b>glimepiride 4 mg</b>
n	240	238	240	122	239
Mean ± SD	8.4 ± 0.9	8.3 ± 1.0	8.4 ± 1.0	8.4 ± 1.1	8.4 ± 1.0
Median	8.3	8.3	8.3	8.4	8.2
Range					
<b>Trial 1573 monotherapy</b>		<b>liraglutide 1.2 mg</b>	<b>liraglutide 1.8 mg</b>		<b>glimepiride 8 mg</b>
n		251	247		248
Mean ± SD		8.2 ± 1.1	8.2 ± 1.1		8.2 ± 1.1
Median		8.0	7.9		8.0
Range					
<b>Trial 1574 add-on to metformin 2 g + rosiglitazone 8 mg (4 mg BID)</b>		<b>liraglutide 1.2 mg</b>	<b>liraglutide 1.8 mg</b>	<b>placebo</b>	
n		178	178	177	
Mean ± SD		8.5 ± 1.2	8.6 ± 1.2	8.4 ± 1.2	
Median		8.2	8.4	8.2	
Range					
<b>Trial 1697 add-on to glimepiride 4 mg + metformin 2 g</b>			<b>liraglutide 1.8 mg</b>	<b>placebo</b>	<b>insulin glargine</b>
n			232	113	234
Mean ± SD			8.3 ± 0.9	8.3 ± 0.9	8.2 ± 0.9
Median			8.2	8.2	8.1
Range					
<i>Note:</i> Baseline HbA1c was recorded at randomization.					
<i>Sources:</i> Clinical reports from Trial 1436 (Table 11-3), Trial 1572 (Table 11-3), Trial 1573 (Tables 11-2 and 14.1-4), Trial 1574 (Tables 11-2 and 14.1-4), Trial 1697 (Table 11-3)					

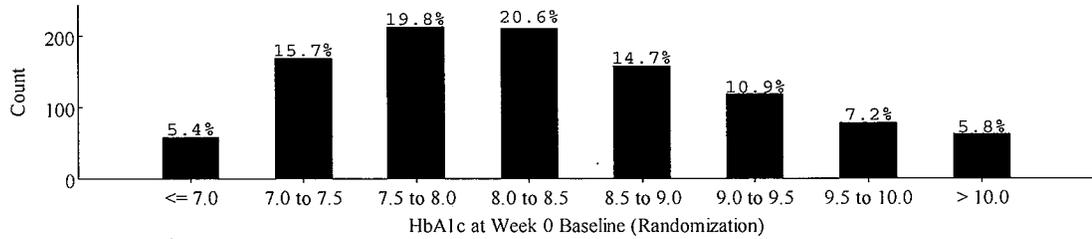
b(4)

FIGURE 7 Distribution of HbA1c at baseline

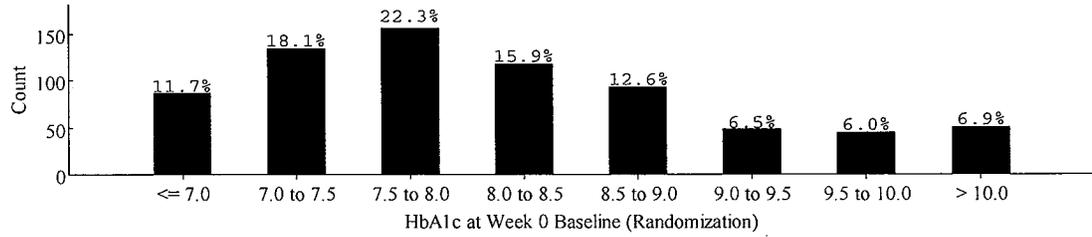
Trial  
1436



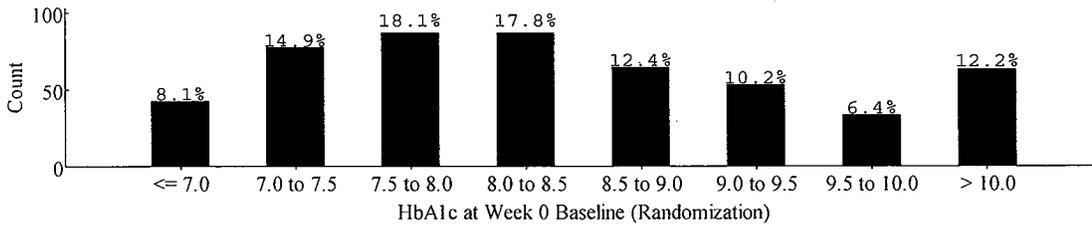
Trial  
1572



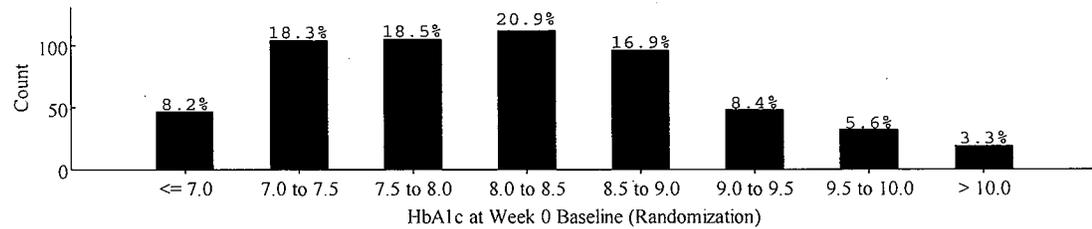
Trial  
1573



Trial  
1574



Trial  
1697



Source: Analysis by this reviewer

### 3.1.3. Analysis populations

All five studies used the same definitions for the analysis populations, with exceptions as described below:

Intention to Treat (ITT) analysis set: The ITT analysis set consisted of all randomized subjects who were exposed to at least one dose of trial product(s). Subjects were analyzed according to the randomized treatment assignment. For Trials 1436, 1572, 1574 and 1697, missing baseline values were not imputed, i.e., subjects without a baseline value of HbA1c were excluded from the analysis. For Trial 1573, missing values of HbA1c at baseline were imputed using the screening value, because there was no change in OAD medication between screening and randomization. For all five studies, subjects who discontinued early had their HbA1c level in the last assessment carried forward to the study endpoint. Similarly, subjects who were withdrawn early due to hyperglycemia (“ineffective therapy”; see TABLE 4) had the HbA1c level in the last assessment prior to withdrawal carried forward to the study endpoint.

A sensitivity analysis for the HbA1c endpoint used a modified version of the ITT analysis set, with no imputation for missing endpoint values of HbA1c.

Per Protocol analysis set (PP): The PP analysis set consisted of all exposed subjects who completed the blinded treatment period (week 26 for Trials 1436, 1572, 1574 and 1697, and week 52 for Trial 1573) with an evaluable HbA1c observation at that week, and who also had no major protocol violations. Subjects were analyzed according to the randomized treatment assignment.

Safety analysis set: The safety analysis set consisted of all randomized subjects who were exposed to at least one dose of trial product(s). If a subject received a different treatment than he/she was randomized to, data for the subject was analyzed, tabulated and/or listed according to the actual treatment he/she received.

### 3.1.4. Primary efficacy variable

The primary efficacy endpoint was the change from baseline in HbA1c after 26 weeks of treatment, for Trials 1436, 1572, 1574 and 1697, and after 52 weeks of treatment for Trial 1573.

### 3.1.5. Statistical analysis methods for primary efficacy endpoint

Primary analysis model: The primary analysis was performed for the ITT analysis set using analysis of covariance (ANCOVA). The primary model included study treatment, country and

previous anti-diabetic treatment stratification categories as fixed effects and baseline HbA1c as a covariate. Supportive analyses were conducted using the PP analysis set, and the modified ITT analysis set (with no imputation), using the same ANCOVA model.

Approach to multiplicity: With the concurrence of the Agency, the applicant used a gate-keeping strategy to control for the overall Type I error associated with the set of comparisons that was used to evaluate the efficacy of liraglutide within each study. The sequence of hypothesis tests for each study was pre-specified in the statistical analysis plan. They encompass comparisons of liraglutide arms against the comparators in each study. The pre-specified sequences do not include comparisons of the active control comparator against placebo comparator in Trials 1436, 1572 and 1697. These comparisons can be used to confirm the efficacy of the active control comparator under the conditions of the study but they were not included in the primary evaluation.

In the statistical analysis plan (SAP) that covered all five Phase 3 studies, the applicant described the hierarchical testing procedure that was used to protect the type I family-wide error. The following description is summarized from the SAP<sup>3</sup>:

Three factors were identified that contribute to multiple testing: (a) up to three different doses or liraglutide treatment in the trials; (2) up to two comparators in the trials; and (c) several secondary endpoints in addition to the primary endpoint.

For the primary HbA1c endpoint, the three doses of liraglutide were tested hierarchically for descending doses of liraglutide: (I) 1.8 mg liraglutide + add-on vs. comparator; (II) 1.2 mg liraglutide + add on vs. comparator; (III) 0.6 mg liraglutide + add-on vs. comparator, where “add-on” refers to the background antidiabetic therapy. The gate-keeping sequence meant that a hypothesis test for a given dose of liraglutide, of superiority or non-inferiority, would only be done if the hypotheses in the gate-keeping sequence were rejected for all higher ranked doses.

For the primary endpoint comparisons with two comparators (i.e., the active control arm and the placebo control arm), the comparisons were done hierarchically within each dose level: (I) Liraglutide + add-on vs. the placebo; (II) Liraglutide + add-on vs. the active control. This means that for the primary endpoint a given liraglutide dose was only tested against the active control if it was superior to the placebo control. Superiority to the placebo control was evaluated at a 2-tailed  $\alpha$  of 0.05, and non-inferiority to the active control was evaluated at a 1-tailed  $\alpha$  of 0.025.

In the event that a conclusion of non-inferiority to the active control is supported for a given dose of liraglutide, then that dose is tested for superiority to the active control. However, the outcome of the superiority evaluation is not part of the gate-keeping sequence.

The applicant noted that this procedure protects the Type I family-wise error at  $\alpha$  for the primary endpoint for each study.

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<sup>3</sup> See the Statistical Analysis Plan (Statistical Methods), Section 7.1

Body weight was a key secondary efficacy endpoint in all trials. Hypotheses for body weight were tested conditional on the outcome of the hypothesis tests for the primary endpoint. The SAP specified that the comparisons of liraglutide to the active comparator were of greatest clinical interest. Dunnett's method was used to protect the family-wise error among this set of pair-wise comparisons involving the active comparator.

### 3.1.6. Results of the statistical analysis of efficacy

Monotherapy: HbA1c at week 52 – baseline: Liraglutide 1.2 mg and 1.8 mg monotherapy produced reductions in HbA1c at week 52 compared to baseline that supported a conclusion of superior efficacy to glimepiride monotherapy ( $p < 0.01$ ; TABLE 8; Trial 1573). The net differences between the liraglutide arms and the glimepiride arm were 0.33 for liraglutide 1.2 mg and 0.62 for liraglutide 1.8 mg in the direction of a greater average reduction of HbA1c compared to glimepiride 8 mg. Analyses of the PP analysis set and the ITT analysis set at week 52 had similar results (not tabulated in this review).

Add-on therapy: HbA1c at week 26 – baseline: In general, all three doses of liraglutide resulted in a greater average reduction in HbA1c at week 26 compared to baseline when given as an add-on to the other anti-diabetic drugs. The net differences between the liraglutide add-on arms and the placebo add-on arms in the four phase 3 studies ranged from 0.78 to 1.36, in the direction of superior efficacy to liraglutide compared to placebo ( $p < 0.0001$ , TABLE 8; Trials 1436, 1572, 1574 and 1697). Specific results for each study are as follows:

*Trial 1572 (metformin background therapy):* The net differences between the liraglutide arms and the placebo arm were 0.78 for liraglutide 0.6 mg, 1.06 for liraglutide 1.2 mg and 1.09 for liraglutide 1.8 mg in the direction of a greater average reduction of HbA1c compared to the placebo arm (TABLE 8). The liraglutide 1.2 mg and 1.8 mg arms were non-inferior to the active comparator arm, glimepiride 4 mg. Analyses of the PP analysis set and the ITT analysis set at week 52 had similar results for the comparisons of liraglutide 1.2 mg and liraglutide 1.8 mg (not tabulated in this review).

The liraglutide 0.6 mg arm did not meet the criterion for non-inferiority to the active comparator arm, and in fact the 95% CI of this comparison was entirely in the region of inferiority to the active comparator arm (TABLE 8). However, the applicant noted that non-inferiority of liraglutide 0.6 mg to glimepiride was demonstrated when the analysis was performed on the PP analysis set and on the ITT/no LOCF analysis set, with the 95% CIs for treatment difference (0.01, 0.36) and (0.04, 0.38) respectively. These confidence intervals are entirely in the region of inferiority of liraglutide 0.6 mg to glimepiride, but the upper bound is less than the margin of 0.4. The applicant suggested that the difference in results between the analysis sets may be due to the larger percentage of early withdrawals due to ineffective therapy in the liraglutide 0.6 mg arm than in the glimepiride arm. For this reason, the applicant chose to evaluate the non-inferiority

of change in body weight for liraglutide 6 mg compared to glimepiride, even though doing so did not strictly follow the pre-specified procedure for evaluating this key secondary efficacy endpoint.

*Trial 1436 (glimepiride background therapy):* The net differences between the liraglutide arms and the placebo arm were 0.83 for liraglutide 0.6 mg, 1.31 for liraglutide 1.2 mg and 1.36 for liraglutide 1.8 mg in the direction of a greater average reduction of HbA1c compared to the placebo arm (TABLE 8). The liraglutide 1.2 mg and 1.8 mg arms were statistically significant in the direction of superiority to the active comparator arm, rosiglitazone 4 mg. The liraglutide 0.6 mg arm met the criterion for non-inferiority to the active comparator arm but was not statistically significant in the direction of superiority (TABLE 8). The same analysis model applied to the ITT analysis set but without data imputation, and on the PP analysis set demonstrated similar results (not tabulated in this review). It is important to note, however, that in this trial, the highest proposed doses of liraglutide are being compared to the half maximal dose of rosiglitazone. The choice of active comparator dose was based on manufacturer's recommendations and the approved doses at the time in the regions where the trial was conducted (21 non-U.S. sites). This explains the difference in rosiglitazone doses between Trial 1436 and Trial 1574 (4 vs. 8 mg/day). Therefore, one should be cautious in concluding that liraglutide is superior to rosiglitazone given at the maximal FDA approved dose.

*Trial 1574 (metformin + rosiglitazone background therapy):* The net differences between the liraglutide and the placebo arm were 0.94 for liraglutide 1.2 mg and 0.94 for liraglutide 1.8 mg in the direction of a greater average reduction of HbA1c compared to the placebo arm (TABLE 8). Analyses of the PP analysis set and the ITT analysis set at week 26 had similar results (not tabulated in this review).

*Trial 1697 (glimepiride + metformin background therapy):* The net difference between the liraglutide 1.8 mg arm and the placebo arm was 1.09 in the direction of a greater reduction of HbA1c compared to the placebo arm (TABLE 8). The liraglutide arm was statistically significant in the direction of superiority to the active comparator arm, insulin glargine (TABLE 8). The same analysis model applied to the ITT analysis set but without data imputation, and on the PP analysis set demonstrated similar results (not tabulated in this review).

I confirmed the results of the primary efficacy analysis from all five studies. The means and 95% confidence intervals of the net differences between the liraglutide arms and the placebo add-on arms, and between the liraglutide arms and the active comparator arms are depicted in FIGURE 8 for each study. The dose response relationship between the 0.6, 1.2 and 1.8 mg doses of liraglutide is illustrated in FIGURE 8. Although the studies were not powered for a comparison between liraglutide dose arms, and these comparisons were not included in the pre-specified sequential testing protocol, it can be noted that the 95% confidence intervals for the 1.2 mg and 1.8 mg dose arms are relatively similar in three of the four studies in which both doses were evaluated (Trials 1436, 1572 and 1574; FIGURE 8). In Trial 1573 the 95% confidence intervals of the 1.8 mg dose arms overlapped less with the 95% CI of the 1.2 mg dose in the direction of a

greater average reduction in HbA1c with the larger dose. The time course of mean HbA1c is illustrated for all five studies in FIGURE 9.

Post-hoc exploration of the active control compared to the placebo control. I conducted a post-hoc exploration of the active control arm in the three studies that were designed with both an active control and a placebo control arm. My purpose in doing this was to gain some insights into the pre-specified non-inferiority margin of 0.4 by comparing it to the placebo-adjusted effect of the active control arm. In doing so I acknowledge the limitations of this assessment compared to a full assessment of historical placebo-controlled studies that would be used to establish the non-inferiority margin for an antidiabetic drug. In addition, from a practical perspective, the assay sensitivity of the active control drugs in these Phase 3 studies was not a review issue, the results supported the superiority of liraglutide 1.2 mg and 1.8 mg compared to the active control.

*Trial 1572 (metformin background therapy):* The placebo-adjusted mean effect of glimepiride 4 mg was statistically significantly different from 0, and was similar to the placebo-adjusted effects of glimepiride (1 to 8 mg; -1.1, -1.9 and -1.9) in the clinical studies reported in the Amaryl™ label<sup>4</sup> (TABLE 9).

*Trial 1436 (glimepiride background therapy):* The placebo-adjusted mean effect of the active control comparator, rosiglitazone 4 mg, was statistically significantly different from 0 (TABLE 9). The mean effect was smaller than the effects reported in the Avandia™ label (-1.1 and -0.9, reported in Table 5 of the Avandia label, for combination studies of Avandia plus sulfonylurea in 24 to 26 weeks. The smaller effect may be due to the population of Trial 1436 which included patients in reasonable glycemic control.

*Trial 1697 (glimepiride + metformin background therapy):* Placebo-adjusted effects of insulin glargine are not reported in the Lantus™ label. Given that insulin can be titrated to effect, the placebo-adjusted mean effect of insulin glargine in this study is challenging to interpret beyond noting that it was statistically significantly different from 0 (TABLE 9).

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<sup>4</sup> The placebo-adjusted effects are not available on the Amaryl label, but are reported in references to the clinical studies used to support the approval of Amaryl; Schade, et al. 1998, J Clin Pharmacol 38:636-641; Goldberg et al. 1996 Diabetes Care 19: 849-856; and Rosenstock et al. 1996, Diabetes Care 19: 1194-1997.

TABLE 8 Analysis of HbA1c, change from baseline (LOCF, ITT analysis set)

	N	LS Mean	SEM	Placebo			Comparator#		
				LS Mean Treatment Diff	95% CI	P-value	LS Mean Treatment Diff	95% CI	P-value
Trial 1573									
Liraglutide 1.2 mg	236	-0.84	(0.080)				-0.33	[-0.53; -0.13]	0.0014
Liraglutide 1.8 mg	234	-1.14	(0.081)				-0.62	[-0.83; -0.42]	<.0001
Comparator	241	-0.51	(0.077)						
Trial 1572									
Liraglutide 0.6 mg	239	-0.70	(0.067)	-0.78	[-0.99; -0.57]	<.0001	0.29	[0.12; 0.46]	0.0009
Liraglutide 1.2 mg	232	-0.97	(0.069)	-1.06	[-1.27; -0.85]	<.0001	0.01	[-0.16; 0.19]	0.8775
Liraglutide 1.8 mg	236	-1.00	(0.066)	-1.09	[-1.30; -0.88]	<.0001	-0.02	[-0.19; 0.15]	0.8592
Placebo	120	0.08	(0.090)						
Comparator	234	-0.99	(0.068)						
Trial 1436									
Liraglutide 0.6 mg	224	-0.60	(0.071)	-0.83	[-1.07; -0.60]	<.0001	-0.16	[-0.35; 0.02]	0.0857
Liraglutide 1.2 mg	223	-1.08	(0.072)	-1.31	[-1.54; -1.08]	<.0001	-0.64	[-0.92; -0.45]	<.0001
Liraglutide 1.8 mg	226	-1.13	(0.072)	-1.36	[-1.60; -1.13]	<.0001	-0.69	[-0.88; -0.51]	<.0001
Placebo	107	0.23	(0.100)						
Comparator	224	-0.44	(0.071)						
Trial 1574									
Liraglutide 1.2 mg	174	-1.48	(0.078)	-0.94	[-1.12; -0.76]	<.0001			
Liraglutide 1.8 mg	177	-1.48	(0.075)	-0.94	[-1.12; -0.75]	<.0001			
Placebo	167	-0.54	(0.080)						
Trial 1697									
Liraglutide 1.8 mg	224	-1.33	(0.088)	-1.09	[-1.28; -0.90]	<.0001	-0.24	[-0.39; -0.08]	0.0029
Placebo	110	-0.24	(0.106)						
Comparator	225	-1.09	(0.090)						

The P-values corresponds to a two-sided test for superiority on a 5% significant level (statistical significance for p <0.05).

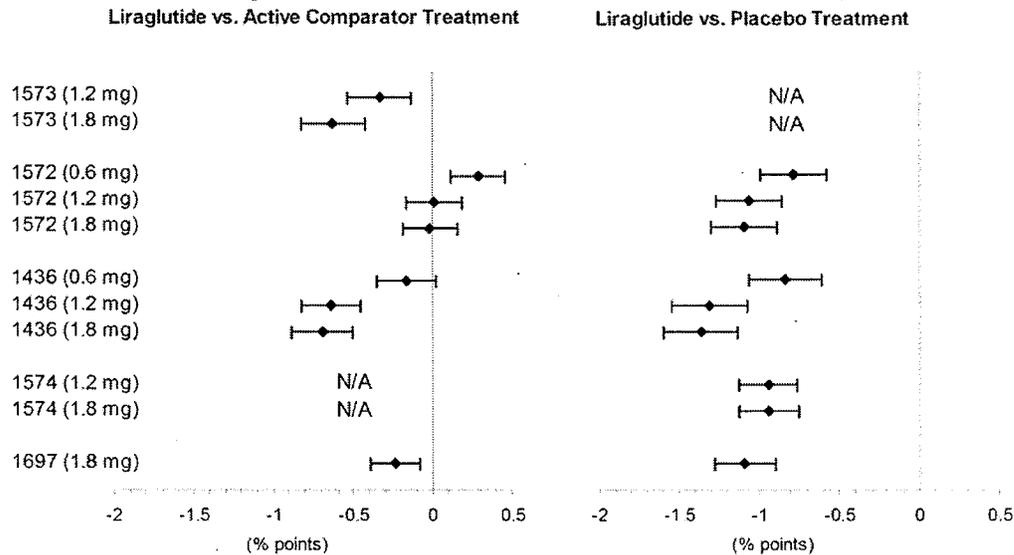
# Test for non-inferiority with switch to superiority if non-inferiority is shown.

Non-inferiority is concluded if the upper limit of the 95% confidence interval for the treatment difference is below 0.4%, i.e. non-inferiority to comparator is shown for all liraglutide groups, except for the 0.6mg liraglutide group in trial 1572.

A hierarchical testing procedure is used.

Source: Clinical Overview, Table 4-2

FIGURE 8 Forest plot of HbA1c, estimated mean difference ± 95% CI (LOCF, ITT analysis set)



Source: Clinical Overview, Figure 4-1

FIGURE 9 Mean HbA1c over time in the five phase 3 studies

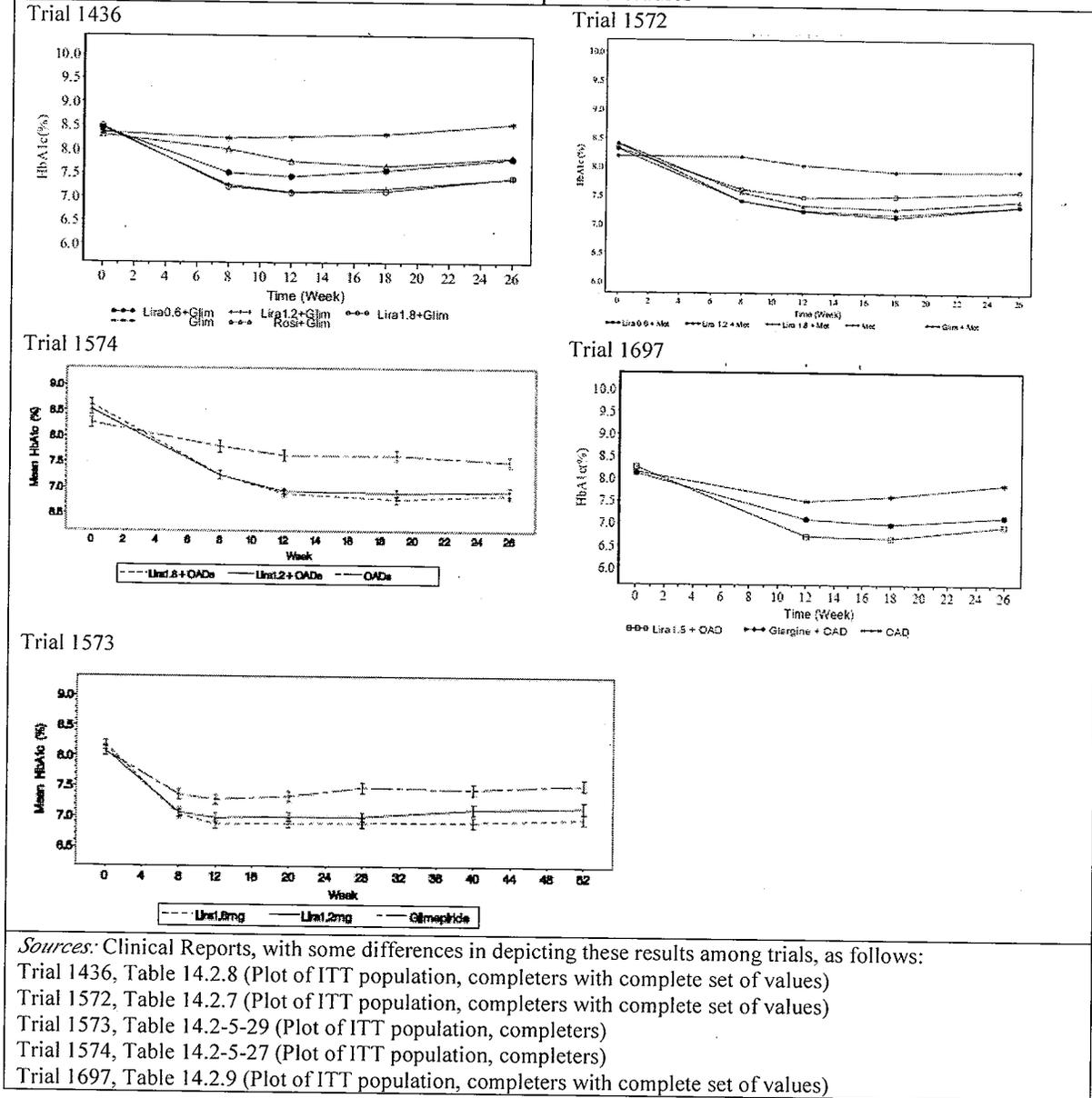


TABLE 9 Comparison of active control comparator arm with placebo control arm, HbA1c primary endpoint (change from baseline), ANCOVA primary model, LOCF/ICC primary analysis population

	Active Control Comparator Arm		Placebo Control Arm		Active - Placebo		p-value	
	N	LSMean	SE	N	LSMean	95% CI		
<b>Trial 1436 (26 weeks)</b>	224	-0.44	0.07	107	0.23	0.10	(-0.90, -0.44)	<0.0001
rosiglitazone 4 mg + glimepiride 4 mg				glimepiride 4 mg				
<b>Trial 1572 (26 weeks)</b>	234	-0.98	0.07	120	0.09	0.09	(-1.28, -0.86)	<0.0001
glimepiride 4 mg + metformin 2 g				metformin 2 g				
<b>Trial 1697 (26 weeks)</b>	225	-1.09	0.09	110	-0.24	0.11	(-1.04, -0.66)	<0.0001
insulin glargine + glimepiride 4 mg + metformin 2 g				glimepiride 4 mg + metformin 2 g				

Sources: Clinical Reports from Trial 1436 (Table 14.2.16), Trial 1572 (Table 14.2.15), Trial 1697 (Table 14.2.17)

### 3.1.7. Other Efficacy Endpoints: Body Weight

Body weight was pre-specified as a key secondary efficacy endpoint in the phase 3 studies. With 43% to 74% of subjects in the five studies classified as obese at baseline with a BMI  $\geq 30$  kg/m<sup>2</sup> (EXHIBIT 1-EXHIBIT 5), weight loss or gain is an important consideration. In my opinion, the results from the phase 3 studies support the conclusion that liraglutide is associated with an average net loss in weight at 26 weeks or at 52 weeks compared to several of the oral antidiabetic therapies used in the phase 3 studies. An overview of the weight change at study endpoint compared to baseline in the five phase 3 studies is given in FIGURE 10.

Liraglutide monotherapy resulted in an average net weight loss of 3.2 kg (liraglutide 1.2 mg) and 3.6 kg (liraglutide 1.8 mg) after 52 weeks, compared to glimepiride monotherapy (EXHIBIT 3; Trial 1573). However, liraglutide as an add-on to glimepiride did not result in an additional weight loss at 26 weeks compared to glimepiride monotherapy (EXHIBIT 1; Trial 1436). The liraglutide arms did result in a average net weight loss ranging from 1.4 kg to 2.3 kg compared to the rosiglitazone arm (EXHIBIT 1). This finding is consistent with findings reported elsewhere concerning the potential for rosiglitazone to cause a weight gain.

Liraglutide as an add-on to background antidiabetic therapies resulted in an average net weight loss ranging from 1.1 kg to 3.4 kg (EXHIBIT 2 - EXHIBIT 5).

About half of the subjects in the liraglutide arms (ranging from 40% to 62%) lost from 0 to 5% of their baseline body weight at the study endpoint. The percentage of subjects who lost 5% or more ranged from 4% to 33%, and the percentage of subjects who gained weight ranged from 17% to 54% across the liraglutide arms of the phase 3 studies (EXHIBIT 1-EXHIBIT 5). The summaries reported in EXHIBIT 1-EXHIBIT 5 are based on the ITT/LOCF analysis set. The applicant provided additional summaries based on the subset of ITT subjects who completed the study, and concluded that the two analysis sets resulted in similar findings. I evaluated a selection of these additional summaries and agree that the set of completers and the ITT/LOCF analysis set produce similar results with respect to body weight.

EXHIBIT 1 Body weight at baseline and change from baseline in Trial 1436

Trial 1436 add-on to glimepiride 4 mg	liraglutide 0.6 mg	liraglutide 1.2 mg	liraglutide 1.8 mg	placebo	rosiglitazone 4 mg
<b>n in ITT analysis set</b>	233	228	234	114	231
<b>Baseline BMI categories (kg/m<sup>2</sup>)</b>					
< 25	37 (15.9%) <sup>1</sup>	39 (17.1%)	37 (11.1%)	16 (14.0%)	49 (21.2%)
25-30	85 (36.5%)	89 (39.0%)	93 (39.7%)	43 (37.7%)	82 (35.5%)
30-35	74 (31.8%)	55 (24.1%)	69 (29.5%)	34 (29.8%)	66 (28.6%)
≥ 35	36 (15.5%)	45 (19.7%)	34 (14.5%)	21 (18.4%)	33 (14.3%)
<b>Baseline Body weight (kg)</b>					
Mean ± SD	82.6 ± 17.7	80.0 ± 17.1	83.0 ± 18.1	81.9 ± 17.1	80.6 ± 17.0
Median	82.0	79.0	81.0	81.0	79.6
Min, Max	43.5, 183.1	40.3, 124.0	43.6, 138.0	50.0, 135.0	51.0, 130.0
<b>Change from baseline at 26-week endpoint (LOCF)</b>					
LS Mean ± SEM	0.72 ± 0.20	0.32 ± 0.20	-0.23 ± 0.20	-0.10 ± 0.27	2.11 ± 0.20
<i>Net Change vs. Glimepiride arm</i>					
LSMean, 95% CI, p-value <sup>2</sup>	0.82 (0.04, 1.60) p=0.0355	0.42 (-0.37, 1.20) p=0.4546	-0.14 (-0.92, 0.64) p=0.9702		
<i>Net Change vs. Rosiglitazone + Glimepiride arm</i>					
LSMean, 95% CI, p-value <sup>2</sup>	-1.38 (-2.03, -0.74) p<0.0001	-1.79 (-2.44, -1.13) p<0.0001	-2.34 (-2.99, -1.69) p<0.0001		
<b>Weight loss as a % of baseline weight (% of ITT set; LOCF)</b>					
No weight loss	126 (54.1%) <sup>1</sup>	110 (48.2%)	98 (41.9%)	46 (40.4%)	171 (74.0%)
0% to < 5%	92 (39.5%)	104 (45.6%)	109 (46.6%)	59 (51.8%)	52 (22.5%)
5% to < 10%	13 (5.6%)	8 (3.5%)	23 (9.8%)	7 (6.1%)	6 (2.6%)
≥ 10%	0 (0.0%)	2 (0.9%)	2 (0.9%)	0 (0.0%)	0 (0.0%)

Mean of Body Weight (kg) by Treatment and Week  
ITT Analysis Set  
Completers with Complete Set of Values

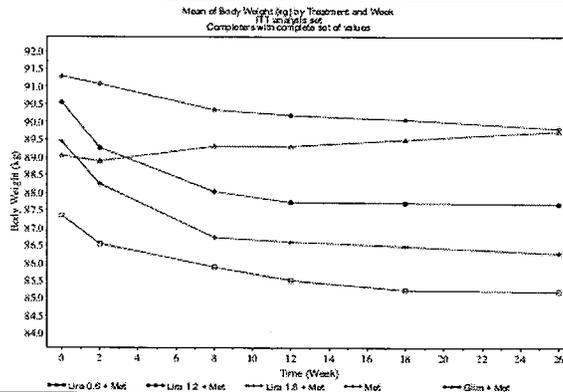
Legend:  
 ●●● Lira0.6+Glim    ●●● Lira1.2+Glim    ●●● Lira1.8+Glim  
 ○○○○ Placebo    ●●● Rosi+Glim

Sources: Clinical report from Trial 1436 (Table 11-15, Table 11-16, Table 11-17, Table 11-18, Figure 14.2.36)  
 (Plot of mean body weight in kg by treatment and week, ITT population, completers with complete set of values)

Notes:  
<sup>1</sup> Percentage of the ITT analysis set  
<sup>2</sup> ANCOVA model with treatment, country, previous treatment as fixed effects and baseline weight as covariate.

EXHIBIT 2 Body weight at baseline and change from baseline in Trial 1572

Trial 1572 add-on to metformin 2 g	liraglutide 0.6 mg	liraglutide 1.2 mg	liraglutide 1.8 mg	placebo	glimepiride 4 mg
<b>n in ITT analysis set</b>	242	240	242	121	242
<b>Baseline BMI categories (kg/m<sup>2</sup>)</b>					
< 25	33 (13.6%) <sup>1</sup>	22 (9.2%)	23 (9.5%)	8 (6.6%)	20 (8.3%)
25-30	84 (34.7%)	85 (35.4%)	86 (35.5%)	33 (27.3%)	79 (32.6%)
30-35	78 (32.2%)	72 (30.0%)	80 (33.1%)	50 (41.3%)	91 (37.6%)
≥ 35	47 (19.4%)	61 (25.4%)	53 (21.9%)	29 (24.0%)	50 (20.7%)
<b>Baseline Body weight (kg)</b>					
Mean ± SD	87.8 ± 17.1	88.5 ± 19.1	88.0 ± 16.3	91.0 ± 17.0	89.0 ± 16.8
Median	86.2	87.3	88.5	91.8	89.7
Min, Max	43.5, 141.0	43.4, 151.0	48.1, 135.2	52.5, 132.0	42.0, 148.0
<b>Change from baseline at 26-week endpoint (LOCF)</b>					
LS Mean ± SEM	-1.78 ± 0.23	-2.58 ± 0.24	-2.79 ± 0.23	-1.51 ± 0.31	0.95 ± 0.23
<i>Net Change vs. Metformin arm</i>					
LSMean, 95% CI, p-value <sup>2</sup>	-0.28 (-1.15, 0.60) p=0.8198	-1.07 (-1.94, -0.19) p=0.0117	-1.29 (-2.16, -0.41) p=0.0016		
<i>Net Change vs. Glimepiride + Metformin arm</i>					
LSMean, 95% CI, p-value <sup>2</sup>	-2.73 (-3.47, -2.00) p<0.0001	-3.53 (-4.27, -2.79) p<0.0001	-3.75 (-4.48, -3.01) p<0.0001		
<b>Weight loss as a % of baseline weight (% of ITT set; LOCF)</b>					
No weight loss	55 (22.7%) <sup>1</sup>	35 (14.6%)	40 (16.5%)	30 (24.8%)	149 (61.6%)
0% to < 5%	139 (57.4%)	148 (61.7%)	121 (50.0%)	71 (58.7%)	71 (29.3%)
5% to < 10%	45 (18.6%)	40 (16.7%)	66 (27.3%)	16 (13.2%)	16 (6.6%)
≥ 10%	3 (1.2%)	13 (5.4%)	14 (5.8%)	4 (3.3%)	1 (0.4%)



Sources: Clinical reports from Trial 1572 (Table 11-14, Table 11-15, Table 11-16, Table 11-17, Figure 14.2.39 (Plot of mean body weight in kg by treatment and week, ITT population, completers with complete set of values))

Notes:

<sup>1</sup> Percentage of the ITT analysis set

<sup>2</sup> ANCOVA model with treatment, country, previous treatment as fixed effects and baseline weight as covariate.

EXHIBIT 3 Body weight at baseline and change from baseline in Trial 1573

Trial 1573 monotherapy	liraglutide 1.2 mg	liraglutide 1.8 mg	glimepiride 8 mg
n in ITT analysis set	251	246	248
<b>Baseline BMI categories (kg/m<sup>2</sup>)</b>			
< 25	17 (6.8%) <sup>1</sup>	20 (8.1%)	15 (6.0%)
25-30	59 (23.5%)	73 (29.7%)	57 (23.0%)
30-35	90 (35.9%)	64 (26.0%)	84 (33.9%)
≥ 35	79 (31.5%)	83 (33.7%)	92 (37.1%)
<b>Baseline Body weight (kg)</b>			
Mean ± SD	92.1 ± 19.0	92.6 ± 20.8	93.3 ± 19.0
Median	90.3	89.4	92.2
Min, Max	50.3, 154.0	49.9, 163.3	46.7, 159.2
<b>Change from baseline at 52-week endpoint (LOCF)</b>			
LS Mean ± SEM <sup>2</sup>	-2.05 ± 0.28	-2.45 ± 0.28	1.12 ± 0.27
<i>Net Change vs. Glimepiride arm</i>			
LSMean, 95% CI, p-value <sup>2</sup>	-3.17 (-3.87, -2.47) p<0.0001	-3.57 (-4.28, -2.87) p<0.0001	
<b>Weight loss as a % of baseline weight (% of ITT set; LOCF)</b>			
No weight loss	66 (26.3%) <sup>1</sup>	60 (24.4%)	154 (62.1%)
0% to < 5%	125 (49.8%)	116 (47.2%)	81 (32.7%)
5% to < 10%	42 (16.7%)	51 (20.7%)	11 (4.4%)
≥ 10%	12 (4.8%)	13 (5.3%)	2 (0.8%)

**Plot of Mean Body Weight (kg) Over Time by Treatment, Completers – ITT Population**

The graph displays the mean body weight in kilograms for completers in the ITT population over a 52-week period. Three treatment groups are compared: Liraglutide 1.8mg (dashed line), Liraglutide 1.2mg (solid line), and Glimepiride (dotted line). All groups start at a mean weight of approximately 92-93 kg at week 0. The Liraglutide 1.2mg group shows a steady decline, reaching approximately 89.5 kg by week 52. The Liraglutide 1.8mg group shows a similar but slightly less pronounced decline, ending at approximately 90.5 kg. The Glimepiride group shows a slight increase in weight, ending at approximately 94.5 kg. Error bars represent standard error of the mean (SEM) at each time point.

*Sources:* Clinical reports from Trial 1573 (Table 11-8, Table 11-9, Table 11-10, Table 14.2-6-6, Figure 14.2-6-17  
(Plot of mean body weight in kg by treatment and week, ITT population, completers))

*Notes:*

<sup>1</sup> Percentage of the ITT analysis set

<sup>2</sup> ANCOVA model with treatment, country, previous treatment as fixed effects and baseline weight as covariate.

EXHIBIT 4 Body weight at baseline and change from baseline in Trial 1574

Trial 1574 add-on to metformin 2 g + rosiglitazone 8 mg (4 mg BID) n in ITT analysis set	liraglutide 1.2 mg	liraglutide 1.8 mg	placebo
n in ITT analysis set	177	178	175
<b>Baseline BMI categories (kg/m<sup>2</sup>)</b>			
< 25	10 (5.6%) <sup>1</sup>	7 (3.9%)	8 (4.6%)
25-30	45 (25.4%)	41 (23.0%)	35 (20.0%)
30-35	66 (37.3%)	63 (35.4%)	66 (37.7%)
≥ 35	55 (31.1%)	67 (37.6%)	64 (36.6%)
<b>Baseline Body weight (kg)</b>			
Mean ± SD	95.3 ± 18.3	94.9 ± 19.2	98.5 ± 18.2
Median	93.7	93.4	96.4
Min, Max	54.2, 152.0.6	52.4, 160.6	53.1, 150.1
<b>Change from baseline at 52-week endpoint (LOCF)</b>			
LS Mean ± SEM <sup>2</sup>	-1.01 ± 0.33	-2.02 ± 0.32	0.60 ± 0.34
<i>Net Change vs. Metformin + Rosiglitazone arm</i>			
LSMean, 95% CI, p-value <sup>2</sup>	-1.62 (-2.39, -0.85) p<0.0001	-2.62 (-3.39, -1.84) p<0.0001	
<b>Weight loss as a % of baseline weight (% of ITT set; LOCF)</b>			
No weight loss	59 (33.3%) <sup>1</sup>	36 (20.2%)	87 (49.7%)
0% to < 5%	83 (46.9%)	99 (55.6%)	72 (41.1%)
5% to < 10%	29 (16.4%)	38 (21.3%)	12 (6.9%)
≥ 10%	5 (2.8%)	5 (2.8%)	2 (1.1%)

**Plot of Mean Body Weight (kg) Over Time by Treatment, Completers – ITT Population**

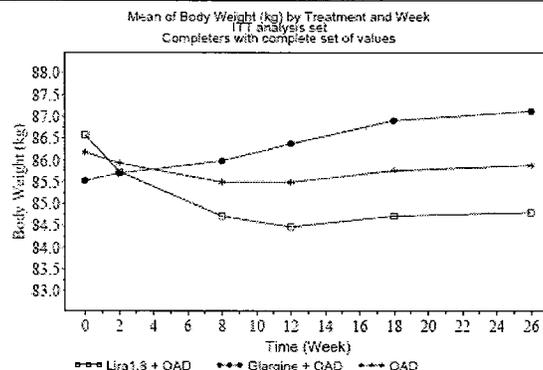
Legend: --- Liraglutide 1.8 mg + OADs    — Liraglutide 1.2 mg + OADs    ··· OADs

Sources: Clinical reports from Trial 1574 (Table 11-8, Table 11-9, Table 11-10, Table 14.2-6-6, Table 14.2-6-17)  
 (Plot of mean body weight in kg by treatment and week, ITT population, completers)

Notes:  
<sup>1</sup> Percentage of the ITT analysis set  
<sup>2</sup> ANCOVA model with treatment, country, previous treatment as fixed effects and baseline weight as covariate.

EXHIBIT 5 Body weight at baseline and change from baseline in Trial 1697

Trial 1697 add-on to glimepiride 4 mg + metformin 2 g	liraglutide 1.8 mg	placebo	insulin glargine
<b>n in ITT analysis set</b>	230	114	232
<b>Baseline BMI categories (kg/m<sup>2</sup>)</b>			
< 25	38 (16.5%) <sup>1</sup>	11 (9.6%)	33 (14.2%)
25-30	79 (34.3%)	39 (34.2%)	87 (37.7%)
30-35	71 (30.9%)	40 (35.1%)	68 (29.3%)
≥ 35	42 (18.3%)	23 (20.2%)	43 (18.5%)
<b>Baseline Body weight (kg)</b>			
Mean ± SD	85.8 ± 19.3	85.4 ± 16.3	85.2 ± 17.9
Median	83.7	85.9	84.0
Min, Max	50.4, 149.5	56.9, 132.2	45.6, 136.0
<b>Change from baseline at 26-week endpoint (LOCF)</b>			
LS Mean ± SEM <sup>2</sup>	-1.81 ± 0.33	-0.42 ± 0.39	1.62 ± 0.33
<b>Net Change vs. Glimepiride + Metformin arm</b>			
LSMean, 95% CI, p-value <sup>2</sup>	-1.39 (-2.10, -0.69) p=0.0001		
<b>Net Change vs. Glimepiride arm +Metformin + Insulin Glargine arm</b>			
LSMean, 95% CI, p-value	-3.43 (-4.00, -2.86) p<0.0001		
<b>Weight loss as a % of baseline weight (% of ITT set; LOCF)</b>			
No weight loss	64 (27.8%) <sup>1</sup>	47 (41.2%)	166 (71.6%)
0% to < 5%	110 (47.8%)	55 (48.2%)	55 (23.7%)
5% to < 10%	48 (20.9%)	9 (7.9%)	4 (1.7%)
≥ 10%	5 (2.2%)	2 (1.8%)	2 (0.9%)



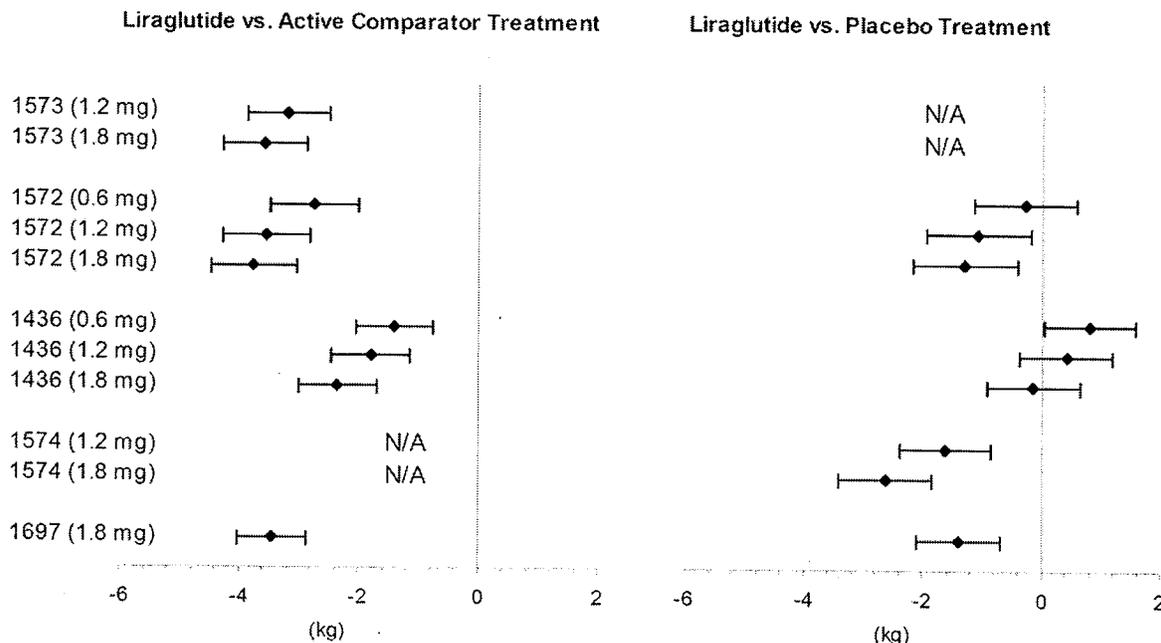
Sources: Clinical reports from Trial 1697 (Table 11-16, Table 11-17, Table 11-18, Table 11-19, Figure 14.2.37)  
(Plot of mean body weight in kg by treatment and week, ITT population, completers with complete set of values)

Notes:

<sup>1</sup> Percentage of the ITT analysis set

<sup>2</sup> ANCOVA model with treatment, country, previous treatment as fixed effects and baseline weight as covariate.

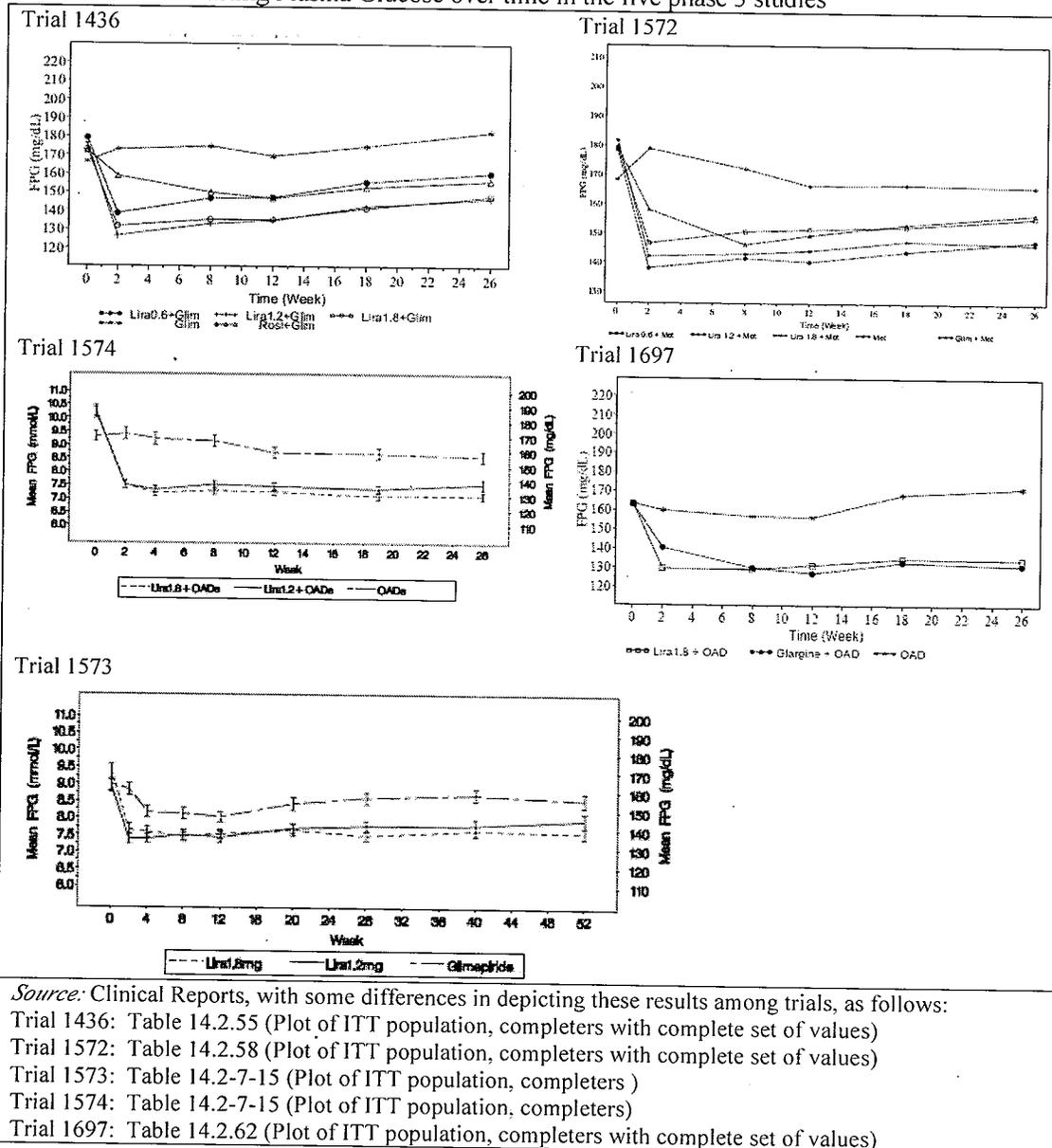
FIGURE 10 Forest plot of body weight (kg), estimated mean difference  $\pm$  95% CI (LOCF, ITT analysis set)



Source: Clinical Overview, Figure 4-2

**Fasting Plasma Glucose (FPG):** Treatment with liraglutide in the five phase 3 studies resulted in a decrease in mean FPG compared to baseline over the first 2-4 weeks of the double blind period, followed by a steady increase over the remaining period of the studies (FIGURE 11). In general, the active control arm followed a similar pattern. The placebo add-on arm did not show a decrease in mean FPG in the first 2-4 weeks. This pattern is supportive of the efficacy of liraglutide as monotherapy and as an add-on to background therapy with the other anti-diabetic drugs used in these studies.

FIGURE 11 Fasting Plasma Glucose over time in the five phase 3 studies



### 3.2 Evaluation of Safety

Liraglutide was the topic of a meeting of the Endocrine and Metabolic Drug Advisory Committee meeting on April 2, 2009. The primary focus was on issues surrounding the safety of liraglutide. An earlier version of this statistics review was provided as a briefing document to the committee on the efficacy of liraglutide. The briefing document for the safety issues, "A Joint Clinical/Statistical Review of Cardiovascular Events and Thyroid Tumors," was written by Karen Mahoney, M.D., and this reviewer. My contribution included a discussion of several statistical methods used to calculate the incidence ratio and associated 95% confidence interval of MACE (Major Adverse Cardiovascular Events) events. I used these methods to analyze and compare the upper 95% confidence bound for the incidence of MACE events in liraglutide-treated patients compared to the incidence in comparator-treated patients, using different versions of the study population and different definitions of the MACE endpoint. These results, along with results provided by the sponsor, illustrated the extent to which the estimates of the upper 95% confidence bound of the risk ratio were sensitive to choice of method, study population and definition of MACE endpoint. This upper bound is compared to non-inferiority margins of 1.8 and 1.3, as specified in the 2008 guidance, "Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes." These margins represent critical decision points regarding the cardiovascular safety of a diabetes therapy.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age

In order to focus on the comparison of "liraglutide vs. comparator" in subgroups of the studies, I combined the liraglutide dose groups together. In addition, because the large majority of patients in each study were Caucasian, I combined all of the non-Caucasian race groups for a "Caucasian vs non-Caucasian" comparison. Results of these comparisons are depicted graphically in FIGURE 12-FIGURE 14. For a more detailed summary of the HbA1c efficacy endpoint in the full set of treatment groups and the full set of racial groups in each study, see the Appendix, TABLE 10 - TABLE 19.

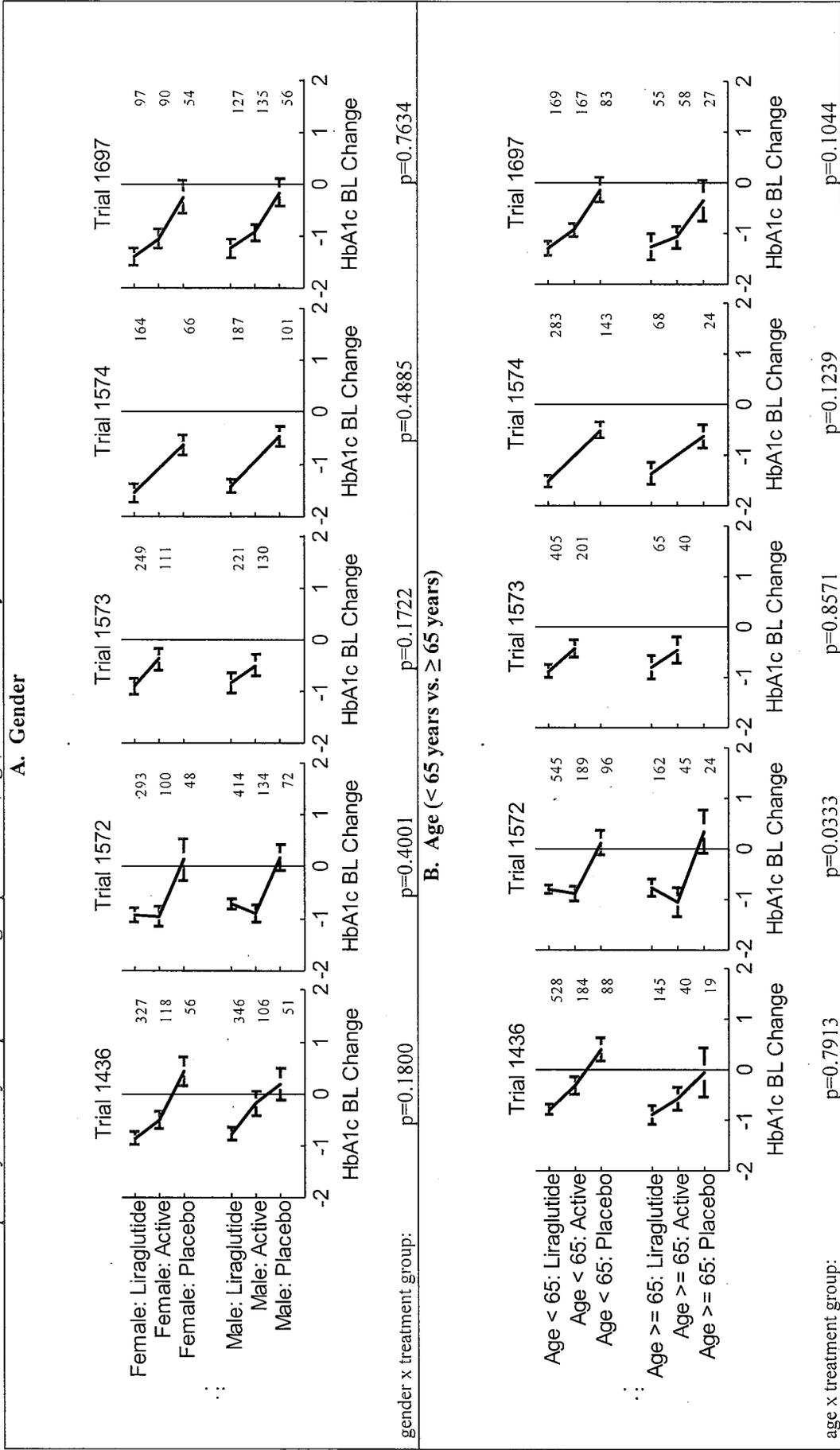
Across the five key studies, the average HbA1c response to liraglutide vs. comparator was not consistently affected by age group, gender, race or ethnicity. Most of the p-values of the interactions of these factors with treatment group were greater than 0.1 (FIGURE 12). In my opinion, the few p-values that were less than 0.1 were not consistent among studies, as follows:

- Age group (< 65 years and ≥ 65 years) by treatment group (liraglutide vs comparator(s)): The interaction of age group by treatment group in Trial 1572 (add-on to metformin) had a p-value of 0.0033. However, the treatment comparison of liraglutide vs. comparator appeared

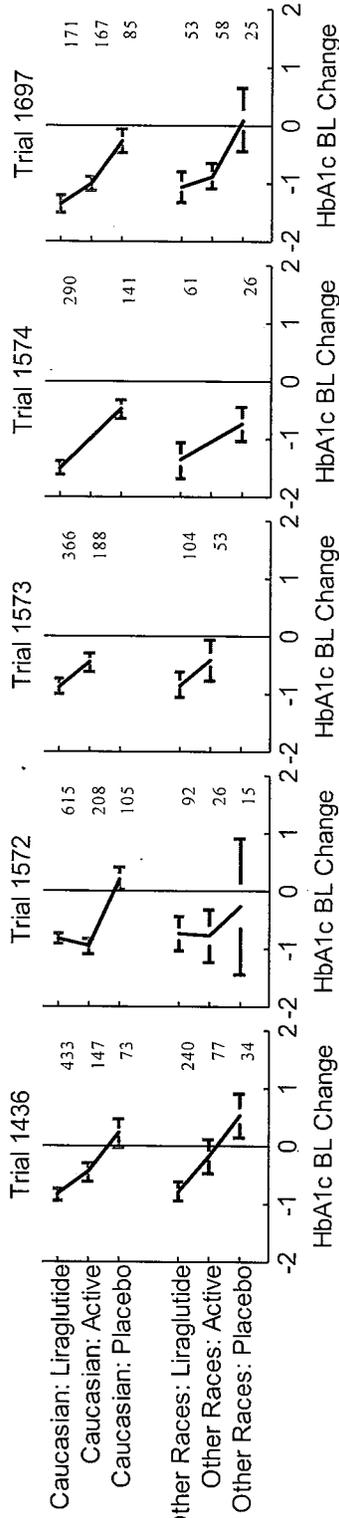
to be relatively similar between the two age groups (< 65 years and  $\geq$  65 years; FIGURE 12B). This interaction was not significant in the other four studies. For this reason I do not believe that this one low p-value signaled an important effect of age on the efficacy of liraglutide.

- Race group (Caucasian and all other non-Caucasian groups combined) by treatment group (liraglutide vs comparator(s)): The interaction of race by treatment group had a p-value < 0.1 in one study (FIGURE 12C). This result was not consistent between the two studies that had a similar composition of non-Caucasian racial groups. Two studies had “Black” as the predominant group among the non-Caucasian racial groups (TABLE 6). The p-value of the race by treatment group was 0.7011 in Trial 1573 and 0.0518 in Trial 1574. Because of this lack of consistency, I do not believe that one low p-value signaled an important effect of race on the efficacy of liraglutide.

FIGURE 12 HbA1c primary efficacy endpoint in subgroups: Gender, age, race and ethnicity

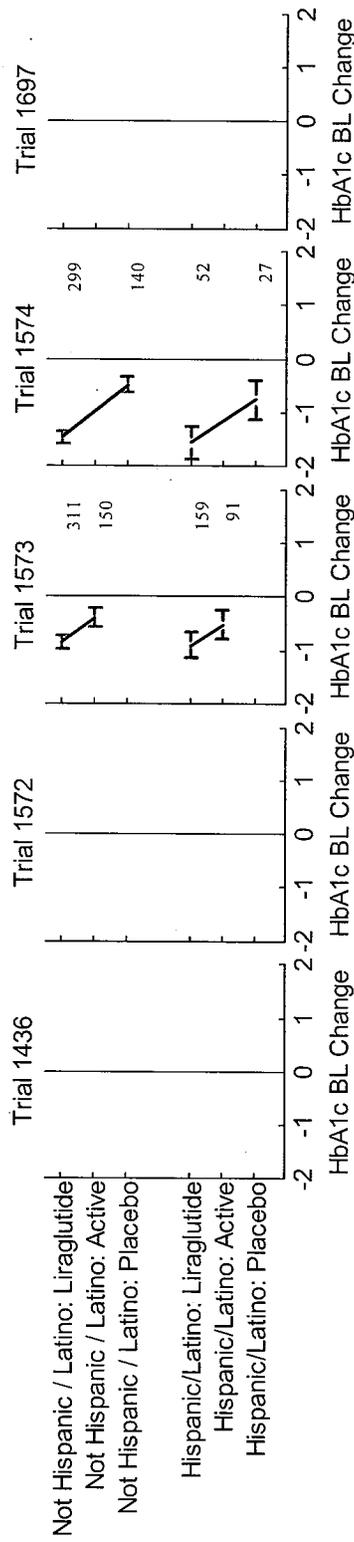


**C. Race (Caucasian vs. Other races combined)**



race by treatment group: p=0.1141 p=0.4424 p=0.7011 p=0.0518 p=0.3379

**D. Ethnicity (Hispanic / Latino vs. not Hispanic / Latino, for Trials 1573 and 1574 only)**



ethnicity by treatment group: (ethnicity not recorded) (ethnicity not recorded) p=0.4940 p=0.4112 (ethnicity not recorded)

*Notes:*

Shown on the graphs are the t-intervals (mean and 95% confidence interval) for HbA1c change from baseline for each subgroup category. The treatment groups in the original study design were combined into all liraglutide groups and all comparator groups. The p-values are from the analysis of covariance model with the following general form: country, baseline HbA1c, combined treatment groups (i.e., liraglutide group and comparator group), subgroup and subgroup by combined treatment group interaction. Only Trials 1573 and 1574 recorded the ethnicity category.

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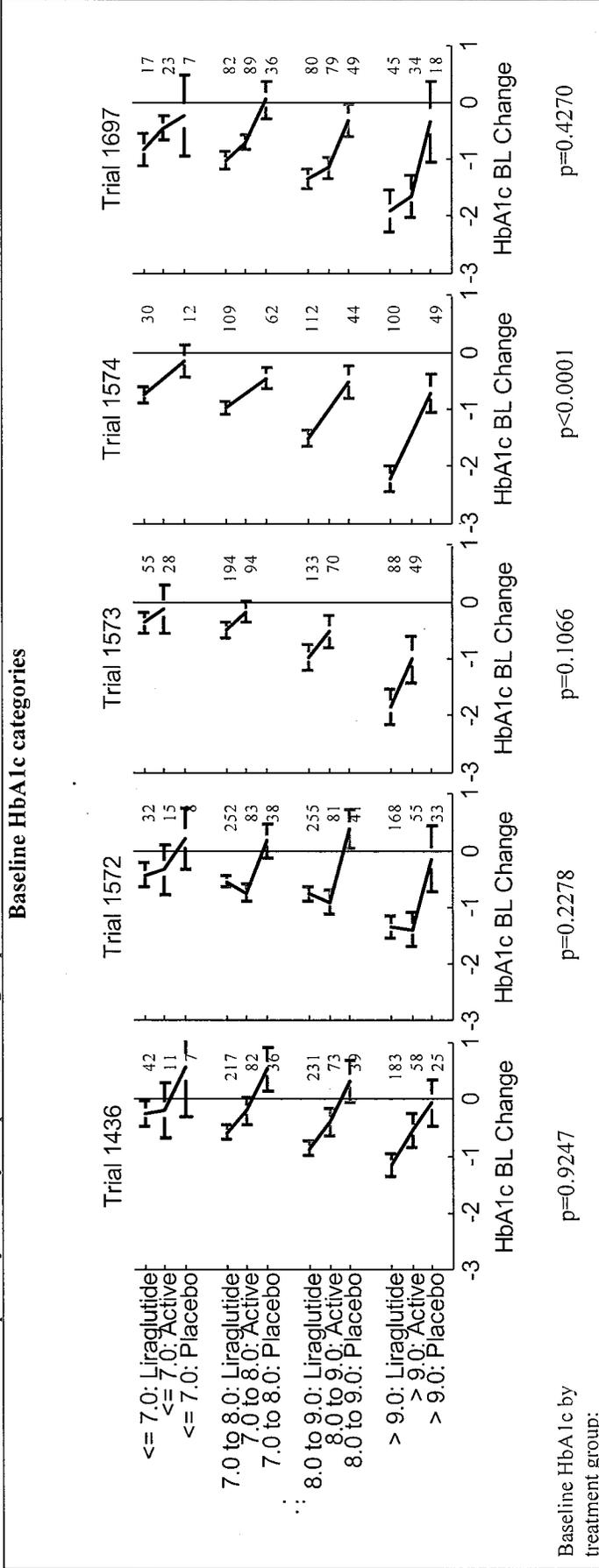
## 4.2 Other Special/Subgroup Populations

Baseline HbA1c: Across the five key studies, subjects in subgroups with higher baseline HbA1c values generally had greater average reductions in HbA1c compared to subjects in subgroups with lower baseline HbA1c values in the liraglutide arms (Figure 13). This relationship is illustrated not only in the liraglutide groups, but also in the arms with other antidiabetic drugs, including the placebo comparator groups and the active control comparator groups. Several explanations are consistent with this finding: (1) The antidiabetic drugs may all promote a greater reduction in HbA1c in subjects with higher baseline values; (2) The regression to the mean effect will tend to cause a greater change from baseline in subjects who had higher than average HbA1c levels at baseline by chance; and (3) The general improvement in diabetes care and management in subjects who participate in these studies may have a greater impact on subjects with higher baseline HbA1c.

In four of the five studies, the baseline level of HbA1c did not appear to affect the comparison between liraglutide and the comparator group(s) (Figure 13). In Trial 1574 (metformin and rosiglitazone background therapy, placebo comparator group), the effect of liraglutide compared to placebo was smaller at the lower levels of baseline HbA1c and larger at the higher levels of baseline HbA1c ( $p < 0.1$ ).

Baseline BMI: Differences in average HbA1c response between categories of baseline BMI were not consistent across the five key studies (FIGURE 14). In four of the five studies, the baseline level of BMI did not appear to affect the comparison between liraglutide and the comparator group(s). In Trial 1697 (add-on to glimepiride + rosiglitazone, with both placebo and active comparator groups), the p-value for the subgroup by treatment interaction was 0.0874. Based on an inspection of FIGURE 14, the lack of parallelism associated with this low p-value appears to be primarily due to the response of the active control, insulin, relative to the placebo in different baseline BMI categories. The response of liraglutide relative to placebo appears to be relatively similar through all of the baseline BMI categories.

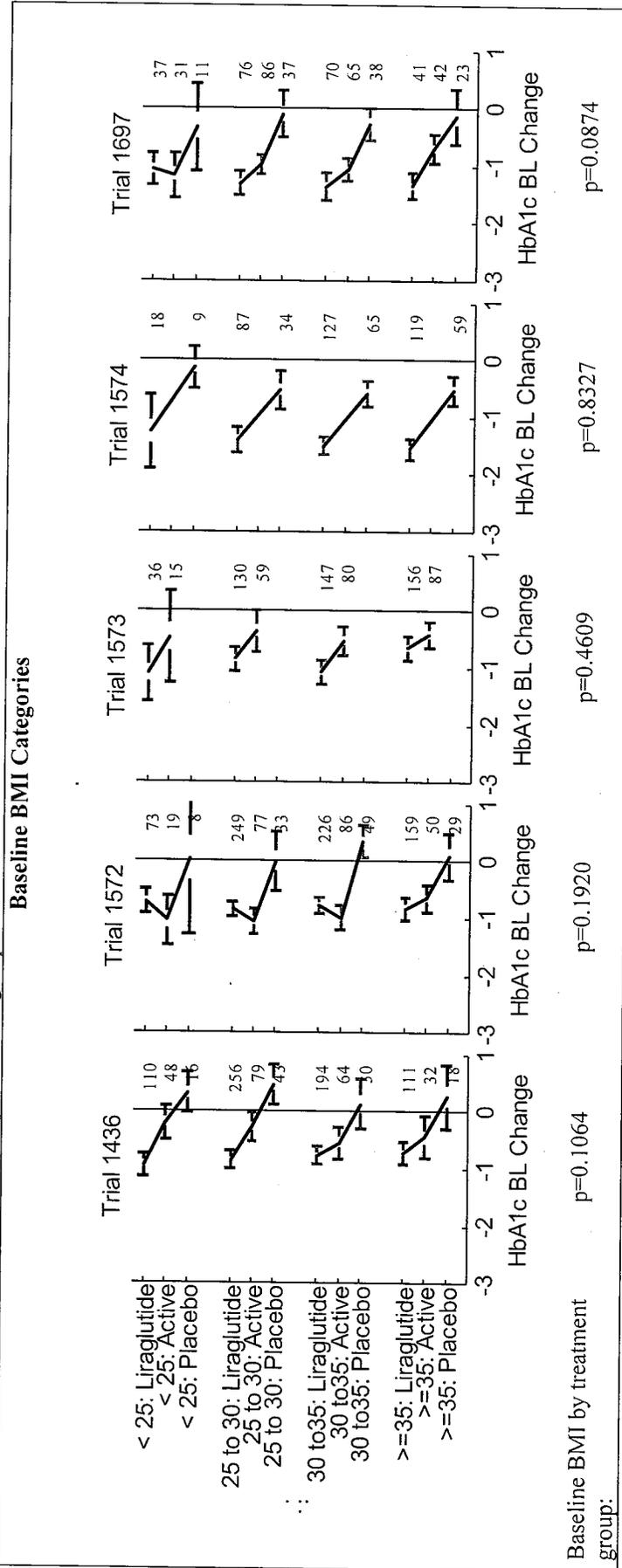
FIGURE 13 HbA1c primary efficacy endpoint, in subgroups: Baseline HbA1c



**Notes:**

Shown on the graphs are the t-intervals (mean and 95% confidence interval) for HbA1c change from baseline for each subgroup category. The treatment groups in the original study design were combined into all liraglutide groups and all comparator groups. The p-values are from the analysis of covariance model with the following form: country, baseline HbA1c category, combined treatment groups (i.e., liraglutide group and comparator group), and baseline HbA1c category by combined treatment group interaction. In the model evaluating the linear effect of baseline HbA1c category, this variable was included as a covariate instead of as a class effect in the model.

FIGURE 14 HbA1c primary efficacy endpoint, in subgroups: Baseline BMI



Shown on the graphs are the t-intervals (mean and 95% confidence interval) for HbA1c change from baseline for each subgroup category. The treatment groups in the original study design were combined into all liraglutide groups and all comparator groups. The p-values are from the analysis of covariance model with the following general form: country, baseline HbA1c, combined treatment groups (i.e., liraglutide group and comparator group), baseline BMI category, and baseline BMI category by combined treatment group interaction. In the model evaluating the linear effect of baseline BMI category, this variable was included as a covariate instead of as class effects in the model.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

I evaluated the collective evidence in support of the efficacy of liraglutide from the results of five key Phase 3 studies. I confirmed a selection of the efficacy results for the primary endpoint, HbA1c at week 26 and 52, expressed as a change from baseline. I concurred with the pre-specified statistical methodology used in evaluating the primary endpoint. Results from the sensitivity analysis of the HbA1c endpoint supported the efficacy of liraglutide 1.2 mg and 1.8 mg. The efficacy of liraglutide 0.6 mg was less well supported, with results from one study supporting a non-inferiority conclusion and results from another study failing to meet the non-inferiority margin.

### 5.2 Conclusions

Monotherapy: HbA1c at week 52 – baseline: Liraglutide 1.2 mg and 1.8 mg monotherapy produced reductions in HbA1c at week 52 compared to baseline that supported a conclusion of superior efficacy to glimepiride monotherapy. The net differences between the liraglutide arms and the glimepiride arm were 0.33 for liraglutide 1.2 mg and 0.62 for liraglutide 1.8 mg in the direction of a greater average reduction of HbA1c compared to glimepiride 8 mg. Analyses of the PP analysis set and the ITT analysis set at week 52 had similar results.

Add-on therapy: HbA1c at week 26 – baseline: In general, all three doses of liraglutide resulted in a greater average reduction in HbA1c at week 26 compared to baseline when given as an add-on to the other anti-diabetic drugs. The net differences between the liraglutide add-on arms and the placebo add-on arms in the four phase 3 studies ranged from 0.78 to 1.36, in the direction of superior efficacy to liraglutide compared to placebo. Analyses of the PP analysis sets were supportive of the results from the ITT/LOCF analysis sets.

### 5.3 Recommendations for Labeling

The following are general recommendations for Part 14 (Clinical Studies) of the proposed patient insert:

1. Report summary statistics to the 0.1 decimal place, in the tables and the text. For example, in part 14.1 (Monotherapy): “In this 52-week study (Table 4) with 746 patients, [liraglutide] 1.8 mg and 1.2 mg resulted in a 12 month sustained mean HbA1c reduction of 0.62 and 0.33, respectively compared to glimepiride.”
2. The text does not consistently report summary statistics for liraglutide that are net changes compared to the comparator group. Some of the summary statistics reported for liraglutide are the average change from baseline to study endpoint in a liraglutide dose group without adjusting for the average change from baseline to study endpoint in the comparator group. We recommend consistently reporting the net effect of liraglutide in comparison to the comparator group. The

text should clearly state the comparison from which the summary statistics are obtained. For example, in Part 14.1 (Monotherapy): “Patients previously treated on diet alone had a mean HbA1c change from baseline of ~~+480.7~~ and ~~+130.4~~ for [liraglutide] 1.8 mg and [liraglutide] 1.2 mg, respectively, compared to glimepiride.”

**APPENDIX: Primary Efficacy Endpoint by Subgroup Categories**

Included in this appendix are summary tables of the HbA<sub>1c</sub> primary efficacy endpoint, in subgroup categories of age, sex, race, ethnicity, baseline HbA<sub>1c</sub> category and baseline BMI category. Categories include the original randomized treatment groups in each study, and the full set of racial categories in each study.

TABLE 10 Trial 1436; Mean changes from baseline in HbA<sub>1c</sub> (%) at endpoint: subgroup analysis of the ITT/LOCF population by age, gender and race

Trial 1436 add-on to gimepiride 4 mg	liraglutide 0.6 mg			liraglutide 1.2 mg			liraglutide 1.8 mg			placebo			rosiglitazone 4 mg		
	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)
<b>Age (years)</b>															
<65	180	8.4	-0.4 (1.1)	171	8.5	-1.0 (1.1)	184	8.5	-1.0 (1.2)	89	8.4	0.4 (1.1)	187	8.4	-0.3 (1.1)
≥ 65	47	8.4	-0.7 (0.9)	57	8.4	-0.9 (1.0)	45	8.5	-1.0 (1.2)	22	8.2	-0.1 (1.0)	41	8.3	-0.6 (0.7)
<b>Sex</b>															
Male	124	8.4	-0.5 (1.2)	102	8.4	-0.9 (1.1)	123	8.5	-0.9 (1.1)	52	8.3	0.2 (1.1)	108	8.3	-0.2 (1.2)
Female	103	8.4	-0.5 (0.8)	126	8.6	-1.0 (1.1)	106	8.5	-1.0 (1.2)	59	8.4	0.4 (1.1)	120	8.5	-0.5 (0.9)
<b>Race</b>															
Caucasian	153	8.4	-0.6 (1.0)	143	8.4	-0.9 (1.0)	145	8.4	-1.0 (1.1)	76	8.2	0.2 (1.1)	149	8.4	-0.4 (1.0)
Black	7	8.0	0.1 (1.1)	7	9.5	-2.2 (1.5)	9	9.0	-1.6 (1.4)	1	8.8	3.0 (---)	5	8.9	-0.8 (0.8)
Asian / Pacific Islander	67	8.6	-0.3 (1.1)	78	8.5	-1.0 (1.1)	74	8.6	-0.8 (1.2)	33	8.7	0.5 (1.0)	71	8.4	-0.2 (1.2)
Other							1	8.5	-1.7 (---)	1	8.6	-1.2 (---)	3	8.3	0.8 (2.7)

Sources: Clinical Report from Trial 1436, Tables 14.2.25, 14.2.26 and 14.2.27

TABLE 11 Trial 1436; Mean changes from baseline in HbA<sub>1c</sub> (%) at endpoint: subgroup analysis of the ITT/LOCF population by baseline HbA<sub>1c</sub> category and baseline BMI category

Trial 1436 add-on to glimepiride 4 mg	liraglutide 0.6 mg			liraglutide 1.2 mg			liraglutide 1.8 mg			placebo			rosiglitazone 4 mg		
	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)
<b>Baseline HbA<sub>1c</sub> (%)</b>															
≤ 7.0	15	6.8	0.1 (0.9)	18	6.8	-0.4 (0.6)	9	6.8	-0.6 (0.5)	7	6.8	0.6 (0.9)	11	6.8	-0.2 (0.7)
7.0 < HbA <sub>1c</sub> ≤ 8.0	81	7.7	-0.4 (0.9)	70	7.6	-0.6 (0.8)	68	7.6	-0.7 (1.0)	38	7.5	0.5 (1.1)	83	7.6	-0.2 (1.1)
8.0 < HbA <sub>1c</sub> ≤ 9.0	70	8.5	-0.5 (1.0)	72	8.5	-0.9 (1.0)	95	8.5	-1.1 (1.1)	41	8.6	0.3 (1.1)	75	8.5	-0.4 (1.1)
> 9.0%	61	9.7	-0.7 (1.2)	68	9.7	-1.5 (1.3)	57	9.8	-1.2 (1.5)	25	9.7	-0.1 (1.0)	59	9.7	-0.5 (1.1)
<b>Baseline BMI (kg/m<sup>2</sup>)</b>															
< 25	36	8.5	-0.6 (0.9)	39	8.7	-1.3 (1.0)	37	8.6	-0.9 (1.1)	16	8.6	0.3 (0.7)	49	8.5	-0.2 (1.0)
25 to < 30	82	8.4	-0.6 (1.0)	89	8.5	-1.0 (1.1)	90	8.6	-1.0 (1.3)	43	8.4	0.5 (1.1)	80	8.3	-0.3 (1.1)
30 to < 35	73	8.5	-0.6 (1.1)	55	8.4	-0.8 (1.1)	68	8.3	-0.9 (1.1)	32	8.4	0.1 (1.2)	66	8.4	-0.5 (1.1)
≥ 35	35	8.2	-0.2 (0.9)	45	8.4	-0.8 (1.0)	33	8.5	-1.2 (1.1)	20	8.0	0.3 (1.1)	32	8.4	-0.4 (1.0)

Sources: Clinical Report from Trial 1436, Table 14.2.28 (BMI) and additional analysis by this reviewer (HbA<sub>1c</sub>)

TABLE 12 Trial 1572; Mean changes from baseline in HbA<sub>1c</sub> (%) at endpoint: subgroup analysis of the ITT/LOCF population by age, gender and race

Trial 1572 add-on to metformin 2 g	liraglutide 0.6 mg			liraglutide 1.2 mg			liraglutide 1.8 mg			placebo			gimepiride 4 mg		
	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)
<b>Age (years)</b>															
<65	183	8.4	-0.6 (1.0)	184	8.3	-0.9 (1.1)	188	8.4	-0.9 (1.1)	97	8.5	0.1 (1.2)	191	8.4	-0.9 (0.9)
≥ 65	57	8.3	-0.6 (0.8)	54	8.5	-0.9 (1.0)	52	8.3	-0.8 (1.1)	24	8.1	0.3 (1.0)	48	8.4	-1.1 (1.0)
<b>Sex</b>															
Male	150	8.4	-0.6 (1.0)	127	8.2	-0.8 (0.9)	140	8.4	-0.9 (1.1)	72	8.3	0.2 (1.1)	138	8.4	-0.9 (0.9)
Female	90	8.5	-0.7 (1.0)	111	8.4	-1.0 (1.2)	100	8.4	-1.0 (1.2)	49	8.6	0.1 (1.4)	101	8.4	-1.0 (1.0)
<b>Race</b>															
Caucasian	200	8.4	-0.6 (0.9)	208	8.3	-0.8 (1.0)	212	8.3	-1.0 (1.0)	106	8.3	0.2 (1.0)	211	8.4	-0.9 (0.9)
Black	4	8.8	-1.1 (1.1)	9	9.1	-1.5 (2.2)	5	9.8	-1.7 (3.0)	3	10.4	-1.8 (3.5)	5	8.9	-1.9 (0.7)
Asian / Pacific Islander	31	8.7	-0.5 (1.2)	19	8.5	-1.2 (1.1)	18	8.4	-0.3 (1.2)	9	8.9	-0.3 (1.5)	21	8.5	-0.6 (1.0)
Other	5	8.0	-0.2 (1.4)	2	8.7	-0.8 (1.7)	5	8.8	-0.2 (1.3)	3	8.7	1.3 (1.8)	2	8.9	0.6 (0.7)

Sources: Clinical Report from Trial 1572, Tables 14.2.28, 14.2.29 and 14.2.30

TABLE 13 Trial 1572; Mean changes from baseline in HbA<sub>1c</sub> (%) at endpoint: subgroup analysis of the ITT/LOCF population by baseline HbA<sub>1c</sub> category and baseline BMI category

Trial 1572 add-on to metformin 2 g	liraglutide 0.6 mg			liraglutide 1.2 mg			liraglutide 1.8 mg			placebo			glimepiride 4 mg		
	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)
<b>Baseline HbA<sub>1c</sub> (%)</b>															
≤ 7.0	9	6.8	-0.3 (0.6)	16	6.6	-0.5 (0.4)	9	6.8	-0.4 (0.8)	8	6.6	0.2 (0.6)	16	6.8	-0.3 (0.8)
7.0 < HbA <sub>1c</sub> ≤ 8.0	82	7.5	-0.3 (0.7)	85	7.6	-0.6 (0.7)	91	7.6	-0.7 (0.9)	39	7.6	0.2 (0.9)	85	7.7	-0.7 (0.7)
8.0 < HbA <sub>1c</sub> ≤ 9.0	84	8.5	-0.5 (1.0)	86	8.5	-0.8 (0.9)	86	8.5	-0.9 (1.0)	41	8.5	0.4 (1.1)	83	8.5	-0.9 (0.9)
> 9.0%	65	9.6	-1.1 (1.1)	51	9.7	-1.6 (1.4)	54	9.8	-1.4 (1.6)	33	9.7	-0.1 (1.6)	55	9.9	-1.4 (1.1)
<b>Baseline BMI (kg/m<sup>2</sup>)</b>															
< 25	33	8.3	-0.7 (0.8)	22	8.2	-0.8 (0.8)	23	8.4	-0.7 (0.9)	8	9.3	0.0 (1.6)	20	8.7	-1.0 (0.9)
25 to < 30	83	8.4	-0.7 (1.0)	84	8.5	-0.9 (1.0)	84	8.4	-0.9 (1.0)	33	8.5	0.0 (1.5)	78	8.3	-1.1 (0.9)
30 to < 35	77	8.4	-0.5 (0.9)	72	8.3	-0.9 (1.1)	79	8.4	-0.9 (1.1)	50	8.4	0.3 (1.0)	89	8.5	-1.0 (1.0)
≥ 35	47	8.5	-0.5 (1.2)	60	8.3	-0.9 (1.1)	53	8.4	-1.1 (1.4)	29	8.1	0.1 (1.1)	50	8.4	-0.6 (0.8)

Sources: Clinical Report from Trial 1572, Table 14.2.31 (BMI) and additional analysis by this reviewer (HbA<sub>1c</sub>)

TABLE 14 Trial 1573; Mean changes from baseline in HbA<sub>1c</sub> (%) at endpoint: subgroup analysis of the ITT/LOCF population by age, gender, race and ethnicity

Trial 1573		liraglutide 1.2 mg		liraglutide 1.8 mg			glimepiride 8 mg		
monotherapy	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)
<b>Age (years)</b>									
<65	208	8.2	-0.7 (1.4)	222	8.2	-1.0 (1.3)	208	8.3	-0.4 (1.2)
≥ 65	43	8.0	-0.8 (1.0)	24	7.7	-0.8 (0.9)	40	7.8	-0.5 (0.8)
<b>Sex<sup>1</sup></b>									
Male	117	8.2	-0.7 (1.3)	121	8.2	-1.0 (1.4)	133	8.2	-0.5 (1.2)
Female	134	8.2	-0.8 (1.3)	125	8.2	-1.0 (1.1)	115	8.2	-0.4 (1.1)
<b>Race</b>									
Caucasian	200	8.1	-0.7 (1.4)	185	8.3	-0.7 (1.4)	192	8.2	-0.5 (1.1)
Black	34	8.5	-0.8 (1.1)	30	7.7	-0.9 (0.9)	30	8.3	0.0 (1.2)
Asian	5	7.8	-1.0 (0.8)	12	8.3	-1.1 (1.0)	9	9.0	-0.9 (1.0)
Native Hawaiian	---			2	7.4	0.2 (0.6)	---		
Other	12	8.2	-0.8 (1.4)	17	8.3	-0.8 (1.8)	17	8.5	-0.8 (1.5)
<b>Ethnicity</b>									
Hispanic/Latino	81	8.2	-0.7 (1.5)	87	8.5	-1.1 (1.5)	93	8.4	-0.5 (1.3)
not Hispanic/Latino	170	8.2	-0.8 (1.3)	159	8.0	-0.9 (1.1)	155	8.1	-0.4 (1.1)

Sources: Clinical Report from Trial 1573, Tables 14.2.5-13, 14.2.5-14, 14.2.5-15, and 14.2.5-16

TABLE 15 Trial 1573; Mean changes from baseline in HbA<sub>1c</sub> (%) at endpoint: subgroup analysis of the ITT/LOCF population by baseline HbA<sub>1c</sub> category and by baseline BMI category

Trial 1573		liraglutide 1.2 mg		liraglutide 1.8 mg			glimepiride 8 mg		
monotherapy	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)
<b>Baseline HbA<sub>1c</sub> (%)</b>									
≤ 7.0	24	6.8	-0.4 (0.7)	31	6.8	-0.3 (0.7)	28	6.8	-0.1 (1.1)
7.0 < HbA <sub>1c</sub> ≤ 8.0	100	7.5	-0.3 (1.1)	94	7.6	-0.7 (1.0)	94	7.6	-0.2 (0.9)
8.0 < HbA <sub>1c</sub> ≤ 9.0	69	8.5	-0.8 (1.3)	64	8.6	-1.1 (1.4)	70	8.5	-0.5 (1.2)
> 9.0%	43	10.0	-1.7 (1.5)	45	9.9	-2.0 (1.3)	49	9.9	-1.0 (1.4)
<b>Baseline BMI (kg/m<sup>2</sup>)</b>									
< 25	18	7.8	-0.5 (1.4)	21	8.8	-1.5 (1.0)	15	8.1	-0.5 (1.4)
25 to < 30	61	8.1	-0.6 (1.3)	75	8.1	-1.0 (1.2)	57	8.1	-0.4 (1.4)
30 to < 35	93	8.3	-1.0 (1.3)	66	8.2	-1.2 (1.3)	84	8.5	-0.5 (1.2)
35 to < 40	40	8.2	-0.6 (1.2)	43	8.3	-0.7 (1.4)	57	8.1	-0.4 (1.1)
≥ 40	39	8.0	-0.5 (1.5)	41	8.0	-0.9 (1.3)	35	8.1	-0.5 (0.9)

Sources: Clinical Report from Trial 1573, Table 14.2.5-17 (BMI), and additional analysis by this reviewer (HbA<sub>1c</sub>)

TABLE 16 Trial 1574; Mean changes from baseline in HbA<sub>1c</sub> (%) at endpoint: subgroup analysis of the ITT/LOCF population by age, gender, race and ethnicity

Trial 1574 add-on to metformin 2 g + rosiglitazone 8 mg (4 mg BID)	liraglutide 1.2 mg			liraglutide 1.8 mg			placebo		
	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)
<b>Age (years)</b>									
<65	146	8.5	-1.5 (1.0)	141	8.6	-1.5 (1.1)	151	8.5	-0.5 (1.0)
≥ 65	31	8.6	-1.3 (0.7)	37	8.6	-1.4 (1.0)	24	8.1	-0.6 (0.6)
<b>Sex<sup>1</sup></b>									
Male	101	8.6	-1.4 (0.9)	87	8.7	-1.4 (0.9)	107	8.6	-0.5 (1.0)
Female	76	8.4	-1.5 (1.1)	91	8.4	-1.6 (1.1)	68	8.2	-0.6 (0.8)
<b>Race</b>									
Caucasian	144	8.5	-1.6 (0.9)	148	8.5	-1.5 (1.0)	148	8.4	-0.5 (0.9)
Black	26	8.0	-1.1 (0.9)	18	8.5	-1.6 (1.4)	18	8.3	-0.7 (0.8)
Asian	2	9.3	-0.1 (2.2)	5	8.7	-1.3 (1.1)	2	7.9	-0.6 (0.7)
American Indian	1	9.9	-3.1 (---)	1	8.3	-1.2 (---)	2	7.9	-1.1 (0.4)
Other	4	9.1	-1.3 (1.0)	6	9.1	-1.9 (1.4)	5	8.8	-0.8 (0.8)
<b>Ethnicity</b>									
Hispanic/Latino	23	8.7	-1.7 (1.1)	29	8.6	-1.5 (1.1)	29	8.7	-0.8 (0.9)
not Hispanic/Latino	154	8.5	-1.5 (0.9)	149	8.6	-1.5 (1.0)	146	8.4	-0.5 (0.9)

*Sources:* Clinical Report from Trial 1574, Tables 14.2.5-13, 14.2-5-14, 14.2-5-15, and 14.2-5-16

TABLE 17 Trial 1574; Mean changes from baseline in HbA<sub>1c</sub> (%) at endpoint: subgroup analysis of the ITT/LOCF population by baseline HbA<sub>1c</sub> category and by baseline BMI category

Trial 1574 add-on to metformin 2 g + rosiglitazone 8 mg (4 mg BID)	liraglutide 1.2 mg			liraglutide 1.8 mg			placebo		
	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)
<b>Baseline HbA<sub>1c</sub> (%)</b>									
≤ 7.0	19	6.7	-0.8 (0.4)	11	6.8	-0.7 (0.3)	12	6.7	-0.2 (0.4)
7.0 < HbA <sub>1c</sub> ≤ 8.0	55	7.6	-1.0 (0.5)	54	7.6	-1.9 (0.7)	62	7.6	-0.4 (0.7)
8.0 < HbA <sub>1c</sub> ≤ 9.0	46	8.5	-1.6 (0.8)	66	8.5	-1.4 (0.8)	44	8.5	-0.5 (0.9)
> 9.0%	54	10.0	-2.1 (1.1)	46	10.2	-2.3 (1.2)	49	9.9	-0.7 (1.2)
<b>Baseline BMI (kg/m<sup>2</sup>)</b>									
< 25	7	9.4	-1.6 (1.7)	11	8.5	-1.2 (1.0)	8	8.5	-0.2 (0.5)
25 to < 30	41	9.0	-1.4 (1.1)	45	8.5	-1.4 (1.1)	35	8.5	-0.5 (1.0)
30 to < 35	63	8.4	-1.5 (0.9)	66	8.5	-1.5 (0.9)	66	8.4	-0.6 (0.9)
35 to < 40	39	8.5	-1.5 (1.1)	33	8.3	-1.5 (0.9)	43	8.4	-0.4 (0.9)
≥ 40	28	8.3	-1.5 (1.1)	22	8.7	-1.7 (1.0)	23	8.4	-0.7 (1.0)

*Sources:* Clinical Report from Trial 1697, Table 14.2-5-17 (BMI) and additional analysis by this reviewer (HbA<sub>1c</sub>)

TABLE 18 Trial 1697; Mean changes from baseline in HbA<sub>1c</sub> (%) at endpoint: subgroup analysis of the ITT/LOCF population by age, gender and race

Trial 1697 add-on to glimpiride 4 mg + metformin 2 g	liraglutide 1.8 mg			placebo			insulin glargine		
	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)
<b>Age (years)</b>									
<65	173	8.3	-1.3 (0.9)	83	8.3	-0.1 (1.1)	172	8.2	-0.9 (0.8)
≥ 65	57	8.3	-1.3 (1.0)	29	8.2	-0.4 (1.0)	60	8.1	-1.1 (0.8)
<b>Sex<sup>1</sup></b>									
Male	130	8.3	-1.2 (1.0)	56	8.4	-0.2 (1.0)	139	8.1	-0.9 (0.8)
Female	100	8.2	-1.4 (0.8)	56	8.1	-0.2 (1.2)	93	8.3	-1.1 (0.9)
<b>Race</b>									
Caucasian	176	8.3	-1.4 (0.9)	87	8.2	-0.3 (1.0)	171	8.1	-1.0 (0.8)
Black	9	8.7	-1.5 (0.9)	5	9.5	0.4 (2.6)	7	8.4	-1.0 (1.1)
Asian / Pacific Islander	32	8.3	-1.0 (1.0)	14	8.0	-0.2 (0.7)	40	7.9	-0.9 (0.8)
Other	2	7.9	-0.3 (0.0)	1	8.9	-0.8 (---)	2	8.1	-0.9 (0.7)
<i>Sources:</i> Clinical Report from Trial 1697, Tables 14.2.26, 14.2.27 and 14.2.28									

TABLE 19 Trial 1697; Mean changes from baseline in HbA<sub>1c</sub> (%) at endpoint: subgroup analysis of the ITT/LOCF population by baseline HbA<sub>1c</sub> category and by baseline BMI category

Trial 1697 add-on to glimpiride 4mg + metformin 2g	liraglutide 1.8 mg			placebo			insulin glargine		
	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)	n	Base- line mean	Change from baseline (SD)
<b>Baseline HbA<sub>1c</sub> (%)</b>									
≤ 7.0	17	6.7	-0.8 (0.6)	7	6.7	-0.2 (0.8)	23	6.6	-0.5 (0.5)
7.0 < HbA <sub>1c</sub> ≤ 8.0	83	7.5	-1.0 (0.7)	37	7.6	0.0 (1.0)	91	7.6	-0.7 (0.6)
8.0 < HbA <sub>1c</sub> ≤ 9.0	85	8.5	-1.3 (0.8)	50	8.5	-0.3 (1.0)	82	8.5	-1.1 (0.8)
> 9.0%	45	9.7	-1.9 (1.2)	18	9.7	-0.3 (1.4)	36	9.6	-1.7 (1.1)
<b>Baseline BMI (kg/m<sup>2</sup>)</b>									
< 25	38	8.2	-1.1 (0.8)	11	8.6	-0.3 (1.1)	33	7.9	-1.2 (1.1)
25 to < 30	79	8.3	-1.3 (1.0)	38	8.3	-0.1 (1.2)	87	8.1	-1.0 (0.7)
30 to < 35	71	8.4	-1.4 (1.0)	39	8.1	-0.3 (0.8)	68	8.2	-1.1 (0.8)
≥ 35	42	8.2	-1.4 (0.7)	23	8.4	-0.1 (1.1)	43	8.3	-0.7 (0.8)
<i>Sources:</i> Clinical Report from Trial 1697, Table 14.2.29 (BMI), and additional analysis by this reviewer (HbA <sub>1c</sub> )									

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**Statistical Review and Evaluation**  
**CARCINOGENICITY STUDIES**

**IND/NDA Number:** NDA 22-341  
**Drug Name:** Victoza (Liraglutide)  
**Applicant:** Sponsor: Novo Nordisk Inc., 100 College Road West, Princeton, NJ 08540.  
Test Facility: \_\_\_\_\_  
**Documents Reviewed:** Electronic data submitted on May 23, 2008  
**Review Priority:** Standard  
**Biometrics Division:** Division of Biometrics -6  
**Statistical Reviewer:** Min Min, Ph.D.  
**Concurring Reviewer:** Karl Lin, Ph.D.  
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**Reviewing Pharmacologist:** Anthony L Parola, Ph.D.  
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## 1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of Victoza (Liraglutide) in rats and mice when administered by subcutaneous injection at appropriate drug levels for about 104 weeks. The test item, Victoza (Liraglutide), a GLP-1 like analogue was developed for the treatment of Type II diabetes in man. Results of this review have been discussed with the reviewing pharmacologist Dr. Parola.

## 2. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one control group. Two hundred Sprague-Dawley rats (Ctrl: CD®(SD) IGS BR) of each sex were randomly allocated to treated and control groups in equal size of 50 animals. The dose levels for groups were 0, 0.075, 0.25, and 0.75 mg/kg/day at a dose volume of 1ml/kg body weight. In this review these dose groups would be referred to as the control, low, medium, and high dose group, respectively.

The animals were dosed once daily by subcutaneous injection for 104 weeks. The control animals received vehicle only at the same dose volume as treated animals. Body weight and food consumption measurements were made regularly throughout the dosing period and clinical observations were recorded as required. After 104 weeks of dosing, all animals (including premature decedents) were subjected to a full necropsy and histopathological evaluation.

### 2.1. Sponsor's analyses

#### 2.1.1. Survival analysis

Survival data were presented graphically using Kaplan-Meier survival curves and pairwise comparisons were made using Wilcoxon's rank sum test modified for censored survival data.

**Sponsor's findings:** Sponsor's analysis showed survival rates of 46.0%, 48.0%, 58.0%, and 52.0% in control, low, medium, and high dose groups, respectively in males and 56.0%, 50.0%, 42.0%, and 58.0%, respectively in females. Sponsor concluded that there was no treatment effect on mortality in either sex.

#### 2.1.2. Tumor data analysis

Pairwise comparisons of the incidence of tumor were made using the Fisher's Exact test function within PLACES 2000. The statistical evaluation of the tumor data was performed in SAS (V8.2) using PROC MULTTEST. All significance tests were one-tailed (testing for an increase) and were performed at the 5% significance level. The analysis of non-fatal tumors was conducted by dividing the experimental period into the following fixed time intervals: 1-52 weeks, 53-78 weeks, 79-92 weeks, over 92 weeks and single interval for any planned sacrifices. For each considered tumor type, the significance of a linear dose related increase in tumor incidence was evaluated using a one-sided trend test. Furthermore, Peto's one-tailed test was also used to test whether or not the tumor incidence in each treated group is significantly higher than that in the control group. For each statistical test performed on a tumor type with 10 or less tumor bearing animals, the discrete permutation trend test was used to calculate the corresponding p-value.

Tests for dose response relationship were conducted at the significance levels of 0.005 (one tailed-level) for common tumors and 0.025 (one tailed-level) for rare tumors. Pairwise comparisons were conducted at the

significance levels of 0.01 (one tailed-level) for common tumors and 0.05 (one tailed-level) for rare tumors. Common tumors were defined as those with an incidence in controls of 1% or higher in the control group and rare tumors as less than 1%.

**Reviewer's comment:** *The above significance levels for dose response relationship test were suggested by Lin and Rahman (1998) and those for pairwise comparisons were suggested by Haseman (1983) to adjust for multiple testing (to keep the false-positive rate at the nominal level of approximately 10%).*

**Sponsor's findings:** Administration of Victoza (Liraglutide) to rats at level 0.075 mg/kg/day and above for a 104 week period was associated with an increase in hyperplasia and neoplasia of the C-cells in the thyroid gland of males and females. Sponsor concluded that there was no other evidence of carcinogenicity at any dose level. Summary of statistically significant results is presented below:

Organ	Tumour Type		P-VALUE <sup>(1)</sup>	P-VALUE <sup>(2)</sup>	P-VALUE <sup>(3)</sup>	P-VALUE <sup>(4)</sup>
Thyroid Gland	C-cell Carcinoma [M]	Males	0.013	0.058	0.17	0.009
		Females	0.027	1.00	0.27	0.12
	C-cell Adenoma [B]	Males	<0.001	0.28	<0.001	<0.001
		Females	<0.001	0.016	0.001	<0.001
	C-cell Tumour	Males	<0.001	0.13	<0.001	<0.001
		Females	<0.001	0.016	<0.001	<0.001
Pituitary Gland	Carcinoma anterior lobe [M], locally invasive	Males	0.30	0.48	1.00	0.47
		Females	0.008	1.00	0.69	0.089

- (1) Linear trend
- (2) Group 2 vs Group 1
- (3) Group 3 vs Group 1
- (4) Group 4 vs Group 1

## 2.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

### 2.2.1. Survival analysis

The survival distributions of animals in all four treatment groups were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested using the Cox test (Cox, 1972) and the Generalized Wilcoxon test (Gehan, 1965). The intercurrent mortality data are given in Tables 1A and 1B in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for males and females, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for males and females, respectively.

**Reviewer's findings:** The tests showed no statistically significant dose response relationship or differences between the control and any of the treated groups in survivals across treatment groups in either sex.

### 2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationship and pairwise differences between control group and each of the treated groups were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of the tumor data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for males and females, respectively.

**Multiple testing adjustment:** Adjustment for the multiple dose response relationship testing was done using the criteria developed by Lin and Rahman (1998). The criteria recommend the use of a significance level  $\alpha=0.025$  for rare tumors and  $\alpha=0.005$  for common tumors for a submission with two species, and a significance level  $\alpha=0.05$  for rare tumors and  $\alpha=0.01$  for common tumors for a submission with only one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the spontaneous tumor rate is less than 1%. The adjustment for multiple pairwise comparisons was done using the criteria developed by Haseman (1983) that recommends the use of significance level  $\alpha=0.05$  for rare tumors and  $\alpha=0.01$  for common tumors, in order to keep the false-positive rate at the nominal level of approximately 10%.

It should be noted that the recommended test levels of significance by Lin and Rahman for the adjustment of multiple testing were originally based on the result of a simulation and an empirical study using the Peto method for dose response relationship analysis. However, some later simulation results by Rahman and Lin (2008) indicate that the criteria apply equally well to the analysis using the poly-3 test.

As suggested by the reviewing pharmacologist Dr. Parola, this reviewer did the analysis of the following tumor/organ combinations:

- hemangiomas and hemangiosarcomas from all sites (include separate analysis for hemangiomas and hemangiosarcomas in both rats and mice)
- mesotheliomas (all sites, rats and mice)
- leukemias (all sites, male rats, male mice)
- lymphomas (rats and mice (all sites)
- chondroma / osteosarcoma / osteoma (all bone-- e.g., bone, cranium, femur, rats and mice)
- lipoma / liposarcoma at same tissue site (rats and mice)
- kidney tubular cell adenomas / carcinomas (male rats, male mice)
- liver hepatocellular adenomas / carcinomas (male rats, male mice)
- pancreas islet cell adenoma and mixed acinar / islet cell adenoma (male rats)
- pancreas mixed acinar / islet cell adenoma and acinar cell adenoma (male rats)
- pituitary anterior lobe adenoma / carcinoma (male rats, female rats)
- skin and subcutis basal cell adenoma / carcinoma (male rats)
- skin and subcutis squamous cell papilloma / carcinoma / keratoacanthoma (male rats, female rats, male mice)
- testis interstitial cell adenoma / mesothelioma / rete testis adenoma / sex cord stromal tumor (male rats, male mice)
- thymus thymoma (benign and malignant) (male rats)
- thyroid c-cell adenoma / carcinoma (rats and mice)
- thyroid follicular cell adenoma / carcinoma (rats and mice)
- duodenum leiomyoma / leiomyosarcoma (female rats)

mammary adenoma / carcinoma (female rats)  
 mammary fibroadenoma / fibrocarcinoma (female rats)  
 uterus stromal polyp / sarcoma (female rats)  
 uterus adenoma / adenocarcinoma (female rats)  
 uterus/vagina stromal neoplasms  
 pituitary adenomas / carcinomas anterior lobes (rats and mice)  
 oral cavity/tongue squamous cell papillomas/ carcinomas

**Reviewer's findings:** The following tumor types showed p-values less than or equal to 0.05 either for dose response relationship and/or pairwise comparisons between control and indicated treated groups.

#### Tumor Types with P-Values $\leq 0.05$ for Dose Response Relationship or Pairwise Comparisons

Sex	Organ Name	Tumor Name	Cont N=50	Low N=50	Med N=50	High N=50	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Male	THYROID GLAND	C-CELL ADENOMA [B]	6	8	21	23	0.000	0.384	0.002	0.000
		C-CELL CARCINOMA [M]	1	4	3	7	0.023	0.187	0.338	0.031
		C-CELL_ ADENOMA+CARCI	7	11	21	28	0.000	0.229	0.005	0.000
Female	PITUITARY GLAND	CARCINOMA, ANTERIOR	1	0	1	5	0.007	0.474	0.727	0.089
	THYROID GLAND	C-CELL_ADENOMA+CARCI	5	13	18	29	0.000	0.022	0.001	0.000
		C-CELL ADENOMA [B]	5	13	16	28	0.000	0.022	0.003	0.000
		C-CELL CARCINOMA [M]	0	0	2	3	0.023	0.228	0.111	
	UTERUS	STROMAL POLYP [B]	5	5	7	10	0.046	0.581	0.324	0.105

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, the positive dose-response relationships in the incidence of C-cell adenoma and combined adenoma and carcinoma in thyroid gland in both sexes, and C-cell carcinoma in thyroid gland in females were considered to be statistically significant. Also based on the criteria by Haseman, the increased tumor incidences of C-cell adenoma and C-cell combined adenoma and carcinoma tumor in thyroid gland in the high and medium dose groups in both male and female rats were considered to be statistically significant when compared to the control group because all the p-values are less than 0.01.

### 3. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were four treated groups and one control group. In main study, two hundred and fifty CD-1 mice (CrI:CD-1TM(ICR)BR) of each sex were randomly allocated to treated and control groups in equal size of 50 animals. The dose levels for groups were 0, 0.03, 0.2, 1.0 and 3.0 mg/kg/day at a dose volume of 5 mL/kg. In this review these dose groups would be referred to as the control, low, medium, medium high, and high dose group, respectively. The nominal Week 78/104 satellite study comprised of control and high dose groups with 29 male and 29 female mice each, and low and 2 medium dose groups with 17 male and female mice each. From the data electronically submitted by sponsor, the animals were allocated to dose groups as detailed below:

Dose group	Male Mice		Female Mice	
	Main study animal number	Week 78/104 satellite group animal number	Main study animal number	Week 78/104 satellite group animal number
Control	1-50	501-529	251-300	610-638
Low	51-100	530-546	301-350	639-655
Medium	101-114, 116-124, 126-137, 139-150, 721, 723, 720	547, 549-563, 719	351-368, 370-396, 398-400, 725, 728	656-672
Medium high	151-183, 185-200, 724	564-580	401-450	673-689
High	201-208, 210-250, 722	581-609	451-500	690-710, 712-718, 726

Once each week all main study animals received a detailed clinical examination, including appearance, movement and behavior patterns, skin and hair conditions, eyes and mucous membranes, respiration and excreta. Body weights were recorded once during the week prior to the start of the treatment period and then daily up until the end of the dosing period. All animals, with the exception of the pretrial antibody animals, were subjected to a detailed necropsy performed under the guidance of a veterinary pathologist. The necropsy consisted of an external and internal examination.

### 3.1. Sponsor's analyses

#### 3.1.1. Survival analysis

Survival data from the mouse study were analyzed using the same statistical methodologies as were used to analyze the survival data from the rat study.

**Sponsor's findings:** In main study, sponsor's analysis showed survival rates of 50.0%, 58.0%, 56.0%, 62.0%, and 38.0% in control, low, medium, medium high and high dose groups, respectively in males and 28.0%, 22.0%, 38.0%, 38.0% and 38.0%, respectively in females. Sponsor concluded that there was no statistically significant treatment related effect on the survival in male mice. Female survival in the 1.0 and 3.0 mg/kg/day groups was found to be significantly greater when compared with the control.

In Week 78/104 satellite group, sponsor's analysis showed survival rates of 48.3%, 29.4%, 52.9%, 41.2%, and 48.3% in control, low, medium, medium high and high dose groups, respectively in males and 34.5%, 17.6%, 23.5%, 29.4% and 31.0%, respectively in females. Sponsor concluded that survival in the low dose group was significantly lower for both males and females when compared with the respective control group.

#### 3.1.2. Tumor data analysis

Tumor data from the mouse study were also analyzed using the same statistical methodologies as were used to analyze the tumor data from the rat study.

**Sponsor's findings:** In conclusion, administration of Victoza (Liraglutide) to mice was associated with focal hyperplasia, adenoma and carcinoma of C-cells in the thyroid gland at dose levels of 0.2 mg/kg/day and above, and pigmented Kupffer cells in the liver in females given 1.0 mg/kg/day and above. Summaries of statistically significant results are presented below:

Table 1: Incidence of neoplastic C-cell findings in the thyroid gland in Main and Extension animals (Peto statistical analysis)

Thyroid Findings	Animals/Dose									
	Males					Females				
Group Number	1	2	3	4	5	1	2	3	4	5
Dose of NNC 90-1170 (mg/kg/day)	0	0.03	0.2	1.0	3.0	0	0.03	0.2	1.0	3.0
Number examined	79	66	65	67	79	75	66	67	66	76
C-cell carcinoma	0	0	0	0	0	0	0	0	0	2
C-cell adenoma	0	0	0	9***	15** *	0	0	0	4*	15** *
C-cell tumour	0	0	0	9***	15** *	0	0	0	4*	17** *

\* Statistically different from the Control:  $p < 0.05$ ; \*\* Statistically different from the Control:  $p < 0.01$ ;  
\*\*\* Statistically different from the Control:  $p < 0.001$

Table 2: Incidence of hyperplastic C-cell findings in the thyroid gland in Main and Extension animals (Fischer statistical analysis)

Thyroid Findings	Animals/Dose									
	Males					Females				
Group Number	1	2	3	4	5	1	2	3	4	5
Dose of NNC 90-1170 (mg/kg/day)	0	0.03	0.2	1.0	3.0	0	0.03	0.2	1.0	3.0
Number examined	79	66	65	67	79	75	66	67	66	76
Focal C-cell hyperplasia	0	0	1	11** *	30** *	0	0	7**	10** *	22** *

\* Statistically different from the Control:  $p < 0.05$ ; \*\* Statistically different from the Control:  $p < 0.01$ ;  
\*\*\* Statistically different from the Control:  $p < 0.001$

Table 3: Incidence of Sarcoma on the Dorsal Surface in Main and Extension animals (Peto statistical analysis)

Thyroid Findings	Animals/Dose									
	Males					Females				
Group Number	1	2	3	4	5	1	2	3	4	5
Dose of NNC 90-1170 (mg/kg/day)	0	0.03	0.2	1.0	3.0	0	0.03	0.2	1.0	3.0
Number examined	79	67	67	67	79	79	67	66	65	78
Sarcoma, dorsal surface	2	3	5	3	16***	6	4	2	0	8

\* Statistically different from the Control:  $p < 0.05$ ; \*\*\* Statistically different from the Control:  $p < 0.001$

### 3.2. Reviewer's analyses

This reviewer independently performed survival and tumor data analyses from the mouse study. For the mouse data analyses, this reviewer used similar methodologies as she used to analyze the data from the rat study. Data

used in this reviewer's analyses were provided by the sponsor electronically. As suggested by the reviewing pharmacologist Dr. Parola, this reviewer did survival analysis for main, Week 78/104 satellite groups separately and combined both studies, and tumor data analysis for main and combined both studies.

### 3.2.1. Survival analysis

In main study, the intercurrent mortality data are given in Tables 4A and 4B in the appendix for males and females, respectively. In Week 78/104 satellite group, the intercurrent mortality data are given in Tables 6A and 6B in the appendix for males and females, respectively. In combined main and week 78/104 satellite groups, the intercurrent mortality data are given in Tables 8A and 8B in the appendix for males and females, respectively.

In main study, the Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for males and females, respectively. In Week 78/104 satellite group, the Kaplan-Meier curves for death rate are given in Figures 3A and 3B in the appendix for males and females, respectively. In combined main and Week 78/104 satellite studies, the Kaplan-Meier curves for death rate are given in Figures 4A and 4B in the appendix for males and females, respectively.

In main study, results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 5A and 5B in the appendix for males and females, respectively. In Week 78/104 satellite group, results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 7A and 7B in the appendix for males and females, respectively. In combined main and week 78/104 satellite studies, results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 9A and 9B in the appendix for males and females, respectively.

**Reviewer's findings:** The tests showed no statistically significant dose response relationship or differences between the control and any of the treated groups in survivals across treatment groups in either the main, or the satellite study, or both studies combined for either sex.

### 3.2.2. Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and pairwise comparisons of control and individual treated groups are given in Table 10A and 10B in the appendix for male, respectively, of the main study, and in Table 11A and 11B in the appendix for male and female, respectively, of both studies combined.

As suggested by the reviewing pharmacologist Dr. Parola, this reviewer also did tumor data analysis for the combined tumor or organ combinations listed below:

- hemangiomas and hemangiosarcomas from all sites (include separate analysis for hemangiomas and hemangiosarcomas in both rats and mice)
- mesotheliomas (all sites, rats and mice)
- leukemias (all sites, male rats, male mice)
- lymphomas (rats and mice (all sites))
- chondroma / osteosarcoma / osteoma (all bone-- e.g., bone, cranium, femur, rats and mice)
- lipoma / liposarcoma at same tissue site (rats and mice)
- kidney tubular cell adenomas / carcinomas (male rats, male mice)
- liver hepatocellular adenomas / carcinomas (male rats, male mice)
- skin and subcutis squamous cell papilloma / carcinoma / keratoacanthoma (male rats, female rats, male mice)

testis interstitial cell adenoma / mesothelioma / rete testis adenoma / sex cord stromal tumor (male rats, male mice)  
 thyroid c-cell adenoma / carcinoma (rats and mice)  
 thyroid follicular cell adenoma / carcinoma (rats and mice)  
 mammary gland adenoma / adenocarcinoma / adenoacanthoma (female mice)  
 uterus/vagina stromal neoplasms  
 harderian gland adenoma / adenocarcinoma (male mice)  
 injection site fibroma / fibrosarcoma (male mice)  
 injection site fibroma, fibrosarcoma / sarcoma / rhabdomyosarcoma (male mice)  
 upper alimentary tract adenomas / carcinomas (stomach, duodenum, jejunum male mice)  
 lower alimentary tract adnomas / carcinomas (colon, cecum male mice)  
 alimentary tract adenomas / carcinomas (stomach, duodenum, jejunum, colon, cecum male mice)  
 lung bronchio-alveolar adenoma / carcinoma (male mice)  
 adrenal cortical adenoma / carcinoma (female mice)  
 adrenal benign and malignant pheochromocytoma (female mice)  
 pituitary adenomas / carcinomas anterior lobes (rats and mice)  
 skin and subcutis sarcoma (not specified) / fibrosarcoma / liposarcoma / rabdomyosarcoma (female mice)  
 uterus stromal polyp / endometrial stromal sarcoma (female mice)  
 uterus schwannoma / malignant schwannoma (female mice)  
 uterus leiomyoma / leiomyosarcoma (female mice)  
 oral cavity/tongue squamous cell papillomas/ carcinomas

**Reviewer’s findings:** The following tumor types showed p-values less than or equal to 0.05 either for dose response relationship or pairwise comparisons between control and individual treated groups for both main and combined studies. The analysis for combination for carcinoma and adenoma in thyroid gland was the same as adenoma because there was no tumor incidence in carcinoma in thyroid gland.

**Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons  
 Main Study in Male Mice**

Organ Name	Tumor Name	0 mg	0.03 mg	0.2 mg	1.0 mg	3.0 mg	P_Value				
		Cont N=50	Low N=50	Med N=50	Midhi N=50	High N=50	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H	P_Value MH
ADRENAL GLAND	SUBCAPSULAR CELL TUMOUR [ 1	1	9	3	3	2	0.886	0.010	0.350	0.380	0.521
ALL_SITES	HAEMANGIOSARCOMA+HAEMANGI	0	2	7	0	6	0.073	0.268	0.009	.	0.018
HAEMOPOIETIC SY	LYMPHOMA, FOLLICULAR CENT	5	0	2	4	6	0.047	0.977	0.817	0.599	0.539
LYMPH NODE (MES	HAEMANGIOMA [B]	0	0	2	0	3	0.032	.	0.274	.	0.136
SKIN AND SUBCUT	FIBROSARCOMA [M]	0	1	1	1	3	0.041	0.527	0.527	0.540	0.136
	RHABDOMYOSARCOMA [M]	0	0	1	1	3	0.017	.	0.533	0.546	0.141
THYROID GLAND	C-CELL_ADENOMA [B]	0	0	0	9	8	0.000	.	.	0.003	0.004

**Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons  
Main Study in Female Mice**

Organ Name	Tumor Name	0 mg	0.03 mg	0.2 mg	1.0 mg	3.0 mg	P_Value			P_Value	
		Cont N=50	Low N=50	Med N=50	Midhi N=50	High N=50	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	C vs. MH	P_Value C vs. H
PITUITARY GLAND	ADENOMA, ANTERIOR LOBE [B]	0	0	2	0	3	0.043	.	0.281	.	0.173
THYROID GLAND	C-CELL ADENOMA [B]	0	0	0	4	6	0.001	.	.	0.094	0.029

In the main studies, based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, the positive dose-response relationships in the incidence of C-cell adenoma in thyroid gland in both male and female mice were considered to be statistically significant since all the p-values are less than 0.025. The positive dose-response relationship in the incidence of rhabdomyosarcoma tumor in skin and subcutis in male mice was considered to be statistically significant because the p-value is 0.017 (<0.025).

Also based on the criteria by Haseman, the increased tumor incidences of C-cell adenoma in thyroid gland in the high and medium high dose groups in male mice and in high dose group in females were considered to be statistically significant when compared to the control group because all the p-values are less than 0.05. The increased tumor incidences of combined haemangiomas and hemangiosarcoms from all sites in medium and high dose groups in male mice were considered to be statistically significant when compared to the control because the p-values are less than 0.05.

**Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons  
Combined Main and Week 78/104 Satellite Studies in Male Mice**

Organ Name	Tumor Name	0 mg	0.03 mg	0.2 mg	1.0 mg	3.0 mg	P_Value			P_Value	
		Cont N=79	Low N=67	Med N=67	Midhi N=67	High N=79	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	C vs. MH	P_Value C vs. H
ADRENAL GLAND	SUBCAPSULAR CELL TUMOUR [	4	11	5	4	5	0.835	0.017	0.443	0.579	0.522
ALL_SITES	HAEMANGIOSARCOMA+HAEMANGI	1	2	10	0	7	0.159	0.421	0.003	0.468	0.034
INJECTION/TREAT	FIBROSARCOMA [M]	0	1	1	0	4	0.015	0.448	0.478	.	0.064
INJECTION_SITE	FIBROMA+FIBROSARCOMA	1	1	1	0	4	0.039	0.697	0.729	0.468	0.193
LYMPH NODE (MES	HAEMANGIOMA [B]	0	0	2	0	3	0.042	.	0.226	.	0.128
SKIN AND SUBCUT	FIBROSARCOMA [M]	0	2	1	2	7	0.002	0.207	0.482	0.221	0.008
	RHABDOMYOSARCOMA [M]	0	0	2	1	4	0.014	.	0.230	0.473	0.064
THYROID GLAND	C-CELL ADENOMA [B]	0	0	0	9	15	0.000	.	.	0.001	0.000

**Tumor Types with P-Values  $\leq 0.05$  for Dose Response Relationship or Pairwise Comparisons  
Combined Main and Week 78/104 Satellite Studies in Female Mice**

Organ Name	Tumor Name	0 mg	0.03 mg	0.2 mg	1.0 mg	3.0 mg	P_Value				
		Cont N=79	Low N=67	Med N=67	Midhi N=67	High N=79	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. MH	P_Value C vs. H
HARDERIAN GLAND	ADENOMA [B]	1	0	1	2	5	0.011	0.448	0.712	0.476	0.127
PITUITARY GLAND	ADENOMA, ANTERIOR LOBE [B]	0	0	2	0	5	0.005	.	0.204	.	0.035
SKIN AND SUBCUT	SARCOMA (NOT OTHERWISE SP	1	0	1	0	5	0.007	0.448	0.712	0.484	0.132
THYROID GLAND	C-CELL_ADENOMA+CARCINOMA	0	0	0	4	17	0.000	.	.	0.056	0.000
	C-CELL ADENOMA [B]	0	0	0	4	15	0.000	.	.	0.056	0.000
UTERUS	LEIOMYOMA [B]	5	5	11	4	10	0.282	0.526	0.047	0.473	0.181
	LEIOMYOMA+LEIOMYOSARCOMA	5	7	14	8	10	0.495	0.272	0.008	0.249	0.181

In the main and Week 78/104 satellite studies combined, based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, the dose-response relationship in the incidence of C-cell adenoma in thyroid gland in both male and female mice were considered to be statistically significant since all the p-values are less than 0.025. The dose-response relationships in the incidences of C-cell adenoma+carcinoma in thyroid gland, and adenoma in pituitary gland anterior lobe in female mice were considered to be statistically significant since all the p-values are less than 0.025. The dose-response relationships in the incidences of rhabdomyosarcoma and fibrosarcoma tumors in skin and subcutis, and fibrosarcoma in injection/treatment in male mice were considered to be statistically significant because the p-values are less than 0.025.

Also based on the criteria by Haseman, the increased tumor incidences of C-cell adenoma in thyroid gland in the high and medium high dose groups in male mice was considered to be statistically significant when compared to the control group because all the p-values are less than 0.05. The increased tumor incidence of fibrosarcoma in skin and subcutis in male mice, adenoma in pituitary gland (anterior lobe) in female mice, C-cell adenoma and C-cell combined adenoma and carcinoma in thyroid gland in female mice in high dose group were considered to be statistically significant compared to the respective control because the p-values are less than 0.05. The increased tumor incidences of combined haemangiomas and hemangiosarcoms from all sites in male mice, and combined leiomyoma and leiomyosarcoma in uterus in females in medium dose group were considered to be statistically significant when compared to the respective control because the p-values are less than 0.01.

#### 4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of Victoza (Liraglutide) in rats and mice when administered by subcutaneous injection at appropriate drug levels for about 104 weeks.

**Rat Study:** Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one control group. Two hundred Sprague-Dawley rats (Crl: CD®(SD) IGS BR) of each sex were randomly allocated to treated and control groups in equal size of 50

animals. The dose levels for groups were 0, 0.075, 0.25 and 0.75 mg/kg/day at a dose volume of 1ml/kg body weight. The tests showed no statistically significant dose response relationship or differences in survival across treatment groups in either sex. Tests showed statistically significant positive dose response relationships in the incidence of C-cell adenoma and combined C-cell adenoma and carcinoma in thyroid gland in both sexes, and C-cell carcinoma in thyroid gland in females. Pairwise comparisons showed statistically significantly increased incidence of C-cell adenoma and combined C-cell adenoma and carcinoma in high and medium dose groups in both sexes when compared to their respective control.

**Mouse Study:** Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were four treated groups and one control group. In main study, two hundred and fifty CD-1 mice (CrI: CD-1 TM(ICR)BR) of each sex were randomly allocated to treated and control groups in equal size of 50 animals. The dose levels for groups were 0, 0.03, 0.2, 1.0 and 3.0 mg/kg/day at a dose volume of 5 ml/kg. The nominal Week 78/104 study comprised of control and high dose groups with 29 male and female mice each, and low and 2 medium dose groups with 17 male and female mice each. The tests showed no statistically significant dose response relationship or differences in survival across treatment groups in either sex.

In the main study, tests showed statistically significant positive dose response relationships in the incidence of C-cell adenoma in thyroid gland in both sexes and rhabdomyosarcoma tumor in skin and subcutis in male mice. Pairwise comparisons showed statistically significantly increased incidences of C-cell adenoma in thyroid gland in high and medium high dose groups in males, C-cell adenoma in thyroid gland in high dose group in females, and combined haemangiomas and haemangiosarcomas from all sites medium and high dose groups in males when compared to their respective control.

In combined main and Week 78/104 satellite studies, tests showed statistically significant positive dose response relationships in the incidence of C-cell adenoma in thyroid gland in both sexes, C-cell combined adenoma and carcinoma in thyroid gland, adenoma in pituitary gland anterior lobe in females, rhabdomyosarcoma and fibrosarcoma in skin and subcutis, and fibrosarcoma in injection/treatment in males. Pairwise comparisons showed statistically significantly increased incidences of C-cell adenoma in thyroid gland in high and medium high dose groups in males, C-cell adenoma and C-cell combined adenoma and carcinoma in thyroid gland in females in high dose group, adenoma (anterior lobe) in pituitary gland in high dose group in females fibrosarcoma in skin and subcutis in males in high dose group, combined haemangiomas and haemangiosarcomas from all sites in males in medium dose group, and combined leiomyoma and leiomyosarcoma in uterus in females in medium dose group when compared to their respective control.

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5. Appendix

**Table 1A: Intercurrent Mortality Rate**

**Male Rats**

Week	CONTROL		LOW		MEDIUM		High	
	No. of Death	Cum. %						
0-52	2	4.0	3	6.0	2	4.0	4	8.0
53-78	6	16.0	5	16.0	5	14.0	7	22.0
79-91	9	34.0	10	36.0	6	26.0	6	34.0
92-104	10	54.0	8	52.0	8	42.0	7	48.0
Term. Sac.	23	100.0	24	100.0	29	100.0	26	100.0

**Table 1B: Intercurrent Mortality Rate**

**Female Rats**

Week	CONTROL		LOW		MEDIUM		High	
	No. of Death	Cum. %						
0-52	.	.	2	4.0	2	4.0	2	4.0
53-78	5	10.0	9	22.0	8	20.0	8	20.0
79-91	10	30.0	7	36.0	9	38.0	6	32.0
92-104	7	44.0	7	50.0	10	58.0	5	42.0
Term. Sac.	28	100.0	25	100.0	21	100.0	29	100.0

**Table 2A: Intercurrent Mortality Comparison**

**Male Rats**

Test	P-Value Cox	P-Value Kruskal-Wallis
Dose Response	0.6919	0.8593
Homogeneity	0.6614	0.6998

**Table 2B: Intercurrent Mortality Comparison**

**Female Rats**

Test	P-Value Cox	P-Value Kruskal-Wallis
Dose Response	0.7021	0.8374
Homogeneity	0.4744	0.5485

**Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Male Rats**

Organ Name	Tumor Name	0 mg	0.075 mg	0.25 mg	0.75 mg	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Cont N=50	Low N=50	Med N=50	High N=50				
ABDOMINAL CAVIT	RHABDOMYOSARCOMA [M]	0	0	0	1	0.245	.	.	0.500
ADRENAL GLAND	CORTICAL ADENOMA [B]	0	1	0	0	0.507	0.507	.	.
	PHAECHROMOCYTOMA [B]	6	6	6	6	0.488	0.397	0.435	0.623
ALL_SITES	HAEMANGIOSARCOMA+HAE	3	3	2	1	0.858	0.350	0.538	0.703
	LEUKAEMIA	2	0	0	0	0.939	0.747	0.766	0.747
	LYMPHOMA	0	2	2	1	0.448	0.247	0.267	0.507
	MESOTHELIOMA	0	2	1	0	0.690	0.253	0.526	.
BONE	OSTEOSARCOMA [M]	0	2	1	1	0.416	0.253	0.520	0.500
BRAIN	GLIOMA [M]	0	1	0	0	0.510	0.500	.	.
HAEMOPOIETIC SY	HISTIOCYTIC SARCOMA	2	3	1	0	0.950	0.525	0.530	0.753
	LEUKAEMIA, GRANULOCY	1	0	0	0	0.755	0.500	0.520	0.500
	LEUKAEMIA, LARGE GRA	1	0	0	0	0.750	0.493	0.513	0.493
	LYMPHOMA, FOLLICULAR	0	1	0	0	0.510	0.500	.	.
	LYMPHOMA, LYMPHOCYTI	0	1	2	1	0.329	0.500	0.267	0.507
HEART	HAEMANGIOSARCOMA [M]	1	0	0	0	0.755	0.500	0.520	0.500
	MESOTHELIOMA [M]	0	0	1	0	0.243	.	0.526	.
JEJUNUM	LEIOMYOSARCOMA [M]	1	0	0	0	0.750	0.493	0.513	0.493
KIDNEY	LIPOMA [B]	1	0	0	0	0.755	0.500	0.520	0.500
	LIPOMA+LIPOSARCOMA	3	0	0	0	0.986	0.880	0.894	0.880
	LIPOSARCOMA [M]	2	0	0	0	0.941	0.753	0.772	0.753
	TUBULAR CELL ADENOMA	0	0	0	1	0.245	.	.	0.500
	TUBULAR CELL CARCINO	0	0	1	0	0.245	.	0.520	.
	TUBULAR CELL TUMOR	0	0	1	1	0.190	.	0.520	0.500
LIVER	HEPATOCELLULAR ADENO	1	0	0	1	0.431	0.500	0.520	0.753
	HEPATOCELLULAR CARCI	0	0	0	1	0.245	.	.	0.500
	HEPATOCELLULAR TUMOR	1	0	0	2	0.149	0.500	0.520	0.500
LYMPH NODE (MES	HAEMANGIOMA [B]	0	1	1	1	0.304	0.500	0.520	0.507
	HAEMANGIOSARCOMA [M]	1	1	1	0	0.738	0.253	0.267	0.500
MAMMARY GLAND	CARCINOMA [M]	0	1	0	0	0.507	0.507	.	.
	FIBROADENOMA [B]	1	3	0	0	0.947	0.318	0.520	0.500
ORAL CAVITY	SQUAMOUS-CELL PAPILL	0	0	1	0	0.245	.	0.520	.
ORAL_CAVITY/TON	PAPILLOMA+CARCINOMA	0	0	1	0	0.245	.	0.520	.
PANCREAS	ACINAR-CELL+MIXED-AC	1	1	0	1	0.529	0.753	0.520	0.753
PANCREAS (ENDOC	ISLET CELL ADENOMA [	6	1	2	1	0.939	0.942	0.885	0.942
	MIXED ACINAR/ISLET C	0	0	0	1	0.245	.	.	0.500
PANCREAS (EXOCR	ACINAR CELL ADENOMA	1	1	0	0	0.820	0.753	0.520	0.500

**Table 3A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Male Rats**

Organ Name	Tumor Name	0 mg	0.075 mg	0.25 mg	0.75 mg	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Cont N=50	Low N=50	Med N=50	High N=50				
PANCREAS ;	ISLET-CELL+MIXED-ACI	6	1	2	2	0.811	0.942	0.885	0.860
PARATHYROID GLA	ADENOMA [B]	1	2	2	1	0.552	0.510	0.530	0.753
PITUITARY	ANTERIOR_LOBE TUMOR	27	23	26	26	0.481	0.656	0.599	0.500
PITUITARY GLAND	ADENOMA, ANTERIOR LO	27	22	26	25	0.556	0.691	0.599	0.586
	CARCINOMA, ANTERIOR	0	1	0	1	0.315	0.507	.	0.507
PREPUTIAL GLAND	ADENOMA [B]	0	0	0	1	0.245	.	.	0.500
SALIVARY GLAND	CARCINOMA [M]	0	1	0	0	0.507	0.507	.	.
SEMINAL VESICLE	ADENOMA [B]	0	1	0	0	0.510	0.500	.	.
SKIN AND SUBCUT	BASAL CELL ADENOMA [	0	2	0	2	0.185	0.253	.	0.247
	BASAL CELL CARCINOMA	0	1	1	0	0.500	0.500	0.520	.
	BASAL-CELL TUMOR	0	3	1	2	0.300	0.125	0.520	0.247
	DERMAL FIBROMA [B]	9	11	3	10	0.457	0.425	0.958	0.527
	FIBROMA [B]	6	5	4	2	0.930	0.481	0.680	0.860
	FIBROSARCOMA [M]	2	1	2	0	0.851	0.500	0.327	0.747
	HAEMANGIOSARCOMA [M]	0	1	0	0	0.507	0.507	.	.
	KERATOACANTHOMA [B]	3	6	5	2	0.831	0.253	0.401	0.500
	LIPOMA [B]	2	3	5	0	0.909	0.513	0.260	0.753
	MALIGNANT SCHWANNOMA	0	0	1	1	0.190	.	0.526	0.500
	MYXOSARCOMA [M]	0	0	1	0	0.245	.	0.520	.
	NEURAL CREST TUMOUR	0	1	0	1	0.316	0.500	.	0.507
	SARCOMA (NOT OTHERWI	0	1	0	0	0.507	0.507	.	.
	SEBACEOUS CELL ADENO	1	0	1	1	0.396	0.500	0.273	0.753
	SQUAMOUS-CELL CARCIN	0	1	0	0	0.510	0.500	.	.
SQUAMOUS-CELL PAPILL	1	1	3	0	0.762	0.753	0.338	0.500	
SQUAMOUS-CELL TUMOR	4	7	8	2	0.900	0.274	0.214	0.663	
STOMACH	SQUAMOUS-CELL CARCIN	0	0	1	0	0.245	.	0.520	.
TESTIS	ADENOCARCINOMA [M]	1	0	0	0	0.755	0.500	0.520	0.500
	ADENOMA+MESOTHELIOMA	5	4	2	5	0.402	0.517	0.816	0.632
	HAEMANGIOSARCOMA [M]	1	0	0	0	0.755	0.500	0.520	0.500
	INTERSTITIAL CELL AD	5	3	2	5	0.333	0.660	0.816	0.632
	MESOTHELIOMA [M]	0	2	0	0	0.758	0.253	.	.
THYMUS	BENNIGN+MALIGNANT_TH	0	1	0	1	0.310	0.500	.	0.500
THYMUS	THYMOMA [B]	0	0	0	1	0.245	.	.	0.500
	THYMOMA [M]	0	1	0	0	0.510	0.500	.	.
THYROID GLAND	C-CELL ADENOMA [B]	6	8	21	23	0.000	0.384	0.002	0.000
	C-CELL CARCINOMA [M]	1	4	3	7	0.023	0.187	0.338	0.031
	C-CELL TUMOR	7	11	21	28	0.000	0.229	0.005	0.000
	FOLLICULAR CELL ADEN	0	2	1	2	0.195	0.253	0.520	0.247
	FOLLICULAR CELL CARC	0	1	1	0	0.497	0.507	0.526	.
	FOLLICULAR-CELL_TUMO	0	3	2	2	0.312	0.125	0.273	0.247

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Female Rats

Organ Name	Tumor Name	0 mg	0.075 mg	0.25 mg	0.75 mg	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Cont N=50	Low N=50	Med N=50	High N=50				
ADRENAL GLAND	CORTICAL ADENOMA [B]	3	1	0	2	0.468	0.653	0.860	0.464
	PHAECHROMOCYTOMA [B]	0	1	2	1	0.317	0.481	0.234	0.487
	SUBCAPSULAR CELL TUM	0	1	0	0	0.493	0.481	.	.
ALL_SITES	HAEMANGIOSARCOMA+HAE	1	0	0	0	0.737	0.481	0.481	0.487
	LYMPHOMA	2	1	1	1	0.601	0.471	0.461	0.481
BRAIN	GRANULAR CELL TUMOUR	0	0	0	1	0.255	.	.	0.494
	OLIGODENDROGLIOMA [M]	1	0	0	0	0.737	0.481	0.481	0.487
DUODENUM	LEIOMYOMA [B]	0	1	0	0	0.493	0.481	.	.
	LEIOMYOMA+LEIOMYOSAR	0	1	1	0	0.497	0.481	0.481	.
	LEIOMYOSARCOMA [M]	0	0	1	0	0.250	.	0.481	.
HAEMOPOIETIC SY	HISTIOCYTIC SARCOMA	0	0	0	1	0.255	.	.	0.494
	LEUKAEMIA, GRANULOCY	0	0	0	1	0.255	.	.	0.494
	LYMPHOMA [M]	1	0	0	0	0.732	0.474	0.474	0.481
	LYMPHOMA, LYMPHOCYTI	1	1	1	1	0.512	0.740	0.733	0.747
LIVER	CHOLANGIOMA [B]	0	0	1	0	0.250	.	0.481	.
	HEPATOCELLULAR ADENO	1	1	1	1	0.506	0.733	0.733	0.740
LYMPH NODE (MES	HAEMANGIOMA [B]	1	0	0	0	0.737	0.481	0.481	0.487
MAMMARY	ADENOMA+CARCINOMA	14	14	12	10	0.864	0.499	0.505	0.743
	FIBROADENOMA+FIBROCA	28	25	26	20	0.927	0.515	0.544	0.876
MAMMARY GLAND	ADENOMA [B]	4	5	5	5	0.429	0.467	0.484	0.500
	CARCINOMA [M]	10	13	8	5	0.968	0.221	0.512	0.838
	FIBROADENOMA [B]	28	25	26	20	0.927	0.515	0.544	0.876
	FIBROCARCINOMA [M]	0	0	1	0	0.248	.	0.487	.
ORAL_CAVITY/TON	PAPILLOMA+CARCINOMA	1	0	0	0	0.737	0.481	0.481	0.487
OVARY	FIBROMA [B]	0	1	0	1	0.306	0.481	.	0.487
	GRANULOSA/THECAL CEL	0	1	0	0	0.493	0.481	.	.
PANCREAS (ENDOC	ISLET CELL ADENOMA [	0	0	0	1	0.250	.	.	0.487
PARATHYROID GLA	ADENOMA [B]	1	0	1	2	0.161	0.474	0.727	0.471
PITUITARY GLAND	ADENOMA, ANTERIOR LO	34	27	35	28	0.665	0.770	0.434	0.696
	ADENOMA, INTERMEDIAT	0	0	1	1	0.184	.	0.481	0.487
	CARCINOMA, ANTERIOR	1	0	1	5	0.007	0.474	0.727	0.089
PITUITARY_ANTER	ADENOMA+CARCINOMA	35	27	36	33	0.252	0.790	0.366	0.510
PREPUTIAL GLAND	SQUAMOUS-CELL CARCIN	1	0	0	0	0.737	0.481	0.481	0.487
SKIN AND SUBCUT	BASAL CELL ADENOMA [	1	1	0	0	0.803	0.733	0.481	0.487
	DERMAL FIBROMA [B]	0	1	1	0	0.497	0.481	0.481	.
	FIBROMA [B]	4	1	1	1	0.841	0.796	0.796	0.804
	FIBROSARCOMA [M]	0	2	0	0	0.745	0.228	.	.

Table 3B (Continue): Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Female Rats

Organ Name	Tumor Name	0 mg	0.075 mg	0.25 mg	0.75 mg	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Cont N=50	Low N=50	Med N=50	High N=50				
	KERATOACANTHOMA [B]	0	1	0	1	0.306	0.481	.	0.487
	LIPOMA [B]	1	1	0	1	0.537	0.733	0.481	0.747
	MYXOMA [B]	0	0	0	1	0.250	.	.	0.487
	SARCOMA [M]	0	0	1	0	0.248	.	0.487	.
	SQUAMOUS-CELL CARCIN	0	1	0	0	0.493	0.481	.	.
	SQUAMOUS-CELL PAPILL	0	1	0	0	0.493	0.481	.	.
SKIN_AND_SUBCUT	PAPILLOMA+KERATOACAN	0	2	0	1	0.431	0.228	.	0.487
SPINAL CORD	MENINGEAL SARCOMA [M]	0	0	1	0	0.248	.	0.487	.
THYROID	C-CELL_ADENOMA+CARCI	5	13	18	29	0.000	0.022	0.001	0.000
	FOLLICULAR-CELL_ADEN	1	0	2	0	0.637	0.481	0.470	0.487
THYROID GLAND	C-CELL ADENOMA [B]	5	13	16	28	0.000	0.022	0.003	0.000
	C-CELL CARCINOMA [M]	0	0	2	3	0.023	.	0.228	0.111
	FOLLICULAR CELL ADEN	1	0	2	0	0.637	0.481	0.470	0.487
TONGUE	SQUAMOUS-CELL CARCIN	1	0	0	0	0.737	0.481	0.481	0.487
UTERUS	ADENOCARCINOMA [M]	1	0	0	0	0.737	0.481	0.481	0.487
	ADENOMA [B]	0	0	0	1	0.255	.	.	0.494
	ADENOMA+ADENOCARCINO	1	0	0	1	0.446	0.481	0.481	0.747
	FIBROMA [B]	1	0	0	0	0.737	0.481	0.481	0.487
	STROMAL POLYP [B]	5	5	7	10	0.046	0.581	0.324	0.105
	STROMAL SARCOMA [M]	3	1	2	0	0.914	0.643	0.452	0.860
UTERUS_STROMAL	POLYP+SARCOMA	8	6	9	10	0.161	0.514	0.386	0.308

**Table 4A: Intercurrent Mortality Rate  
Male Mice in Main Study**

Week	CONTROL		LOW		MEDIUM		MEDIUM HIGH		HIGH	
	NO.OF		NO.OF		NO.OF		NO.OF		NO.OF	
	DEATH	Cum %	DEATH	Cum %	DEATH	Cum %	DEATH	Cum %	DEATH	Cum %
0-52	3	6.0	5	10.0	3	6.0	3	6.0	2	4.0
53-78	11	28.0	6	22.0	8	22.0	4	14.0	7	18.0
79-91	7	42.0	2	26.0	4	30.0	4	22.0	10	38.0
92-104	4	50.0	8	42.0	7	44.0	8	38.0	12	62.0
Term. Sac.	25	100.0	29	100.0	28	100.0	31	100.0	19	100.0

**Table 4B: Intercurrent Mortality Rate  
Female Mice in Main Study**

Week	CONTROL		LOW		MEDIUM		MEDIUM HIGH		HIGH	
	NO.OF		NO.OF		NO.OF		NO.OF		NO.OF	
	DEATH	Cum %	DEATH	Cum %	DEATH	Cum %	DEATH	Cum %	DEATH	Cum %
0-52	7	14.0	4	8.0	4	8.0	3	6.0	3	6.0
53-78	18	50.0	10	28.0	14	36.0	11	28.0	10	26.0
79-91	5	60.0	16	60.0	7	50.0	8	44.0	9	44.0
92-104	6	72.0	9	78.0	6	62.0	9	62.0	9	62.0
Term. Sac.	14	100.0	11	100.0	19	100.0	19	100.0	19	100.0

**Table 5A: Intercurrent Mortality Comparison  
Male Mice in Main Study**

Test	P-Value	P-Value
	Cox	Kruskal-Wallis
Dose Response	0.1504	0.3752
Homogeneity	0.2060	0.3001

**Table 5B: Intercurrent Mortality Comparison  
Female Mice in Main Study**

Test	P-Value	P-Value
	Cox	Kruskal-Wallis
Dose Response	0.1004	0.0538
Homogeneity	0.2826	0.1700

**Table 6A: Intercurrent Mortality Rate  
Male Mice in Week 78/104 satellite group**

Week	CONTROL		LOW		MEDIUM		MEDIUM HIGH		HIGH	
	NO.OF DEATH	Cum %								
0-52	1	3.4	4	23.5	1	5.9	2	11.8	1	3.4
53-78	4	17.2	3	41.2	.	.	7	52.9	6	24.1
79-91	2	24.1	2	52.9	2	17.6	.	.	3	34.5
92-104	8	51.7	3	70.6	5	47.1	1	58.8	5	51.7
Term. Sac.	14	100.0	5	100.0	9	100.0	7	100.0	14	100.0

**Table 6B: Intercurrent Mortality Rate  
Female Mice in Week 78/104 satellite group**

Week	CONTROL		LOW		MEDIUM		MEDIUM HIGH		HIGH	
	NO.OF DEATH	Cum %								
0-52	3	10.3	5	29.4	2	11.8	1	5.9	5	17.2
53-78	3	20.7	4	52.9	5	41.2	4	29.4	7	41.4
79-91	5	37.9	2	64.7	3	58.8	4	52.9	1	44.8
92-104	9	69.0	3	82.4	3	76.5	3	70.6	7	69.0
Term. Sac.	9	100.0	3	100.0	4	100.0	5	100.0	9	100.0

**Table 7A: Intercurrent Mortality Comparison  
Male Mice in Week 78/104 satellite group**

Test	P-Value Cox	P-Value Kruskal- Wallis
Dose Response	0.8124	0.8719
Homogeneity	0.2625	0.1028

**Table 7B: Intercurrent Mortality Comparison  
Female Mice in Week 78/104 satellite group**

Test	P-Value Cox	P-Value Kruskal- Wallis
Dose Response	0.7930	0.9751
Homogeneity	0.5190	0.2562

**Table 8A: Intercurrent Mortality Rate  
Male Mice in Combined Main and Week 78/104 Satellite Studies**

Week	CONTROL		LOW		MEDIUM		MEDIUM HIGH		HIGH	
	NO.OF		NO.OF		NO.OF		NO.OF		NO.OF	
	DEATH	Cum %	DEATH	Cum %	DEATH	Cum %	DEATH	Cum %	DEATH	Cum %
0-52	4	5.1	9	13.4	4	6.0	5	7.5	3	3.8
53-78	15	24.1	9	26.9	8	17.9	11	23.9	13	20.3
79-91	9	35.4	4	32.8	6	26.9	4	29.9	13	36.7
92-104	12	50.6	11	49.3	12	44.8	9	43.3	17	58.2
Term. Sac.	39	100.0	34	100.0	37	100.0	38	100.0	33	100.0

**Table 8B: Intercurrent Mortality Rate  
Female Mice in Combined Main and Week 78/104 Satellite Studies**

Week	CONTROL		LOW		MEDIUM		MEDIUM HIGH		HIGH	
	NO.OF		NO.OF		NO.OF		NO.OF		NO.OF	
	DEATH	Cum %	DEATH	Cum %	DEATH	Cum %	DEATH	Cum %	DEATH	Cum %
0-52	10	12.7	9	13.4	6	9.0	4	6.0	8	10.1
53-78	21	39.2	14	34.3	19	37.3	15	28.4	17	31.6
79-91	10	51.9	18	61.2	10	52.3	12	46.3	10	44.3
92-104	14	69.6	12	79.1	9	65.7	12	64.2	16	64.6
Term. Sac.	24	100.0	14	100.0	23	100.0	24	100.0	28	100.0

**Table 9A: Intercurrent Mortality Comparison  
Male Mice in Combined Main and Week 78/104 Satellite Studies**

Test	P-Value	P-Value
	Cox	Kruskal-Wallis
Dose Response	0.2903	0.5184
Homogeneity	0.5051	0.5900

**Table 9B: Intercurrent Mortality Comparison  
Female Mice in Combined Main and Week 78/104 Satellite Studies**

Test	P-Value	P-Value
	Cox	Kruskal-Wallis
Dose Response	0.1639	0.1404
Homogeneity	0.3284	0.3512

Table 10A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Male Mice in Main Study

Organ Name	Tumor Name	0 mg	0.03 mg	0.2 mg	1.0 mg	3.0 mg	P_Value				
		Cont N=50	Low N=50	Med N=50	Midhi N=50	High N=50	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	C vs. MH	P_Value C vs. H
ADRENAL GLAND	PHAECHROMOCYTOMA [B]	1	0	1	0	1	0.390	0.514	0.267	0.533	0.253
	SUBCAPSULAR CELL TUMOUR [	1	9	3	3	2	0.886	0.010	0.350	0.380	0.521
ALIMENTARY_TRAC	ADENOMA+CARCINOMA	0	0	0	2	1	0.124	.	.	0.294	0.514
ALL_BONE	CHONDROMA+OSTEOSARCOMA+OS	0	2	0	0	0	0.851	0.274	.	.	.
ALL_SITES	HAEMANGIOSARCOMA+HAEMANGI	0	2	7	0	6	0.073	0.268	0.009	.	0.018
	LEUKEMIA	1	0	0	0	0	0.816	0.521	0.527	0.540	0.514
	LYMPHOMA	7	2	2	5	6	0.173	0.930	0.935	0.710	0.521
	MESOTHELIOMA	0	0	0	1	0	0.414	.	.	0.546	.
CAECUM	ADENOCARCINOMA [M]	0	1	0	0	0	0.616	0.521	.	.	.
COLON	ADENOCARCINOMA [M]	0	0	0	1	0	0.414	.	.	0.546	.
DUODENUM	OSTEOSARCOMA [M]	0	1	0	0	0	0.616	0.521	.	.	.
EPIDIDYMIS	HISTIOCYTIC SARCOMA [M]	1	0	0	0	0	0.816	0.521	0.527	0.540	0.514
	INTERSTITIAL CELL ADENOMA	0	0	0	1	1	0.122	.	.	0.540	0.514
EYE	AMELANOTIC MELANOMA [M]	0	0	0	1	0	0.411	.	.	0.540	.
FEMUR	CHONDROMA [B]	0	1	0	0	0	0.616	0.521	.	.	.
FOOT/LEG	HAEMANGIOSARCOMA [M]	0	0	1	0	0	0.411	.	0.527	.	.
GALL BLADDER	ADENOMA [B]	0	1	0	0	0	0.616	0.521	.	.	.
HAEMOPOIETIC SY	HISTIOCYTIC SARCOMA [M]	0	0	1	0	0	0.411	.	0.527	.	.
	LEUKAEMIA, GRANULOCYTIC [	1	0	0	0	0	0.816	0.521	0.527	0.540	0.514
HAEMOPOIETIC SY	LYMPHOMA [M]	1	2	0	0	0	0.951	0.521	0.520	0.533	0.507
	LYMPHOMA, FOLLICULAR CENT	5	0	2	4	6	0.047	0.977	0.817	0.599	0.539
	LYMPHOMA, LYMPHOCYTIC [M]	1	0	0	1	0	0.574	0.521	0.527	0.288	0.514
HARDERIAN GLAND	ADENOCARCINOMA [M]	0	0	2	0	0	0.654	.	0.274	.	.
	ADENOMA [B]	2	3	1	1	2	0.520	0.540	0.541	0.560	0.329
HARDERIAN_GLAND	ADENOMA+ADENOCARCINOMA	2	3	3	1	2	0.641	0.540	0.552	0.560	0.329
INJECTION/TREAT	FIBROSARCOMA [M]	0	1	1	0	2	0.125	0.521	0.527	.	0.268
	RHABDOMYOSARCOMA [M]	1	0	0	0	0	0.816	0.521	0.527	0.540	0.514
	SARCOMA (NOT OTHERWISE SP	1	0	1	0	0	0.778	0.521	0.274	0.540	0.514
	SQUAMOUS-CELL PAPILLOMA [	0	0	0	0	1	0.199	.	.	.	0.521
INJECTION_SITE	FIBROMA+FIBROSARCOMA	0	1	1	0	2	0.125	0.521	0.527	.	0.268
	SARCOMA+RHABDOMYOSARCOMA+	2	1	2	0	2	0.421	0.531	0.350	0.791	0.339
JEJUNUM	ADENOMA [B]	0	0	0	1	0	0.411	.	.	0.540	.
KIDNEY	ADENOMA+CARCINOMA	2	0	4	2	0	0.897	0.774	0.391	0.370	0.767

**Table 10A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Male Mice in Main Study**

Organ Name	Tumor Name	0 mg	0.03 mg	0.2 mg	1.0 mg	3.0 mg	P_Value				
		Cont N=50	Low N=50	Med N=50	Midhi N=50	High N=50	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H	
	TUBULAR CELL ADENOMA [B]	2	0	2	2	0	0.815	0.774	0.350	0.370	0.767
	TUBULAR CELL CARCINOMA [M]	0	0	2	0	0	0.654	.	0.274	.	.
LIVER	ADENOMA+CARCINOMA	8	5	4	6	9	0.129	0.796	0.885	0.750	0.577
	HAEMANGIOMA [B]	0	1	0	0	1	0.280	0.521	.	.	0.514
	HAEMANGIOSARCOMA [M]	0	1	0	0	0	0.616	0.521	.	.	.
	HEPATOCELLULAR ADENOMA [B]	6	4	4	4	7	0.176	0.700	0.715	0.743	0.545
	HEPATOCELLULAR CARCINOMA	3	2	0	2	2	0.439	0.540	0.899	0.587	0.527
	ITO CELL TUMOUR [B]	0	1	1	0	0	0.695	0.521	0.527	.	.
LOWER_ALIMENTAR	ADENOMA+CARCINOMA	0	0	0	1	0	0.414	.	.	0.546	.
LUNG	ADENOMA+CARCINOMA	12	16	18	11	7	0.994	0.327	0.238	0.671	0.885
	BRONCHIOLO-ALVEOLAR ADENO	10	14	12	6	4	0.998	0.307	0.488	0.883	0.946
	BRONCHIOLO-ALVEOLAR CARCI	3	2	9	5	5	0.392	0.540	0.091	0.463	0.403
LYMPH NODE (MES	HAEMANGIOMA [B]	0	0	2	0	3	0.032	.	0.274	.	0.136
PANCREAS (EXOCR	MESOTHELIOMA [M]	0	0	0	1	0	0.414	.	.	0.546	.
PITUITARY GLAND	ADENOMA, ANTERIOR LOBE [B]	1	0	1	1	0	0.652	0.521	0.274	0.288	0.514
SEMINAL VESICLE	GRANULAR CELL TUMOUR [M]	1	0	0	0	0	0.816	0.521	0.527	0.540	0.514
	LEIOMYOSARCOMA [M]	0	1	0	0	0	0.616	0.521	.	.	.
SKIN AND SUBCUT	FIBROSARCOMA [M]	0	1	1	1	3	0.041	0.527	0.527	0.540	0.136
	HAEMANGIOSARCOMA [M]	0	0	1	0	1	0.202	.	0.527	.	0.514
	KERATOACANTHOMA [B]	0	0	1	0	0	0.411	.	0.527	.	.
	LEIOMYOSARCOMA [M]	0	0	1	0	1	0.202	.	0.527	.	0.514
	MALIGNANT SCHWANNOMA [M]	0	0	1	0	0	0.411	.	0.527	.	.
	MYXOMA [B]	1	0	0	0	0	0.812	0.514	0.520	0.533	0.507
	NEUROFIBROSARCOMA [M]	0	0	0	0	1	0.195	.	.	.	0.514
	PAPILLOMA+CARCINOMA+KERAT	0	0	2	0	0	0.654	.	0.274	.	.
	RHABDOMYOSARCOMA [M]	0	0	1	1	3	0.017	.	0.533	0.546	0.141
	SARCOMA (NOT OTHERWISE SP	1	0	0	0	0	0.816	0.521	0.527	0.540	0.514
	SEBACEOUS CELL ADENOMA [B]	1	0	0	0	0	0.816	0.521	0.527	0.540	0.514
	SQUAMOUS-CELL PAPILLOMA [	0	0	1	0	0	0.411	.	0.527	.	.
SPINAL CORD	ASTROCYTOMA [B]	0	1	0	0	0	0.616	0.521	.	.	.
	MENINGEAL SARCOMA [M]	0	0	1	0	0	0.411	.	0.527	.	.
STERNUM	MAST CELL TUMOUR [B]	0	0	0	1	0	0.411	.	.	0.540	.
STOMACH	ADENOMA [B]	0	0	0	0	1	0.195	.	.	.	0.514
TESTIS	HAEMANGIOMA [B]	0	0	3	0	0	0.797	.	0.141	.	.
	INTERSTITIAL CELL ADENOMA	9	2	0	3	3	0.693	0.982	0.999	0.966	0.955
	INTERSTITIAL_ADENOMA+RET	9	4	0	5	3	0.773	0.909	0.999	0.876	0.955
	RETE TESTIS ADENOMA [B]	0	1	0	2	0	0.518	0.521	.	0.288	.
	SEX CORD/STROMAL TUMOUR [	0	1	0	0	0	0.616	0.521	.	.	.

**Table 10A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Male Mice in Main Study**

Organ Name	Tumor Name	0 mg	0.03 mg	0.2 mg	1.0 mg	3.0 mg	P_Value			P_Value	
		Cont N=50	Low N=50	Med N=50	Midhi N=50	High N=50	Dos Resp P_Value	C vs. L P_Value	C vs. M P_Value	C vs. MH P_Value	C vs. H P_Value
THYROID	C-CELL_ADENOMA+CARCINOMA	0	0	0	9	8	0.000	.	.	0.003	0.004
	FOLLICULAR-CELL_ADENOMA+C	0	1	0	2	2	0.079	0.527	.	0.288	0.268
THYROID GLAND	C-CELL ADENOMA [B]	0	0	0	9	8	0.000	.	.	0.003	0.004
	FOLLICULAR CELL ADENOMA [	0	1	0	2	1	0.221	0.527	.	0.288	0.514
	FOLLICULAR CELL CARCINOMA	0	0	0	0	1	0.199	.	.	.	0.521
UPPER_ALIMENTAR	ADENNOMA+CARCINOMA	0	0	0	1	1	0.122	.	.	0.540	0.514
VERTEBRAE	HAEMANGIOMA [B]	0	0	0	0	1	0.195	.	.	.	0.514

**APPEARS THIS WAY  
ON ORIGINAL**

Table 10B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Female Mice in Main Study

Organ Name	Tumor Name	0 mg	0.03 mg	0.2 mg	1.0 mg	3.0 mg	P_Value				
		Cont N=50	Low N=50	Med N=50	Midhi N=50	High N=50	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	C vs. MH	P_Value C vs. H
ADRENAL	PHEOCHROMOCYTOMA_BENIGN+M	2	0	0	1	0	0.798	0.771	0.771	0.560	0.799
ADRENAL GLAND	CORTICAL CARCINOMA [M]	0	0	1	0	0	0.437	.	0.535	.	.
	PHAECHROMOCYTOMA [B]	2	0	0	1	0	0.798	0.771	0.771	0.560	0.799
	SUBCAPSULAR CELL TUMOUR [	0	0	0	1	0	0.440	.	.	0.565	.
ADRENAL_CORTICA	ADENOMA+CARCINOMA	0	0	1	0	0	0.437	.	0.535	.	.
ALL_BONE	CHONDROMA+OSTEOSARCOMA+OS	0	0	1	0	0	0.434	.	0.542	.	.
ALL_SITES	HAEMANGIOSARCOMA+HAEMANGI	4	6	8	3	2	0.982	0.456	0.259	0.610	0.776
	LYMPHOMA	12	9	17	11	11	0.827	0.729	0.220	0.660	0.687
	MESOTHELIOMA	0	1	0	0	0	0.633	0.535	.	.	.
BONE	HAEMANGIOSARCOMA [M]	1	0	0	0	0	0.824	0.525	0.525	0.548	0.556
BRAIN	LIPOMA [B]	0	0	0	1	0	0.437	.	.	0.557	.
	MALIGNANT ASTROCYTOMA [M]	1	0	0	0	0	0.829	0.535	0.535	0.557	0.565
CAECUM	LEIOMYOMA [B]	0	2	0	0	0	0.867	0.281	.	.	.
	LEIOMYOSARCOMA [M]	0	0	0	1	0	0.440	.	.	0.565	.
	PLASMACYTOMA [B]	0	1	0	0	0	0.633	0.535	.	.	.
COLON	ADENOCARCINOMA [M]	1	0	0	0	0	0.829	0.535	0.535	0.557	0.565
CRANIUM	OSTEOMA [B]	0	0	1	0	0	0.434	.	0.542	.	.
DUODENUM	ADENOMA [B]	0	0	0	1	0	0.440	.	.	0.565	.
	HAEMANGIOMA [B]	0	1	0	0	0	0.633	0.535	.	.	.
FEMUR	OSTEOMA [B]	0	0	1	0	0	0.434	.	0.542	.	.
HAEMOPOIETIC SY	HISTIOCYTIC SARCOMA [M]	4	5	3	3	1	0.970	0.565	0.557	0.607	0.882
	LEUKAEMIA, GRANULOCYTIC [	0	0	0	1	0	0.440	.	.	0.565	.
	LYMPHOMA [M]	6	2	5	4	4	0.626	0.891	0.546	0.726	0.726
	LYMPHOMA, FOLLICULAR CENT	6	7	11	6	6	0.865	0.604	0.183	0.540	0.561
	LYMPHOMA, LYMPHOCYTIC [M]	0	0	0	0	1	0.222	.	.	.	0.565
	LYMPHOMA, PLASMACYTIC [M]	0	0	1	1	0	0.440	.	0.535	0.557	.
HARDERIAN GLAND	ADENOMA [B]	1	0	1	1	3	0.065	0.535	0.290	0.307	0.411
INJECTION/TREAT	KERATOACANTHOMA [B]	0	0	0	1	0	0.440	.	.	0.565	.
	SARCOMA (NOT OTHERWISE SP	0	1	0	0	0	0.633	0.535	.	.	.
LIVER	HAEMANGIOMA [B]	0	1	2	0	0	0.831	0.535	0.281	.	.
	HEPATOCELLULAR ADENOMA [B	1	0	0	3	0	0.649	0.535	0.535	0.399	0.565
	HEPATOCELLULAR CARCINOMA	0	1	1	1	0	0.644	0.535	0.535	0.565	.
LUNG	BRONCHIOLO-ALVEOLAR ADENO	3	6	8	3	4	0.822	0.327	0.137	0.434	0.626
	BRONCHIOLO-ALVEOLAR CARCI	2	0	4	1	3	0.303	0.771	0.384	0.571	0.590
	MESOTHELIOMA [M]	0	1	0	0	0	0.633	0.535	.	.	.

**Table 10B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Female Mice in Main Study**

Organ Name	Tumor Name	0 mg	0.0 3 mg	0.2 mg	1.0 mg	3.0 mg	P_Value				
		Cont N=50	Low N=50	Med N=50	Midhi N=50	High N=50	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. MH	P_Value C vs. H
LYMPH NODE (MES	HAEMANGIOMA [B]	2	1	1	0	0	0.966	0.553	0.553	0.808	0.814
MAMMARY GLAND	ADENOACANTHOMA [M]	0	1	0	1	1	0.269	0.535	.	0.557	0.565
	ADENOCARCINOMA [M]	1	2	4	1	1	0.830	0.539	0.233	0.297	0.313
	ADENOMA [B]	0	0	0	0	1	0.222	.	.	.	0.565
MAMMARY_GLAND	ADENOMA+ADENOACANTHOMA+AD	1	3	4	2	3	0.482	0.346	0.233	0.574	0.407
MESENTERY	HAEMANGIOSARCOMA [M]	0	0	1	0	0	0.437	.	0.535	.	.
ORAL CAVITY	SQUAMOUS-CELL CARCINOMA [	0	0	0	0	1	0.222	.	.	.	0.565
ORAL_CAVITY/VAG	PAPILLOMA+CARCINOMA	0	1	0	0	1	0.319	0.535	.	.	0.565
OVARY	CYSTADENOMA [B]	0	1	1	0	0	0.722	0.535	0.535	.	.
	DECIDUOMA [B]	0	1	0	0	0	0.633	0.535	.	.	.
	GRANULOSA CELL TUMOUR [B]	0	0	1	0	0	0.437	.	0.535	.	.
	HAEMANGIOMA [B]	0	1	0	0	0	0.633	0.535	.	.	.
	LEIOMYOMA [B]	0	0	1	0	0	0.437	.	0.535	.	.
	LUTEOMA [B]	0	1	1	1	2	0.153	0.535	0.535	0.557	0.315
	SARCOMA (NOT OTHERWISE SP	0	0	0	1	0	0.437	.	.	0.557	.
	SERTOLI CELL TUMOUR [B]	0	0	0	1	1	0.144	.	.	0.557	0.565
SEX CORD/STROMAL TUMOUR [	0	0	1	0	0	0.437	.	0.535	.	.	
	TUBULOSTROMAL ADENOMA [B]	1	0	1	1	3	0.066	0.535	0.281	0.307	0.411
PITUITARY GLAND	ADENOMA, ANTERIOR LOBE [B	0	0	2	0	3	0.043	.	0.281	.	0.173
	ADENOMA, INTERMEDIATE LOB	0	0	0	2	1	0.154	.	.	0.315	0.565
SKELETAL MUSCLE	LIPOSARCOMA [M]	0	0	0	0	1	0.222	.	.	.	0.565
	RHABDOMYOSARCOMA [M]	1	0	0	0	0	0.824	0.525	0.525	0.548	0.556
	SARCOMA (NOT OTHERWISE SP	1	0	0	0	0	0.829	0.535	0.535	0.557	0.565
SKIN AND SUBCUT	BASAL CELL CARCINOMA [M]	2	0	0	0	1	0.540	0.788	0.788	0.808	0.598
	FIBROSARCOMA [M]	0	1	1	0	2	0.154	0.535	0.535	.	0.315
	LIPOSARCOMA [M]	0	2	0	0	0	0.864	0.290	.	.	.
	MALIGNANT FIBROUS HISTIOC	1	0	0	0	0	0.824	0.525	0.525	0.548	0.556
	RHABDOMYOSARCOMA [M]	2	1	1	0	0	0.964	0.539	0.539	0.800	0.807
	SARCOMA (NOT OTHERWISE SP	1	0	1	0	3	0.061	0.525	0.272	0.548	0.407
SKIN_AND_SUBCUT	SARCOMA+FIBROSARCOMA+LIPO	3	4	3	0	5	0.319	0.574	0.384	0.908	0.500
SPINAL CORD	MENINGEAL SARCOMA [M]	0	0	0	2	0	0.440	.	.	0.307	.
SPLEEN	HAEMANGIOMA [B]	0	0	1	0	0	0.437	.	0.535	.	.
	HAEMANGIOSARCOMA [M]	0	0	1	0	1	0.231	.	0.535	.	0.565
	STROMAL SARCOMA [M]	0	0	1	0	0	0.437	.	0.535	.	.
STOMACH	SQUAMOUS-CELL PAPILLOMA [	1	0	0	1	1	0.318	0.535	0.535	0.307	0.315
THORACIC CAVITY	OSTEOSARCOMA [M]	0	0	1	0	0	0.434	.	0.542	.	.

Table 10B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Female Mice in Main Study

Organ Name	Tumor Name	0 mg	0.03 mg	0.2 mg	1.0 mg	3.0 mg	P_Value				
		Cont N=50	Low N=50	Med N=50	Midhi N=50	High N=50	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. MH	P_Value C vs. H
THYROID	C-CELL_ADENOMA+CARCINOMA	0	0	0	4	6	0.001	.	.	0.094	0.029
THYROID GLAND	C-CELL ADENOMA [B]	0	0	0	4	6	0.001	.	.	0.094	0.029
URINARY BLADDER	MESENCHYMAL TUMOUR [B]	0	0	0	0	1	0.222	.	.	.	0.565
UTERUS	DECIDUOMA [B]	1	1	2	0	0	0.922	0.281	0.565	0.557	0.565
	ENDOMETRIAL ADENOMA [B]	0	0	0	0	1	0.222	.	.	.	0.565
	ENDOMETRIAL CARCINOMA [M]	0	0	1	3	0	0.580	.	0.535	0.166	.
	ENDOMETRIAL STROMAL SARCO	1	0	0	2	0	0.590	0.525	0.525	0.574	0.556
	GRANULAR CELL TUMOUR [B]	0	1	0	0	1	0.319	0.535	.	.	0.565
	HAEMANGIOMA [B]	0	1	3	3	0	0.813	0.535	0.146	0.166	.
	HAEMANGIOSARCOMA [M]	2	1	2	0	1	0.750	0.553	0.373	0.808	0.598
	HISTIOCYTIC SARCOMA [M]	0	1	1	0	0	0.717	0.542	0.542	.	.
	LEIOMYOMA [B]	3	5	6	3	7	0.266	0.452	0.290	0.449	0.275
	LEIOMYOMA+LEIOMYOSARCOMA	3	7	9	7	7	0.506	0.243	0.076	0.259	0.275
	LEIOMYOSARCOMA [M]	0	2	3	4	0	0.843	0.290	0.146	0.089	.
	MALIGNANT SCHWANNOMA [M]	0	0	0	0	1	0.222	.	.	.	0.565
	SCHWANNOMA [B]	0	0	0	0	1	0.226	.	.	.	0.571
SCHWANNOMA_MALIGNANT+BENN	0	0	0	0	2	0.050	.	.	.	0.323	
STROMAL POLYP [B]	4	2	4	2	4	0.468	0.711	0.412	0.750	0.484	
STROMAL_SARCOMA+POLYP	4	2	4	4	4	0.458	0.711	0.412	0.466	0.484	
UTERUS_VAGINA	STROMAL_NEOPLASMS	4	3	4	2	4	0.540	0.557	0.412	0.750	0.484
VAGINA	STROMAL SARCOMA [M]	0	1	0	0	0	0.633	0.535	.	.	.
VERTEBRAE	OSTEOMA [B]	0	0	1	0	0	0.434	.	0.542	.	.
ZYMBAL'S GLAND	CARCINOMA [M]	1	0	0	0	0	0.829	0.535	0.535	0.557	0.565

**Table 11A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Male Mice in Combined Main and Week 78/104 Satellite Studies**

Organ Name	Tumor Name	0 mg	0.03 mg	0.2 mg	1.0 mg	3.0 mg	P_Value				
		Cont N=79	Low N=67	Med N=67	Midhi N=67	High N=79	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	C vs. MH	P_Value C vs. H
ADRENAL GLAND	PHAECHROMOCYTOMA [B]	1	0	1	0	1	0.423	0.443	0.725	0.464	0.752
	SUBCAPSULAR CELL TUMOUR [	4	11	5	4	5	0.835	0.017	0.443	0.579	0.522
ALIMENTARY_TRAC	ADENOMA+CARCINOMA	0	0	1	2	1	0.236	.	0.478	0.221	0.504
ALL_BONE	CHONDROMA+OSTEOSARCOMA+OS	0	2	0	0	0	0.846	0.203	.	.	.
ALL_SITES	HAEMANGIOSARCOMA+HAEMANGI	1	2	10	0	7	0.159	0.421	0.003	0.468	0.034
	LEUKEMIA	2	1	0	0	1	0.604	0.422	0.725	0.715	0.500
	LYMPHOMA	9	6	2	6	10	0.132	0.554	0.955	0.602	0.500
	MESOTHELIOMA	0	0	0	1	0	0.413	.	.	0.473	.
CAECUM	ADENOCARCINOMA [M]	0	1	0	1	0	0.504	0.448	.	0.473	.
	LYMPHOMA, PLASMACYTIC [M]	0	0	1	0	0	0.410	.	0.478	.	.
COLON	ADENOCARCINOMA [M]	0	0	0	1	0	0.413	.	.	0.473	.
DUODENUM	ADENOMA [B]	0	0	1	0	0	0.410	.	0.478	.	.
	OSTEOSARCOMA [M]	0	1	0	0	0	0.606	0.453	.	.	.
EPIDIDYMIS	HISTIOCYTIC SARCOMA [M]	1	0	0	0	1	0.393	0.448	0.478	0.468	0.252
	INTERSTITIAL CELL ADENOMA	0	0	0	1	1	0.132	.	.	0.468	0.504
EYE	AMELANOTIC MELANOMA [M]	0	0	0	1	0	0.410	.	.	0.468	.
EYELIDS	ADENOCARCINOMA [M]	0	0	1	0	0	0.410	.	0.478	.	.
FEMUR	CHONDROMA [B]	0	1	0	0	0	0.608	0.448	.	.	.
	MYXOMA [B]	1	0	0	0	0	0.784	0.448	0.478	0.468	0.504
FOOT/LEG	HAEMANGIOSARCOMA [M]	0	0	1	0	0	0.410	.	0.478	.	.
GALL BLADDER	ADENOMA [B]	0	1	0	0	0	0.608	0.448	.	.	.
HAEMOPOIETIC SY	HISTIOCYTIC SARCOMA [M]	0	0	1	0	0	0.410	.	0.478	.	.
	LEUKAEMIA [M]	0	0	0	0	1	0.220	.	.	.	0.504
	LEUKAEMIA, GRANULOCYTIC [	2	1	0	0	0	0.965	0.422	0.725	0.715	0.752
	LYMPHOMA [M]	1	4	0	1	2	0.500	0.129	0.473	0.720	0.506
	LYMPHOMA, FOLLICULAR CENT	7	1	2	4	8	0.056	0.940	0.886	0.648	0.500
LYMPHOMA, LYMPHOCYTIC [M]	1	1	0	1	0	0.726	0.697	0.478	0.719	0.504	
HARDERIAN GLAND	ADENOCARCINOMA [M]	0	0	3	0	0	0.797	.	0.106	.	.
	ADENOMA [B]	4	3	1	1	2	0.739	0.395	0.789	0.776	0.669
HARDERIAN_GLAND	ADENOMA+ADENOCARCINOMA	4	3	4	1	2	0.853	0.395	0.590	0.776	0.669
INJECTION/TREAT	FIBROMA [B]	1	0	0	0	0	0.784	0.448	0.478	0.468	0.504
	FIBROSARCOMA [M]	0	1	1	0	4	0.015	0.448	0.478	.	0.064
	RHABDOMYOSARCOMA [M]	1	0	0	0	1	0.391	0.443	0.473	0.464	0.752
	SARCOMA (NOT OTHERWISE SP	1	0	1	0	0	0.762	0.448	0.729	0.468	0.504
	SQUAMOUS-CELL PAPILLOMA [	0	0	0	0	1	0.220	.	.	.	0.504
INJECTION_SITE	FIBROMA+FIBROSARCOMA	1	1	1	0	4	0.039	0.697	0.729	0.468	0.193
	SARCOMA+RHABDOMYOSARCOMA+	3	1	2	0	5	0.083	0.601	0.449	0.849	0.368

**Table 11A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Male Mice in Combined Main and Week 78/104 Satellite Studies**

Organ Name	Tumor Name	0 mg	0.03 mg	0.2 mg	1.0 mg	3.0 mg	P_Value				
		Cont N=79	Low N=67	Med N=67	Midhi N=67	High N=79	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	C vs. MH	P_Value C vs. H
JEJUNUM	ADENOMA [B]	0	0	0	1	0	0.410	.	.	0.468	.
	OSTEOSARCOMA [M]	1	0	0	0	0	0.784	0.448	0.478	0.468	0.504
KIDNEY	ADENOMA+CARCINOMA	3	0	4	2	0	0.941	0.835	0.449	0.439	0.881
	TUBULAR CELL ADENOMA [B]	3	0	2	2	0	0.894	0.835	0.457	0.439	0.881
	TUBULAR CELL CARCINOMA [M]	0	0	2	0	0	0.653	.	0.226	.	.
LIVER	ADENOMA+CARCINOMA	14	7	6	6	14	0.159	0.826	0.935	0.930	0.435
LIVER	HAEMANGIOMA [B]	0	1	0	0	1	0.297	0.448	.	.	0.504
	HAEMANGIOSARCOMA [M]	1	1	2	0	0	0.901	0.697	0.473	0.468	0.504
	HEPATOCELLULAR ADENOMA [B]	12	6	5	4	11	0.271	0.804	0.923	0.953	0.536
	HEPATOCELLULAR CARCINOMA	4	2	1	2	3	0.444	0.556	0.789	0.607	0.510
	ITO CELL TUMOUR [B]	0	1	1	0	0	0.691	0.448	0.482	.	.
LOWER_ALIMENTAR	ADENOMA+CARCINOMA	0	0	0	1	0	0.413	.	.	0.473	.
LUNG	ADENOMA+CARCINOMA	24	21	23	13	15	0.993	0.464	0.467	0.923	0.947
	BRONCHIOLO-ALVEOLAR ADENO	18	19	16	7	10	0.996	0.248	0.435	0.970	0.941
	BRONCHIOLO-ALVEOLAR CARCI	8	3	12	7	7	0.646	0.810	0.181	0.395	0.514
LYMPH NODE (MES	HAEMANGIOMA [B]	0	0	2	0	3	0.042	.	0.226	.	0.128
PANCREAS (ENDOC	ISLET CELL ADENOMA [B]	1	0	1	0	0	0.762	0.448	0.729	0.468	0.504
PANCREAS (EXOCR	MESOTHELIOMA [M]	0	0	0	1	0	0.413	.	.	0.473	.
PITUITARY GLAND	ADENOMA, ANTERIOR LOBE [B]	1	0	1	1	0	0.660	0.448	0.729	0.719	0.504
SEMINAL VESICLE	GRANULAR CELL TUMOUR [M]	1	0	0	0	0	0.784	0.448	0.478	0.468	0.504
	LEIOMYOSARCOMA [M]	0	1	0	0	0	0.608	0.448	.	.	.
SKIN AND SUBCUT	FIBROSARCOMA [M]	0	2	1	2	7	0.002	0.207	0.482	0.221	0.008
	HAEMANGIOSARCOMA [M]	0	0	1	0	1	0.219	.	0.478	.	0.504
	KERATOACANTHOMA [B]	0	0	1	0	0	0.410	.	0.478	.	.
	LEIOMYOSARCOMA [M]	0	0	1	0	1	0.219	.	0.482	.	0.504
	MALIGNANT SCHWANNOMA [M]	0	0	1	0	0	0.409	.	0.482	.	.
	MYXOMA [B]	1	0	0	0	0	0.781	0.443	0.473	0.464	0.500
	NEUROFIBROSARCOMA [M]	0	0	0	0	1	0.220	.	.	.	0.504
	PAPILLOMA+CARCINOMA+KERAT	0	1	2	0	0	0.804	0.448	0.226	.	.
SKIN AND SUBCUT	RHABDOMYOSARCOMA [M]	0	0	2	1	4	0.014	.	0.230	0.473	0.064
	SARCOMA (NOT OTHERWISE SP	1	0	0	0	1	0.393	0.448	0.478	0.468	0.252
	SEBACEOUS CELL ADENOMA [B]	1	0	0	0	0	0.784	0.448	0.478	0.468	0.504
	SQUAMOUS-CELL CARCINOMA [	0	1	0	0	0	0.608	0.448	.	.	.
	SQUAMOUS-CELL PAPILLOMA [	0	0	1	0	0	0.410	.	0.478	.	.
SPINAL CORD	ASTROCYTOMA [B]	0	1	0	0	0	0.608	0.448	.	.	.
	MENINGEAL SARCOMA [M]	0	0	1	0	0	0.409	.	0.482	.	.
SPLEEN	HAEMANGIOSARCOMA [M]	0	0	1	0	1	0.219	.	0.478	.	0.504

**Table 11A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Male Mice in Combined Main and Week 78/104 Satellite Studies**

Organ Name	Tumor Name	0 mg	0.03 mg	0.2 mg	1.0 mg	3.0 mg	P_Value				
		Cont N=79	Low N=67	Med N=67	Midhi N=67	High N=79	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	C vs. MH	P_Value C vs. H
STERNUM	MAST CELL TUMOUR [B]	0	0	0	1	0	0.410	.	.	0.468	.
STOMACH	ADENOMA [B]	0	0	0	0	1	0.220	.	.	.	0.504
TESTIS	HAEMANGIOMA [B]	0	0	3	0	0	0.795	.	0.109	.	.
	HAEMANGIOSARCOMA [M]	0	0	0	0	1	0.220	.	.	.	0.504
	INTERSTITIAL CELL ADENOMA	11	3	0	4	7	0.317	0.944	1.000	0.916	0.790
	INTERSTITIAL_ADENOMA+RET	12	5	0	6	7	0.482	0.862	1.000	0.830	0.851
	RETE TESTIS ADENOMA [B]	1	1	0	2	0	0.698	0.697	0.478	0.452	0.504
	SEX CORD/STROMAL TUMOUR [	0	1	0	0	0	0.608	0.448	.	.	.
THYROID	C-CELL_ADENOMA+CARCINOMA	0	0	0	9	15	0.000	.	.	0.001	0.000
	FOLLICULAR-CELL_ADENOMA+C	1	1	0	2	2	0.182	0.703	0.478	0.452	0.507
THYROID GLAND	C-CELL ADENOMA [B]	0	0	0	9	15	0.000	.	.	0.001	0.000
	FOLLICULAR CELL ADENOMA [	1	1	0	2	1	0.393	0.703	0.478	0.452	0.252
	FOLLICULAR CELL CARCINOMA	0	0	0	0	1	0.220	.	.	.	0.504
UPPER_ALIMENTAR	ADENOMA+CARCINOMA	0	0	1	1	1	0.197	.	0.478	0.468	0.504
VERTEBRAE	HAEMANGIOMA [B]	0	0	0	0	1	0.220	.	.	.	0.504

**Table 11B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Female Mice in Combined Main and Week 78/104 Satellite Studies**

Organ Name	Tumor Name	0 mg	0.03 mg	0.2 mg	1.0 mg	3.0 mg	P_Value				
		Cont N=79	Low N=67	Med N=67	Midhi N=67	High N=79	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	C vs. MH	P_Value C vs. H
ADRENAL	PHEOCHROMOCYTOMA_BENIGN+M	5	0	1	1	0	0.977	0.951	0.845	0.877	0.976
ADRENAL GLAND	CORTICAL ADENOMA [B]	0	0	1	0	0	0.431	.	0.461	.	.
	CORTICAL CARCINOMA [M]	0	0	1	0	0	0.433	.	0.455	.	.
	PHAECHROMOCYTOMA [B]	4	0	0	1	0	0.940	0.909	0.913	0.792	0.948
	PHAECHROMOCYTOMA [M]	1	0	1	0	0	0.773	0.448	0.705	0.484	0.520
	SUBCAPSULAR CELL TUMOUR [	0	0	0	1	0	0.436	.	.	0.489	.
ADRENAL_CORTICA	ADENNOMA+CARCINOMA	0	0	2	0	0	0.678	.	0.209	.	.
ALL_BONE	CHONDROMA+OSTEOSARCOMA+OS	0	0	1	0	0	0.431	.	0.461	.	.
ALL_SITES	HAEMANGIOSARCOMA+HAEMANGI	5	8	8	4	5	0.881	0.159	0.184	0.459	0.422
	LYMPHOMA	20	13	20	14	16	0.835	0.695	0.276	0.739	0.728
	MESOTHELIOMA	0	1	0	1	0	0.523	0.448	.	0.484	.
BONE	HAEMANGIOSARCOMA [M]	1	0	0	0	0	0.782	0.443	0.449	0.479	0.515
BRAIN	LIPOMA [B]	0	0	0	1	0	0.433	.	.	0.484	.
	MALIGNANT ASTROCYTOMA [M]	1	0	0	0	0	0.786	0.448	0.455	0.484	0.520
	MENINGIOMA [B]	0	0	1	0	0	0.431	.	0.461	.	.
CAECUM	LEIOMYOMA [B]	0	2	0	0	0	0.850	0.198	.	.	.
	LEIOMYOSARCOMA [M]	0	0	0	1	0	0.436	.	.	0.489	.
	PLASMACYTOMA [B]	0	1	0	0	0	0.612	0.448	.	.	.
COLON	ADENOCARCINOMA [M]	1	0	0	1	0	0.595	0.448	0.455	0.742	0.520
	ADENOMA [B]	1	0	0	0	0	0.786	0.448	0.455	0.484	0.520
CRANIUM	OSTEOMA [B]	0	0	1	0	0	0.431	.	0.461	.	.
DUODENUM	ADENOMA [B]	0	0	0	1	0	0.436	.	.	0.489	.
	HAEMANGIOMA [B]	0	1	0	0	0	0.612	0.448	.	.	.
FEMUR	OSTEOMA [B]	0	0	1	0	0	0.431	.	0.461	.	.
FOOT/LEG	RHABDOMYOSARCOMA [M]	0	0	0	0	1	0.232	.	.	.	0.520
HAEMOPOIETIC SY	HISTIOCYTIC SARCOMA [M]	5	6	4	4	1	0.986	0.348	0.377	0.448	0.906
	LEUKAEMIA, GRANULOCYTIC [	0	0	1	1	0	0.449	.	0.461	0.489	.
	LYMPHOMA [M]	7	5	5	4	4	0.836	0.480	0.480	0.676	0.748
	LYMPHOMA, FOLLICULAR CENT	13	8	14	7	11	0.790	0.645	0.304	0.853	0.651
	LYMPHOMA, LYMPHOCYTIC [M]	0	0	0	1	1	0.149	.	.	0.484	0.525
	LYMPHOMA, PLASMACYTIC [M]	0	0	1	2	0	0.555	.	0.455	0.237	.
HARDERIAN GLAND	ADENOMA [B]	1	0	1	2	5	0.011	0.448	0.712	0.476	0.127
HEART	MESOTHELIOMA [M]	0	0	0	1	0	0.433	.	.	0.484	.
INJECTION/TREAT	FIBROSARCOMA [M]	1	0	0	0	2	0.139	0.448	0.455	0.484	0.538
	KERATOACANTHOMA [B]	0	0	0	1	0	0.436	.	.	0.489	.
	SARCOMA (NOT OTHERWISE SP	1	1	0	0	0	0.880	0.699	0.455	0.484	0.520

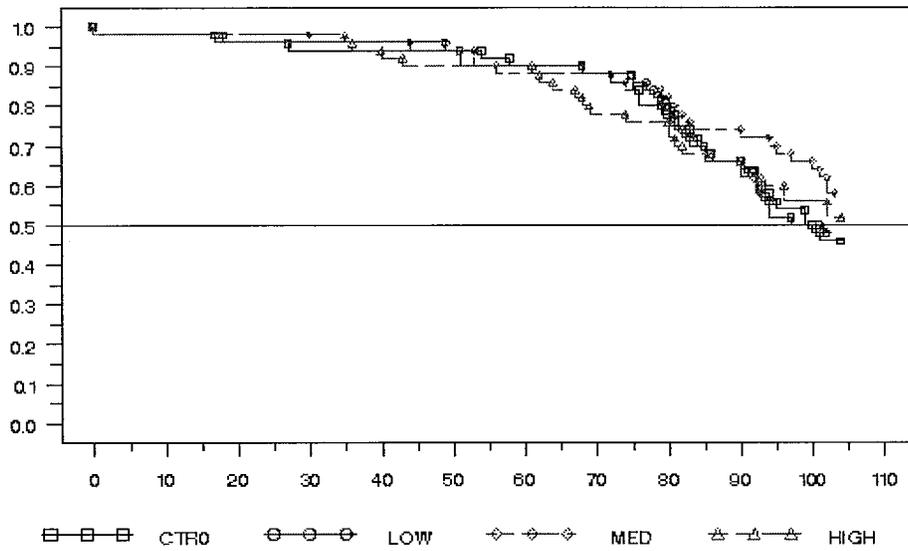
**Table 11B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Female Mice in Combined Main and Week 78/104 Satellite Studies**

Organ Name	Tumor Name	0 mg	0.03 mg	0.2 mg	1.0 mg	3.0 mg	P_Value				
		Cont N=79	Low N=67	Med N=67	Midhi N=67	High N=79	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	C vs. MH	P_Value C vs. H
LIVER	HAEMANGIOMA [B]	0	1	2	0	0	0.823	0.448	0.209	.	.
	HEPATOCELLULAR ADENOMA [B]	2	0	0	3	0	0.761	0.699	0.705	0.469	0.772
	HEPATOCELLULAR CARCINOMA	0	1	1	1	1	0.356	0.448	0.455	0.489	0.520
LUNG	BRONCHIOLO-ALVEOLAR ADENO	11	8	11	5	4	0.995	0.510	0.410	0.883	0.962
	BRONCHIOLO-ALVEOLAR CARCI	3	1	6	2	5	0.299	0.601	0.172	0.470	0.392
	MESOTHELIOMA [M]	0	1	0	0	0	0.612	0.448	.	.	.
LYMPH NODE (MES)	HAEMANGIOMA [B]	2	1	1	0	0	0.954	0.422	0.441	0.736	0.772
LYMPH NODE (MES)	OSTEOSARCOMA [M]	0	0	0	1	0	0.436	.	.	0.489	.
MAMMARY GLAND	ADENOACANTHOMA [M]	0	1	0	1	1	0.263	0.448	.	0.484	0.520
	ADENOCARCINOMA [M]	1	2	4	2	3	0.422	0.422	0.142	0.484	0.347
	ADENOMA [B]	0	0	0	0	1	0.232	.	.	.	0.520
	FIBROADENOMA [B]	1	0	0	0	0	0.786	0.448	0.455	0.484	0.520
MAMMARY_GLAND	ADENOMA+ADENOACANTHOMA+AD	1	3	4	3	5	0.206	0.234	0.142	0.292	0.132
MESENTERY	HAEMANGIOSARCOMA [M]	0	0	1	0	0	0.433	.	0.455	.	.
ORAL CAVITY	SQUAMOUS-CELL CARCINOMA [	0	0	0	0	1	0.232	.	.	.	0.520
ORAL_CAVITY/VAG	PAPILLOMA+CARCINOMA	0	1	0	0	1	0.311	0.448	.	.	0.520
OVARY	CYSTADENOMA [B]	1	1	1	0	1	0.542	0.699	0.705	0.484	0.268
	DECIDUOMA [B]	0	1	0	0	0	0.612	0.448	.	.	.
	GRANULOSA CELL TUMOUR [B]	0	0	1	0	0	0.433	.	0.455	.	.
	HAEMANGIOMA [B]	0	2	0	0	0	0.850	0.198	.	.	.
	LEIOMYOMA [B]	0	0	1	0	0	0.433	.	0.455	.	.
	LUTEOMA [B]	1	1	2	1	2	0.362	0.699	0.431	0.736	0.530
	SARCOMA (NOT OTHERWISE SP	0	0	0	1	0	0.433	.	.	0.484	.
	SERTOLI CELL TUMOUR [B]	0	0	0	1	1	0.147	.	.	0.484	0.520
	SEX CORD/STROMAL TUMOUR [	1	0	1	0	0	0.773	0.448	0.705	0.484	0.520
	TUBULOSTROMAL ADENOMA [B]	1	0	1	1	3	0.072	0.448	0.705	0.736	0.340
PANCREAS (EXOCR)	HAEMANGIOMA [B]	1	0	0	0	0	0.786	0.448	0.455	0.484	0.520
PITUITARY GLAND	ADENOMA, ANTERIOR LOBE [B]	0	0	2	0	5	0.005	.	0.204	.	0.035
	ADENOMA, INTERMEDIATE LOB	0	0	0	2	1	0.163	.	.	0.237	0.520
SKELETAL MUSCLE	LIPOSARCOMA [M]	0	0	0	0	1	0.232	.	.	.	0.520
	RHABDOMYOSARCOMA [M]	1	0	0	0	0	0.786	0.448	0.455	0.484	0.520
	SARCOMA (NOT OTHERWISE SP	1	0	0	0	0	0.786	0.448	0.455	0.484	0.520
SKIN AND SUBCUT	BASAL CELL CARCINOMA [M]	2	0	0	0	1	0.557	0.699	0.705	0.736	0.530
	FIBROSARCOMA [M]	1	1	1	0	2	0.286	0.699	0.705	0.484	0.530
	LIPOSARCOMA [M]	0	2	0	0	0	0.848	0.204	.	.	.
	MALIGNANT FIBROUS HISTIOC	1	0	0	0	0	0.786	0.448	0.455	0.484	0.520
	RHABDOMYOSARCOMA [M]	2	1	1	0	0	0.954	0.422	0.441	0.736	0.772
	SARCOMA (NOT OTHERWISE SP	1	0	1	0	5	0.007	0.448	0.712	0.484	0.132
	SQUAMOUS-CELL CARCINOMA [	1	0	0	0	0	0.786	0.448	0.455	0.484	0.520
	SQUAMOUS-CELL PAPILLOMA [	0	0	0	1	0	0.433	.	.	0.484	.

**Table 11B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons  
Female Mice in Combined Main and Week 78/104 Satellite Studies**

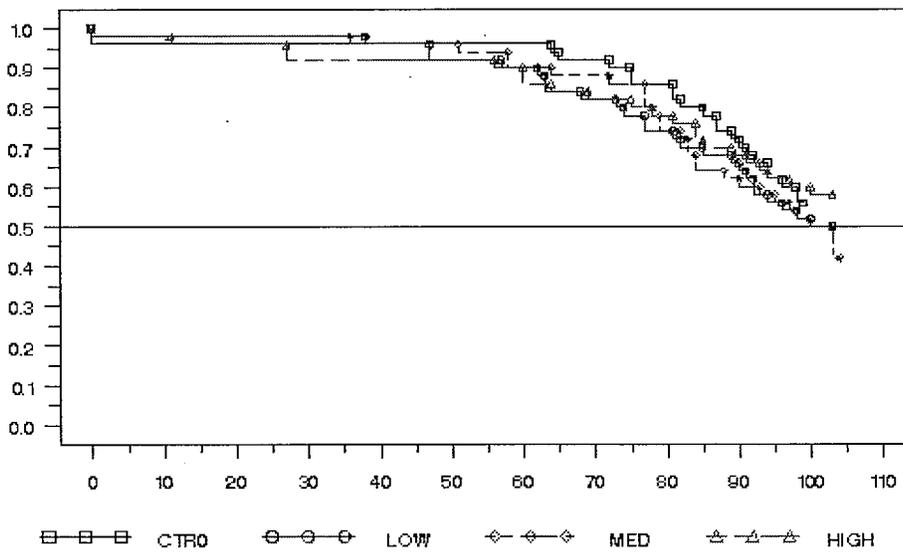
Organ Name	Tumor Name	0 mg	0.03 mg	0.2 mg	1.0 mg	3.0 mg	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value	
		Cont N=79	Low N=67	Med N=67	Midhi N=67	High N=79				C vs. MH	C vs. H
SKIN_AND_SUBCUT	SARCOMA+FIBROSARCOMA+LIPO	4	4	3	0	7	0.163	0.524	0.414	0.931	0.322
SPINAL CORD	MENINGEAL SARCOMA [M]	0	0	0	2	0	0.451	.	.	0.231	.
SPLEEN	HAEMANGIOMA [B]	0	0	1	0	0	0.431	.	0.461	.	.
	HAEMANGIOSARCOMA [M]	0	0	1	0	1	0.230	.	0.455	.	0.520
	STROMAL SARCOMA [M]	0	0	1	0	0	0.433	.	0.455	.	.
STOMACH	SQUAMOUS-CELL PAPILLOMA [	1	0	0	1	1	0.324	0.448	0.455	0.736	0.268
THORACIC CAVITY	OSTEOSARCOMA [M]	0	0	1	0	0	0.431	.	0.461	.	.
THYROID	C-CELL_ADENOMA+CARCINOMA	0	0	0	4	17	0.000	.	.	0.056	0.000
THYROID GLAND	C-CELL ADENOMA [B]	0	0	0	4	15	0.000	.	.	0.056	0.000
	C-CELL CARCINOMA [M]	0	0	0	0	2	0.055	.	.	.	0.273
URINARY BLADDER	LEIOMYOMA [B]	1	0	0	0	0	0.786	0.448	0.455	0.484	0.520
URINARY BLADDER	MESENCHYMAL TUMOUR [B]	0	0	0	0	1	0.232	.	.	.	0.520
UTERUS	DECIDUOMA [B]	1	1	2	0	0	0.913	0.699	0.441	0.484	0.520
	ENDOMETRIAL ADENOMA [B]	0	0	0	0	1	0.232	.	.	.	0.520
	ENDOMETRIAL CARCINOMA [M]	0	0	1	3	0	0.580	.	0.455	0.109	.
	ENDOMETRIAL STROMAL SARCO	1	0	0	2	0	0.599	0.448	0.455	0.484	0.520
	GRANULAR CELL TUMOUR [B]	0	1	0	0	1	0.311	0.448	.	.	0.520
	HAEMANGIOMA [B]	0	2	3	3	3	0.258	0.198	0.090	0.113	0.137
	HAEMANGIOSARCOMA [M]	2	1	2	1	1	0.715	0.422	0.630	0.476	0.530
	HISTIOCYTIC SARCOMA [M]	0	2	1	1	3	0.113	0.204	0.461	0.484	0.137
	LEIOMYOMA [B]	5	5	11	4	10	0.282	0.526	0.047	0.473	0.181
	LEIOMYOMA+LEIOMYOSARCOMA	5	7	14	8	10	0.495	0.272	0.008	0.249	0.181
	LEIOMYOSARCOMA [M]	0	2	3	4	0	0.845	0.198	0.090	0.051	.
	MALIGNANT SCHWANNOMA [M]	0	0	0	0	1	0.232	.	.	.	0.520
	SCHWANNOMA [B]	0	0	1	0	1	0.234	.	0.461	.	0.525
	SCHWANNOMA_MALIGNANT+BENN	0	0	1	0	2	0.075	.	0.461	.	0.273
STROMAL POLYP [B]	9	3	6	2	5	0.809	0.875	0.556	0.965	0.836	
STROMAL_SARCOMA+POLYP	9	3	6	4	5	0.795	0.875	0.556	0.858	0.836	
UTERUS_VAGINA	STROMAL_NEOPLASMS	9	4	6	2	5	0.847	0.778	0.556	0.965	0.836
VAGINA	STROMAL SARCOMA [M]	0	1	0	0	0	0.612	0.448	.	.	.
VERTEBRAE	OSTEOMA [B]	0	0	1	0	0	0.431	.	0.461	.	.
ZYMBAL'S GLAND	CARCINOMA [M]	1	0	0	0	0	0.786	0.448	0.455	0.484	0.520

**Figure 1A: Kaplan-Meier Survival Functions for Male Rats**  
Male Rats



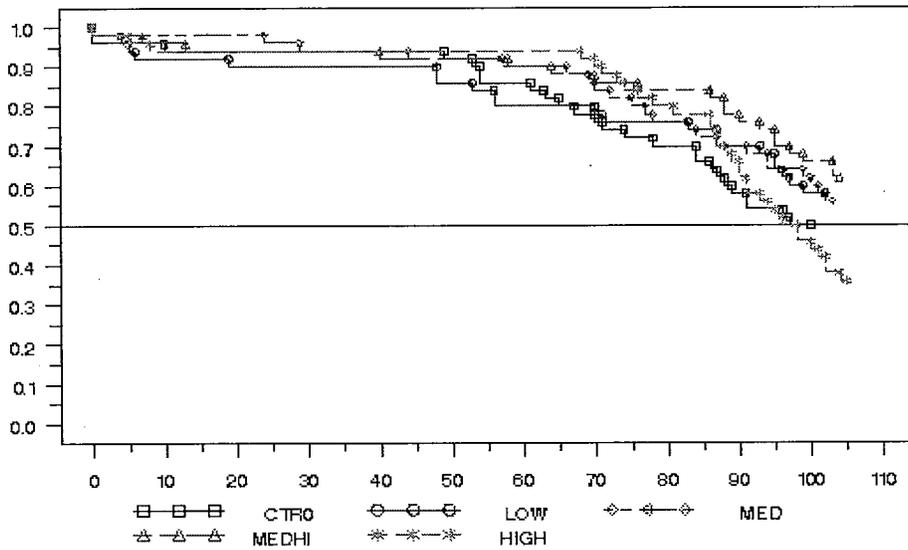
X-Axis: Weeks, Y-Axis: Survival rates

**Figure 1B: Kaplan-Meier Survival Functions for Female Rats**  
Female Rats



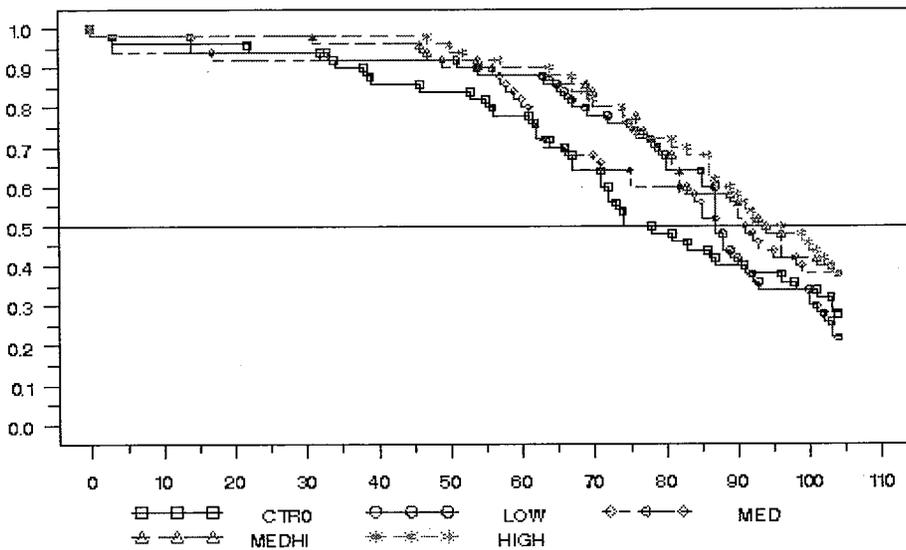
X-Axis: Weeks, Y-Axis: Survival rates

**Figure 2A: Kaplan-Meier Survival Functions for Male Mice in Main Study**  
Male Mice



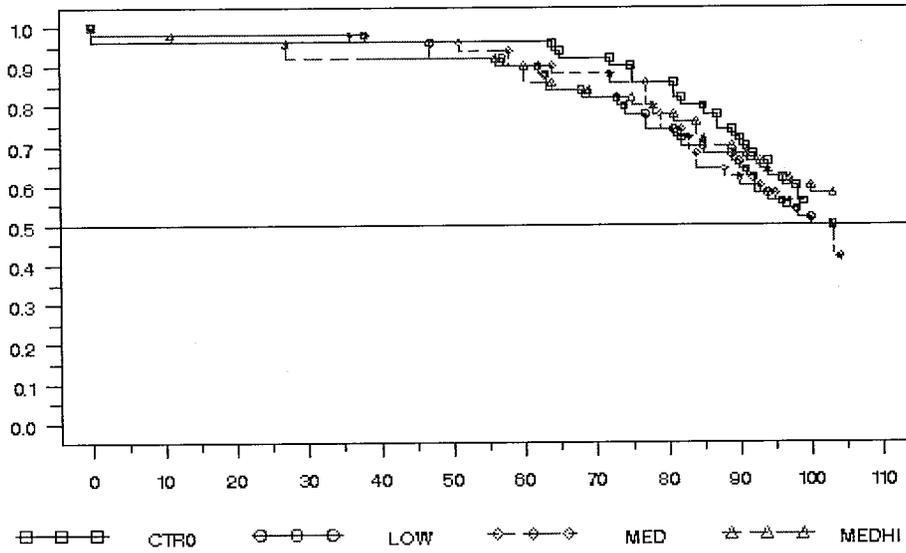
X-Axis: Weeks, Y-Axis: Survival rates

**Figure 2B: Kaplan-Meier Survival Functions for Female Mice in Main Study**  
Female Mice



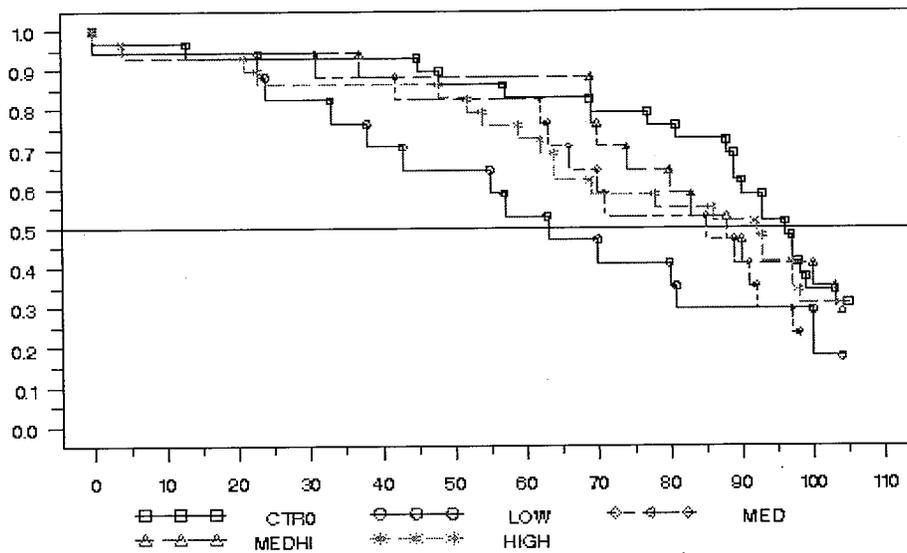
X-Axis: Weeks, Y-Axis: Survival rates

**Figure 3A: Kaplan-Meier Survival Functions for Male Mice  
in Week 78/104 satellite group**  
Male Mice



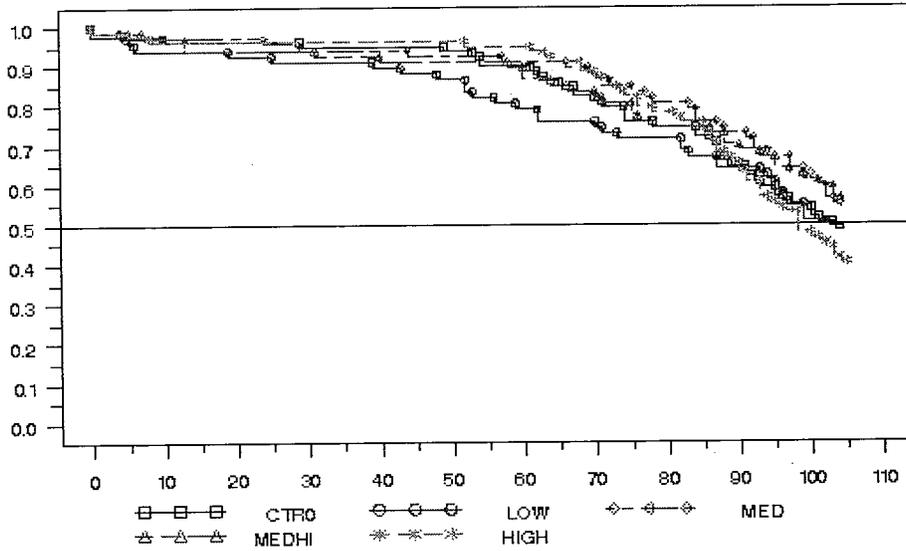
X-Axis: Weeks, Y-Axis: Survival rates

**Figure 3B: Kaplan-Meier Survival Functions for Female Mice  
in Week 78/104 satellite group**  
Female Mice



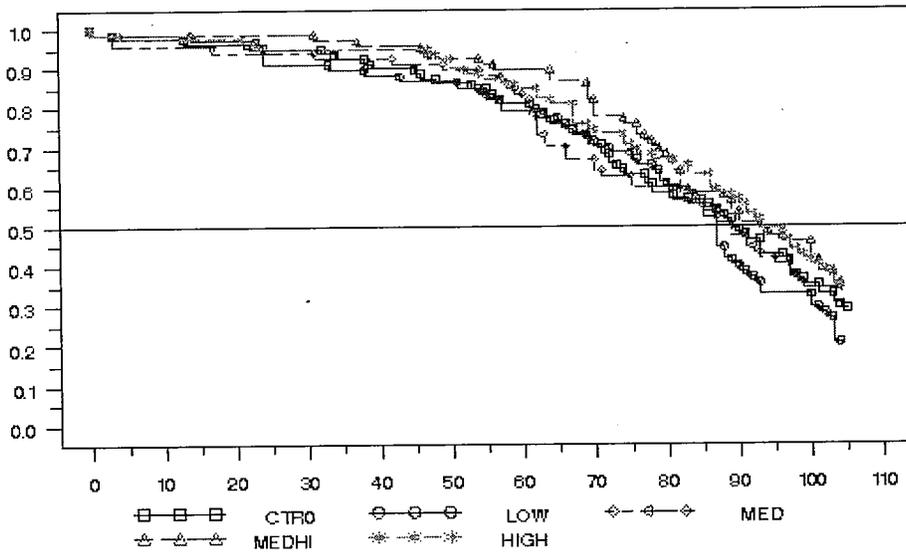
X-Axis: Weeks, Y-Axis: Survival rates

**Figure 4A: Kaplan-Meier Survival Functions for Male Mice  
in Combined Main and Week 78/104 Satellite Studies**  
Male Mice



X-Axis: Weeks, Y-Axis: Survival rates

**Figure 4B: Kaplan-Meier Survival Functions for Female Mice  
in Combined Main and Week 78/104 Satellite Studies**  
Female Mice



X-Axis: Weeks, Y-Axis: Survival rates

## 6. References:

1. Bailer AJ, Portier CJ (1988). "Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples." *Biometrics*, 44, 417-431.
2. Bieler, G. S. and Williams, R. L. (1993). "Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity". *Biometrics* 49, 793-801.
3. Cox D. R. (1972) "Regression models and life tables", *Journal of the Royal Statistical Society*, B, 34, 187-220.
4. Gehan (1965) "A generalized Wilcoxon test for comparing arbitrarily singly censored samples", *Biometrika*, 52, 203-223.
5. Haseman, J (1983), "A re-examination of false-positive rates for carcinogenesis studies", *Fundamental and Applied Toxicology*, 3: 334-339.
6. Lin, K.K. and Rahman, M.A. (1998), "Overall false positive rates in tests for linear trend in tumor incidence in animal carcinogenicity studies of new drugs", *Journal of Biopharmaceutical Statistics*, 8(1), 1-15.
7. Lin, K.K. and Rahman, M.A. (2008), "A comparison of False Positive Rates of Peto and Poly-3 Methods for Long-Term Carcinogenicity Data Analysis Using Multiple Comparison Adjustment Method Suggested by Lin and Rahman", *Journal of Biopharmaceutical Statistics*, 18:5, 849-858.
8. Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, Richards, and J. Wahrendorf (1980), "Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments", Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, *Annex to supplement, World Health Organization, Geneva*, 311-426.
9. Tarone RE (1975), "Test for trend in life table analysis", *Biometrika*, 62: 679-82.
10. U.S. Department of Health and Human Services, "Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals", Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, 2001.

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