# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 209637Orig1s000

# STATISTICAL REVIEW(S)

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 (ADDENDUM)

CLINICAL STUDIES

| | |
|---|---|
| **NDA/BLA #:** | NDA 209637 |
| **Drug Name:** | Semaglutide Injection |
| **Indication(s):** | Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus (T2DM) |
| **Applicant:** | Novo Nordisk Inc. |
| **Date(s):** | Date submitted: December 5, 2016<br>Review due date: August 11, 2017<br>PDUFA due date: December 5, 2017 |
| **Review Priority:** | Standard |
| **Biometrics Division:** | Division of Biometrics II |
| **Statistical Reviewer:** | Jiwei He, Ph.D. |
| **Concurring Reviewers:** | Yun Wang, Ph.D. (Acting Team Leader) |
| **Medical Division:** | Metabolism and Endocrinology Products (DMEP) |
| **Clinical Team:** | Andreea Lungu, M.D.<br>William Chong, M.D. (Team Leader)<br>Jean-Marc Guettier, M.D. (Division Director) |
| **Project Manager:** | Peter Franks, M.S. |

**Keywords:** subgroup analysis

We requested the applicant to examine the treatment effect of each of semaglutide 0.5 mg and semaglutide 1.0 mg on the change in HbA1c from baseline within each sex, age, race, and ethnicity subgroup and the differences in the treatment effect between the subgroups. The information request we sent on 11/21/2017 is included in the Appendix of this document.

# FINDINGS IN SUBGROUP POPULATIONS

The results in this section were provided by the applicant. They are consistent with the results in the subgroup section of the statistical review for this NDA (documented in DARRTS on 8/11/2017). In the statistical review, the placebo-controlled studies were not pooled, and the race subgroups were analyzed as White versus non-White.

In general, the treatment effect of each of semaglutide 0.5 mg and semaglutide 1.0 mg was consistent in different subgroups. The few significant differences found between subgroups were quantitative instead of qualitative. An evaluation of whether differences in the treatment effect across subgroups is real should consider whether the finding has been reproduced and how strong is the evidence of a finding (which needs to consider how many possible comparisons can be done).

- For subgroup analyses by sex,
    - Each of semaglutide 0.5 mg and semaglutide 1.0 mg is superior to placebo with respect to the change in HbA1c from baseline within each sex.
    - In trial 3625 (SUSTAIN 4), a slightly higher effect was seen in females compared to males with the 0.5 mg dose (-0.45 versus -0.11, nominal p-value = 0.03), but there was no difference with the 1.0 mg dose.

- For subgroup analyses by age group ($< 65$, $\geq 65$ years of age),
    - Each of semaglutide 0.5 mg and semaglutide 1.0 mg is superior to placebo with respect to the change in HbA1c from baseline within each age group.
    - In trial 3625 (SUSTAIN 4), a slightly higher effect was seen in younger patients as compared to older patients with the 1.0 mg dose (-0.7 versus -0.21, nominal p-value = 0.01), but no difference was observed with the 0.5 mg dose.

- For subgroup analyses by race (White, Black or African American, Asian, Other),
    - Each of semaglutide 0.5 mg and semaglutide 1.0 mg is superior to placebo with respect to the change in HbA1c from baseline within each race group.
    - In the placebo pool, a slightly higher effect was seen in Asians and Black/African Americans as compared to White patients with both doses (-1.42 and -2.23 versus -1.07, nominal p-value = 0.05 for semaglutide 0.5 mg; -1.92 and -2.23 versus -1.33, nominal p-value = 0.02 for semaglutide 1.0 mg).

- For subgroup analyses by ethnic group (Hispanic, Non-Hispanic),
    - Each of semaglutide 0.5 mg and semaglutide 1.0 mg is superior to placebo with respect to the change in HbA1c from baseline within each ethnic group.

- In the placebo pool, a slightly lower effect was seen in Hispanic/Latino patients compared to non-Hispanic/non-Latino patients with both doses (-0.75 versus -1.28, nominal p-value = 0.04 for semaglutide 0.5 mg; -1.03 versus -1.62, nominal p-value = 0.04 for semaglutide 1.0 mg).

# Result Tables:

**Table 1. Effect of semaglutide on HbA1c by subgroup (Placebo-controlled trials)**

| Demographic Parameters | Semaglutide 0.5 mg | | | Semaglutide 1.0 mg | | | Control | | | Treatment Difference [95% Confidence Interval] (Semaglutide 0.5 mg minus Control) | Test for Treatment by Subgroup Interaction (p-value) | Treatment Difference [95% Confidence Interval] (Semaglutide 1.0 mg minus Control) | Test for Treatment by Subgroup Interaction (p-value) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean HbA1c at baseline | LS Mean Change from Baseline | N | Mean HbA1c at baseline | LS Mean Change from Baseline | N | Mean HbA1c at baseline | LS Mean Change from Baseline | | | | |
| **Sex** | | | | | | | | | | | 0.60 | | 0.45 |
| Male | 134 | 8.35 | -1.38 | 157 | 8.28 | -1.72 | 141 | 8.17 | -0.16 | -1.21 [-1.515 ; -0.912] | | -1.56 [-1.843 ; -1.287] | |
| Female | 126 | 8.1 | -1.29 | 104 | 8.13 | -1.58 | 121 | 8.22 | -0.17 | -1.11 [-1.42 ; -0.791] | | -1.41 [-1.728 ; -1.084] | |
| **Age Group** | | | | | | | | | | | 0.32 | | 0.13 |
| below 65 years | 195 | 8.32 | -1.36 | 212 | 8.26 | -1.7 | 191 | 8.18 | -0.11 | -1.25 [-1.501 ; -0.997] | | -1.58 [-1.825 ; -1.345] | |
| 65 years and above | 65 | 7.94 | -1.27 | 49 | 8.05 | -1.5 | 71 | 8.22 | -0.29 | -0.98 [-1.419 ; -0.546] | | -1.22 [-1.67 ; -0.777] | |
| **Race** | | | | | | | | | | | 0.05 | | 0.02 |
| White | 191 | 8.2 | -1.27 | 186 | 8.21 | -1.53 | 179 | 8.16 | -0.21 | -1.07 [-1.326 ; -0.806] | | -1.33 [-1.574 ; -1.076] | |
| Black or African American | 15 | 8.39 | -1.72 | 20 | 8.27 | -1.74 | 17 | 8.51 | 0.48 | -2.23 [-3.258 ; -1.211] | | -2.23 [-3.139 ; -1.315] | |
| Asian | 45 | 8.32 | -1.58 | 48 | 8.24 | -2.09 | 56 | 8.27 | -0.16 | -1.42 [-1.873 ; -0.975] | | -1.92 [-2.369 ; -1.47] | |
| Other | | | | | | | | | | | | | |
| **Ethnicity** | | | | | | | | | | | 0.04 | | 0.04 |
| Hispanic or Latino | 49 | 8.3 | -0.98 | 57 | 8.22 | -1.25 | 55 | 8.16 | -0.24 | -0.75 [-1.25 ; -0.246] | | -1.03 [-1.509 ; -0.546] | |
| Not Hispanic or Latino | 211 | 8.21 | -1.43 | 204 | 8.22 | -1.77 | 207 | 8.2 | -0.15 | -1.28 [-1.519 ; -1.044] | | -1.62 [-1.852 ; -1.391] | |

**Table 2. Effect of semaglutide on HbA1c by subgroup (Trial 3624 - vs exenatide)**

| Demographic Parameters | Semaglutide 0.5 mg | | | Semaglutide 1.0 mg | | | Control | | | Treatment Difference [95% Confidence Interval] (Semaglutide 0.5 mg minus Control) | Test for Treatment by Subgroup Interaction (p-value) | Treatment Difference [95% Confidence Interval] (Semaglutide 1.0 mg minus Control) | Test for Treatment by Subgroup Interaction (p-value) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean HbA1c at baseline | LS Mean Change from Baseline | N | Mean HbA1c at baseline | LS Mean Change from Baseline | N | Mean HbA1c at baseline | LS Mean Change from Baseline | | | | |
| **Sex** | | | | | | | | | | | | | 0.24 |
| Male | | | | 219 | 8.39 | -1.28 | 228 | 8.33 | -0.89 | | | -0.38 [-0.638 ; -0.131] | |
| Female | | | | 185 | 8.33 | -1.53 | 177 | 8.33 | -0.92 | | | -0.6 [-0.873 ; -0.333] | |
| **Age Group** | | | | | | | | | | | | | 0.95 |
| below 65 years | | | | 316 | 8.39 | -1.4 | 298 | 8.42 | -0.9 | | | -0.49 [-0.708 ; -0.275] | |
| 65 years and above | | | | 88 | 8.24 | -1.38 | 107 | 8.09 | -0.9 | | | -0.48 [-0.844 ; -0.113] | |
| **Race** | | | | | | | | | | | | | 1.00 |
| White | | | | 341 | 8.32 | -1.44 | 338 | 8.34 | -0.95 | | | -0.49 [-0.696 ; -0.292] | |
| Black or African American | | | | 28 | 8.59 | -0.86 | 30 | 8.51 | -0.4 | | | -0.45 [-1.145 ; 0.236] | |
| Asian | | | | 8 | 9.34 | -1.26 | 6 | 7.98 | -0.89 | | | -0.36 [-1.797 ; 1.076] | |
| Other | | | | 27 | 8.35 | -1.38 | 31 | 8.19 | -0.9 | | | -0.48 [-1.169 ; 0.209] | |
| **Ethnicity** | | | | | | | | | | | | | 0.59 |
| Hispanic or Latino | | | | 91 | 8.54 | -1.14 | 106 | 8.52 | -0.57 | | | -0.58 [-0.943 ; -0.213] | |
| Not Hispanic or Latino | | | | 313 | 8.31 | -1.48 | 299 | 8.26 | -1.01 | | | -0.46 [-0.675 ; -0.247] | |

Table 3. Effect of semaglutide on HbA1c by subgroup (Trial 3625 - vs IGlar)

| Demographic Parameters | Semaglutide 0.5 mg | | | Semaglutide 1.0 mg | | | Control | | | Treatment Difference [95% Confidence Interval] (Semaglutide 0.5 mg minus Control) | Test for Treatment by Subgroup Interaction (p-value) | Treatment Difference [95% Confidence Interval] (Semaglutide 1.0 mg minus Control) | Test for Treatment by Subgroup Interaction (p-value) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean HbA1c at baseline | LS Mean Change from Baseline | N | Mean HbA1c at baseline | LS Mean Change from Baseline | N | Mean HbA1c at baseline | LS Mean Change from Baseline | | | | |
| **Sex** | | | | | | | | | | | 0.03 | | 0.38 |
| Male | 197 | 8.14 | -1.13 | 182 | 8.23 | -1.55 | 195 | 8.23 | -1.02 | -0.11 [-0.362 ; 0.14] | | -0.53 [-0.788 ; -0.275] | |
| Female | 165 | 8.12 | -1.19 | 178 | 8.26 | -1.41 | 165 | 8.02 | -0.73 | -0.45 [-0.687 ; -0.221] | | -0.67 [-0.91 ; -0.44] | |
| **Age Group** | | | | | | | | | | | 0.94 | | 0.01 |
| below 65 years | 278 | 8.22 | -1.16 | 281 | 8.28 | -1.59 | 281 | 8.19 | -0.89 | -0.27 [-0.474 ; -0.065] | | -0.7 [-0.906 ; -0.495] | |
| 65 years and above | 84 | 7.82 | -1.15 | 79 | 8.14 | -1.11 | 79 | 7.92 | -0.9 | -0.25 [-0.592 ; 0.082] | | -0.21 [-0.56 ; 0.132] | |
| **Race** | | | | | | | | | | | 0.81 | | 0.97 |
| White | 279 | 8.12 | -1.18 | 279 | 8.2 | -1.51 | 276 | 8.05 | -0.89 | -0.3 [-0.49 ; -0.102] | | -0.62 [-0.815 ; -0.425] | |
| Black or African American | 32 | 8.32 | -1.17 | 34 | 8.36 | -1.65 | 33 | 8.59 | -1.09 | -0.08 [-0.614 ; 0.451] | | -0.56 [-1.105 ; -0.014] | |
| Asian | 42 | 8.12 | -0.88 | 39 | 8.44 | -1.23 | 38 | 8.31 | -0.71 | -0.16 [-0.687 ; 0.361] | | -0.51 [-1.053 ; 0.023] | |
| Other | 9 | 7.93 | -1.45 | 8 | 8.26 | -1.47 | 13 | 8.14 | -0.99 | -0.46 [-1.368 ; 0.439] | | -0.48 [-1.423 ; 0.463] | |
| **Ethnicity** | | | | | | | | | | | 0.27 | | 0.41 |
| Hispanic or Latino | 61 | 8.24 | -1.16 | 74 | 8.44 | -1.44 | 78 | 8.04 | -0.73 | -0.43 [-0.801 ; -0.054] | | -0.71 [-1.079 ; -0.342] | |
| Not Hispanic or Latino | 301 | 8.11 | -1.15 | 286 | 8.2 | -1.49 | 281 | 8.15 | -0.94 | -0.21 [-0.404 ; -0.008] | | -0.55 [-0.751 ; -0.35] | |

**Table 4. Effect of semaglutide on HbA1c by subgroup (Trial 3626 - vs sitagliptin)**

| Demographic Parameters | Semaglutide 0.5 mg | | | Semaglutide 1.0 mg | | | Control | | | Treatment Difference [95% Confidence Interval] (Semaglutide 0.5 mg minus Control) | Test for Treatment by Subgroup Interaction (p-value) | Treatment Difference [95% Confidence Interval] (Semaglutide 1.0 mg minus Control) | Test for Treatment by Subgroup Interaction (p-value) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean HbA1c at baseline | LS Mean Change from Baseline | N | Mean HbA1c at baseline | LS Mean Change from Baseline | N | Mean HbA1c at baseline | LS Mean Change from Baseline | | | | |
| **Sex** | | | | | | | | | | | 0.78 | | 0.46 |
| Male | 207 | 8.01 | -1.31 | 205 | 8.16 | -1.47 | 208 | 8.12 | -0.76 | -0.55 [-0.761 ; -0.337] | | -0.71 [-0.914 ; -0.503] | |
| Female | 202 | 8.02 | -1.27 | 204 | 7.91 | -1.49 | 199 | 8.22 | -0.67 | -0.59 [-0.812 ; -0.373] | | -0.82 [-1.037 ; -0.601] | |
| **Age Group** | | | | | | | | | | | 0.24 | | 0.27 |
| below 65 years | 333 | 8.02 | -1.3 | 332 | 8.08 | -1.49 | 328 | 8.2 | -0.69 | -0.61 [-0.786 ; -0.444] | | -0.8 [-0.972 ; -0.636] | |
| 65 years and above | 76 | 8 | -1.23 | 77 | 7.89 | -1.44 | 79 | 8.06 | -0.85 | -0.39 [-0.736 ; -0.035] | | -0.59 [-0.934 ; -0.253] | |
| **Race** | | | | | | | | | | | 0.99 | | 0.58 |
| White | 279 | 7.98 | -1.27 | 279 | 7.99 | -1.47 | 281 | 8.12 | -0.72 | -0.55 [-0.735 ; -0.368] | | -0.75 [-0.933 ; -0.57] | |
| Black or African American | 18 | 8.54 | -1.41 | 24 | 8.06 | -1.56 | 17 | 8.31 | -0.86 | -0.56 [-1.39 ; 0.279] | | -0.7 [-1.429 ; 0.028] | |
| Asian | 106 | 7.99 | -1.31 | 99 | 8.13 | -1.44 | 102 | 8.29 | -0.7 | -0.61 [-0.907 ; -0.315] | | -0.74 [-1.038 ; -0.45] | |
| Other | 6 | 8.42 | -1.48 | 7 | 8.56 | -2.35 | 7 | 7.97 | -0.79 | -0.69 [-1.806 ; 0.422] | | -1.56 [-2.628 ; -0.485] | |
| **Ethnicity** | | | | | | | | | | | 0.35 | | 0.68 |
| Hispanic or Latino | 69 | 8 | -1.47 | 67 | 8.15 | -1.57 | 73 | 8.28 | -0.74 | -0.72 [-1.074 ; -0.37] | | -0.83 [-1.177 ; -0.48] | |
| Not Hispanic or Latino | 340 | 8.02 | -1.25 | 342 | 8.02 | -1.46 | 334 | 8.15 | -0.71 | -0.54 [-0.709 ; -0.367] | | -0.75 [-0.916 ; -0.58] | |

## Forest Plots:

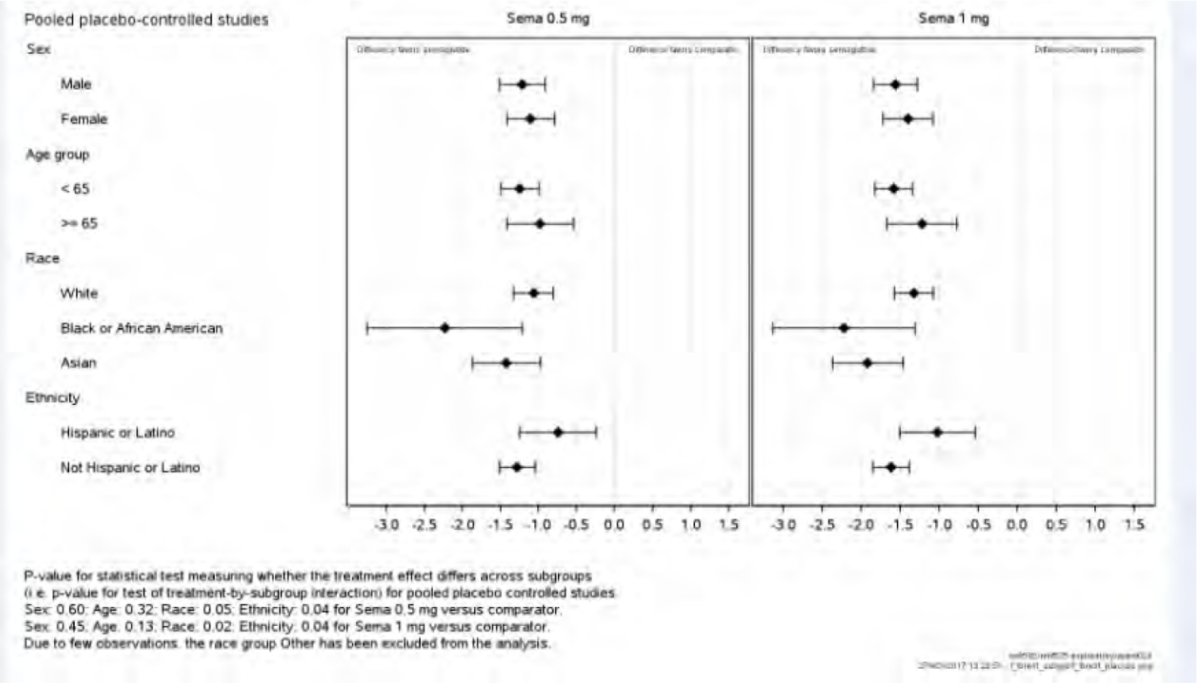


**Figure 1 Forest Plot for Placebo Controlled Trials**

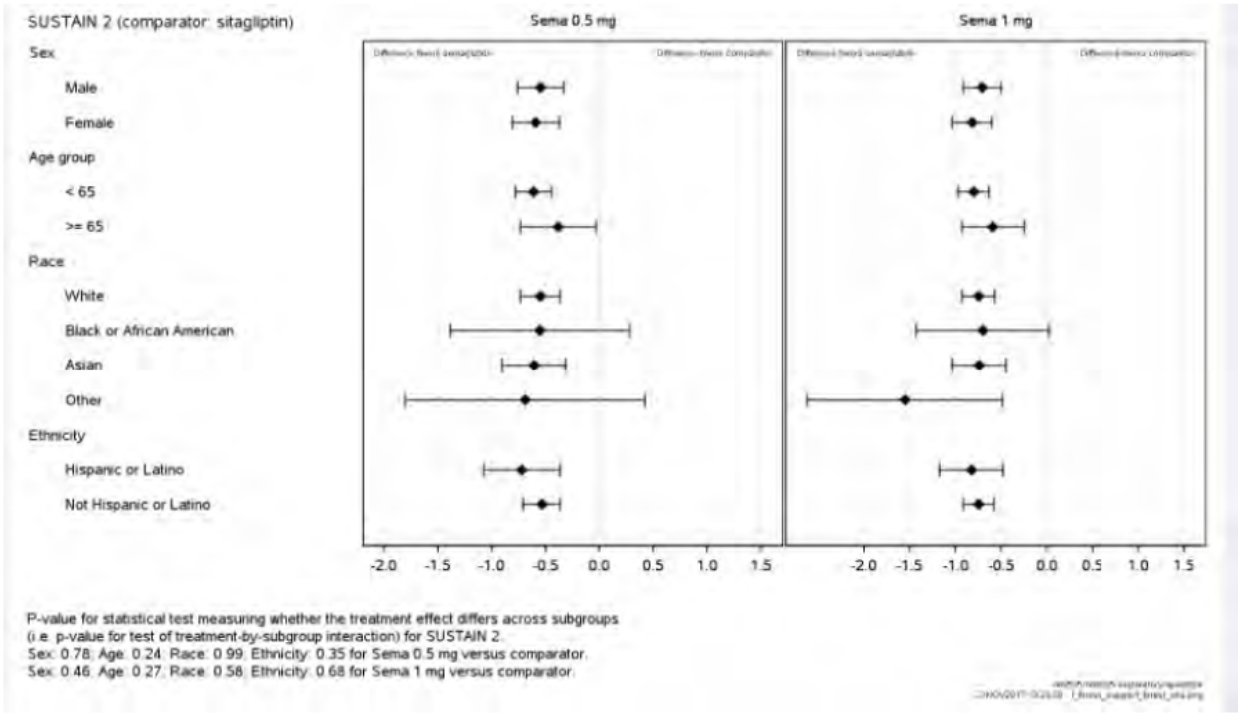


**Figure 2 Forest Plot for SUSTAIN 2 (Trial NN9535-3626)**

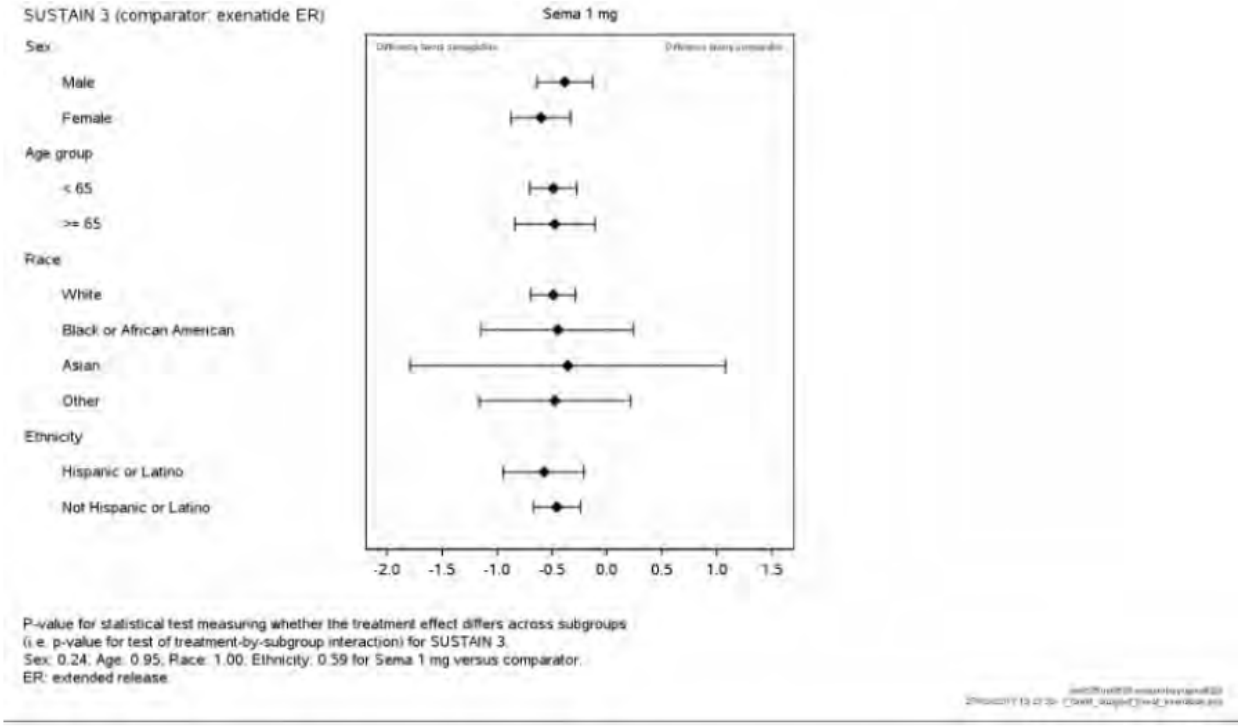


**Figure 3 Forest Plot for SUSTAIN 3 (Trial NN9535-3624)**

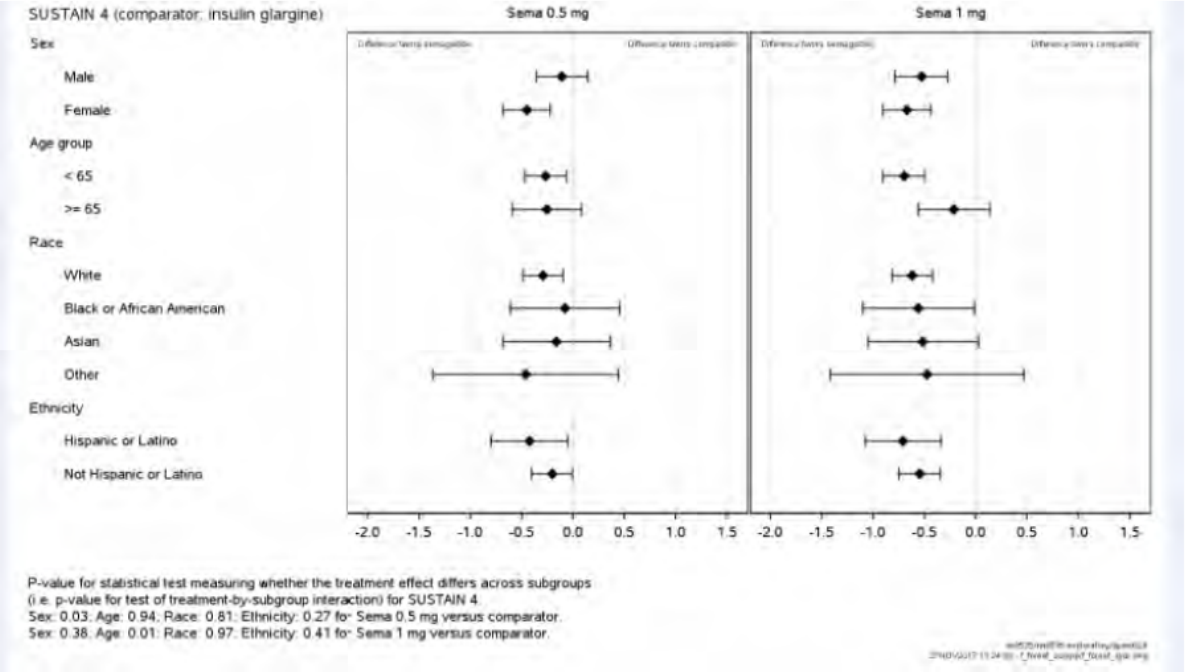


**Figure 4 Forest Plot for SUSTAIN 4 (Trial NN9535-3625)**

# APPENDIX: FDA's Information Request

Please complete the shell table for HbA1c results by subgroup using the retrieved dropout analysis method in Section 14 of the proposed product label based on analyses in each of the following studies or combinations of studies:

- Placebo-controlled key efficacy studies 3623 and 3627 combined
- Active-controlled key efficacy studies 3626, 3624, 3625 individually

For the individual active-controlled studies, estimate the treatment effect of each of semaglutide 0.5 mg and semaglutide 1.0 mg relative to the active comparator within subgroups and test for the difference in overall treatment effect across subgroups. For the combination of placebo-controlled studies, estimate the treatment effect of each of semaglutide 0.5 mg and semaglutide 1.0 mg relative to the placebo within subgroups by combining the estimates for individual studies inversely weighted by their variances.

With respect to the interaction tests of the treatment effect by subgroup factor (e.g., race), for an individual study the ANCOVA model should include the factors/terms:

- race (as a categorical factor)
- treatment

- treatment by race interaction term
- the covariates used in the primary analysis

When performing an interaction test of the treatment effect by subgroup factor (e.g., race) for a combination of studies, additionally include the factors/terms:

- race by study interaction term
- treatment by study interaction term
- interaction terms with study for each covariate used in the primary analysis

In addition, please provide a forest plot for each set of subgroup analysis. An example forest plot may be found at: https://www.fda.gov/Drugs/InformationOnDrugs/ucm532714.htm under the MORE INFO section of the question addressing whether there were any differences in how well the drug worked in clinical trials among sex, race and age.

Please provide the code and a description of the statistical methods used to generate these analyses.

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/s/

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JIWEI HE
12/04/2017

YUN WANG
12/04/2017

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

# Statistical Review and Evaluation

## CARCINOGENICITY STUDIES

| | |
|---|---|
| IND/NDA Number: | NDA 209637 (IND 79754) |
| Drug Name: | Semaglutide |
| Indication: | Treatment of Type 2 Diabetes Mellitus (T2D) |
| Studies: | 104 Weeks of Carcinogenicity Studies in Rats and Mice |
| Applicant: | Sponsor:<br>Novo Nordisk A/S,<br>Novo Nordisk Park,<br>DK-2760 Måløv,<br>Denmark. |
| | Testing Facility:<br>(b) (4) |
| Review Priority: | Standard |
| Biometrics Division: | Division of Biometrics - VI |
| Statistical Reviewer: | Hepei Chen |
| Concurring Reviewer: | Karl Lin, Ph.D. |
| Medical Division: | Division of Metabolism and Endocrinology Products |
| Reviewing Pharmacologist: | Federica Basso, Ph.D. |
| Keywords: | Carcinogenicity, Dose response |

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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 to assess the carcinogenic potential of NNC 0113-0217 (a GLP-1 agonist being developed for the treatment of Type 2 diabetes), when administered to CD rats and CD-1 mice by daily subcutaneous administration over a period of 104 weeks.

In this review the phrase "dose response relationship" refers to the linear component (trend) of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

## 2. Rat Study

Two separate experiments, one in male rats and one in female rats were conducted. As indicated in Table 1, in each of these two experiments there were four treated groups and one vehicle control group. Three hundred fifty CD rats of each sex were assigned randomly in size of 70 rats per group. The dose levels for the four treated groups were 0.0025, 0.01, 0.025, and 0.1 mg/kg/day for both male and female rats. In this review these dose groups were referred to as the low (Group 2), mid (Group 3), mid-high (Group 4), and high (Group 5) dose groups, respectively. The rats in the vehicle control group were administrated with the vehicle [1.42 mg/mL disodium (b) (4) phosphate, dihydrate; 14.0 mg/mL propylene glycol; 5.50 mg/mL phenol in water for injection, adjusted to pH 7.4], and handled for the same duration and in the same manner as the treated groups.

**Table 1: Experimental Design in Rat Study**

| Group No. | No. of Animals | | Test Material | Dosage Level (mg/kg/day) | |
|---|---|---|---|---|---|
| | Male | Female | | Male | Female |
| 1 | 70 | 70 | Vehicle Control | 0 | 0 |
| 2 | 70 | 70 | NNC 0113-0217 Low | 0.0025 | 0.0025 |
| 3 | 70 | 70 | NNC 0113-0217 Mid | 0.01 | 0.01 |
| 4 | 70 | 70 | NNC 0113-0217 Mid-High | 0.025 | 0.025 |
| 5 | 70 | 70 | NNC 0113-0217 High | 0.1 | 0.1 |

Animals were inspected visually at least twice daily for evidence of ill-health or reaction to treatment. In addition, a more detailed weekly physical examination, which included palpation, was performed on each animal to monitor general health. Particular attention was paid to any superficial or palpable swellings, for which the location, size, consistency, time of first observation and subsequent history were recorded. Animals were killed for reasons of animal welfare where necessary. Animals killed during the study and those surviving until the end of the scheduled treatment period were killed by carbon dioxide asphyxiation. All animals were subject to a detailed necropsy. After a review of the history of each animal, a full macroscopic examination of the tissues was performed. All external features and orifices were examined visually including the parenteral sites. Any abnormal position, morphology or interaction was recorded. The organs and tissues were examined as appropriate. Any abnormality in the appearance or size of any organ and tissue was recorded and the required tissue samples preserved in appropriate fixative. All tissues preserved for examination (as specified above) were

examined for all animals sacrificed on completion of the scheduled treatment period and for all animals killed or dying during the study. Tissues reported at macroscopic examination as being grossly abnormal were examined for all animals in line with current practice.

## 2.1. Sponsor's analyses

### 2.1.1. Survival analysis

In the sponsor's analysis, the numbers of animal deaths during the study, up to terminal sacrifice, were analyzed by logrank tests for a trend across the groups. The numbers of animal deaths during the study were presented as life-tables and Kaplan-Meier survival curves. The following statistical tests were carried out: 1) a two-tailed test for a trend with dose level, and 2) a two-tailed pairwise comparison test of each treatment group against the control group. Where the test for trend was statistically significant, the highest dose group was excluded and the trend test was repeated (using a one-tailed test), until the test was no longer statistically significant.

As a check, tests for non-linearity (not presented) were carried out. In this study, the non-linearity test was statistically significant for the females (p=0.006) and thus the results of the pairwise tests are to be preferred to the trend test. For the males the non-linearity test was not statistically significant at the 1% level and thus the result of the trend test is to be preferred. P-values were calculated using $\chi 2$ tests and adjusted with a continuity correction where there was only one degree of freedom.

**Sponsor's findings**:

The sponsor's analysis showed that the numbers of rats surviving to their terminal necropsy were 35 (50%), 32 (46%), 28 (40%), 40 (57%), and 33 (47%) in Groups 1, 2, 3, 4, and 5 for male rats, respectively, and 34 (49%), 31 (44%), 20 (29%), 19 (27%), and 31 (44%) for female rats respectively. For male rats, the trend test was not statistically significant when all groups were included in the analysis ($p$=0.699), without any statistically significant pairwise comparisons. For female rats, statistically significant pairwise comparisons of the control group with the mid and mid-high dose groups were noted ($p$=0.028 and $p$=0.019 respectively), while the trend test was not statistically significant ($p$=0.649).

### 2.1.2. Tumor data analysis

In the sponsor's report, the analyses were carried out for benign, malignant and benign and malignant tumors combined. If an animal had a benign and a malignant non-palpable tumor then only the malignant tumor was included in the analysis of both tumors together. Also, if an animal had more than one palpable tumor of the same category, benign or malignant, then only the first observed tumor was included in the analysis. Tumor types were selected for full statistical analysis where at least two tumors were observed in treated groups for which all animals were examined.

For the life-table analysis the study was divided into time strata. For non-incidental tumors, the strata are defined as those weeks during which there were deaths. For incidental tumors, the

following fixed time intervals were used to adjust for differential mortality between the treatment groups: 1-52, 53-78, 79-92, 93-104 weeks and terminal sacrifice (FDA 2001).

Log-rank methods were used to analyze the number of animals with tumors across treatment groups. The following $\chi 2$ statistical tests were carried out: 1) a one-tailed test for a trend using nominal dose levels, with the control group; 2) a one-tailed pairwise comparison test of each treatment group against the control group. Where the test for trend was statistically significant, the highest dose group was excluded and the trend test was repeated, using a one-tailed test until the test was no longer statistically significant. The p-values were adjusted using a continuity correction where there was one degree of freedom.

As a check, tests for non-linearity were carried out (but not presented in this report). For benign C-cell adenoma and benign C-cell adenoma and malignant C-cell carcinoma combined (thyroids) in males and females ($p<0.001$) and for benign adenoma (mammary areas) in females ($p=0.007$) the non-linearity tests were significant, therefore the pairwise tests are to be preferred to the trend test. For all other analyses the non-linearity tests were not statistically significant at the 1% level, hence the trend tests are to be preferred.

Where there were fewer than ten observed tumor bearing animals across all treatment groups, exact one-tailed p-values were calculated using permutation tests for stratified contingency tables, to test for trend and for pairwise comparisons of each treatment group against the control group.

**Adjustment for multiple testing:**

In the sponsor's report, no text can be located in terms of the criteria used for the significance adjustment for multiple testing. Based on the sponsor's discussion of the tumor findings, no adjustment for multiple testing in the context of rare or common tumors was considered in the sponsor's analysis.

**Sponsor's findings:**

In the sponsor's analysis, for benign C-cell adenoma of thyroids in male rats, the trend test was statistically significant ($p<0.001$), along with statistically significant pairwise comparisons of the control group versus the low, mid, mid-high, and high groups ($p=0.012$, $p<0.001$, $p<0.001$ and $p<0.001$ respectively). For malignant C-cell carcinoma, the trend test was statistically significant ($p<0.001$), along with statistically significant pairwise comparisons of the control group versus the mid, mid-high, and high groups ($p=0.014$, $p=0.008$ and $p<0.001$ respectively). For benign C-cell adenoma and malignant C-cell carcinoma combined, the trend test was statistically significant ($p<0.001$), along with statistically significant pairwise comparisons of the control group versus the low, mid, mid-high, and high groups ($p=0.020$, $p<0.001$, $p<0.001$ and $p<0.001$ respectively).

For malignant large granular cell lymphoma of haematopoietic in male rats, the trend test was statistically significant ($p=0.049$), while no statistically significant pairwise comparisons was noted.

For benign C-cell adenoma of thyroids in female rats, the trend test was statistically significant ($p<0.001$), along with statistically significant pairwise comparisons of the control group versus the low, mid, mid-high, and high groups ($p=0.009$, $p<0.001$, $p<0.001$ and $p<0.001$ respectively). For malignant C-cell carcinoma, the trend test was not statistically significant ($p=0.057$), while a pairwise comparison of the control group versus the high dose group was statistically significant ($p=0.043$). For benign C-cell adenoma and malignant C-cell carcinoma combined, the trend test was statistically significant ($p<0.001$), along with statistically significant pairwise comparisons of the control group versus the low, mid, mid-high, and high groups ($p=0.011$, $p<0.001$, $p<0.001$ and $p<0.001$ respectively).

For benign adenoma of Pituitary (pars distalis) in female rats, the trend test was not statistically significant ($p=0.803$), along with a statistically significant pairwise comparison of the control group versus the mid-high dose group ($p=0.029$). For benign adenoma and malignant carcinoma combined, the trend test was not statistically significant ($p=0.818$), while the pairwise comparison of the control group versus the mid-high dose group was statistically significant ($p=0.029$).

For malignant adenocarcinoma in mammary areas of female rats, the trend test was not statistically significant ($p=0.875$), while the pairwise comparison of the control group versus the mid dose group was statistically significant ($p=0.038$).

For benign squamous papilloma and malignant squamous cell carcinoma combined in uterus of female rats, the trend test was statistically significant when all groups were included in the analysis ($p=0.032$), while no statistically significant pairwise comparisons was noted.

## 2.2. Reviewer's analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing toxicologist, this reviewer independently performed the survival and tumor data analyses using the data provided by the sponsor electronically.

### 2.2.1. Survival analysis

In the reviewer's analysis, the survival distributions of rats in all five groups (Groups 1, 2, 3, 4, and 5) were estimated using the Kaplan-Meier product limit method. The dose response relationship was tested across Groups 1, 2, 3, 4, and 5 using the likelihood ratio test, and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for all five groups in male and female rats, respectively. The intercurrent mortality data of all five groups, and the results of the tests for dose response relationship and homogeneity of survivals for Groups 1, 2, 3, 4, and 5 are given in Tables 1A and 1B in the appendix for male and female rats, respectively.

**Reviewer's findings**:

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy

were 33 (47%), 32 (46%), 28 (40%), 40 (57%), and 33 (47%) in Groups 1, 2, 3, 4, and 5 for male rats, respectively, and 34 (49%), 31 (44%), 20 (29%), 19 (27%), and 31 (44%) for female rats respectively. No statistically significant dose response relationship and pairwise comparisons in mortality was noted for male rats; while for female rats, statistically significant pairwise comparisons in mortality were noted when comparing the control group versus the mid and mid-high dose groups ($p$=0.0227 and $p$=0.0151 respectively), but without the corresponding statistically significant dose response relationship.

For the control group in male rats, there is a discrepancy of the number of animal surviving to their terminal sacrifice between the sponsor's and reviewer's report (35 vs. 33). The reason is that, two animals (#46 and #60) in the control group of male rats that died during the Week 105, were labeled by the sponsor as "Natural Death" instead of "Terminal Sacrifice" in the tumor.xpt dataset. Therefore the reviewer considered them as the natural death, whereas the sponsor considered them as the surviving animals.

### 2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships across Groups 1, 2, 3, 4, and 5, and pairwise comparisons of each of the four treated groups (Groups 2, 3, 4, and 5) against the vehicle control group (Group 1), using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993).

In the ploy-k method, the adjustment for differences in mortality among treatment groups is made by modifying the number of animals at risk in the denominators in the calculations of overall tumor rates in the Cochran-Armitage test to reflect less-than-whole-animal contributions for animals that die without tumor before the end of the study (Bailer and Portier 1988). The modification is made by defining a new number of animals at risk for each treatment group. The number of animals at risk for the $i$-th treatment group $R^*$ i is defined as $R^*_i = \sum W_{ij}$ where $w_{ij}$ is the weight for the $j$-th animal in the $i$-th treatment group, and the sum is over all animals in the group.

Bailer and Portier (1988) proposed the weight $w_{ij}$ as follows:

$w_{ij} = 1$ to animals dying with the tumor, and

$w_{ij} = ( t_{ij} / tsacr )^3$ to animals dying without the tumor,

where $t_{ij}$ is the time of death of the $j$-th animal in the $i$-th treatment group, and tsacr is the planned (or intended) time of terminal sacrifice. The above formulas imply that animals living up to the end of the planned terminal sacrifice date without developing any tumor will also be assigned $w_{ij}$ =1 since $t_{ij}$ = tsacr. Also animals developed the tumor type being tested before the end of the study will be assigned as $w_{ij}$ = 1.

Certain treatment groups of a study or the entire study may be terminated earlier than the planned (or intended) time of terminal sacrifice due to excessive mortalities. However, based on the principle of the Intention-to-treat (ITT) analysis in randomized trials, the tsacr should not be affected by the unplanned early terminations. The tsacr should always be equal to the planned (or intended) time of terminal sacrifice. For those animals that were sacrificed later than tsacr,

regardless their actual terminal sacrifice time, tsacr was used as their time of terminal sacrifice in the analysis.

One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. 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 this data.

**Multiple testing adjustment**:

For the adjustment of multiple testing, this reviewer used the methodologies suggested in the FDA guidance for statistical design and analysis of carcinogenicity studies (2001). For dose response relationship tests, the guidance suggests the use of test levels of $\alpha$=0.005 for common tumors and $\alpha$=0.025 for rare tumors for a submission with two species where both are two-years studies, in order to keep the false-positive rate at the nominal level of approximately 10%. For multiple pairwise comparisons of treated group with control, the guidance suggests the use of test levels of $\alpha$=0.01 for common tumors and $\alpha$=0.05 for rare tumors, in order to keep the false-positive rate at the nominal level of approximately 10% for both submissions with two or one species.

A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. However, if the background information for the common or rare tumor is not available, the number of animals bearing tumors in the vehicle control group in the present study was used to determine the common or rare tumor status in the review report. That is, if the number of animals bearing tumors in the vehicle control group is 0, then this tumor is considered as the rare tumor; otherwise, if the number of animals bearing tumors in the control group is greater than or equal to 1, then this tumor is considered as the common tumor.

**Reviewer's findings**:

The tumor rates and the p-values of the tested tumor types are listed in Tables 2A and 2B in the appendix for male and female rats, respectively. The tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons of treated groups and vehicle control are reported in Table 2.

Based on the criteria of adjustment for multiple testing discussed above, the reviewer's analysis showed that in male rats, statistically significant dose response relationships were noted for both of benign C-cell adenoma and malignant C-cell carcinoma of thyroids ($p<0.0001$ and $p<0.0001$, respectively), along with statistically significant pairwise comparisons of the control group versus the mid, mid-high, and high groups for benign C-cell adenoma ($p<0.0001$, $p<0.0001$ and $p<0.0001$, respectively), and the control group versus the mid-high and high groups for malignant C-cell carcinoma ($p=0.0081$ and $p<0.0001$, respectively), regardless the tumor type (rare or common). In addition, a statistically significant dose response relationship was noted for the combined C-cell adenoma and carcinoma ($p<0.0001$), along with statistically significant pairwise comparisons of the control group versus the mid, mid-high, and high groups ($p<0.0001$, $p<0.0001$ and $p<0.0001$, respectively).

Similarly, based on the criteria of adjustment for multiple testing discussed above, in female rats, statistically significant dose response relationships were noted for both of C-cell adenoma alone and the combined C-cell adenoma and carcinoma of thyroids ($p<0.0001$ and $p<0.0001$, respectively), along with statistically significant pairwise comparisons of the control group versus the mid, mid-high, and high groups for C-cell adenoma alone ($p<0.0001$, $p<0.0001$ and $p<0.0001$, respectively), and for the combined C-cell adenoma and carcinoma ($p<0.0001$, $p<0.0001$ and $p<0.0001$, respectively), regardless the tumor type (rare or common).

No other statistically significant findings were noted in tumor data for both male and female rats.

**Table 2. Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Vehicle Control Group in Rats**

| Organ name | Tumor name | 0 mg Vehicle (C) | 0.0025 mg Low (L) | 0.01 mg Mid (M) | 0.025 mg Mid-High (MH) | 0.1 mg High (H) |
|---|---|---|---|---|---|---|
| | | P-Trend | P-L vs. C | P-M vs. C | P-C vs. MH | P-C vs. H |
| *Male* | | | | | | |
| H-Poietic Tumor | Large Granular Cell Lymphoma | 0/70 (55) | 0/70 (50) | 0/70 (54) | 0/70 (58) | 2/70 (56) |
| | | 0.0415 @ | NC | NC | NC | 0.2523 |
| Thyroids | C-Cell Adenoma | 7/70 (56) | 17/68 (52) | 29/69 (59) | 42/69 (63) | 41/69 (63) |
| | | <0.0001 $ | 0.0106 @ | <0.0001 $ | <0.0001 $ | <0.0001 $ |
| | C-Cell Carcinoma | 3/70 (56) | 3/68 (50) | 12/69 (55) | 13/69 (58) | 24/69 (59) |
| | | <0.0001 $ | 0.6053 | 0.0108 @ | 0.0081 $ | <0.0001 $ |
| | C-Cell Adenoma/ C-Cell Carcinoma | 10/70 (57) | 19/68 (53) | 32/69 (59) | 48/69 (63) | 53/69 (66) |
| | | <0.0001 $ | 0.0246 @ | <0.0001 $ | <0.0001 $ | <0.0001 $ |
| *Female* | | | | | | |
| Mammary | Mammary Adenocarcinoma | 18/70 (61) | 20/70 (59) | 27/70 (56) | 19/69 (53) | 16/69 (56) |
| | | 0.8252 | 0.3743 | 0.0294 @ | 0.3010 | 0.4628 |
| | Mammary Adenoma | 1/70 (54) | 5/70 (55) | 0/70 (47) | 0/69 (46) | 0/69 (52) |
| | | 0.9916 | 0.1071 | 0.4653 | 0.4600 | 0.4906 |
| | Mammary Adenocarcinoma/ Mammary Adenoma | 19/70 (61) | 23/70 (59) | 27/70 (56) | 19/69 (53) | 16/69 (56) |
| | | 0.8965 | 0.2395 | 0.0446 @ | 0.3696 | 0.5401 |
| Thyroids | C-Cell Adenoma | 6/70 (53) | 17/70 (56) | 28/69 (52) | 31/70 (53) | 45/70 (62) |
| | | <0.0001 $ | 0.0130 @ | <0.0001 $ | <0.0001 $ | <0.0001 $ |
| | C-Cell Carcinoma | 2/70 (53) | 4/70 (54) | 6/69 (48) | 5/70 (47) | 8/70 (54) |
| | | 0.0598 | 0.3482 | 0.1049 | 0.1715 | 0.0495 @ |
| | C-Cell Adenoma/ C-Cell Carcinoma | 8/70 (53) | 19/70 (56) | 34/69 (54) | 32/70 (53) | 50/70 (63) |
| | | <0.0001 $ | 0.0192 @ | <0.0001 $ | <0.0001 $ | <0.0001 $ |
| Uterus | Endometrial Polyp | 8/69 (54) | 4/70 (55) | 6/70 (48) | 13/70 (50) | 12/70 (54) |
| | | 0.0446 @ | 0.8291 | 0.5185 | 0.1199 | 0.2290 |

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;

$ = Statistically significant in common tumor at 0.005 level for test of dose response relationship and at 0.01 level for test of pairwise comparisons, or in rare tumor at 0.025 level for test of dose response relationship and at 0.05 level for test of pairwise comparisons;

@ = Not statistically significant in common tumor at 0.005 level for test of dose response relationship and at 0.01 level for test of pairwise comparisons; or in rare tumor at 0.025 level for test of dose response relationship and at 0.05 level for test of pairwise comparisons;

NC = Not calculable

Based on the request of the pharm/tox reviewer, the latency tables of tumors in mammary and pituitary for male and female rats are reported in Table 3A and 3B.

**Table 3A. Latency Tables with Mammary/Pituitary Tumors in Male Rats**

| | | | | Dose levels (mg/kg/day) | | | | |
|---|---|---|---|---|---|---|---|---|
| Organ | Tumor | Type | Weeks | 0 | 0.0025 | 0.01 | 0.025 | 0.1 |
| *Male* | | | | | | | | |
| Mammary | Mammary Adenocarcinoma | Incidental | 105+ | 1 | 0 | 0 | 0 | 0 |
| | | Total | | 1 | 0 | 0 | 0 | 0 |
| | Mammary Fibroadenoma | Non-incidental | 79 - 92 | 0 | 0 | 1 | 0 | 0 |
| | | | 93 - 104 | 0 | 0 | 0 | 0 | 1 |
| | | Incidental | 93 - 104 | 0 | 0 | 1 | 0 | 0 |
| | | | 105+ | 0 | 2 | 0 | 0 | 0 |
| | | Total | | 0 | 2 | 2 | 0 | 1 |
| Pituitary | Adenoma, Pars Distalis | Non-incidental | 53 - 78 | 1 | 3 | 2 | 5 | 4 |
| | | | 79 - 92 | 5 | 4 | 9 | 2 | 11 |
| | | | 93 - 104 | 2 | 0 | 7 | 4 | 9 |
| | | Incidental | 53 - 78 | 1 | 1 | 0 | 0 | 0 |
| | | | 79 - 92 | 4 | 2 | 1 | 2 | 1 |
| | | | 93 - 104 | 5 | 5 | 5 | 1 | 2 |
| | | | 105+ | 14 | 17 | 10 | 15 | 11 |
| | | Total | | 32 | 32 | 34 | 29 | 38 |
| | Adenoma, Pars Intermed | Incidental | 93 - 104 | 1 | 0 | 0 | 0 | 1 |
| | | | 105+ | 1 | 1 | 0 | 2 | 2 |
| | | Total | | 2 | 1 | 0 | 2 | 3 |

**Table 3B. Latency Tables with Mammary/Pituitary Tumors in Female Rats**

| | | | | Dose levels (mg/kg/day) | | | | |
|---|---|---|---|---|---|---|---|---|
| Organ | Tumor | Cause of Death | Weeks | 0 | 0.0025 | 0.01 | 0.025 | 0.1 |
| *Female* | | | | | | | | |
| Mammary | Mammary Adenocarcinoma | Non-incidental | 0 - 52 | 3 | 0 | 2 | 3 | 1 |
| | | | 53 - 78 | 8 | 4 | 14 | 4 | 1 |
| | | | 79 - 92 | 1 | 6 | 4 | 8 | 5 |
| | | | 93 - 104 | 0 | 5 | 1 | 1 | 3 |
| | | Incidental | 53 - 78 | 0 | 1 | 0 | 0 | 1 |
| | | | 79 - 92 | 1 | 2 | 2 | 1 | 1 |
| | | | 93 - 104 | 2 | 1 | 1 | 1 | 0 |
| | | | 105+ | 3 | 1 | 3 | 1 | 3 |
| | | Total | | 18 | 20 | 27 | 19 | 15 |
| | Mammary Adenoma | Non-incidental | 0 - 52 | 0 | 1 | 0 | 0 | 0 |
| | | | 79 - 92 | 0 | 2 | 0 | 0 | 0 |
| | | | 93 - 104 | 0 | 1 | 0 | 0 | 0 |
| | | Incidental | 79 - 92 | 1 | 0 | 0 | 0 | 0 |
| | | | 93 - 104 | 0 | 1 | 0 | 0 | 0 |
| | | Total | | 1 | 5 | 0 | 0 | 0 |
| | Mammary Fibroadenoma | Non-incidental | 0 - 52 | 2 | 1 | 1 | 3 | 1 |
| | | | 53 - 78 | 10 | 10 | 8 | 12 | 9 |
| | | | 79 - 92 | 7 | 11 | 9 | 3 | 5 |
| | | | 93 - 104 | 10 | 6 | 6 | 2 | 2 |
| | | Incidental | 53 - 78 | 0 | 1 | 1 | 0 | 0 |
| | | | 79 - 92 | 2 | 1 | 4 | 0 | 1 |
| | | | 93 - 104 | 0 | 2 | 1 | 1 | 1 |
| | | | 105+ | 2 | 3 | 2 | 3 | 4 |
| | | Total | | 33 | 35 | 32 | 24 | 23 |
| Pituitary | Adenoma, Pars Distalis | Non-incidental | 0 - 52 | 0 | 0 | 1 | 1 | 0 |
| | | | 53 - 78 | 5 | 5 | 7 | 7 | 5 |
| | | | 79 - 92 | 6 | 8 | 8 | 7 | 7 |
| | | | 93 - 104 | 3 | 8 | 6 | 7 | 6 |
| | | Incidental | 0 - 52 | 0 | 0 | 0 | 1 | 0 |
| | | | 53 - 78 | 2 | 2 | 5 | 2 | 1 |
| | | | 79 - 92 | 8 | 1 | 7 | 5 | 3 |
| | | | 93 - 104 | 5 | 3 | 7 | 9 | 4 |
| | | | 105+ | 19 | 22 | 13 | 14 | 20 |
| | | Total | | 48 | 49 | 54 | 53 | 46 |
| | Adenoma, Pars Intermed | Incidental | 93 - 104 | 0 | 0 | 0 | 0 | 1 |
| | | | 105+ | 0 | 0 | 0 | 1 | 0 |
| | | Total | | 0 | 0 | 0 | 1 | 1 |
| | Carcinoma, Pars Distal | Incidental | 93 - 104 | 0 | 1 | 0 | 0 | 0 |
| | | Total | | 0 | 1 | 0 | 0 | 0 |

### 3. Mouse Study

Two separate experiments, one in male mice and one in female mice were conducted. As indicated in Table 4, in each of these two experiments there were three treated groups and one vehicle control groups. Two hundred and forty CD-1 mice of each sex were assigned randomly to these four groups in size of 60 mice per group. The three treated groups received 0.3, 1, and 3 mg/kg/day, referred to as Groups3, 4, and 5 (low, mid, and high dose group) for male mice respectively, and 0.1, 0.3, and 1 mg/kg/day, referred to as Groups 2, 3 and 4 (low, mid, and high dose group) for female mice, respectively. Animals in the control group were administrated with the vehicle (1.42 mg/mL disodium hydrogen phosphate, dehydrate, 14.0 mg/mL propylene glycol and 5.50 mg/mL phenol in water for injection, adjusted to pH 7.4), and handled for the same duration and in the same manner as the treated groups.

**Table 4. Experimental Design in Mouse Study**

| Group No. | No. of Toxicity Animals | | | Dosage Level (mg/kg/day) | |
|---|---|---|---|---|---|
| | Male | Female | Test Material | Male | Female |
| 1 | 60 | 60 | Vehicle Control | 0 | 0 |
| 2 | 0 | 60 | NNC 0113-0217 | N/A | 0.1 |
| 3 | 60 | 60 | NNC 0113-0217 | 0.3 | 0.3 |
| 4 | 60 | 60 | NNC 0113-0217 | 1 | 1 |
| 5 | 60 | 0 | NNC 0113-0217 | 3 | N/A |

Animals were inspected visually at least twice daily for evidence of ill-health or reaction to treatment. In addition, a more detailed weekly physical examination, which included palpation, was performed on each animal to monitor general health. Particular attention was paid to any superficial or palpable swellings, for which the location, size, consistency, time of first observation and subsequent history were recorded. Main group animals killed during the study and those surviving until the end of the scheduled treatment period were killed by carbon dioxide asphyxiation followed by exsanguination. The sequence in which the animals were killed after completion of treatment was selected to allow satisfactory inter-group comparison. After a review of the history of each animal, a full macroscopic examination of the tissues was performed. All external features and orifices were examined visually including the parenteral sites. All tissues preserved for examination were examined for all animals sacrificed on completion of the scheduled treatment period and for all animals killed or dying during the study. Tissues reported at macroscopic examination as being grossly abnormal were examined for all animals in line with current practice.

## 3.1. Sponsor's analyses

### 3.1.1. Survival analysis

The sponsor used similar methodologies to analyze the mouse tumor data as those used to analyze the rat tumor data.

**Sponsor's findings**:

The sponsor's analysis showed that the numbers of mice surviving to their terminal necropsy were 27 (45%), 17 (28%), 35 (58%), and 35 (58%) in vehicle control, the low, mid and high dose groups for male mice, respectively, and 29 (48%), 23 (38%), 24 (40%), and 24 (40%) for female mice, respectively. The sponsor did not report any statistically significant trend in mortality for male and female mice ($p$=0.639 and 0.707, respectively), while a statistically significant pairwise comparison of the control group with the low dose group was noted ($p$=0.006) for male mice, and no statistically significant pairwise comparison was noted for female mice.

### 3.1.2. Tumor data analysis

The sponsor used similar methodologies to analyze the mouse tumor data as those used to analyze the rat tumor data.

**Multiple testing adjustment**:

In the sponsor's report, no text can be located in terms of the criteria used for the significance adjustment. Based on the sponsor's discussion of the tumor findings, no adjustment for multiple testing in the context of rare or common tumors was considered in the sponsor's analysis.

**Sponsor's findings:**

In the sponsor's analysis, for benign C-cell adenoma in thyroids of male mice, the trend test was not statistically significant ($p$=0.065), along with statistically significant pairwise comparisons of the control group versus the low, mid, and high groups (p<0.001, p<0.001 and p<0.001 respectively). For the combined benign C-cell adenoma and malignant C-cell carcinoma, the trend test was statistically significant ($p$=0.021), along with statistically significant pairwise comparisons of the control group versus the low, mid, and high dose groups (p<0.001, p<0.001 and p<0.001 respectively).

For benign C-cell adenoma in thyroids of female mice, the trend test was statistically significant ($p$<0.001), along with statistically significant pairwise comparisons of the control group versus the low, mid, and high dose groups (p<0.001, p<0.001 and p<0.001 respectively). For the combined benign C-cell adenoma and malignant C-cell carcinoma, the trend test was statistically significant ($p$<0.001), along with statistically significant pairwise comparisons of the control group versus the low, mid, and high dose groups were (p<0.001, p<0.001 and p<0.001 respectively).

For malignant adenocarcinoma and the combined benign adenoma and malignant adenocarcinoma in harderian glands of female mice, the trend tests were statistically significant ($p$=0.016 and $p$=0.003, respectively), without any statistically significant pairwise comparisons.

For benign luteoma in ovaries of female mice, the trend test was not statistically significant ($p$=0.195), while a statistically significant pairwise comparison was noted between the control group and the mid dose group ($p$=0.036).

## 3.2. Reviewer's analyses

Similar to the rat study, this reviewer independently performed survival and tumor data analyses of mouse data to verify sponsor's analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

For the analysis of both the survival data and the tumor data in mice, this reviewer used similar methodologies that were used for the analyses of the rat survival and tumor data.

### 3.2.1. Survival analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data, and the results of the tests for dose response relationship and homogeneity of survivals for the combined vehicle control, low, mid, and high dose groups were given in Tables 3A and 3B in the appendix for male and female mice, respectively.

**Reviewer's findings**:

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 25 (42%), 17 (28%), 34 (57%), and 35 (58%) in vehicle control, the low, mid and high dose groups for male mice, respectively, and 29 (48%), 23 (38%), 24 (40%), and 24 (40%) for female mice, respectively. The reviewer's analysis showed no statistically significant dose response relationship in mortality for both male and female mice. For female mice, a statistically significant pairwise comparison was noted when comparing the control group versus the low dose groups ($p$=0.0014), while no statistically significant pairwise comparison was noted for male mice.

For the control and mid dose groups in male mice, there are discrepancies of the number of animal surviving to their terminal sacrifice between the sponsor's and reviewer's report (27 vs 25, and 35 vs 34, respectively). The reason is that, two animals (#25 and #42) in the control group and one animal (#182) in the mid dose group that died during the Week 105, were labeled by the sponsor as "Natural Death" instead of "Terminal Sacrifice" in the tumor.xpt dataset. Therefore the reviewer considered them as the natural death in the report, whereas the sponsor considered them as the surviving animals.

### 3.2.2. Tumor data analysis

**Reviewer's findings**:

The tumor rates and the p-values of the tested tumor types are listed in Tables 4A and Table 4B in the appendix for male and female mice, respectively. The tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons of treated groups and vehicle control are reported in Table 5.

Based on the criteria of adjustment for multiple testing discussed above, the reviewer's analysis showed that for thyroids in male mice, statistically significant pairwise comparisons were noted when comparing the control group versus the low, mid, and high groups for both of benign C-cell adenoma alone ($p<0.0001$, $p<0.0001$ and $p<0.0001$, respectively) and the combined C-cell adenoma and carcinoma ($p<0.0001$, $p<0.0001$ and $p<0.0001$, respectively), while there is no statistically significant dose response relationship, regardless the tumor type (rare or common).

For thyroids in female mice, statistically significant dose response relationship were noted for both of benign C-cell adenoma alone ($p=0.0001$) and the combined C-cell adenoma and carcinoma of thyroids ($p=0.0001$), along with statistically significant pairwise comparisons of the control group versus the low, mid, and high groups for benign C-cell adenoma alone ($p<0.0001$, $p<0.0001$ and $p<0.0001$, respectively) and for the combined C-cell adenoma and carcinoma ($p<0.0001$, $p<0.0001$ and $p<0.0001$, respectively).

No other statistically significant findings were noted in tumor data for both male and female mice.

**Table 5. Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Vehicle Control Group in Mice**

| Organ name | Tumor name | Vehicle (C)<br>P - Trend | Low (L)<br>P - C vs. L | Mid (M)<br>P - C vs. M | High (H)<br>P - C vs. H |
|---|---|---|---|---|---|
| *Male* | | 0 mg | 0.3 mg | 1 mg | 3 mg |
| Thyroids | C-Cell Adenoma | 0/60 (41) | 24/60 (51) | 23/59 (49) | 18/59 (49) |
| | | 0.0620 | <0.0001 $ | <0.0001 $ | <0.0001 $ |
| | C-Cell Carcinoma | 0/60 (41) | 2/60 (50) | 2/59 (47) | 2/59 (48) |
| | | 0.2426 | 0.2991 | 0.2824 | 0.2880 |
| | C-Cell Adenoma/C-Cell Carcinoma | 0/60 (41) | 24/60 (51) | 24/59 (49) | 20/59 (49) |
| | | 0.0233 @ | <0.0001 $ | <0.0001 $ | <0.0001 $ |
| *Female* | | 0 mg | 0.1 mg | 0.3 mg | 1 mg |
| Harderian Glands | Adenocarcinoma | 0/60 (45) | 0/60 (45) | 0/60 (42) | 3/60 (45) |
| | | 0.0156 @ | NC | NC | 0.1208 |
| | Adenoma | 4/60 (45) | 2/60 (45) | 5/60 (43) | 7/60 (44) |
| | | 0.0683 | 0.6617 | 0.4707 | 0.2477 |
| | Adenocarcinoma/Adenoma | 4/60 (45) | 2/60 (45) | 5/60 (43) | 10/60 (45) |
| | | 0.0077 @ | 0.6617 | 0.4707 | 0.0721 |
| Ovaries | Luteoma | 0/60 (45) | 1/59 (44) | 4/59 (41) | 2/60 (44) |
| | | 0.2257 | 0.4944 | 0.0477 @ | 0.2416 |
| Thyroids | C-Cell Adenoma | 0/58 (43) | 16/59 (45) | 20/58 (43) | 24/60 (47) |
| | | 0.0001 $ | <0.0001 $ | <0.0001 $ | <0.0001 $ |
| | C-Cell Carcinoma | 0/58 (43) | 1/59 (44) | 2/58 (42) | 2/60 (44) |
| | | 0.1434 | 0.5057 | 0.2412 | 0.2529 |
| | C-Cell Adenoma/C-Cell Carcinoma | 0/58 (43) | 16/59 (45) | 21/58 (43) | 24/60 (47) |
| | | 0.0001 $ | <0.0001 $ | <0.0001 $ | <0.0001 $ |

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
$ = Statistically significant in common tumor at 0.005 level for test of dose response relationship and at 0.01 level for test of pairwise comparisons, or in rare tumor at 0.025 level for test of dose response relationship and at 0.05 level for test of pairwise comparisons;
@ = Not statistically significant in common tumor at 0.005 level for test of dose response relationship and at 0.01 level for test of pairwise comparisons; or in rare tumor at 0.025 level for test of dose response relationship and at 0.05 level for test of pairwise comparisons;
NC = Not calculable.

## 4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were to assess the carcinogenic potential of NNC 0113-0217 (a GLP-1 agonist being developed for the treatment of Type 2 diabetes), when administered to CD rats and CD-1 mice by daily subcutaneous administration over a period of 104 weeks.

### Rat Study:

Two separate experiments, one in male rats and one in female rats were conducted. In each of these two experiments there were four treated groups and one vehicle control group. Three hundred fifty CD rats of each sex were assigned randomly in size of 70 rats per group. The dose levels for the four treated groups were 0.0025, 0.01, 0.025, and 0.1 mg/kg/day for both male and

female rats.

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 33 (47%), 32 (46%), 28 (40%), 40 (57%), and 33 (47%) in Groups 1, 2, 3, 4, and 5 for male rats, respectively, and 34 (49%), 31 (44%), 20 (29%), 19 (27%), and 31 (44%) for female rats respectively. No statistically significant dose response relationship and pairwise comparisons in mortality was noted for male rats; while for female rats, statistically significant pairwise comparisons in mortality were noted when comparing the control group versus the mid and mid-high dose groups ($p$=0.0227 and $p$=0.0151 respectively), but without the corresponding statistically significant dose response relationship.

Based on the criteria of adjustment for multiple testing discussed above, the reviewer's analysis showed that in male rats, statistically significant dose response relationships were noted for both of benign C-cell adenoma and malignant C-cell carcinoma of thyroids ($p<0.0001$ and $p<0.0001$, respectively), along with statistically significant pairwise comparisons of the control group versus the mid, mid-high, and high groups for benign C-cell adenoma ($p<0.0001$, $p<0.0001$ and $p<0.0001$, respectively), and the control group versus the mid-high and high groups for malignant C-cell carcinoma ($p=0.0081$ and $p<0.0001$, respectively), regardless the tumor type (rare or common). In addition, a statistically significant dose response relationship was noted for the combined C-cell adenoma and carcinoma ($p<0.0001$), along with statistically significant pairwise comparisons of the control group versus the mid, mid-high, and high groups ($p<0.0001$, $p<0.0001$ and $p<0.0001$, respectively).

Similarly, based on the criteria of adjustment for multiple testing discussed above, in female rats, statistically significant dose response relationships were noted for both of C-cell adenoma alone and the combined C-cell adenoma and carcinoma of thyroids ($p<0.0001$ and $p<0.0001$, respectively), along with statistically significant pairwise comparisons of the control group versus the mid, mid-high, and high groups for C-cell adenoma alone ($p<0.0001$, $p<0.0001$ and $p<0.0001$, respectively), and for the combined C-cell adenoma and carcinoma ($p<0.0001$, $p<0.0001$ and $p<0.0001$, respectively), regardless the tumor type (rare or common).

No other statistically significant findings were noted in tumor data for both male and female rats.

**Mouse Study:**

Two separate experiments, one in male mice and one in female mice were conducted. In each of these two experiments there were three treated groups and one vehicle control groups. Two hundred and forty CD-1 mice of each sex were assigned randomly to these four groups (Groups 1 to 4) in size of 60 mice per group. The three treated groups received 0.3, 1, and 3 mg/kg/day for male mice, referred to as Groups 3, 4, and 5 (low, mid, and high dose group) respectively, and 0.1, 0.3, and 1 mg/kg/day for female mice, referred to as Groups 2, 3 and 4 (low, mid, and high dose group) respectively.

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 25 (42%), 17 (28%), 34 (57%), and 35 (58%) in vehicle control, the low, mid and high dose groups for male mice, respectively, and 29 (48%), 23 (38%), 24 (40%), and 24 (40%) for female

mice, respectively. The reviewer's analysis showed no statistically significant dose response relationship in mortality for both male and female mice. For female mice, a statistically significant pairwise comparison was noted when comparing the control group versus the low dose groups ($p$=0.0014), while no statistically significant pairwise comparison was noted for male mice.

Based on the criteria of adjustment for multiple testing discussed above, the reviewer's analysis showed that for thyroids in male mice, statistically significant pairwise comparisons were noted when comparing the control group versus the low, mid, and high groups for both of benign C-cell adenoma alone ($p<0.0001$, $p<0.0001$ and $p<0.0001$, respectively) and the combined C-cell adenoma and carcinoma ($p<0.0001$, $p<0.0001$ and $p<0.0001$, respectively), while there is no statistically significant dose response relationship, regardless the tumor type (rare or common).

For thyroids in female mice, statistically significant dose response relationship were noted for both of benign C-cell adenoma alone ($p=0.0001$) and the combined C-cell adenoma and carcinoma of thyroids ($p=0.0001$), along with statistically significant pairwise comparisons of the control group versus the low, mid, and high groups for benign C-cell adenoma alone ($p<0.0001$, $p<0.0001$ and $p<0.0001$, respectively) and for the combined C-cell adenoma and carcinoma ($p<0.0001$, $p<0.0001$ and $p<0.0001$, respectively).

No other statistically significant findings were noted in tumor data for both male and female mice.

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Mathematical Statistician

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Dr. Lillian Patrician

# 5. Appendix

## Table 1A: Intercurrent Mortality Rate in Male Rats

| | 0 mg/kg/day | | 0.0025 mg/kg/day Low | | 0.01 mg/kg/day Mid | | 0.025 mg/kg/day Mid-High | | 0.1 mg/kg/day High | |
|---|---|---|---|---|---|---|---|---|---|---|
| Week / Type of Death | No. of Death | Cum % | No. of Death | Cum % | No. of Death | Cum % | No. of Death | Cum % | No. of Death | Cum % |
| 0 - 52 | 2 | 5.71 | 5 | 7.14 | 1 | 1.43 | . | . | . | . |
| 53 - 78 | 7 | 15.71 | 10 | 21.43 | 8 | 12.86 | 9 | 12.86 | 7 | 10.00 |
| 79 - 91 | 10 | 30.00 | 11 | 37.14 | 13 | 31.43 | 8 | 24.29 | 14 | 30.00 |
| 92 - 104 | 16 | 52.86 | 12 | 54.29 | 20 | 60.00 | 13 | 42.86 | 16 | 52.86 |
| >105 | 2 | 2.86 | . | . | . | . | . | . | . | . |
| Terminal sacrifice | 33 | 47.14 | 32 | 45.71 | 28 | 40.00 | 40 | 57.14 | 33 | 47.14 |
| Total | 70 | . | 70 | . | 70 | . | 70 | . | 70 | . |

| Test | All Dose Groups | Control vs. Low | Control vs. Mid | Control vs. MId-high | Control vs. High |
|---|---|---|---|---|---|
| Dose-Response (Likelihood Ratio) | 0.6199 | 0.5669 | 0.4060 | 0.2636 | 0.9655 |
| Homogeneity (Log-Rank) | 0.3707 | 0.5640 | 0.4003 | 0.2591 | 0.9652 |

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

## Table 1B: Intercurrent Mortality Rate in Female Rats

| | 0 mg/kg/day | | 0.0025 mg/kg/day Low | | 0.01 mg/kg/day Mid | | 0.025 mg/kg/day Mid-High | | 0.1 mg/kg/day High | |
|---|---|---|---|---|---|---|---|---|---|---|
| Week / Type of Death | No. of Death | Cum % | No. of Death | Cum % | No. of Death | Cum % | No. of Death | Cum % | No. of Death | Cum % |
| 0 - 52 | 2 | 2.86 | 1 | 1.43 | 3 | 4.29 | 3 | 4.29 | 1 | 1.43 |
| 53 - 78 | 8 | 14.29 | 10 | 15.71 | 13 | 22.86 | 15 | 25.71 | 9 | 14.29 |
| 79 - 91 | 14 | 34.29 | 11 | 31.43 | 17 | 47.14 | 14 | 45.71 | 14 | 34.29 |
| 92 - 104 | 12 | 51.43 | 17 | 55.71 | 17 | 71.43 | 19 | 72.86 | 15 | 55.71 |
| Terminal sacrifice | 34 | 48.57 | 31 | 44.29 | 20 | 28.57 | 19 | 27.14 | 31 | 44.29 |
| Total | 70 | . | 70 | . | 70 | . | 70 | . | 70 | . |

| Test | All Dose Groups | Control vs. Low | Control vs. Mid | Control vs. MId-High | Control vs. High |
|---|---|---|---|---|---|
| Dose-Response (Likelihood Ratio) | 0.6486 | 0.8326 | 0.0227* | 0.0151* | 0.7437 |
| Homogeneity (Log-Rank) | 0.0122* | 0.8311 | 0.0213* | 0.0139* | 0.7414 |

#All Cum. % Cumulative Percentage except for Terminal sacrifice;
* = Significant at 5% level;

**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats**

| Organ name | Tumor name | 0 mg Vehicle (C) | 0.0025 mg Low (L) | 0.01 mg Mid (M) | 0.025 mg Mid-high (MH) | 0.1 mg High (H) |
|---|---|---|---|---|---|---|
| | | P-Trend | P-L vs. C | P-M vs. C | P-C vs. MH | P-C vs. H |
| Abdomen | Sarcoma | 0/69 (0) | 1/70 (2) | 0/70 () | 0/70 () | 0/70 () |
| | | 0.5000 | 0.5000 | NC | NC | NC |
| Adrenals | Cortical Adenoma | 2/70 (55) | 0/70 (50) | 4/70 (54) | 4/70 (58) | 4/70 (56) |
| | | 0.1492 | 0.7280 | 0.3306 | 0.3651 | 0.3480 |
| | Cortical Carcinoma | 0/70 (55) | 1/70 (51) | 0/70 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.6131 | 0.4811 | NC | NC | NC |
| | Cortical Adenoma/ Cortical Carcinoma | 2/70 (55) | 1/70 (51) | 4/70 (54) | 4/70 (58) | 4/70 (56) |
| | | 0.1959 | 0.4714 | 0.3306 | 0.3651 | 0.3480 |
| | Phaeochromocytoma | 14/70 (56) | 10/70 (51) | 10/70 (55) | 8/70 (58) | 5/70 (56) |
| | | 0.9857 | 0.6676 | 0.7391 | 0.8997 | 0.9790 |
| | Malignant Phaeochromocytoma | 5/70 (56) | 3/70 (50) | 0/70 (54) | 1/70 (58) | 2/70 (56) |
| | | 0.7162 | 0.5767 | 0.9688 | 0.9048 | 0.7810 |
| | Malignant Phaeochromocytoma/ Phaeochromocytoma | 16/70 (56) | 12/70 (51) | 10/70 (55) | 9/70 (59) | 6/70 (57) |
| | | 0.9891 | 0.6445 | 0.8573 | 0.9341 | 0.9862 |
| Brain | Astrocytoma | 0/70 (55) | 2/70 (51) | 0/70 (54) | 0/70 (58) | 2/70 (56) |
| | | 0.1577 | 0.2291 | NC | NC | 0.2523 |
| | Granular Cell Tumor | 0/70 (55) | 1/70 (51) | 0/70 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.6131 | 0.4811 | NC | NC | NC |
| | Malignant Granular Cell Tumor | 1/70 (55) | 0/70 (50) | 0/70 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.7985 | 0.4762 | 0.4954 | 0.5133 | 0.5045 |
| | Granular Cell Tumor/ Malignant Granular Cell Tumor | 1/70 (55) | 1/70 (51) | 0/70 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.8853 | 0.7332 | 0.4954 | 0.5133 | 0.5045 |
| | Medulloblastoma | 1/70 (56) | 0/70 (50) | 0/70 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.7956 | 0.4717 | 0.4909 | 0.5088 | 0.5000 |
| | Meningioma | 0/70 (55) | 0/70 (50) | 0/70 (54) | 1/70 (58) | 0/70 (56) |
| | | 0.2051 | NC | NC | 0.5133 | NC |
| | Mixed Glioma | 1/70 (55) | 0/70 (50) | 0/70 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.7985 | 0.4762 | 0.4954 | 0.5133 | 0.5045 |

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)**

| Organ name | Tumor name | 0 mg Vehicle (C) | 0.0025 mg Low (L) | 0.01 mg Mid (M) | 0.025 mg Mid-high (MH) | 0.1 mg High (H) |
|---|---|---|---|---|---|---|
| | | P-Trend | P-L vs. C | P-M vs. C | P-C vs. MH | P-C vs. H |
| Colon | Lipoma | 0/70 (55) | 2/70 (50) | 0/70 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.8529 | 0.2244 | NC | NC | NC |
| H-Poietic Tumor | Histiocytic Sarcoma | 3/70 (57) | 1/70 (51) | 3/70 (54) | 1/70 (58) | 0/70 (56) |
| | | 0.9582 | 0.6478 | 0.6345 | 0.6974 | 0.8750 |
| | Large Granular Cell Lymphoma | 0/70 (55) | 0/70 (50) | 0/70 (54) | 0/70 (58) | 2/70 (56) |
| | | 0.0415 @ | NC | NC | NC | 0.2523 |
| | Malignant Lymphoma | 2/70 (56) | 3/70 (51) | 2/70 (54) | 4/70 (59) | 0/70 (56) |
| | | 0.9394 | 0.4554 | 0.6771 | 0.3648 | 0.7523 |
| | Large Granular Cell Lymphoma/ Malignant Lymphoma | 2/70 (56) | 3/70 (51) | 2/70 (54) | 4/70 (59) | 2/70 (56) |
| | | 0.5766 | 0.4554 | 0.6771 | 0.3648 | NC |
| Harderian Glands | Adenoma | 0/70 (55) | 0/69 (50) | 0/70 (54) | 0/70 (58) | 1/69 (56) |
| | | 0.2051 | NC | NC | NC | 0.5045 |
| Kidneys | Nephroblastoma | 1/70 (56) | 0/70 (50) | 0/70 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.7956 | 0.4717 | 0.4909 | 0.5088 | 0.5000 |
| | Renal Liposarcoma | 0/70 (55) | 0/70 (50) | 2/70 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.6617 | NC | 0.2431 | NC | NC |
| | Transitional Cell Papilloma | 0/70 (55) | 1/70 (51) | 0/70 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.6131 | 0.4811 | NC | NC | NC |
| | Tubular Adenoma | 0/70 (55) | 0/70 (50) | 0/70 (54) | 0/70 (58) | 1/70 (56) |
| | | 0.2051 | NC | NC | NC | 0.5045 |
| Liver | Hepatocellular Adenoma | 3/70 (56) | 2/70 (51) | 0/70 (54) | 3/70 (58) | 1/70 (56) |
| | | 0.7078 | 0.4554 | 0.8716 | 0.3564 | 0.6909 |
| | Hepatocellular Carcinoma | 1/70 (55) | 0/70 (50) | 0/70 (54) | 2/70 (58) | 0/70 (56) |
| | | 0.5597 | 0.4762 | 0.4954 | 0.5201 | 0.5045 |
| | Hepatocellular Adenoma/ Hepatocellular Carcinoma | 4/70 (56) | 2/70 (51) | 0/70 (54) | 5/70 (58) | 1/70 (56) |
| | | 0.7819 | 0.6151 | 0.9364 | 0.5224 | 0.8182 |
| Ln Mesenteric | Haemangioma | 0/67 (54) | 0/70 (50) | 3/70 (54) | 2/69 (57) | 0/69 (55) |
| | | 0.7066 | NC | 0.1215 | 0.2614 | NC |
| Lungs + Bronchi | Bronchioloalveolar Adenoma | 1/70 (56) | 0/70 (50) | 0/70 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.7956 | 0.4717 | 0.4909 | 0.5088 | 0.5000 |

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)**

| Organ name | Tumor name | 0 mg Vehicle (C) | 0.0025 mg Low (L) | 0.01 mg Mid (M) | 0.025 mg Mid-high (MH) | 0.1 mg High (H) |
|---|---|---|---|---|---|---|
| | | P-Trend | P-L vs. C | P-M vs. C | P-C vs. MH | P-C vs. H |
| Mammary | Mammary Adenocarcinoma | 1/68 (54) | 0/70 (50) | 0/69 (53) | 0/69 (57) | 0/69 (55) |
| | | 0.7993 | 0.4808 | 0.4953 | 0.5135 | 0.5046 |
| | Mammary Fibroadenoma | 0/68 (54) | 2/70 (50) | 2/69 (53) | 0/69 (57) | 1/69 (55) |
| | | 0.5723 | 0.2287 | 0.2430 | NC | 0.5046 |
| Pancreas | Acinar Cell Adenoma | 0/70 (55) | 1/70 (51) | 0/70 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.6131 | 0.4811 | NC | NC | NC |
| | Islet Cell Adenoma | 5/70 (56) | 2/70 (50) | 2/70 (54) | 1/70 (58) | 1/70 (56) |
| | | 0.9157 | 0.7319 | 0.7658 | 0.9048 | 0.8970 |
| | Islet Cell Carcinoma | 2/70 (56) | 1/70 (50) | 1/70 (54) | 0/70 (58) | 1/70 (56) |
| | | 0.6366 | 0.4572 | 0.4862 | 0.7609 | 0.5000 |
| | Islet Cell Adenoma/ Islet Cell Carcinoma | 6/70 (56) | 3/70 (50) | 3/70 (54) | 1/70 (58) | 2/70 (56) |
| | | 0.8697 | 0.6958 | 0.7369 | 0.9486 | 0.8645 |
| | Mixed Cell Adenoma | 0/70 (55) | 1/70 (51) | 0/70 (54) | 0/70 (58) | 2/70 (56) |
| | | 0.0822 | 0.4811 | NC | NC | 0.2523 |
| Parathyroids | Chief Cell Adenoma | 0/67 (53) | 3/66 (49) | 2/65 (50) | 0/65 (54) | 0/63 (51) |
| | | 0.9350 | 0.1073 | 0.2332 | NC | NC |
| Pituitary | Adenoma, Pars Distalis | 32/69 (62) | 32/70 (57) | 34/70 (62) | 29/68 (62) | 38/70 (66) |
| | | 0.2912 | 0.3781 | 0.4286 | 0.6402 | 0.3087 |
| | Adenoma, Pars Intermedia | 2/69 (55) | 1/70 (50) | 0/70 (54) | 2/68 (56) | 3/70 (56) |
| | | 0.1257 | 0.4640 | 0.7477 | 0.3159 | 0.5086 |
| | Adenoma, Pars Distalis/ Adenoma, Pars Intermedia | 34/69 (62) | 33/70 (57) | 34/70 (62) | 31/68 (62) | 41/70 (67) |
| | | 0.2136 | 0.4402 | NC | 0.6404 | 0.2903 |
| Prostate | Adenocarcinoma | 0/70 (55) | 0/70 (50) | 1/69 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.4176 | NC | 0.4954 | NC | NC |
| | Leiomyosarcoma | 0/70 (55) | 0/70 (50) | 0/69 (53) | 0/70 (58) | 1/70 (56) |
| | | 0.2059 | NC | NC | NC | 0.5045 |
| Seminal Vesicles | Adenocarcinoma | 0/70 (55) | 0/70 (50) | 0/69 (53) | 1/70 (58) | 0/70 (56) |
| | | 0.2059 | NC | NC | 0.5133 | NC |
| Skeletal Muscle | Chordoma | 0/70 (55) | 0/70 (50) | 0/70 (54) | 1/70 (58) | 0/70 (56) |
| | | 0.2051 | NC | NC | 0.5133 | NC |

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)**

| Organ name | Tumor name | 0 mg Vehicle (C) | 0.0025 mg Low (L) | 0.01 mg Mid (M) | 0.025 mg Mid-high (MH) | 0.1 mg High (H) |
|---|---|---|---|---|---|---|
| | | P-Trend | P-L vs. C | P-M vs. C | P-C vs. MH | P-C vs. H |
| Skin | Basal Cell Tumor | 0/70 (55) | 1/70 (51) | 0/70 (54) | 0/70 (58) | 1/70 (56) |
| | | 0.2852 | 0.4811 | NC | NC | 0.5045 |
| | Fibroma | 10/70 (57) | 14/70 (52) | 11/70 (55) | 11/70 (60) | 13/70 (57) |
| | | 0.3947 | 0.1714 | 0.4636 | 0.5520 | 0.3207 |
| | Fibrosarcoma | 2/70 (56) | 2/70 (51) | 1/70 (54) | 0/70 (58) | 1/70 (56) |
| | | 0.7206 | 0.6549 | 0.4862 | 0.7609 | 0.5000 |
| | Fibroma/ Fibrosarcoma | 12/70 (57) | 16/70 (53) | 12/70 (55) | 11/70 (60) | 14/70 (57) |
| | | 0.4682 | 0.1894 | 0.5519 | 0.5549 | 0.4119 |
| | Fibrous Histiocytoma | 1/70 (56) | 0/70 (50) | 0/70 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.7956 | 0.4717 | 0.4909 | 0.5088 | 0.5000 |
| | Haemangioma | 0/70 (55) | 0/70 (50) | 1/70 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.4176 | NC | 0.4954 | NC | NC |
| | Haemangiopericytoma | 0/70 (55) | 0/70 (50) | 0/70 (54) | 1/70 (58) | 0/70 (56) |
| | | 0.2051 | NC | NC | 0.5133 | NC |
| | Haemangiosarcoma | 0/70 (55) | 0/70 (50) | 1/70 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.4176 | NC | 0.4954 | NC | NC |
| | Haemangiopericytoma/ Haemangiosarcoma | 0/70 (55) | 0/70 (50) | 1/70 (54) | 1/70 (58) | 0/70 (56) |
| | | 0.4133 | NC | 0.4954 | 0.5133 | NC |
| | Keratoacanthoma | 5/70 (56) | 7/70 (51) | 6/70 (54) | 5/70 (58) | 2/70 (57) |
| | | 0.9619 | 0.3159 | 0.4742 | 0.3938 | 0.7882 |
| | Lipoma | 2/70 (55) | 4/70 (51) | 3/70 (55) | 2/70 (58) | 3/70 (56) |
| | | 0.4901 | 0.3038 | 0.5000 | 0.3295 | 0.5086 |
| | Sarcoma, Nos | 0/70 (55) | 1/70 (51) | 0/70 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.6131 | 0.4811 | NC | NC | NC |
| | Sebaceous Cell Adenoma | 2/70 (56) | 0/70 (50) | 0/70 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.9588 | 0.7233 | 0.7431 | 0.7609 | 0.7523 |
| | Squamous Cell Papilloma | 1/70 (55) | 0/70 (50) | 0/70 (54) | 1/70 (58) | 1/70 (56) |
| | | 0.2895 | 0.4762 | 0.4954 | 0.2612 | 0.2523 |
| Spleen | Haemangiosarcoma | 0/70 (55) | 0/70 (50) | 0/70 (54) | 1/70 (58) | 0/70 (56) |
| | | 0.2051 | NC | NC | 0.5133 | NC |
| | Stromal Cell Sarcoma | 1/70 (55) | 0/70 (50) | 0/70 (54) | 0/70 (58) | 0/70 (56) |
| | | 0.7985 | 0.4762 | 0.4954 | 0.5133 | 0.5045 |

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)**

| Organ name | Tumor name | 0 mg Vehicle (C) | 0.0025 mg Low (L) | 0.01 mg Mid (M) | 0.025 mg Mid-high (MH) | 0.1 mg High (H) |
|---|---|---|---|---|---|---|
| | | P-Trend | P-L vs. C | P-M vs. C | P-C vs. MH | P-C vs. H |
| Testes | Interstitial (Leydig) Cell Adenoma | 3/70 (55) | 6/70 (51) | 8/70 (55) | 5/70 (58) | 3/70 (56) |
| | | 0.8428 | 0.2078 | 0.1011 | 0.3884 | 0.3480 |
| Thyroids | C-Cell Adenoma | 7/70 (56) | 17/68 (52) | 29/69 (59) | 42/69 (63) | 41/69 (63) |
| | | <0.0001 $ | 0.0106 @ | <0.0001 $ | <0.0001 $ | <0.0001 $ |
| | C-Cell Carcinoma | 3/70 (56) | 3/68 (50) | 12/69 (55) | 13/69 (58) | 24/69 (59) |
| | | <0.0001 $ | 0.6053 | 0.0108$ | 0.0081 $ | <0.0001 $ |
| | C-Cell Adenoma/ C-Cell Carcinoma | 10/70 (57) | 19/68 (53) | 32/69 (59) | 48/69 (63) | 53/69 (66) |
| | | <0.0001 $ | 0.0246 @ | <0.0001 $ | <0.0001 $ | <0.0001 $ |
| | Follicular Cell Adenoma | 2/70 (55) | 1/68 (51) | 1/69 (53) | 0/69 (57) | 0/69 (56) |
| | | 0.9535 | 0.4714 | 0.4860 | 0.7611 | 0.7568 |
| | Follicular Cell Carcinoma | 1/70 (55) | 0/68 (50) | 0/69 (53) | 1/69 (57) | 0/69 (56) |
| | | 0.5753 | 0.4762 | 0.4907 | 0.2568 | 0.5045 |
| | Follicular Cell Adenoma/ Follicular Cell Carcinoma | 3/70 (55) | 1/68 (51) | 1/69 (53) | 1/69 (57) | 0/69 (56) |
| | | 0.9449 | 0.6620 | 0.6769 | 0.7043 | 0.8817 |

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

**Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats**

| Organ name | Tumor name | 0 mg Vehicle (C) | 0.0025 mg Low (L) | 0.01 mg Mid (M) | 0.025 mg Mid-high (MH) | 0.1 mg High (H) |
|---|---|---|---|---|---|---|
| | | P-Trend | P-L vs. C | P-M vs. C | P-C vs. MH | P-C vs. H |
| Adrenals | Cortical Adenoma | 2/70 (53) | 3/70 (54) | 3/70 (48) | 0/70 (47) | 0/70 (53) |
| | | 0.9832 | 0.5089 | 0.4527 | 0.7216 | 0.7524 |
| | Cortical Carcinoma | 0/70 (53) | 0/70 (54) | 1/70 (47) | 1/70 (47) | 1/70 (53) |
| | | 0.1759 | NC | 0.4700 | 0.4700 | 0.5000 |
| | Cortical Adenoma/ Cortical Carcinoma | 2/70 (53) | 3/70 (54) | 4/70 (48) | 1/70 (47) | 1/70 (53) |
| | | 0.8568 | 0.5089 | 0.2929 | 0.4546 | 0.5000 |
| | Malignant Phaeochromocytoma | 0/70 (53) | 1/70 (54) | 1/70 (47) | 1/70 (47) | 1/70 (53) |
| | | 0.3035 | 0.5047 | 0.4700 | 0.4700 | 0.5000 |
| | Phaeochromocytoma | 6/70 (54) | 6/70 (55) | 3/70 (48) | 1/70 (47) | 2/70 (53) |
| | | 0.9339 | 0.3936 | 0.6936 | 0.9191 | 0.8588 |
| | Malignant Phaeochromocytoma/ Phaeochromocytoma | 6/70 (54) | 7/70 (55) | 4/70 (48) | 2/70 (47) | 3/70 (53) |
| | | 0.8804 | 0.5143 | 0.5521 | 0.8155 | 0.7463 |
| Brain | Astrocytoma | 0/70 (53) | 0/70 (54) | 1/70 (47) | 1/70 (47) | 0/70 (53) |
| | | 0.4081 | NC | 0.4700 | 0.4700 | NC |
| | Oligodendroglioma | 0/70 (53) | 0/70 (54) | 1/70 (48) | 1/70 (47) | 0/70 (53) |
| | | 0.4065 | NC | 0.4752 | 0.4700 | NC |
| Colon | Adenocarcinoma | 0/70 (53) | 0/69 (54) | 1/70 (48) | 1/70 (47) | 0/70 (53) |
| | | 0.4065 | NC | 0.4752 | 0.4700 | NC |
| H-Poietic Tumor | Histiocytic Sarcoma | 0/70 (53) | 1/70 (55) | 0/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.5765 | 0.5093 | NC | NC | NC |
| | Malignant Lymphoma | 1/70 (54) | 0/70 (54) | 1/70 (47) | 2/70 (47) | 1/70 (54) |
| | | 0.3419 | 0.5000 | 0.7166 | 0.4476 | NC |
| | Myeloid Cell Leukaemia | 0/70 (53) | 0/70 (54) | 1/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.3937 | NC | 0.4700 | NC | NC |
| Heart | Atriocaval Mesothelioma | 0/70 (53) | 0/70 (54) | 0/70 (47) | 1/70 (47) | 0/70 (53) |
| | | 0.2087 | NC | NC | 0.4700 | NC |

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

**Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)**

| Organ name | Tumor name | 0 mg Vehicle (C) | 0.0025 mg Low (L) | 0.01 mg Mid (M) | 0.025 mg Mid-high (MH) | 0.1 mg High (H) |
|---|---|---|---|---|---|---|
| | | P-Trend | P-L vs. C | P-M vs. C | P-C vs. MH | P-C vs. H |
| Jejunum | Adenocarcinoma | 0/70 (53) | 0/69 (54) | 1/69 (46) | 0/70 (47) | 0/70 (53) |
| | | 0.3953 | NC | 0.4646 | NC | NC |
| Liver | Hepatocellular Adenoma | 1/70 (53) | 3/70 (55) | 1/70 (47) | 2/70 (47) | 0/70 (53) |
| | | 0.8791 | 0.3231 | 0.7216 | 0.4546 | 0.5000 |
| Ln Renal | Leiomyosarcoma | 1/70 () | 3/70 (4) | 1/70 (2) | 2/70 (2) | 0/70 (1) |
| | | 0.2500 | NC | NC | NC | NC |
| Mammary | Mammary Adenocarcinoma | 18/70 (61) | 20/70 (59) | 27/70 (56) | 19/69 (53) | 16/69 (56) |
| | | 0.8252 | 0.3743 | 0.0294 @ | 0.3010 | 0.4628 |
| | Mammary Adenoma | 1/70 (54) | 5/70 (55) | 0/70 (47) | 0/69 (46) | 0/69 (52) |
| | | 0.9916 | 0.1071 | 0.4653 | 0.4600 | 0.4906 |
| | Mammary Adenocarcinoma/ Mammary Adenoma | 19/70 (61) | 23/70 (59) | 27/70 (56) | 19/69 (53) | 16/69 (56) |
| | | 0.8965 | 0.2395 | 0.0446 @ | 0.3696 | 0.5401 |
| | Mammary Fibroadenoma | 33/70 (60) | 35/70 (60) | 32/70 (56) | 24/69 (53) | 23/69 (59) |
| | | 0.9896 | 0.4270 | 0.4821 | 0.8002 | 0.9416 |
| Ovaries | Cystadenoma | 0/70 (53) | 0/69 (54) | 1/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.3937 | NC | 0.4700 | NC | NC |
| | Granulosa Cell Tumor | 1/70 (53) | 0/69 (54) | 0/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.7913 | 0.5047 | 0.4700 | 0.4700 | 0.5000 |
| | Luteoma | 0/70 (53) | 1/69 (54) | 0/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.5787 | 0.5047 | NC | NC | NC |
| | Malignant Granulosa Cell Tumor | 0/70 (53) | 0/69 (54) | 0/70 (47) | 1/70 (47) | 0/70 (53) |
| | | 0.2087 | NC | NC | 0.4700 | NC |
| | Sertoliform Tubular Adenoma | 1/70 (53) | 1/69 (54) | 2/70 (47) | 2/70 (47) | 0/70 (53) |
| | | 0.8034 | 0.2523 | 0.4546 | 0.4546 | 0.5000 |
| | Thecal Cell Tumor | 1/70 (54) | 0/69 (54) | 0/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.7882 | 0.5000 | 0.4653 | 0.4653 | 0.4953 |
| | Yolk Sac Cell Tumor | 0/70 (53) | 1/69 (55) | 0/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.5765 | 0.5093 | NC | NC | NC |

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

**Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)**

| Organ name | Tumor name | 0 mg Vehicle (C) | 0.0025 mg Low (L) | 0.01 mg Mid (M) | 0.025 mg Mid-high (MH) | 0.1 mg High (H) |
|---|---|---|---|---|---|---|
| | | P-Trend | P-L vs. C | P-M vs. C | P-C vs. MH | P-C vs. H |
| Pancreas | Acinar Cell Adenoma | 1/70 (54) | 0/70 (54) | 0/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.7882 | 0.5000 | 0.4653 | 0.4653 | 0.4953 |
| | Islet Cell Adenoma | 0/70 (53) | 1/70 (54) | 0/70 (47) | 1/70 (47) | 0/70 (53) |
| | | 0.4768 | 0.5047 | NC | 0.4700 | NC |
| | Islet Cell Carcinoma | 1/70 (53) | 0/70 (54) | 0/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.7913 | 0.5047 | 0.4700 | 0.4700 | 0.5000 |
| | Islet Cell Adenoma/ Islet Cell Carcinoma | 1/70 (53) | 1/70 (54) | 0/70 (47) | 1/70 (47) | 0/70 (53) |
| | | 0.7110 | 0.2523 | 0.4700 | 0.7216 | 0.5000 |
| | Mixed Cell Adenoma | 0/70 (53) | 0/70 (54) | 0/70 (47) | 1/70 (47) | 0/70 (53) |
| | | 0.2087 | NC | NC | 0.4700 | NC |
| Pituitary | Adenoma, Pars Distalis | 48/70 (66) | 49/70 (65) | 54/70 (65) | 53/69 (62) | 46/70 (64) |
| | | 0.7802 | 0.4415 | 0.1118 | 0.0597 | 0.4654 |
| | Carcinoma, Pars Distalis | 0/70 (53) | 1/70 (55) | 0/70 (47) | 0/69 (46) | 0/70 (53) |
| | | 0.5748 | 0.5093 | NC | NC | NC |
| | Adenoma, Pars Distalis/ Carcinoma, Pars Distalis | 48/70 (66) | 50/70 (65) | 54/70 (65) | 53/69 (62) | 46/70 (64) |
| | | 0.8060 | 0.3627 | 0.1118 | 0.0597 | 0.4654 |
| | Adenoma, Pars Intermedia | 0/70 (53) | 0/70 (54) | 0/70 (47) | 1/69 (46) | 1/70 (53) |
| | | 0.1197 | NC | NC | 0.4646 | 0.5000 |
| | Adenoma, Pars Distalis/ Carcinoma, Pars Distalis/ Adenoma, Pars Intermedia | 48/70 (66) | 50/70 (65) | 54/70 (65) | 53/69 (62) | 46/70 (64) |
| | | 0.8060 | 0.3627 | 0.1118 | 0.0597 | 0.4654 |
| Salivary Glands | Adenocarcinoma | 0/70 (53) | 0/70 (54) | 1/69 (47) | 1/70 (47) | 0/69 (53) |
| | | 0.4081 | NC | 0.4700 | 0.4700 | NC |

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

**Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)**

| Organ name | Tumor name | 0 mg Vehicle (C) | 0.0025 mg Low (L) | 0.01 mg Mid (M) | 0.025 mg Mid-high (MH) | 0.1 mg High (H) |
|---|---|---|---|---|---|---|
| | | P-Trend | P-L vs. C | P-M vs. C | P-C vs. MH | P-C vs. H |
| Skin | Basal Cell Tumor | 0/70 (53) | 0/70 (54) | 1/70 (48) | 0/70 (47) | 0/70 (53) |
| | | 0.3922 | NC | 0.4752 | NC | NC |
| | Fibroma | 4/70 (54) | 1/70 (54) | 0/70 (47) | 1/70 (47) | 1/70 (53) |
| | | 0.7537 | 0.8184 | 0.9225 | 0.7724 | 0.8126 |
| | Fibrosarcoma | 0/70 (53) | 1/70 (55) | 0/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.5765 | 0.5093 | NC | NC | NC |
| | Fibroma/ Fibrosarcoma | 4/70 (54) | 2/70 (55) | 0/70 (47) | 1/70 (47) | 1/70 (53) |
| | | 0.8139 | 0.6694 | 0.9225 | 0.7724 | 0.8126 |
| | Fibrous Histiocytoma | 0/70 (53) | 1/70 (55) | 0/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.5765 | 0.5093 | NC | NC | NC |
| | Leiomyosarcoma | 1/70 (53) | 0/70 (54) | 0/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.7913 | 0.5047 | 0.4700 | 0.4700 | 0.5000 |
| | Lipoma | 1/70 (53) | 3/70 (55) | 2/70 (48) | 1/70 (47) | 0/70 (53) |
| | | 0.9230 | 0.3231 | 0.4625 | 0.7216 | 0.5000 |
| | Liposarcoma | 1/70 (53) | 0/70 (54) | 0/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.7913 | 0.5047 | 0.4700 | 0.4700 | 0.5000 |
| | Lipoma/ Liposarcoma | 2/70 (53) | 3/70 (55) | 2/70 (48) | 1/70 (47) | 0/70 (53) |
| | | 0.9571 | 0.5177 | 0.6529 | 0.4546 | 0.7524 |
| | Sarcoma, Nos | 1/70 (53) | 2/70 (54) | 1/70 (47) | 0/70 (47) | 1/70 (53) |
| | | 0.6097 | 0.5071 | 0.7216 | 0.4700 | NC |
| | Keratoacanthoma | 1/70 (53) | 1/70 (54) | 0/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.8680 | 0.2523 | 0.4700 | 0.4700 | 0.5000 |
| | Squamous Cell Carcinoma | 0/70 (53) | 0/70 (54) | 1/70 (48) | 0/70 (47) | 0/70 (53) |
| | | 0.3922 | NC | 0.4752 | NC | NC |
| | Squamous Cell Papilloma | 1/70 (54) | 2/70 (55) | 0/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.9335 | 0.5069 | 0.4653 | 0.4653 | 0.4953 |
| | Squamous Cell Carcinoma/ Squamous Cell Papilloma/ Keratoacanthoma | 2/70 (54) | 3/70 (55) | 1/70 (48) | 0/70 (47) | 0/70 (53) |
| | | 0.9826 | 0.5088 | 0.4555 | 0.7166 | 0.7477 |
| Spinal C. Thor. | Astrocytoma | 0/70 (53) | 0/70 (54) | 0/70 (47) | 0/70 (47) | 1/70 (53) |
| | | 0.2087 | NC | NC | NC | 0.5000 |
| Spleen | Stromal Cell Sarcoma | 0/70 (53) | 1/70 (55) | 0/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.5765 | 0.5093 | NC | NC | NC |
| Thymus | Thymoma (Epithelial) | 0/66 (50) | 0/69 (54) | 0/67 (45) | 0/67 (45) | 1/69 (53) |
| | | 0.2146 | NC | NC | NC | 0.5146 |

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

**Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)**

| Organ name | Tumor name | 0 mg Vehicle (C) | 0.0025 mg Low (L) | 0.01 mg Mid (M) | 0.025 mg Mid-high (MH) | 0.1 mg High (H) |
|---|---|---|---|---|---|---|
| | | P-Trend | P-L vs. C | P-M vs. C | P-C vs. MH | P-C vs. H |
| Thyroids | C-Cell Adenoma | 6/70 (53) | 17/70 (56) | 28/69 (52) | 31/70 (53) | 45/70 (62) |
| | | <0.0001 $ | 0.0130 @ | <0.0001 $ | <0.0001 $ | <0.0001 $ |
| | C-Cell Carcinoma | 2/70 (53) | 4/70 (54) | 6/69 (48) | 5/70 (47) | 8/70 (54) |
| | | 0.0598 | 0.3482 | 0.1049 | 0.1715 | 0.0495 @ |
| | C-Cell Adenoma/ C-Cell Carcinoma | 8/70 (53) | 19/70 (56) | 34/69 (54) | 32/70 (53) | 50/70 (63) |
| | | <0.0001 $ | 0.0192 @ | <0.0001 $ | <0.0001 $ | <0.0001 $ |
| | Follicular Cell Adenoma | 0/70 (53) | 1/70 (55) | 0/69 (47) | 1/70 (47) | 0/70 (53) |
| | | 0.4747 | 0.5093 | NC | 0.4700 | NC |
| Uterine Cervix | Fibrosarcoma | 0/69 (53) | 0/70 (54) | 0/70 (47) | 1/70 (47) | 0/70 (53) |
| | | 0.2087 | NC | NC | 0.4700 | NC |
| | Leiomyosarcoma | 0/69 (53) | 0/70 (54) | 0/70 (47) | 0/70 (47) | 1/70 (53) |
| | | 0.2087 | NC | NC | NC | 0.5000 |
| | Squamous Cell Papilloma | 0/69 (53) | 0/70 (54) | 0/70 (47) | 0/70 (47) | 1/70 (53) |
| | | 0.2087 | NC | NC | NC | 0.5000 |
| Uterus | Endometrial Adenocarcinoma | 3/69 (53) | 1/70 (55) | 3/70 (48) | 4/70 (47) | 6/70 (55) |
| | | 0.0563 | 0.7049 | 0.6126 | 0.4326 | 0.2632 |
| | Endometrial Adenoma | 0/69 (53) | 3/70 (55) | 2/70 (47) | 1/70 (47) | 1/70 (53) |
| | | 0.6156 | 0.1285 | 0.2184 | 0.4700 | 0.5000 |
| | Endometrial Adenocarcinoma/ Endometrial Adenoma | 3/69 (53) | 4/70 (55) | 5/70 (48) | 5/70 (47) | 7/70 (55) |
| | | 0.1282 | 0.5208 | 0.3033 | 0.2922 | 0.1756 |
| | Endometrial Polyp | 8/69 (54) | 4/70 (55) | 6/70 (48) | 13/70 (50) | 12/70 (54) |
| | | 0.0446 @ | 0.8291 | 0.5185 | 0.1199 | 0.2290 |
| | Endometrial Stromal Cell Sarcoma | 0/69 (53) | 0/70 (54) | 1/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.3937 | NC | 0.4700 | NC | NC |
| | Leiomyosarcoma | 0/69 (53) | 0/70 (54) | 0/70 (47) | 0/70 (47) | 1/70 (53) |
| | | 0.2087 | NC | NC | NC | 0.5000 |
| | Malignant Schwannoma | 0/69 (53) | 0/70 (54) | 0/70 (47) | 1/70 (47) | 1/70 (53) |
| | | 0.1204 | NC | NC | 0.4700 | 0.5000 |
| | Squamous Cell Carcinoma | 1/69 (53) | 0/70 (54) | 0/70 (47) | 0/70 (47) | 2/70 (54) |
| | | 0.1144 | 0.5047 | 0.4700 | 0.4700 | 0.5071 |
| | Squamous Papilloma | 0/69 (53) | 0/70 (54) | 0/70 (47) | 0/70 (47) | 1/70 (53) |
| | | 0.2087 | NC | NC | NC | 0.5000 |
| Vagina | Schwannoma | 1/69 (53) | 0/70 (54) | 0/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.7913 | 0.5047 | 0.4700 | 0.4700 | 0.5000 |
| | Squamous Cell Carcinoma | 0/69 (53) | 1/70 (54) | 0/70 (47) | 0/70 (47) | 0/70 (53) |
| | | 0.5787 | 0.5047 | NC | NC | NC |

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

**Table 3A: Intercurrent Mortality Rate in Male Mice**

| | Vehicle Control | | 0.3 mg/kg/day Low | | 1 mg/kg/day Mid | | 3 mg/kg/day High | |
|---|---|---|---|---|---|---|---|---|
| Week / Type of Death | No. of Death | Cum % | No. of Death | Cum % | No. of Death | Cum % | No. of Death | Cum % |
| 0 - 52 | 5 | 11.67 | 2 | 3.33 | 6 | 11.67 | 4 | 6.67 |
| 53 - 78 | 12 | 31.67 | 9 | 18.33 | 4 | 18.33 | 2 | 10.00 |
| 79 - 91 | 8 | 45.00 | 2 | 21.67 | 5 | 26.67 | 9 | 25.00 |
| 92 - 104 | 8 | 13.33 | 4 | 6.67 | 10 | 16.67 | 10 | 16.67 |
| >105 | 2 | 3.33 | | | 1 | 1.67 | | |
| Terminal sacrifice | 25 | 41.67 | 43 | 71.67 | 34 | 56.67 | 35 | 58.33 |
| Total | 60 | | 60 | | 60 | | 60 | |

| Test | All Dose Groups | Vehicle Control vs. Low | Vehicle Control vs. Mid | Vehicle Control vs. High |
|---|---|---|---|---|
| Dose-Response (Likelihood Ratio) | 0.5024 | 0.0014** | 0.0984 | 0.0554 |
| Homogeneity (Log-Rank) | 0.0118* | 0.0014** | 0.0967 | 0.0540 |

#All Cum. % Cumulative Percentage except for Terminal sacrifice;
* = Significant at 5% level; ** = Significant at 1% level.

**Table 3B: Intercurrent Mortality Rate in Female Mice**

| | Vehicle Control | | 0.1 mg/kg/day Low | | 0.3 mg/kg/day Mid | | 1 mg/kg/day High | |
|---|---|---|---|---|---|---|---|---|
| Week / Type of Death | No. of Death | Cum % | No. of Death | Cum % | No. of Death | Cum % | No. of Death | Cum % |
| 0 - 52 | 3 | 5.00 | 1 | 1.67 | 3 | 5.00 | 5 | 8.33 |
| 53 - 78 | 9 | 20.00 | 10 | 18.33 | 14 | 28.33 | 6 | 18.33 |
| 79 - 91 | 8 | 33.33 | 9 | 33.33 | 7 | 40.00 | 10 | 35.00 |
| 92 - 104 | 11 | 18.33 | 17 | 28.33 | 12 | 20.00 | 15 | 25.00 |
| Terminal sacrifice | 29 | 48.33 | 23 | 38.33 | 24 | 40.00 | 24 | 40.00 |
| Total | 60 | | 60 | | 60 | | 60 | |

| Test | All Dose Groups | Vehicle Control vs. Low | Vehicle Control vs. Mid | Vehicle Control vs. High |
|---|---|---|---|---|
| Dose-Response (Likelihood Ratio) | 0.6872 | 0.4625 | 0.3451 | 0.4888 |
| Homogeneity (Log-Rank) | 0.7990 | 0.4569 | 0.3400 | 0.4829 |

**Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice**

| Organ name | Tumor name | 0 mg<br>Vehicle (C)<br>P - Trend | 0.3 mg<br>Low (L)<br>P - C vs. L | 1 mg<br>Mid (M)<br>P - C vs. M | 3 mg<br>High (H)<br>P - C vs. H |
|---|---|---|---|---|---|
| Adrenals | Cortical Adenoma | 2/59 (42) | 1/59 (49) | 0/58 (46) | 1/60 (48) |
| | | 0.6516 | 0.5582 | 0.7751 | 0.5505 |
| | Phaeochromocytoma | 1/59 (41) | 1/59 (49) | 0/58 (46) | 0/60 (48) |
| | | 0.8320 | 0.2936 | 0.5287 | 0.5393 |
| | Subcapsular Cell Adenoma | 3/59 (41) | 1/59 (49) | 1/58 (46) | 2/60 (48) |
| | | 0.5347 | 0.7559 | 0.7342 | 0.5751 |
| | Subcapsular Cell Carcinoma | 1/59 (41) | 0/59 (49) | 0/58 (46) | 0/60 (48) |
| | | 0.7772 | 0.5444 | 0.5287 | 0.5393 |
| | Subcapsular Cell Adenoma/ Subcapsular Cell Carcinom | 4/59 (41) | 1/59 (49) | 1/58 (46) | 2/60 (48) |
| | | 0.6625 | 0.8700 | 0.8536 | 0.7338 |
| Brain | Glioma | 0/59 (40) | 1/60 (50) | 0/60 (47) | 0/60 (48) |
| | | 0.5135 | 0.5556 | NC | NC |
| | Meningeal Sarcoma | 0/59 (40) | 0/60 (50) | 0/60 (47) | 1/60 (49) |
| | | 0.2634 | NC | NC | 0.5506 |
| Caecum | Adenocarcinoma | 0/60 (41) | 1/60 (50) | 0/60 (47) | 0/60 (48) |
| | | 0.5108 | 0.5495 | NC | NC |
| Duodenum | Sarcoma Nos | 0/59 (41) | 1/60 (51) | 0/58 (46) | 0/60 (48) |
| | | 0.5054 | 0.5543 | NC | NC |
| Femur Inc. Joint | Osteosarcoma | 0/60 (41) | 0/60 (50) | 1/60 (47) | 0/60 (48) |
| | | 0.2581 | NC | 0.5341 | NC |
| Gall Bladder | Adenoma | 1/60 (41) | 2/59 (49) | 0/60 (47) | 0/59 (47) |
| | | 0.9030 | 0.5672 | 0.5341 | 0.5341 |
| H-Poietic Tumour | Malignant Lymphoma | 5/60 (43) | 4/60 (51) | 4/60 (49) | 3/60 (49) |
| | | 0.7606 | 0.6084 | 0.5835 | 0.7139 |
| | Myeloid Cell Leukaemia | 1/60 (42) | 0/60 (50) | 0/60 (47) | 0/60 (48) |
| | | 0.7754 | 0.5435 | 0.5281 | 0.5333 |
| | Malignant Mast Cell Tumour | 0/60 (41) | 1/60 (50) | 0/60 (47) | 0/60 (48) |
| | | 0.5108 | 0.5495 | NC | NC |
| Harderian Glands | Adenocarcinoma | 1/60 (41) | 0/60 (50) | 1/60 (47) | 1/60 (48) |
| | | 0.4076 | 0.5495 | 0.2824 | 0.2880 |
| | Adenoma | 5/60 (42) | 4/60 (51) | 3/60 (47) | 3/60 (49) |
| | | 0.7664 | 0.6229 | 0.7048 | 0.7261 |
| | Adenocarcinoma/Adenoma | 6/60 (42) | 4/60 (51) | 4/60 (47) | 4/60 (49) |
| | | 0.7003 | 0.7466 | 0.7005 | 0.7245 |

& X/ZZ (YY): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

**Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice (Continued)**

| Organ name | Tumor name | 0 mg<br>Vehicle (C)<br>P - Trend | 0.3 mg<br>Low (L)<br>P - C vs. L | 1 mg<br>Mid (M)<br>P - C vs. M | 3 mg<br>High (H)<br>P - C vs. H |
|---|---|---|---|---|---|
| Jejunum | Adenocarcinoma | 0/60 (41) | 1/60 (51) | 0/60 (47) | 1/60 (48) |
| | | 0.3353 | 0.5543 | NC | 0.5393 |
| Kidneys | Haemangiosarcoma | 0/60 (41) | 0/60 (50) | 0/60 (47) | 1/60 (49) |
| | | 0.2620 | NC | NC | 0.5444 |
| Liver | Haemangioma | 1/60 (41) | 1/60 (50) | 0/60 (47) | 1/60 (48) |
| | | 0.4633 | 0.2991 | 0.5341 | 0.2880 |
| | Haemangiosarcoma | 0/60 (41) | 0/60 (50) | 1/60 (47) | 1/60 (48) |
| | | 0.1967 | NC | 0.5341 | 0.5393 |
| | Haemangioma/<br>Haemangiosarcoma | 1/60 (41) | 1/60 (50) | 1/60 (47) | 2/60 (48) |
| | | 0.2817 | 0.2991 | 0.2824 | 0.5595 |
| | Hepatocellular Adenoma | 7/60 (43) | 8/60 (52) | 2/60 (47) | 3/60 (48) |
| | | 0.9579 | 0.4377 | 0.9402 | 0.8833 |
| Ln Mesenteric | Haemangioma | 0/60 (41) | 2/59 (49) | 1/60 (47) | 1/58 (48) |
| | | 0.4482 | 0.2936 | 0.5341 | 0.5393 |
| | Haemangiosarcoma | 0/60 (41) | 0/59 (49) | 0/60 (47) | 1/58 (48) |
| | | 0.2595 | NC | NC | 0.5393 |
| | Haemangioma/<br>Haemangiosarcoma | 0/60 (41) | 2/59 (49) | 1/60 (47) | 2/58 (48) |
| | | 0.2221 | 0.2936 | 0.5341 | 0.2880 |
| Lungs + Bronchi | Bronchioloalveolar Adenocarcinoma | 4/60 (43) | 6/60 (50) | 9/60 (48) | 5/60 (49) |
| | | 0.5362 | 0.4699 | 0.1624 | 0.5835 |
| | Bronchioloalveolar Adenoma | 21/60 (45) | 12/60 (51) | 19/60 (49) | 11/60 (49) |
| | | 0.9570 | 0.9850 | 0.7137 | 0.9883 |
| | Bronchioloalveolar Adenocarcinoma/<br>Bronchioloalveolar Adenoma | 24/60 (46) | 17/60 (51) | 25/60 (49) | 13/60 (50) |
| | | 0.9844 | 0.9527 | 0.4630 | 0.9925 |
| Pancreas | Islet Cell Adenoma | 0/60 (41) | 1/60 (50) | 0/60 (47) | 1/60 (48) |
| | | 0.3362 | 0.5495 | NC | 0.5393 |
| Prostate | Decidual Reaction | 1/59 (41) | 0/60 (50) | 0/60 (47) | 0/59 (48) |
| | | 0.7796 | 0.5495 | 0.5341 | 0.5393 |
| Seminal Vesicles | Adenoma | 0/60 (41) | 0/60 (50) | 1/60 (47) | 0/59 (48) |
| | | 0.2581 | NC | 0.5341 | NC |

& X/ZZ (YY): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

**Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice (Continued)**

| Organ name | Tumor name | 0 mg<br>Vehicle (C)<br>P - Trend | 0.3 mg<br>Low (L)<br>P - C vs. L | 1 mg<br>Mid (M)<br>P - C vs. M | 3 mg<br>High (H)<br>P - C vs. H |
|---|---|---|---|---|---|
| Skin | Fibrosarcoma | 0/59 (40) | 1/60 (51) | 0/59 (46) | 1/59 (48) |
| | | 0.3398 | 0.5604 | NC | 0.5455 |
| | Leiomyosarcoma | 0/59 (40) | 1/60 (51) | 0/59 (46) | 0/59 (48) |
| | | 0.5081 | 0.5604 | NC | NC |
| Spleen | Haemangioma | 0/60 (41) | 1/60 (50) | 0/60 (47) | 0/60 (48) |
| | | 0.5108 | 0.5495 | NC | NC |
| Stomach | Adenoma | 1/60 (42) | 0/60 (50) | 1/60 (47) | 0/60 (48) |
| | | 0.6458 | 0.5435 | 0.2760 | 0.5333 |
| Testes | Adenoma, Rete Testis | 0/60 (41) | 0/60 (50) | 1/60 (47) | 0/60 (48) |
| | | 0.2581 | NC | 0.5341 | NC |
| | Haemangioma | 0/60 (41) | 0/60 (50) | 0/60 (47) | 2/60 (49) |
| | | 0.0676 | NC | NC | 0.2936 |
| | Interstitial (Leydig) Cell Adenoma | 3/60 (42) | 4/60 (50) | 0/60 (47) | 2/60 (48) |
| | | 0.7684 | 0.5976 | 0.8989 | 0.5638 |
| Thymus | C Cell Adenoma (Ectopic Thyroid Tissue) | 0/52 (36) | 1/57 (48) | 0/55 (45) | 0/55 (46) |
| | | 0.5200 | 0.5714 | NC | NC |
| Thyroids | C-Cell Adenoma | 0/60 (41) | 24/60 (51) | 23/59 (49) | 18/59 (49) |
| | | 0.0620 | <0.0001 $ | <0.0001 $ | <0.0001 $ |
| | C-Cell Carcinoma | 0/60 (41) | 2/60 (50) | 2/59 (47) | 2/59 (48) |
| | | 0.2426 | 0.2991 | 0.2824 | 0.2880 |
| | C-Cell Adenoma/<br>C-Cell Carcinoma | 0/60 (41) | 24/60 (51) | 24/59 (49) | 20/59 (49) |
| | | 0.0233 $ | <0.0001 $ | <0.0001 $ | <0.0001 $ |
| | Follicular Cell Adenoma | 0/60 (41) | 0/60 (50) | 0/59 (47) | 1/59 (47) |
| | | 0.2541 | NC | NC | 0.5341 |
| Treated Site 1 | Fibrosarcoma | 0/60 (41) | 0/60 (50) | 1/60 (47) | 0/60 (48) |
| | | 0.2581 | NC | 0.5341 | NC |
| Urinary Bladder | Mesenchymal Tumour | 1/59 (42) | 0/53 (44) | 0/60 (47) | 0/58 (48) |
| | | 0.7680 | 0.5116 | 0.5281 | 0.5333 |
| | Sarcoma Nos | 1/59 (42) | 0/53 (44) | 0/60 (47) | 0/58 (48) |
| | | 0.7680 | 0.5116 | 0.5281 | 0.5333 |

& X/ZZ (YY): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

**Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice**

| Organ name | Tumor name | 0 mg<br>Vehicle (C)<br>P - Trend | 0.1 mg<br>Low (L)<br>P - L vs. C | 0.3 mg<br>Mid (M)<br>P - M vs. C | 1 mg<br>High (H)<br>P - H vs. C |
|---|---|---|---|---|---|
| Adrenals | Phaeochromocytoma | 0/60 (45) | 1/59 (44) | 0/59 (41) | 0/59 (43) |
| | | 0.4855 | 0.4944 | NC | NC |
| | Subcapsular Cell Adenoma | 3/60 (45) | 1/59 (44) | 1/59 (41) | 0/59 (43) |
| | | 0.9408 | 0.6833 | 0.6559 | 0.8707 |
| Brain | Astrocytoma | 0/60 (45) | 1/60 (45) | 0/60 (42) | 0/60 (44) |
| | | 0.4886 | 0.5000 | NC | NC |
| Caecum | Adenocarcinoma | 0/60 (45) | 0/60 (45) | 0/60 (42) | 1/60 (44) |
| | | 0.2500 | NC | NC | 0.4944 |
| Clitoral Glands | Adenocarcinoma | 0/59 (44) | 0/59 (44) | 0/59 (41) | 1/58 (43) |
| | | 0.2500 | NC | NC | 0.4943 |
| Gall Bladder | Adenoma | 0/60 (45) | 0/58 (43) | 1/59 (41) | 0/60 (44) |
| | | 0.2543 | NC | 0.4767 | NC |
| H-Poietic Tumour | Histiocytic Sarcoma | 1/60 (45) | 5/60 (45) | 3/60 (43) | 3/60 (45) |
| | | 0.4394 | 0.1014 | 0.2911 | 0.3082 |
| | Malignant Lymphoma | 11/60 (48) | 9/60 (49) | 10/60 (45) | 10/60 (47) |
| | | 0.4921 | 0.6188 | 0.4329 | 0.4781 |
| | Myeloid Cell Leukaemia | 1/60 (45) | 0/60 (45) | 1/60 (42) | 1/60 (44) |
| | | 0.3833 | 0.5000 | 0.7354 | 0.7472 |
| Harderian Glands | Adenocarcinoma | 0/60 (45) | 0/60 (45) | 0/60 (42) | 3/60 (45) |
| | | 0.0156 @ | NC | NC | 0.1208 |
| | Adenoma | 4/60 (45) | 2/60 (45) | 5/60 (43) | 7/60 (44) |
| | | 0.0683 | 0.6617 | 0.4707 | 0.2477 |
| | Adenocarcinoma/Adenoma | 4/60 (45) | 2/60 (45) | 5/60 (43) | 10/60 (45) |
| | | 0.0077 @ | 0.6617 | 0.4707 | 0.0721 |
| Liver | Cholangiocarcinoma | 0/60 (45) | 0/60 (45) | 1/60 (42) | 0/60 (44) |
| | | 0.2500 | NC | 0.4828 | NC |
| | Haemangioma | 0/60 (45) | 1/60 (45) | 0/60 (42) | 0/60 (44) |
| | | 0.4886 | 0.5000 | NC | NC |
| | Hepatocellular Adenoma | 0/60 (45) | 1/60 (45) | 0/60 (42) | 0/60 (44) |
| | | 0.4886 | 0.5000 | NC | NC |
| Ln Mesenteric | Haemangioma | 4/60 (45) | 0/60 (45) | 0/60 (42) | 0/59 (43) |
| | | 0.9961 | 0.9417 | 0.9331 | 0.9361 |

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

**Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)**

| Organ name | Tumor name | 0 mg<br>Vehicle (C)<br>P - Trend | 0.1 mg<br>Low (L)<br>P - L vs. C | 0.3 mg<br>Mid (M)<br>P - M vs. C | 1 mg<br>High (H)<br>P - H vs. C |
|---|---|---|---|---|---|
| Lungs + Bronchi | Bronchioloalveolar Adenocarcinoma | 4/60 (45) | 2/60 (45) | 0/60 (42) | 2/60 (44) |
| | | 0.6670 | 0.6617 | 0.9331 | 0.6509 |
| | Bronchioloalveolar Adenoma | 8/60 (46) | 8/60 (47) | 4/60 (43) | 7/60 (45) |
| | | 0.5517 | 0.4106 | 0.7890 | 0.4812 |
| | Bronchioloalveolar Adenocarcinoma/ Bronchioloalveolar Adenoma | 12/60 (46) | 10/60 (47) | 4/60 (43) | 9/60 (46) |
| | | 0.6742 | 0.6185 | 0.9643 | 0.6900 |
| Mammary | Adenoacanthoma | 2/56 (42) | 1/57 (42) | 0/56 (39) | 0/60 (44) |
| | | 0.9375 | 0.5000 | 0.7343 | 0.7644 |
| | Mammary Adenocarcinoma | 7/56 (43) | 2/57 (43) | 3/56 (40) | 1/60 (44) |
| | | 0.9710 | 0.9219 | 0.8125 | 0.9733 |
| | Mammary Adenoma | 0/56 (42) | 0/57 (42) | 1/56 (39) | 0/60 (44) |
| | | 0.2635 | NC | 0.4815 | NC |
| | Mammary Adenocarcinoma/ Mammary Adenoma | 7/56 (43) | 2/57 (43) | 4/56 (40) | 1/60 (44) |
| | | 0.9682 | 0.9219 | 0.6964 | 0.9733 |
| Ovaries | Cystadenoma | 1/60 (45) | 1/59 (44) | 1/59 (41) | 0/60 (44) |
| | | 0.7273 | 0.7472 | 0.7291 | 0.4944 |
| | Fibrosarcoma | 0/60 (45) | 0/59 (44) | 1/59 (41) | 0/60 (44) |
| | | 0.2529 | NC | 0.4767 | NC |
| | Granulosa Cell Tumour | 1/60 (45) | 0/59 (44) | 1/59 (41) | 0/60 (44) |
| | | 0.6172 | 0.4944 | 0.7291 | 0.4944 |
| | Haemangioma | 1/60 (45) | 0/59 (44) | 0/59 (41) | 1/60 (44) |
| | | 0.4429 | 0.4944 | 0.4767 | 0.7472 |
| | Leiomyosarcoma | 0/60 (45) | 0/59 (44) | 1/59 (41) | 0/60 (44) |
| | | 0.2529 | NC | 0.4767 | NC |
| | Luteoma | 0/60 (45) | 1/59 (44) | 4/59 (41) | 2/60 (44) |
| | | 0.2257 | 0.4944 | 0.0477 @ | 0.2416 |
| | Sertoli Cell Like Adenoma | 1/60 (45) | 0/59 (44) | 1/59 (41) | 0/60 (44) |
| | | 0.6172 | 0.4944 | 0.7291 | 0.4944 |
| | Sex Cord Stromal Mixed Adenoma | 0/60 (45) | 1/59 (44) | 0/59 (41) | 0/60 (44) |
| | | 0.4885 | 0.4944 | NC | NC |
| | Tubulostromal Adenoma | 2/60 (45) | 1/59 (44) | 2/59 (41) | 0/60 (44) |
| | | 0.8493 | 0.4915 | 0.6559 | 0.7472 |
| Pancreas | Islet Cell Adenoma | 1/60 (45) | 0/60 (45) | 1/60 (42) | 2/60 (45) |
| | | 0.1674 | 0.5000 | 0.7354 | 0.5000 |

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

**Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)**

| Organ name | Tumor name | 0 mg<br>Vehicle (C)<br>P - Trend | 0.1 mg<br>Low (L)<br>P - L vs. C | 0.3 mg<br>Mid (M)<br>P - M vs. C | 1 mg<br>High (H)<br>P - H vs. C |
|---|---|---|---|---|---|
| Pituitary | Adenoma, Pars Distalis | 2/56 (43) | 1/57 (44) | 1/56 (38) | 1/55 (41) |
| | | 0.5888 | 0.5087 | 0.4532 | 0.4819 |
| Skin | Fibrosarcoma | 2/57 (43) | 0/57 (42) | 0/59 (41) | 0/60 (44) |
| | | 0.9371 | 0.7471 | 0.7410 | 0.7586 |
| | Haemangiosarcoma | 0/57 (42) | 0/57 (42) | 0/59 (41) | 1/60 (44) |
| | | 0.2604 | NC | NC | 0.5116 |
| | Keratoacanthoma | 0/57 (42) | 1/57 (43) | 1/59 (42) | 0/60 (44) |
| | | 0.5088 | 0.5059 | 0.5000 | NC |
| | Mammary Adenoma | 0/57 (42) | 1/57 (42) | 1/59 (41) | 0/60 (44) |
| | | 0.5118 | 0.5000 | 0.4940 | NC |
| | Osteosarcoma | 1/57 (43) | 0/57 (42) | 0/59 (41) | 0/60 (44) |
| | | 0.7471 | 0.4941 | 0.4881 | 0.5057 |
| | Sarcoma Nos | 1/57 (42) | 0/57 (42) | 0/59 (41) | 1/60 (44) |
| | | 0.4541 | 0.5000 | 0.4940 | 0.2588 |
| Spleen | Haemangiosarcoma | 0/60 (45) | 0/60 (45) | 2/60 (42) | 0/60 (44) |
| | | 0.4386 | NC | 0.2302 | NC |
| Stomach | Neuroendocrine Carcinoma | 0/60 (45) | 0/60 (45) | 1/60 (42) | 0/59 (43) |
| | | 0.2457 | NC | 0.4828 | NC |
| Thorax | Osteosarcoma | 1/4 (3) | 0/5 (3) | 0/3 (3) | 1/7 (5) |
| | | 0.6044 | 0.5000 | 0.5000 | 0.3571 |
| Thymus | C Cell Adenoma (Ectopic Thyroid Tissue) | 0/57 (43) | 0/55 (41) | 1/57 (39) | 0/52 (40) |
| | | 0.2454 | NC | 0.4756 | NC |
| | Thymoma (Epithelial) | 0/57 (43) | 0/55 (41) | 1/57 (39) | 0/52 (40) |
| | | 0.2454 | NC | 0.4756 | NC |
| Thyroids | C-Cell Adenoma | 0/58 (43) | 16/59 (45) | 20/58 (43) | 24/60 (47) |
| | | 0.0001 $ | <0.0001 $ | <0.0001 $ | <0.0001 $ |
| | C-Cell Carcinoma | 0/58 (43) | 1/59 (44) | 2/58 (42) | 2/60 (44) |
| | | 0.1434 | 0.5057 | 0.2412 | 0.2529 |
| | C-Cell Adenoma/<br>C-Cell Carcinoma | 0/58 (43) | 16/59 (45) | 21/58 (43) | 24/60 (47) |
| | | 0.0001 $ | <0.0001 $ | <0.0001 $ | <0.0001 $ |
| Urinary Bladder | Mesenchymal Tumour | 0/57 (42) | 1/53 (40) | 0/58 (40) | 0/57 (42) |
| | | 0.5000 | 0.4878 | NC | NC |

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

**Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)**

| Organ name | Tumor name | 0 mg<br>Vehicle (C)<br>P - Trend | 0.1 mg<br>Low (L)<br>P - L vs. C | 0.3 mg<br>Mid (M)<br>P - M vs. C | 1 mg<br>High (H)<br>P - H vs. C |
|---|---|---|---|---|---|
| Uterine Cervix | Endometrial Stromal Polyp | 3/60 (45) | 1/59 (44) | 1/58 (40) | 0/60 (44) |
| | | 0.9414 | 0.6833 | 0.6461 | 0.8750 |
| | Haemangioma | 0/60 (45) | 0/59 (44) | 1/58 (40) | 0/60 (44) |
| | | 0.2543 | NC | 0.4706 | NC |
| | Leiomyoma | 1/60 (45) | 1/59 (44) | 2/58 (40) | 1/60 (44) |
| | | 0.4381 | 0.7472 | 0.4554 | 0.7472 |
| | Leiomyosarcoma | 1/60 (45) | 0/59 (44) | 0/58 (40) | 0/60 (44) |
| | | 0.7399 | 0.4944 | 0.4706 | 0.4944 |
| | Leiomyoma/<br>Leiomyosarcoma | 2/60 (45) | 1/59 (44) | 2/58 (40) | 1/60 (44) |
| | | 0.5957 | 0.4915 | 0.6461 | 0.4915 |
| Uterus | Deciduoma | 0/60 (45) | 0/60 (45) | 1/60 (42) | 0/60 (44) |
| | | 0.2500 | NC | 0.4828 | NC |
| | Endometrial Adenocarcinoma | 0/60 (45) | 1/60 (45) | 0/60 (42) | 0/60 (44) |
| | | 0.4886 | 0.5000 | NC | NC |
| | Endometrial Polyp | 0/60 (45) | 1/60 (45) | 3/60 (42) | 0/60 (44) |
| | | 0.6740 | 0.5000 | 0.1083 | NC |
| | Endometrial Stromal Cell Sarcoma | 0/60 (45) | 1/60 (45) | 1/60 (42) | 2/60 (44) |
| | | 0.1161 | 0.5000 | 0.4828 | 0.2416 |
| | Fibrosarcoma | 1/60 (45) | 0/60 (45) | 1/60 (42) | 0/60 (44) |
| | | 0.6172 | 0.5000 | 0.7354 | 0.4944 |
| | Haemangioma | 1/60 (45) | 1/60 (45) | 1/60 (42) | 1/60 (44) |
| | | 0.5061 | 0.2472 | 0.7354 | 0.7472 |
| | Leiomyoma | 3/60 (45) | 3/60 (45) | 4/60 (42) | 4/60 (45) |
| | | 0.3416 | NC | 0.4609 | 0.5000 |
| | Leiomyosarcoma | 1/60 (45) | 1/60 (45) | 0/60 (42) | 0/60 (44) |
| | | 0.8042 | 0.2472 | 0.4828 | 0.4944 |
| | Leiomyoma/Leiomyosarcoma | 4/60 (45) | 4/60 (45) | 4/60 (42) | 4/60 (45) |
| | | 0.4766 | 0.3568 | 0.6036 | NC |
| | Malignant Schwannoma | 0/60 (45) | 0/60 (45) | 0/60 (42) | 1/60 (45) |
| | | 0.2542 | NC | NC | 0.5000 |

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

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

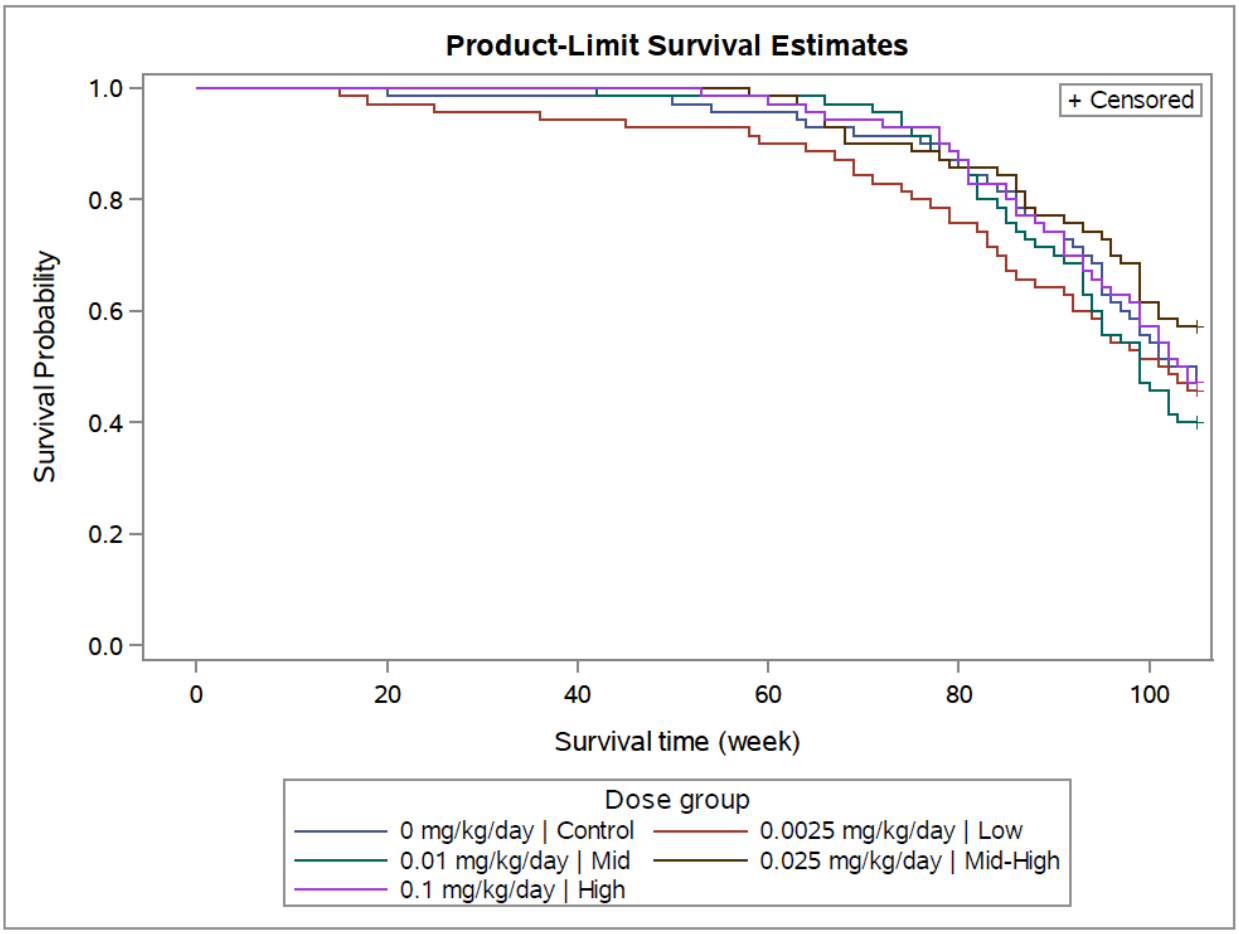


**Figure 1B: Kaplan-Meier Survival Functions for Female Rats**

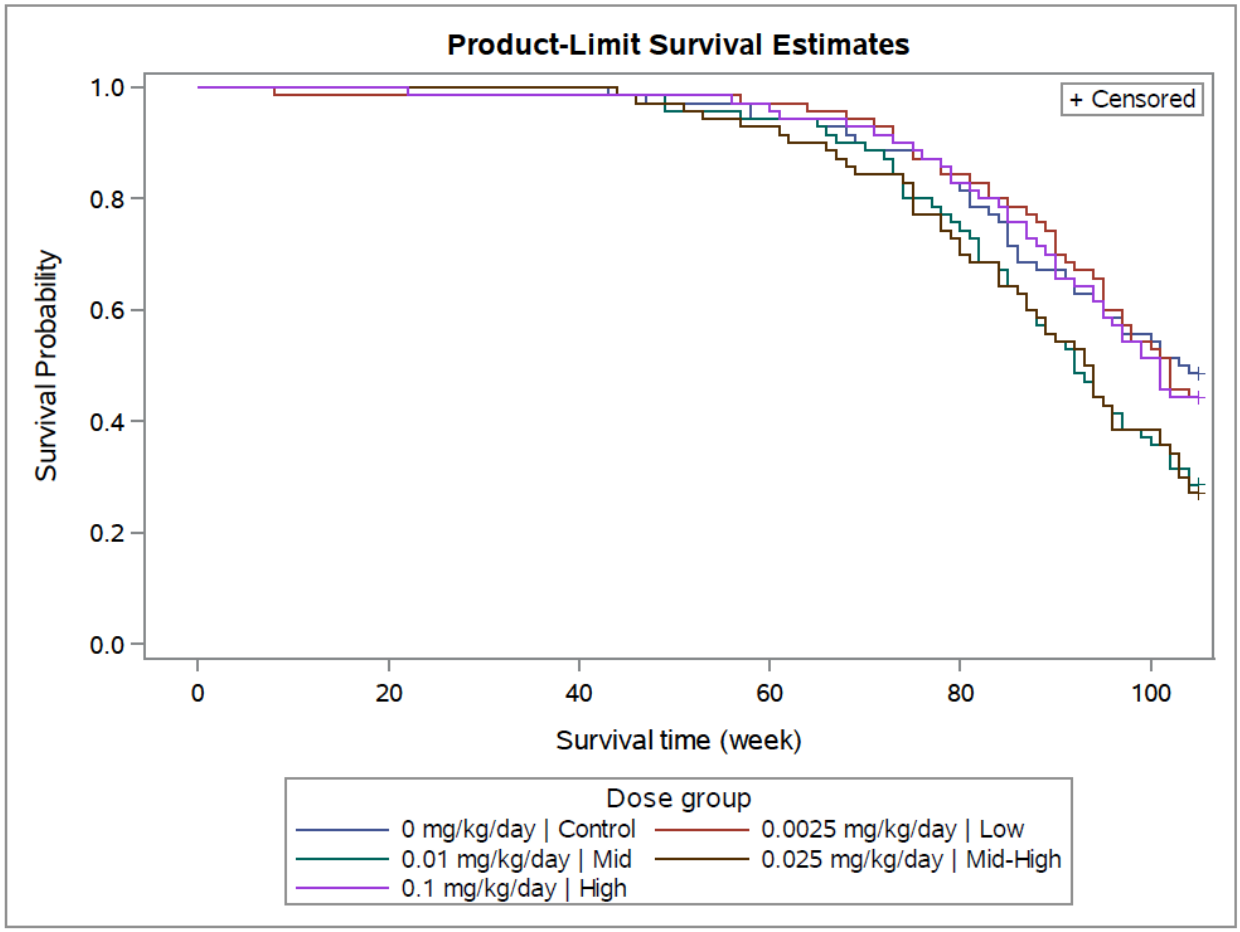


**Figure 2A: Kaplan-Meier Survival Functions for Male Mice**

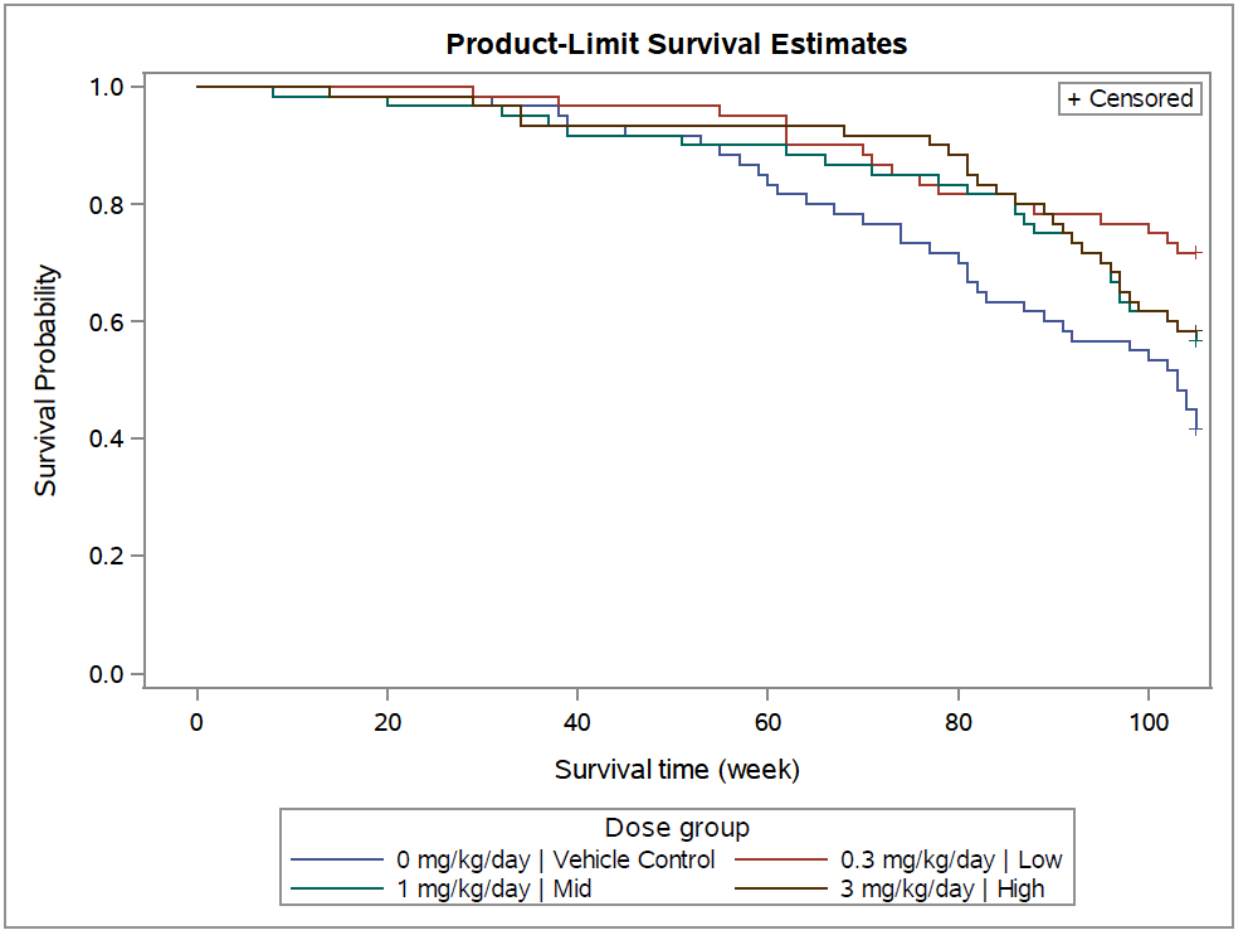
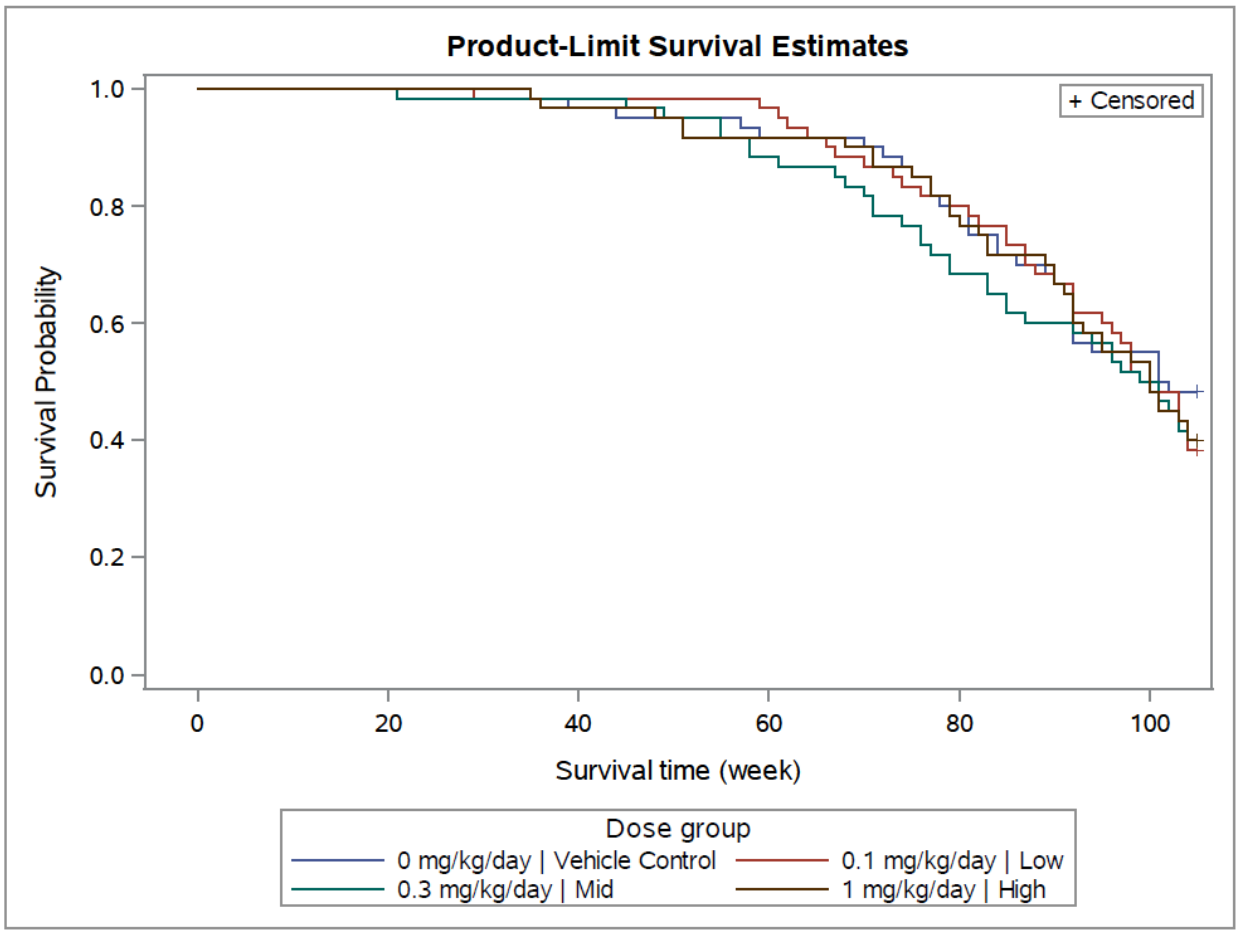


**Figure 2B: Kaplan-Meier Survival Functions for Female Mice**



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HEPEI CHEN
11/02/2017

KARL K LIN
11/02/2017
Concur with review.

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA / Serial Number:** | 209637 |
| **Supplement #:** | Sequence 0001 |
| **Drug Name:** | Semaglutide |
| **Indication(s):** | Treatment of type 2 diabetes |
| **Applicant:** | Novo Nordisk |
| **Date(s):** | Submitted: 12/05/2016<br>PDUFA Goal Date: 12/05/2017 |
| **Review Priority:** | Standard |
| **Biometrics Division:** | Division of Biometrics VII |
| **Statistical Reviewer:** | Ya-Hui (Catherine) Hsueh, Ph.D. |
| **Concurring Reviewers:** | Eugenio Andraca-Carrera, Ph.D., Team Lead<br>Mark Levenson, Ph.D., Division Director |
| **Medical Division:** | Division of Metabolism and Endocrinology Products (DMEP) |
| **Clinical Team:** | Medical Officer: Andreea Lungu<br>Medical Team Leader: William Chong |
| **Project Manager:** | Peter Franks (DMEP) |

**Keywords:** type 2 diabetes mellitus, cardiovascular safety, retinopathy

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# 1. Executive Summary

Ozempic® (semaglutide), a long-acting glucagon-like-peptide-1 (GLP-1) receptor agonist, is proposed to indicate as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The proposed therapeutic dosage is 0.5 mg or 1 mg, once weekly subcutaneous administration. In 2013, Novo Nordisk (the Sponsor) initiated a cardiovascular outcomes trial (SUSTAIN 6) to evaluate the cardiovascular (CV) risk associated with the use of semaglutide in support of the application of NDA 209637.

SUSTAIN 6 was an event-driven trial designed and powered to demonstrate the non-inferiority of semaglutide relative to placebo, both added on to standard-of-care, for the risk of major adverse cardiovascular events (MACE). MACE is a 3-component composite endpoint of CV death (including deaths of unknown cause), non-fatal myocardial infarction (MI), and non-fatal stroke. The statistical goal of this evaluation is to assess whether the hazard ratio of MACE associated with semaglutide relative to placebo met the risk margin of 1.8 in accordance with the FDA Diabetes Guidance of 2008[1].

During the trial, an increased incidence of retinopathy with semaglutide was observed. Thus, in addition to the pre-marketing evaluation of cardiovascular safety of semaglutide, this statistical review also discusses the assessment of the diabetic retinopathy safety of semaglutide.

## 1.1 Conclusions and Recommendations

The SUSTAIN 6 trial was a multi-national, randomized, double-blind, and placebo-controlled cardiovascular outcome trial designed to assess cardiovascular safety of semaglutide. The pre-specified primary CV endpoint was time from randomization to first MACE. In addition to the primary MACE endpoint, some secondary CV-related endpoints including expanded MACE, all-cause death, and primary MACE (on-treatment +42 days) were also investigated using time to event analysis methods. All events included in these primary and secondary endpoints were adjudicated by an external independent Event Adjudication Committee (EAC).

SUSTAIN 6 was designed to test whether the upper bound of the 95% confidence interval for the hazard ratio of MACE associated with semaglutide met the 1.8 risk margin specified by the 2008 FDA Diabetes Guidance. A total of 3297 subjects were included in the intent to treat (ITT) population, with 1648 randomized to semaglutide and 1649 randomized to placebo (both administered in addition to their standard-of-care treatment). Approximately 95% of the subjects had one or more years of follow-up, and about 89% had at least two years of follow-up; no subjects were followed up to 3 years. The median treatment exposure time was 104 weeks for both treatment arms. Vital status was available for about 99.6% of subjects.

A total of 254 adjudicated primary MACE events occurred during the course of the trial: 108 MACE were observed in the semaglutide arm (3.2 per 100 person-years), and 146 MACE were observed in the placebo arm (4.3 per 100 person-years). The pre-specified stratified Cox proportional hazards model for the primary MACE analysis estimated a hazard ratio of **0.74** with an associated 95% confidence interval of **(0.58, 0.95)** associated with semaglutide. The upper bound of 0.95 ruled out the risk margin of 1.8 in accordance with the 2008 FDA Diabetes

Guidance. No component of the primary MACE endpoint raised any statistical concerns. Table 1 shows the results for the pre-specified primary analysis and the secondary analyses of cardiovascular safety in the ITT population. The pre-specified secondary analyses of cardiovascular endpoints showed consistent results with the primary MACE, and were thus supportive of the findings for MACE. Subgroup analyses showed no evidence of an increased risk of MACE associated with semaglutide in subgroups defined by gender, age, race and country of randomization. Detailed results are provided in Section 3.1.5.

The results of SUSTAIN 6 suggest that semaglutide is not associated with increased cardiovascular risk relative to placebo, both added to standard-of-care.

Table 1. Primary and Secondary Analyses of Cardiovascular Endpoints

| | **Semaglutide** N=1648 PY=3408.2 | **Placebo** N=1649 PY=3401.1 | **Hazard Ratio (95% CI)** |
|---|---|---|---|
| **Primary Analysis- MACE** | **108 [3.2]** | **146 [4.3]** | **0.74 (0.58, 0.95)** |
| **Secondary Analysis** | | | |
| Expanded CV outcome | 199 | 264 | 0.74 (0.62, 0.89) |
| Cardiovascular death | 44 | 46 | 0.98 (0.65, 1.48) |
| Non-fatal MI | 47 | 64 | 0.74 (0.51, 1.08) |
| Non-fatal Stroke | 27 | 44 | 0.61 (0.38, 0.99) |
| Revascularization | 83 | 126 | 0.65 (0.50, 0.86) |
| Hospitalization for Unstable Angina | 22 | 27 | 0.82 (0.47, 1.44) |
| Hospitalization for Heart Failure | 59 | 54 | 1.11 (0.77, 1.61) |
| All-Cause Death | 62 | 60 | 1.05 (0.74, 1.50) |
| MACE (on-treatment + 42 days)* | 88 | 124 | 0.73 (0.56, 0.96) |

*included all randomized subjects exposed to at least one dose of randomized treatment
[] indicates incidence rate per 100 person-years
Source: Created by the reviewer

A total of 79 subjects experienced diabetic retinopathy complications during the course of the trial: 50 in the semaglutide arm (1.5 per 100 person-years), and 29 in the placebo arm (0.9 per 100 person-years). The pre-specified Cox proportional hazards model for the secondary endpoint of diabetic retinopathy complications obtained a hazard ratio of 1.76 with 95% confidence interval of (1.11, 2.78) associated with semaglutide (Table 2). This analysis showed evidence of increased risk of diabetic retinopathy complications associated with semaglutide. The Sponsor conducted a *post hoc* analysis to further assess the effect of semaglutide on retinopathy risk. This *post hoc* analysis resulted in an estimated hazard ratio of semaglutide relative to placebo of 1.22 with 95% confidence interval of (0.71, 2.09); a reduction of hazard ratio in comparison to the hazard ratio of the pre-specified analysis. The change in HbA1c from baseline to week 16 was found to have a statistically significant effect on the risk of retinopathy. Based on these results, the Sponsor concluded the increased risk of diabetic retinopathy complication appeared to be mediated through the larger initial rapid reduction in HbA1c observed for semaglutide. We caution that the results of this *post hoc* analysis may have limitations and should be interpreted with caution due to the following limitations: 1) adjusting for the variable of "change in HbA1c at week 16 from baseline" as an independent variable in a Cox proportional hazard model is

likely to bias the estimated hazard ratio of retinopathy associated with semaglutide towards the null (so-called overadjustment bias), and 2) the post hoc analysis is hypothesis generating and additional independent data may be needed to corroborate its findings.

Subjects with a baseline history of retinopathy were more likely to experience retinopathy complications during the trial (8.2% of subjects on semaglutide, 5.2% on placebo) than subjects without a baseline history of retinopathy (0.7% on semaglutide, 0.4% on placebo). In our exploratory analysis, the group of subjects with baseline retinopathy and more than 1.5% HbA1c reduction from baseline to week 16 was found to have the highest observed risk of developing diabetic retinopathy.

Additional data are needed to assess whether a slower reduction in HbA1c among subjects with a history of retinopathy treated with semaglutide would result in a lower risk of retinopathy. One potential source to collect these data is a future dedicated clinical trial

Table 2. Analyses of Diabetic Retinopathy Complications

| | **HR (95% CI)**<br>**Semaglutide vs. Placebo**<br>50/1648 29/1649 |
|---|---|
| **Pre-Specified Analysis** | **1.76 (1.11, 2.78)** |
| **Sponsor's post hoc analysis** | |
| Controlled direct effect of treatment | 1.22 (0.71, 2.09) |
| Effect of change in HbA1c at week 16 | 1.26 (1.02, 1.56) |

Source: Created by the reviewer

# 2. Introduction

## 2.1 Product Description and Regulatory Background

Ozempic® (semaglutide) is a long-acting glucagon-like-peptide-1 (GLP-1) receptor agonist for once weekly (OW) subcutaneous administration. The proposed indication of semaglutide is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The proposed therapeutic dosage is 0.5 mg or 1 mg. The proposed dosing regimens are: the starting dose of 0.25 mg (not a therapeutic dose), after 4 weeks the dose should be increased to 0.5 mg, and then after 4 more weeks the dose may be increased to 1 mg.

In 2013, Novo Nordisk (the Sponsor) initiated a cardiovascular outcomes trial (SUSTAIN 6) to evaluate the cardiovascular (CV) risk associated with the use of semaglutide. The SUSTAIN 6 trial entitled "A long-term, randomised, double-blind, placebo-controlled, multinational, multi-centre trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes" was completed in 2016. On 5 December 2016, the Sponsor submitted the SUSTAIN 6 trial report along with their application package for NDA 209637.

During the trial, an increased incidence of retinopathy with semaglutide was observed. Therefore, this review primarily focuses on the assessment of cardiovascular safety and retinopathy safety of semaglutide from the SUSTAIN 6 trial.

## 2.2 Data Sources

The sponsor submitted electronic documents and analysis datasets for the SUSTAIN 6 trial in support of NDA 209637 on 12/5/2016. The CDER Electronic Document Room (EDR) link to the clinical trial report and the analysis datasets of SUSTAIN 6 are provided below:

\\cdsesub1\evsprod\nda209637\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-cv-risk\5351-stud-rep-contr\study-report-nn9535-3744
\\cdsesub1\evsprod\nda209637\0001\m5\datasets\nn9535-3744\analysis\adam\datasets

The Sponsor submitted responses to two statistics Information Requests (IRs) on 4/5/2017 and 6/16/2017. The links to each IR are provided below:

\\cdsesub1\evsprod\nda209637\0010\m5\datasets\nn9535-3744\analysis\adam\programs\3744-002-t2e-retin-hba1c.txt
\\cdsesub1\evsprod\nda209637\0010\m5\datasets\nn9535-3744\analysis\adam\programs\3744-003-inc-retin-hba1c.txt
\\cdsesub1\evsprod\nda209637\0024\m1\us\resp-ir-stats-06142017.pdf

The format, content and documentation of the data submitted in support of this application were adequate to conduct a statistical review of the cardiovascular risk and the risk of retinopathy associated with semaglutide based on the SUSTAIN 6 trial.

# 3. Statistical Evaluation

This statistical review focuses on the single Phase 3a cardiovascular outcomes trial, SUSTAIN 6, that was conducted to evaluate the long term safety (CV and retinopathy safety). For a statistical evaluation of efficacy for this NDA, please refer to the review by Dr. Jiwei He.

## 3.1 Evaluation of Safety

### 3.1.1 Study Design

**SUSTAIN 6** was a Phase 3a trial titled: "A long-term, randomised, double-blind, placebo-controlled, multinational, multi-centre trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes". This trial was a long-term, multi-center, multi-national, randomized, double-blind, placebo-controlled trial conducted to evaluate the effect of semaglutide on the 3-component composite MACE endpoint (cardiovascular death including deaths of unknown cause, non-fatal myocardial infarction (MI), and non-fatal stroke) and long term outcomes in adults with type 2 diabetes mellitus at high risk of cardiovascular

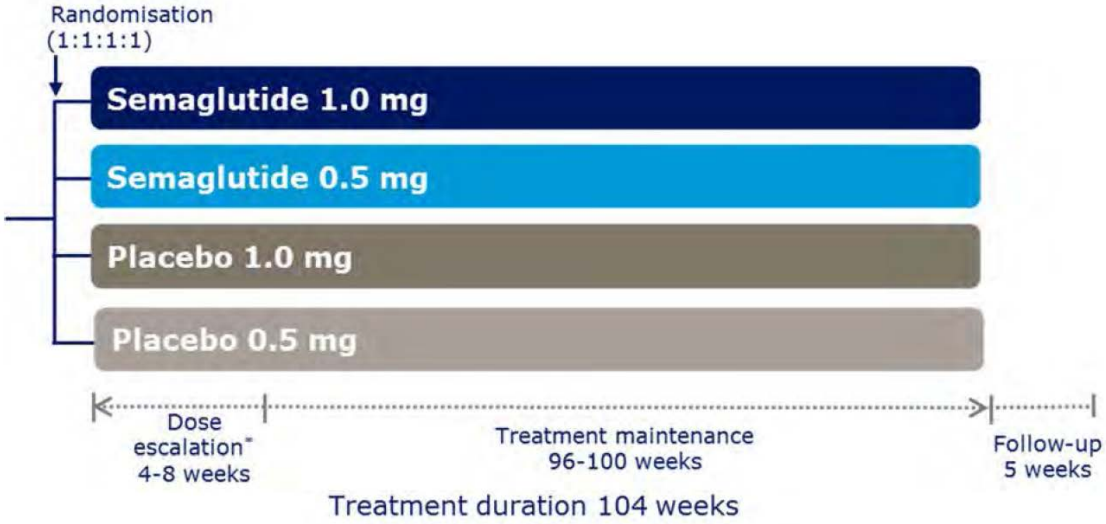
events. The trial had the following inclusion criteria: a) men or women with type 2 diabetes mellitus, b) HbA1c ≥7.0%, c) age ≥50 years with clinical evidence of cardiovascular disease or age ≥60 years with subclinical evidence of cardiovascular disease, and d) anti-diabetic drug naïve, or treated with one or two oral anti-diabetic drugs OAD(s), or treated with basal insulin (human Neutral Protamine Hagedorn (NPH) insulin or long-acting insulin analogue) or pre-mixed insulin, alone or in combination with one or two OAD(s). The trial had no exclusion criteria directly related to retinopathy. For the list of exclusion criteria of this trial, please refer to the SUSTAIN 6 clinical trial report.

Subjects meeting all enrollment criteria were randomly assigned 1:1:1:1 to treatment with 0.5 mg semaglutide, 1.0 mg semaglutide, 0.5 mg placebo, or 1.0 mg placebo after an initial dose escalation step of 0.25 mg for 4 weeks, as an add-on to their standard-of-care treatment. Randomization was stratified by three variables (total of 9 strata): 1) evidence of cardiovascular disease at baseline (clinical or subclinical), 2) insulin treatment at baseline (none, basal insulin or pre-mixed insulin), and 3) renal impairment with GFR value <30 mL/min/1.73m$^2$ per MDRD at baseline (presence or absence). Note that subjects with severe renal impairment (GFR value <30 mL/min/1.73m$^2$ per MDRD at baseline), by trial design, always fall into the "clinical evidence of CV disease" stratum. Therefore, this resulted in a total of 9 strata.

The primary safety objective of this trial was to demonstrate that the upper bound of the two-sided 95% confidence interval for the estimated hazard ratio of primary MACE associated with semaglutide relative to placebo was less than 1.8. Therefore, SUSTAIN 6 was designed as an event-driven trial and was planned to be terminated when the number of subjects with adjudicated primary composite outcome MACE were at least 122, and at the earliest 104 weeks after the last subject had been randomized. Because the projected number of MACE was reached earlier than predicted, the median on trial follow up was 109 weeks per subject and the median on treatment exposure was 104 weeks. Figure 1 presents the design of SUSTAIN 6.

The trial was conducted at 229 sites in 20 countries. A total of 3297 subjects were randomized, 1648 to the semaglutide arm and 1649 to the placebo arm.

Figure 1. SUSTAIN 6 Design




Source: Clinical trial report, page 95/12143

### 3.1.2 Study Endpoints

#### 3.1.2.1 Primary Composite Endpoint

The pre-specified primary endpoint was the time from randomization to the first occurrence of a Major Adverse Cardiovascular Event (MACE), defined as the composite of cardiovascular death (including deaths of unknown cause), non-fatal myocardial infarction (MI), and non-fatal stroke.

#### 3.1.2.2 Secondary Endpoints

The study protocol included a long list of secondary endpoints. This review only discusses the following secondary endpoints for cardiovascular safety and retinopathy safety. For the complete list and results of secondary endpoints, please refer to the SUSTAIN 6 clinical trial report.

- Time from randomization to first occurrence of an expanded composite cardiovascular outcome, defined as MACE, revascularization (coronary and peripheral), unstable angina requiring hospitalization or hospitalization for chronic heart failure.
- Time from randomization to each individual component of the expanded composite cardiovascular outcome.
- Time from randomization to all-cause death.
- Time from randomization to primary MACE (on-treatment + 42 days).
- Time from randomization to first occurrence of diabetic retinopathy complications (defined as a need for retinal photocoagulation, treatment with intravitreal agents, vitreous hemorrhage, and diabetes-related blindness (defined as Snellen visual acuity of 20/200 [6/60] or less, or visual field of less than 20 degrees, in the better eye with best correction possible)).

Sensitivity analyses (conducted by the statistical reviewer) for the time from randomization to first MI (fatal + non-fatal) or first stroke (fatal + non-fatal) are also discussed in this review.

#### 3.1.2.3 Adjudication Methods

An external independent Event Adjudication Committee (EAC) was constituted for the trial to adjudicate cardiovascular events and diabetic retinopathy events for randomized subjects in an independent and blinded manner. The EAC is composed of permanent members covering required medical specialties (cardiology, neurology, oncology, endocrinology, gastroenterology, nephrology and ophthalmology). The EAC charter was submitted to the FDA as part of the application package for NDA 209637.

According to the EAC charter, its members adjudicated and classified the following events in a blinded manner: fatal events, acute coronary syndrome (MI or unstable angina), cerebrovascular event (stroke or transient ischemic attack), heart failure requiring hospitalization, coronary revascularization procedures, nephropathy, diabetic retinopathy, pancreatitis or clinical suspicion

pancreatitis, neoplasm, and thyroid disease. The EAC members, procedures and event definitions are detailed in the submitted charter.

### 3.1.3 Statistical Methodology

#### 3.1.3.1 Analysis Populations

There were two pre-specified analysis populations defined in the study protocol: Full Analysis Set (FAS) and Safety Analysis Set (SAS).

FAS consisted of all randomized subjects followed from the time of randomization to the last recorded study visit, date of loss of follow-up, or event date, regardless of their treatment adherence. The statistical evaluation of the FAS followed the intention-to-treat (ITT) principle and subjects contributed to the evaluation "as randomized".

SAS consisted of all randomized subjects exposed to at least one dose of randomized treatment. Subjects in the SAS contributed to the statistical evaluation "as treated". Subjects were followed until the earliest of the following dates: last recorded study visit, date of loss of follow-up, event date, last date on trial product plus an ascertainment window of 42 days.

The primary and secondary analyses of all endpoints in this review were conducted based on the FAS unless noted otherwise.

#### 3.1.3.2 Primary Analysis of MACE

The primary analysis of MACE was pre-specified as a time to first event analysis. This analysis was conducted to rule out a hazard ratio greater than 1.8 at two-sided 5% alpha level based on a stratified Cox proportional hazard model with treatment arm as fixed factor. The stratification factor was categorized into 9 strata based on three stratification variables. This analysis will successfully rule out a hazard ratio of 1.8 if the upper bound of the two-sided 95% CI for the hazard ratio is below 1.8.

The hypothesis for the primary composite endpoint of MACE was to test non-inferiority of semaglutide versus placebo at the two-sided 5% alpha level:

$H_0$: $HR_{semaglutide/placebo} \geq 1.8$ vs. $H_a$: $HR_{semaglutide/placebo} < 1.8$

The proportional hazards assumption of the primary Cox model was evaluated graphically by plotting the scaled-Schoenfeld residuals of the model against time.

The sample size projection was based on the following assumptions: 1.98% annual event rate in each group, less than 10% dropout rate, an average observation time of 2.1 years, and a true hazard ratio of 1. Based on these assumptions, 3260 randomized subjects were needed to achieve

122 subjects with primary outcome, giving 95% power to reject a hazard ratio of at least 1.8. No interim analyses were planned for this trial.

#### 3.1.3.3 Secondary Analyses of Cardiovascular Safety

Stratified Cox proportional hazards models were conducted for the following secondary analyses of cardiovascular safety:

- Analysis of expanded MACE
- Analysis of individual components of expanded MACE
- Analysis of all-cause death
- Analysis of the primary MACE based on the SAS (on-treatment + 42 days)
- Sensitivity analyses of MI (fatal+no-fatal) and stroke (fatal+non-fatal)

#### 3.1.3.4 Analysis of Retinopathy

The analysis of diabetic retinopathy complications was pre-specified as a time to first event analysis. In order for an event to qualify as a diabetic retinopathy complication, it had to fulfill one or more of the following criteria:

- Need for retinal photocoagulation
- Vitreous hemorrhage
- Need for treatment with intravitreal agents
- Onset of diabetes-related blindness (defined as Snellen visual acuity of 20/200 [6/60] or less, or visual field of less than 20 degrees, in the better eye with best correction possible)

The analysis of the time to first event of diabetic retinopathy complications was based on the same stratified Cox proportional hazard model as the primary analysis of MACE.

### 3.1.4 Subject Disposition and Baseline Characteristics

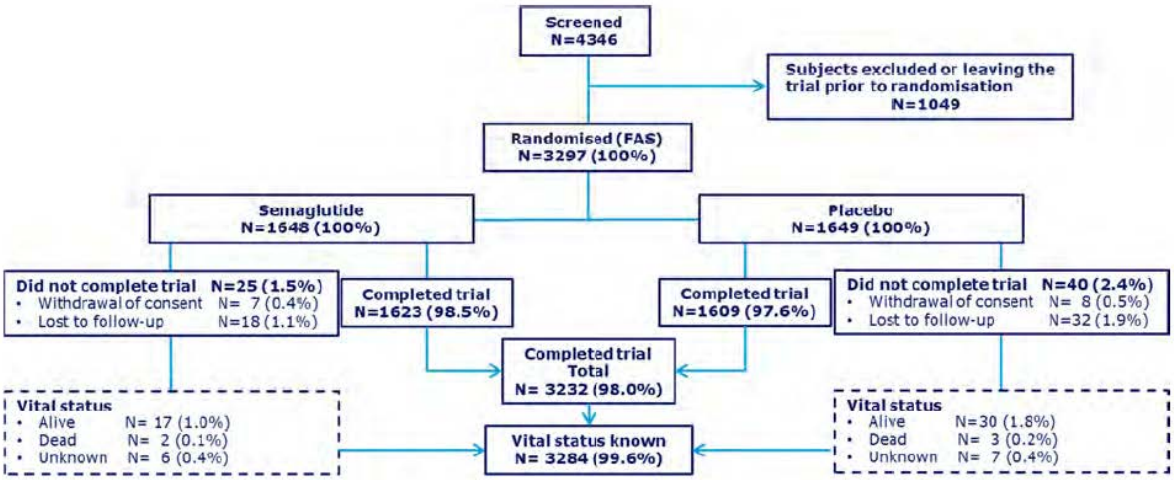
#### 3.1.4.1 Subject Disposition

SUSTAIN 6 was conducted at 229 sites in 20 countries: United States (96), Canada (13), Russian Federation (11), Turkey (10), Mexico (9), Australia (8), Brazil (8), United Kingdom (8), Argentina (7), Germany (7), Israel (6), Italy (6), Malaysia (6), Spain (6), Bulgaria (5), Denmark (5), Poland (5), Thailand (5), Algeria (4), and Taiwan (4).

The trial was initiated on 2/21/2013 (first subject first visit) and was completed on 3/15/2016 (last subject last visit). Figure 2 describes subject disposition for the ITT population (FAS). A total of 4346 subjects were screened, and 3297 subjects were randomized (1648 subjects to semaglutide and 1649 subjects to placebo). Of the 3297 subjects randomized, 3232 (98%) subjects completed the trial. There were 50 subjects (18 with semaglutide and 32 with placebo) who were lost to follow-up and 15 subjects (7 with semaglutide; 8 with placebo) who withdrew

from the trial in relation to or after treatment discontinuation. Of the 3297 subjects randomized in the trial, the last known vital status was unknown for only 13 subjects.

Figure 2. CONSORT Diagram of SUSTAIN 6




Trial completer: a subject that either attend the last follow-up visit or dies while considered an active trial participant.
FAS: full analysis set

Source: Clinical trial report, page 196/12143

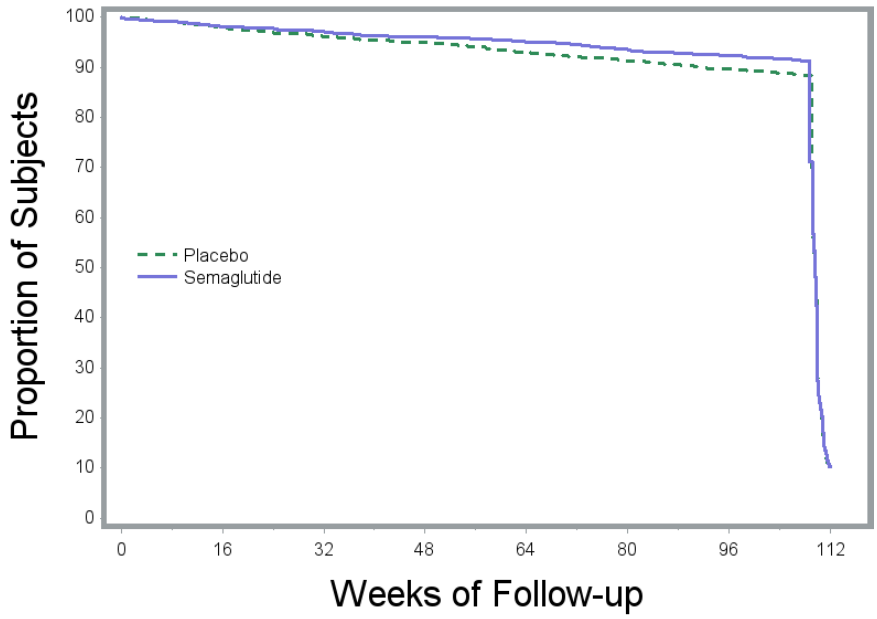
The follow-up duration for the primary MACE endpoint in the ITT population (FAS) is summarized in Table 3 and Figure 3. The mean and median follow-up duration were similar in both treatment arms. Approximately 95% of subjects had at least one year of follow-up for the primary MACE, about 90% of subjects had 2 or more years of follow-up, and no subjects had three or more years of follow-up. Follow-up duration was similar across both arms.

Table 3. Subjects Follow-up until First MACE or Trial Discontinuation

| | **Semaglutide N=1648** | **Placebo N=1649** |
|---|---|---|
| Weeks of Follow-up | | |
| Mean (SD) | 105.6 (19.0) | 104.0 (21.4) |
| Median | 109.7 | 109.7 |
| Max | 151.0 | 136.3 |
| % Subject with Follow-up | | |
| ≥ 1 year | 96.1% | 94.7% |
| ≥ 2 years | 91.8% | 88.8% |
| ≥ 3 years | 0 | 0 |

Source: Created by the reviewer

Figure 3. Study Follow-up for Primary MACE




Source: Created by the reviewer

Summary statistics in Table 4 shows similar distribution of treatment exposure across both arms for the subset of ITT population who had been exposed to the study treatment. The median treatment exposure time was 104 weeks for both treatment arms.

Table 4. Statistics on Weeks of Exposure in Subjects Exposed to Study Treatment

| | **Semaglutide N=1642*** | **Placebo N=1644*** |
|---|---|---|
| Weeks of Treatment Exposure | | |
| Mean (SD) | 88.3 (33.0) | 91.5 (29.0) |
| Median | 104.0 | 104.0 |
| Max | 116.3 | 116.1 |

*Including all randomized subjects (ITT) except those who never took any dose of study treatment.
Note: exposure times for three subjects with invalid date of last exposure to treatment were replaced by the follow-up time until first MACE or trial discontinuation for calculation purpose.
Source: Created by the reviewer

### 3.1.4.2 Baseline Characteristics

Table 5 shows baseline demographics and clinical characteristics for the ITT population (FAS) in SUSTAIN 6. All of these baseline demographic characteristics appeared balanced between the two treatment arms. The mean age at baseline was 65 years old. Approximately 61% of all

randomized subjects were male. Most subjects were White (83%) followed by Asian (8%) and Black or African American (7%). Approximately 35% of all randomized subjects were recruited from U.S. sites, 19% from Europe, and 46% from the rest of the world. The clinical characteristics were balanced between treatment arms. For both arms, a majority of subjects (83%) had clinical evidence of CV disease at baseline, average body mass index (BMI) was around 33, average baseline HbA1c was 8.7%, average duration of diabetes was about 14 years, and approximately 28% of subjects had baseline eGFR less than 60 mL/min/1.73m$^2$.

Table 5. Baseline Demographics and Clinical Characteristics in SUSTAIN 6

| | **Semaglutide** (*N=1648*) | **Placebo** (*N=1649*) | **Total (N=3297)** |
|---|---|---|---|
| Age, Mean ± SD | 64.7 ± 7.2 | 64.6 ± 7.5 | 64.6 ± 7.4 |
| <65 | 51.9% | 51.2% | 51.5% |
| ≥65 | 48.1% | 48.8% | 48.5% |
| Sex | | | |
| Female | 38.5% | 40.0% | 39.3% |
| Male | 60.0% | 61.5% | 60.7% |
| Race | | | |
| White | 84.0% | 82.0% | 83.0% |
| Asian | 7.3% | 9.2% | 8.3% |
| Black or African American | 6.6% | 6.9% | 6.7% |
| Other | 2.1% | 1.9% | 2.0% |
| Country | | | |
| United States | 34.6% | 34.4% | 34.5% |
| EU | 19.8% | 18.6% | 19.2% |
| Rest of the World | 45.6% | 47.1% | 46.3% |
| BMI[a], Mean ± SD, kg/m2 | 32.8 ± 6.2 | 32.8 ± 6.2 | 32.8 ± 6.2 |
| Duration of Diabetes, Mean ± SD, yrs | 14.2 ± 8.2 | 13.6 ± 8.0 | 13.9 ± 8.1 |
| Baseline HbA1c, Mean ± SD, % | 8.7 ± 1.5 | 8.7 ± 1.5 | 8.7 ± 1.5 |
| Clinical Evidence of CV Disease | 82.1% | 83.8% | 83.0% |
| Baseline eGFR, mL/min/1.73m$^2$ | | | |
| < 60 | 27.6% | 27.3% | 27.5% |
| 60-90 | 44.1% | 43.9% | 44.0% |
| > 90 | 28.3% | 28.8% | 28.5% |

[a] The calculation ignored missing values
Source: Created by the reviewer

## 3.1.5 Analysis Results

### 3.1.5.1 Primary Analysis of MACE

Results of the pre-specified primary analysis of MACE based on a stratified Cox proportional hazards model are shown in Table 6. The estimated hazard ratio of MACE associated with semaglutide relative to placebo was 0.74 with 95% confidence interval of (0.58, 0.95). Based on

this result alone, the upper bound of the 95% confidence interval for the hazard ratio successfully ruled out a hazard ratio of MACE greater than 1.8 associated with semaglutide. Table 6 also presents the results of the components of the primary MACE endpoint. The same stratified Cox proportional hazard model was used to calculate the time to first event analyses. The estimated hazard ratio and 95% CI for cardiovascular death: 0.98 (0.65, 1.48); non-fatal myocardial infarction: 0.74 (0.51, 1.08); and non-fatal stroke: 0.61 (0.38, 0.99) show no evidence of increased risk associated with semaglutide.

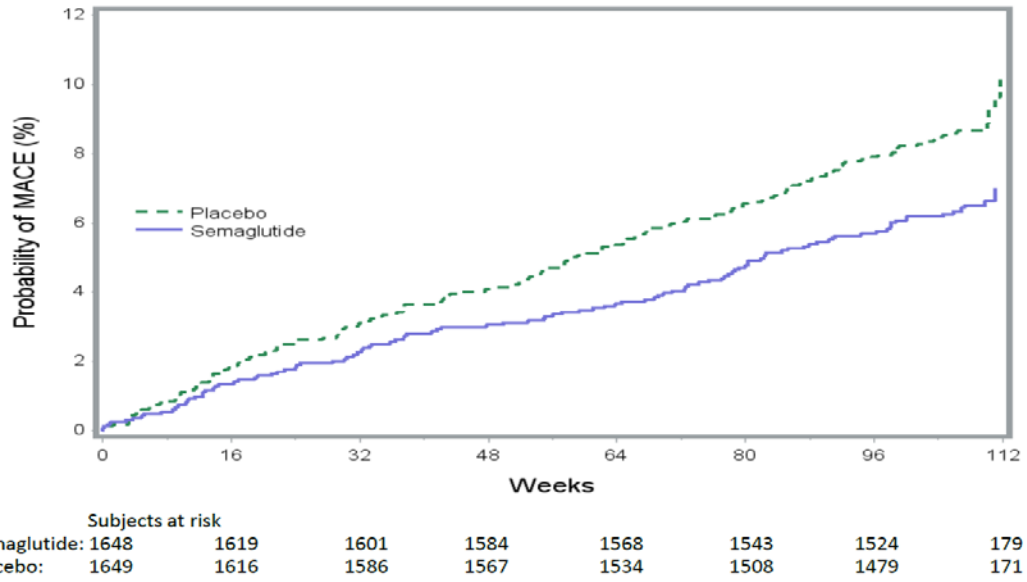
Table 6. Primary Analysis of MACE – Number of Events

| | **Semaglutide** N=1648 PY=3408.2 | **Placebo** N=1649 PY=3401.1 | **Hazard Ratio (95% CI)** |
|---|---|---|---|
| MACE (FAS) | 108 [3.2] | 146 [4.3] | 0.74 (0.58, 0.95) |
| Cardiovascular death | 44 | 46 | 0.98 (0.65, 1.48) |
| Non-fatal MI | 47 | 64 | 0.74 (0.51, 1.08) |
| Non-fatal Stroke | 27 | 44 | 0.61 (0.38, 0.99) |

[] indicates incidence rate per 100 person-years
Source: Created by the reviewer

Figure 4 shows the Kaplan-Meier cumulative probability of developing MACE by treatment arm. The curves separated gradually over time. The cumulative probability of MACE appeared to be higher in the placebo arm over time. The assumption of proportional hazards appears to hold for the primary MACE analysis (Figure 14 in Appendix shows the plot of the scaled Schoenfeld residuals).

Figure 4. Kaplan-Meier Cumulative Probability of Primary MACE by Treatment




Source: Created by the reviewer

### 3.1.5.2 Secondary Analyses of Cardiovascular Endpoints

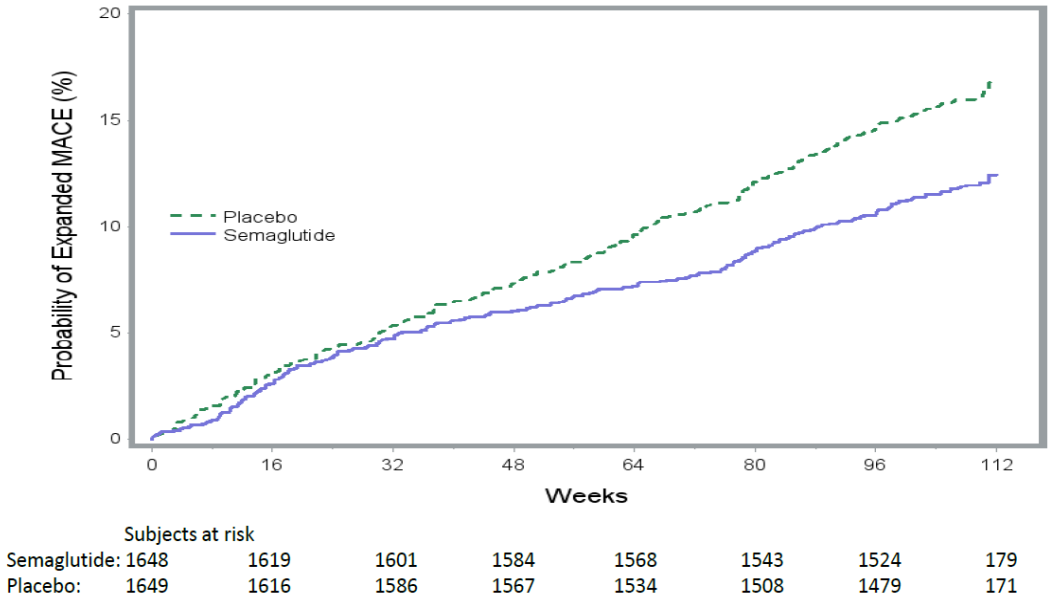
The pre-specified secondary cardiovascular endpoints that were included in this review are the expanded MACE, the individual components of the expanded MACE, all-cause death, and the primary MACE based on SAS (on-treatment + 42 days). Table 7 presents the time to first event analysis for the expanded MACE and its individual components. The hazard ratio for the expanded MACE was 0.74 with 95% confidence interval of (0.62, 0.89). The Kaplan-Meier curves for the two arms were plotted in Figure 5. The curves were close in the beginning of the trial and then separated gradually over time. Subjects in the placebo arm had higher observed probability of developing expanded MACE than those in the semaglutide arm. The estimated hazard ratio and 95% confidence interval for cardiovascular death: 0.98 (0.65, 1.48); non-fatal myocardial infarction: 0.74 (0.51, 1.08); non-fatal stroke: 0.61 (0.38, 0.99); revascularization: 0.65 (0.50, 0.86); hospitalization for unstable angina: 0.82 (0.47, 1.44); and hospitalization for heart failure: 1.11 (0.77, 1.61) show no evidence of increased risk associated with semaglutide. A graphical check (Figure 15 in Appendix) shows that the assumption of proportional hazards appears reasonable for the Expanded MACE analysis.

Table 7. Secondary Analysis of Expanded MACE – Number of Events

| | **Semaglutide** N=1648 PY=3408.2 | **Placebo** N=1649 PY=3401.1 | **Hazard Ratio (95% CI)** |
|---|---|---|---|
| Expanded CV outcome (FAS) | 199 [5.8] | 264 [7.8] | 0.74 (0.62, 0.89) |
| Cardiovascular death | 44 | 46 | 0.98 (0.65, 1.48) |
| Non-fatal MI | 47 | 64 | 0.74 (0.51, 1.08) |
| Non-fatal Stroke | 27 | 44 | 0.61 (0.38, 0.99) |
| Revascularization | 83 | 126 | 0.65 (0.50, 0.86) |
| Hospitalization for Unstable Angina | 22 | 27 | 0.82 (0.47, 1.44) |
| Hospitalization for Heart Failure | 59 | 54 | 1.11 (0.77, 1.61) |

[] indicates incidence rate per 100 person-years
Source: Created by the reviewer

Figure 5. Kaplan-Meier Plot for Expanded MACE




Source: Created by the reviewer

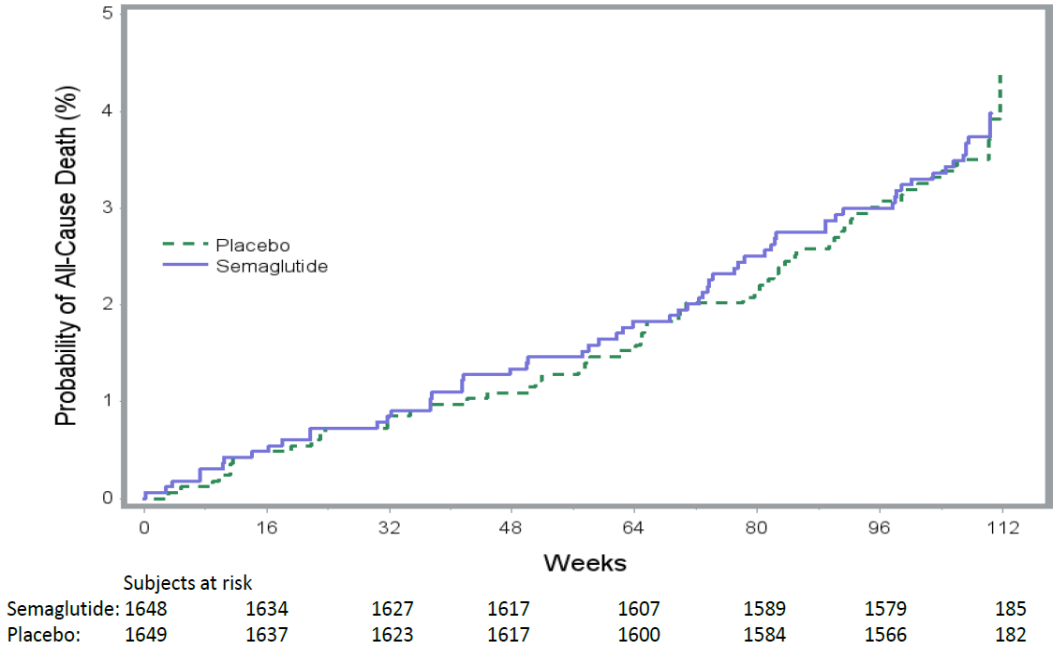
Time to all-cause death was pre-specified as a secondary endpoint. A total of 62 deaths (3.8%) were observed in the semaglutide arm and 60 deaths (3.6%) were observed in the placebo arm. As discussed in section 3.2.3, vital status was available for 99.6% of all randomized subjects; only 13 subjects lacked vital status follow-up (6 with semaglutide; 7 with placebo). Table 8 shows the analysis results for the time to all-cause death. This analysis resulted in an estimated hazard ratio of 1.05 with an associated 95% confidence interval of (0.74, 1.50). The Kaplan-Meier plot in Figure 6 indicates that the curves for the two treatment arms were generally close to each other throughout the course of the trial. A graphical check (Figure 16 in Appendix) shows that the assumption of proportional hazards appears reasonable for the all-cause death analysis.

Table 8. Secondary Analysis of All-Cause Death- Number of Events

| | **Semaglutide** N=1648 PY=3408.2 | **Placebo** N=1649 PY=3401.1 | **Hazard Ratio (95% CI)** |
|---|---|---|---|
| All-Cause Death | 62 [1.8] | 60 [1.8] | 1.05 (0.74, 1.50) |

[] indicates incidence rate per 100 person-years
Source: Created by the reviewer

Figure 6. Kaplan-Meier Plot for All-Cause Death




Source: Created by the reviewer

The time to first event analysis for the primary composited MACE based on SAS (on-treatment + 42 days) is presented in Table 9. The estimated hazard ratio for primary MACE based on the SAS was 0.73 with 95% confidence interval of (0.56, 0.96). Another two on-treatment analyses (+ 7 days and + 30 days) were also assessed for the same endpoint and the results were similar to the on-treatment + 42 days analysis. The Kaplan-Meier curves for these analyses were similar to the primary analysis of MACE shown in Figure 5 and are not shown in this document.

Table 9. Secondary Analysis of MACE based on SAS – Number of Events

| | **Semaglutide** N=1642 | **Placebo** N=1644 | **Hazard Ratio (95% CI)** |
|---|---|---|---|
| MACE (on-Treatment +42 days) | 88 | 124 | 0.73 (0.56, 0.96) |
| +7 days | 76 | 109 | 0.72 (0.54, 0.97) |
| +30 days | 86 | 120 | 0.74 (0.56, 0.97) |

Source: Created by the reviewer

The sensitivity analyses for time to first event of MI (fatal + non-fatal) and time to first event of stroke (fatal + non-fatal) are presented in Table 10. The estimated hazard ratios and 95% confidence intervals were 0.81 (0.57, 1.16) and 0.65 (0.41, 1.03) for MI (fatal and non-fatal) and stroke (fatal and non-fatal), respectively.

Table 10. Sensitivity Analyses of MI (fatal + non-fatal) and Stroke (fatal + non-fatal)

| | **Semaglutide** N=1648 | **Placebo** N=1649 | **Hazard Ratio (95% CI)** |
|---|---|---|---|
| MI (fatal + non-fatal) | 54 | 67 | 0.81 (0.57, 1.16) |
| Stroke (fatal + non-fatal) | 30 | 46 | 0.65 (0.41, 1.03) |

Source: Created by the reviewer

### 3.1.5.3 Pre-specified Analysis of Retinopathy

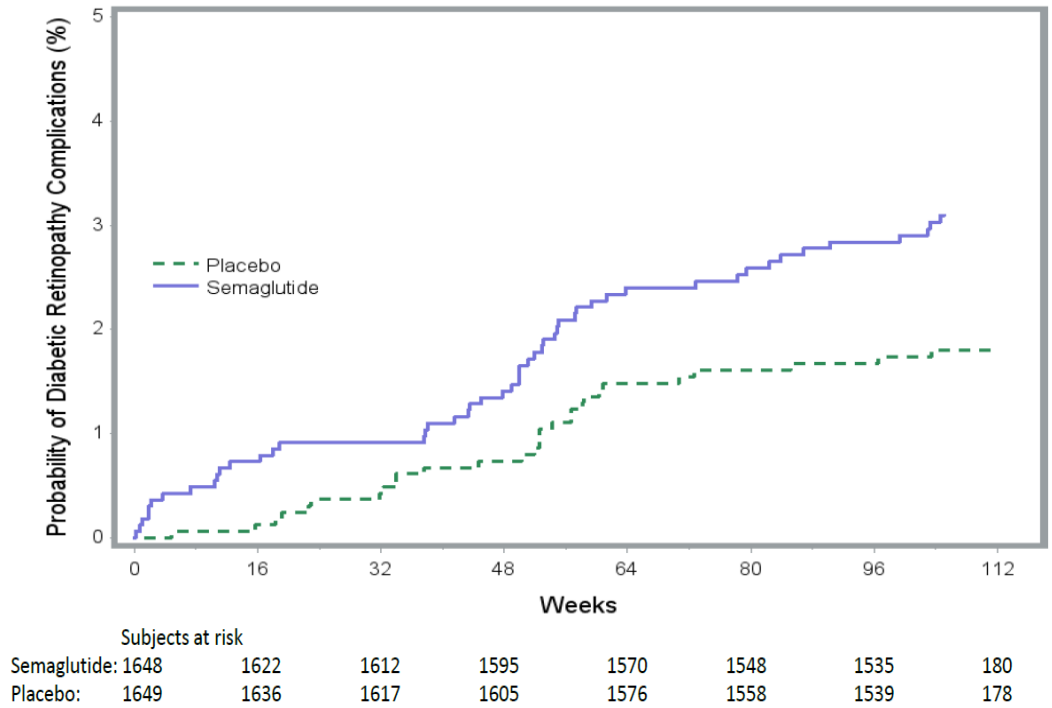
The time to first event of diabetic retinopathy complication was pre-specified as a secondary endpoint. Table 11 presents the analysis results for the composite endpoint of diabetic retinopathy complications and its four individual components. A total of 79 subjects were identified as experiencing diabetic retinopathy complications (50 subjects with semaglutide; 29 subjects with placebo). The estimated hazard ratio was 1.76 with an associated 95% confidence interval of (1.11, 2.78). This analysis showed evidence of increased risk of diabetic retinopathy complications associated with semaglutide. The Kaplan-Meier plot in Figure 7 shows the imbalance appeared from the beginning of the trial and continued throughout the trial. The observed probability of diabetic retinopathy complications was higher in the semaglutide arm. Figure 17 in the Appendix shows possible evidence of non-proportional hazards with a steep slope (high rate of events) observed in the semaglutide arm during the early part of the trial.

Table 11. Pre-Specified Analysis of Diabetic Retinopathy Complications

| | **Semaglutide** N=1648 PY=3408.2 | **Placebo** N=1649 PY=3401.1 | **Hazard Ratio (95% CI)** |
|---|---|---|---|
| Diabetic Retinopathy Complications | 50 | 29 | 1.76 (1.11, 2.78) |
| Need for Retinal Photocoagulation | 38 | 20 | |
| Vitreous Hemorrhage | 16 | 7 | |
| Need for Treatment with Intravitreal agents | 16 | 13 | |
| Onset of Diabetes-Related Blindness | 5 | 1 | |

Source: Created by the reviewer

Figure 7. Kaplan-Meier Plot for Diabetic Retinopathy Complications




Source: Created by the reviewer

### 3.1.5.3.1 Baseline Characteristics of Subjects with Retinopathy

Table 12 presents baseline characteristic for subjects with diabetic retinopathy complications and all subjects randomized in the SUSTAIN 6. In contrast to all randomized subjects in the trial, subjects who experienced an event of diabetic retinopathy complication on average were younger (age of 62.6), had longer duration of diabetes (17.5 years), had higher HbA1c (9.4%) at baseline, and approximately 76% had insulin treatment (basal or premix) at baseline. The largest difference was observed in terms of diabetic retinopathy at baseline: approximately 84% of the subjects who experienced diabetic retinopathy complications had diabetic retinopathy at baseline compared to 29.4% in the overall population (which includes subjects who experienced retinopathy complications). The baseline characteristics of subjects with an event of diabetic retinopathy complications were similar between the two treatment arms.

Table 12. Baseline Characteristics for Subjects with Event of Diabetic Retinopathy Complications and All Randomized Subjects in SUSTAIN 6

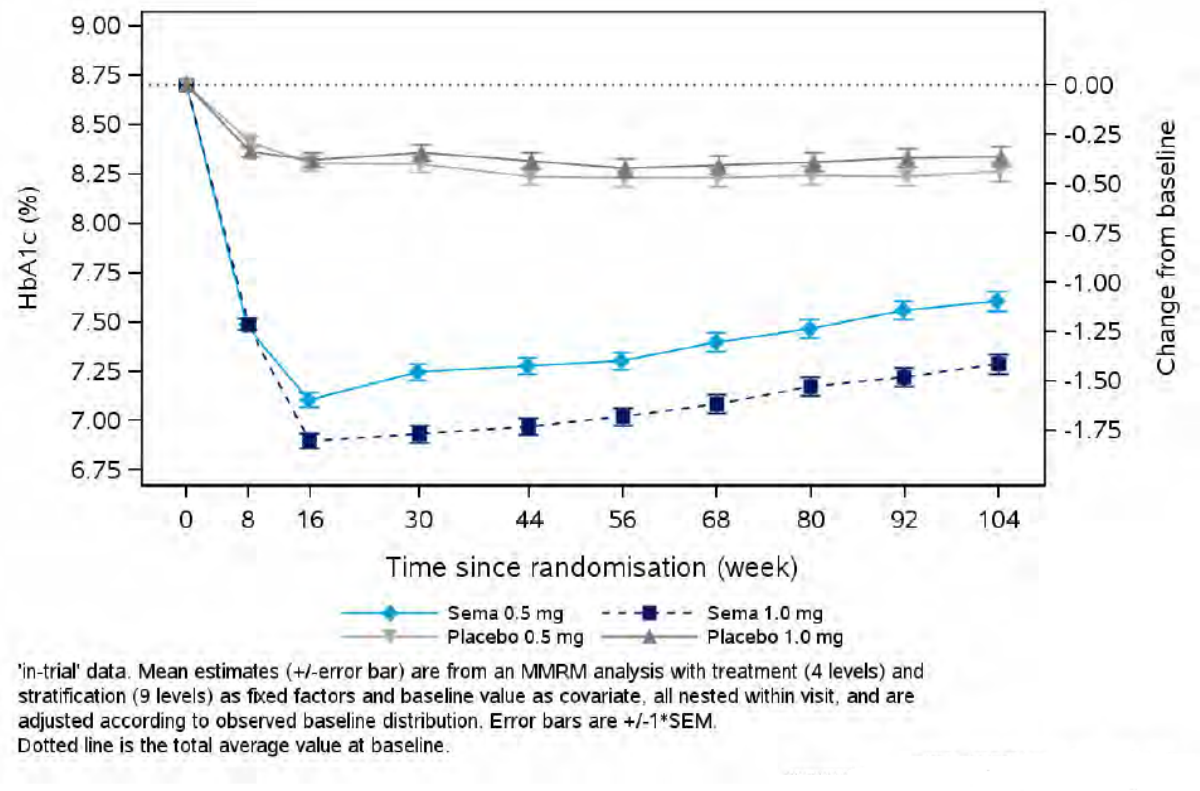
| Baseline Characteristics | Subjects with event of Diabetic Retinopathy Complications | | | All Randomized subjects (N=3297) |
|---|---|---|---|---|
| | Semaglutide (N=50) | Placebo (N=29) | All subjects (N=79) | |
| Age, Mean ± SD | 63.0 ± 5.6 | 61.8 ± 7.0 | 62.6 ± 6.1 | 64.6 ± 7.4 |
| <65 | 70.0% | 69.0% | 69.6% | 51.5% |
| ≥65 | 30.0% | 31.0% | 30.4% | 48.5% |
| Sex | | | | |
| Female | 32.0% | 41.4% | 35.4% | 39.3% |
| Male | 68.0% | 58.6% | 65.6% | 60.7% |
| Race | | | | |
| White | 86.0% | 86.2% | 86.1% | 83.0% |
| Asian | 14.0% | 0.0% | 8.9% | 8.3% |
| Black | 0.0% | 10.3% | 3.8% | 6.7% |
| Other | 0.0% | 3.5% | 1.3% | 2.0% |
| Country of Randomization | | | | |
| US | 26.0% | 17.2% | 22.8% | 34.5% |
| Non-US | 74.0% | 82.8% | 77.2% | 65.5% |
| Insulin treatment at Baseline | | | | |
| Basal insulin | 28.0% | 41.4% | 32.9% | 31.7% |
| Premix insulin | 48.0% | 34.5% | 43.0% | 26.3% |
| None | 24.0% | 24.1% | 24.1% | 42.0% |
| Duration of Diabetes, Mean ± SD, yrs | 17.1 ± 9.2 | 18.3 ± 6.9 | 17.5 ± 8.4 | 13.9 ± 8.1 |
| Baseline HbA1c, Mean ± SD, % | 9.2 ± 2.0 | 9.7 ± 1.8 | 9.4 ± 1.9 | 8.7 ± 1.5 |
| Diabetic Retinopathy at Baseline | | | | |
| Yes | 84.0% | 82.8% | 83.5% | 29.4% |
| No | 10.0% | 13.8% | 11.4% | 64.1% |
| Unknown | 6.0% | 3.5% | 5.1% | 6.6% |

Source: Created by the reviewer

### 3.1.5.4 Post-hoc Analyses of Retinopathy Conducted by the Sponsor

As a result of the increased risk of diabetic retinopathy complications observed with semaglutide during the trial, the Sponsor conducted a *post hoc* analysis to further investigate the effect of semaglutide on this risk. The Sponsor attempted to control for the effect of the rapid decrease in HbA1c. Because the effect of the rapid decrease in HbA1c is a post-baseline factor, such an analysis is known as a mediator analysis. The Sponsor noted that subjects randomized to semaglutide experienced a rapid reduction in HbA1c relative to placebo, as shown in Figure 8. In the *post hoc* analysis, the change in HbA1c from baseline to week 16 was chosen as a marker for the initial rapid decline in blood glucose (BG).

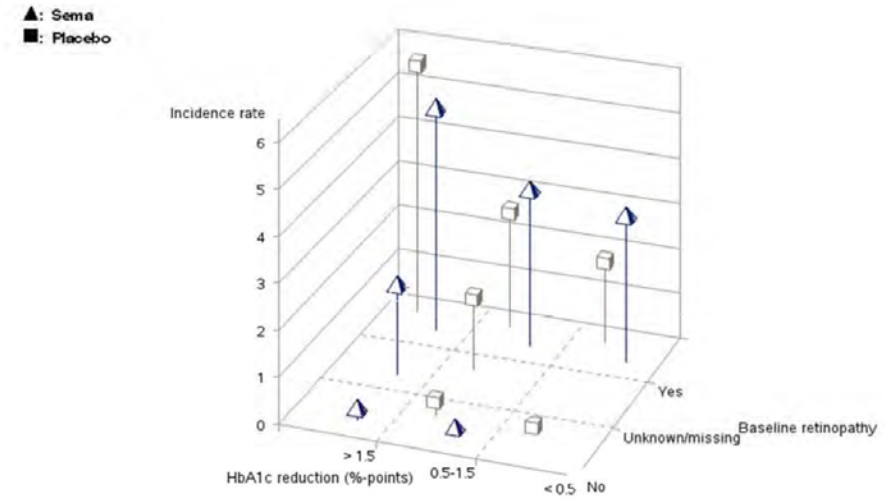
Figure 8. Mean HbA1c by Treatment Group and Week




Source: Clinical trial report, page 3111/12143

The Sponsor summarized the incidence rate of first event of diabetic retinopathy complications between treatment arms by diabetic retinopathy at baseline (3 groups: Yes, No, Unknown) and change in HbA1c at week 16 from baseline (3 groups: decrease > 1.5%, 0.5%-1.5%, <0.5%) as shown in Figure 9. The Sponsor argued that the observed difference in incidence rates of first event of diabetic retinopathy complications between the two treatment arms within these 9 subgroups defined by diabetic retinopathy at baseline and decrease in HbA1c was minimal. Subjects with a large reduction in HbA1c at week 16 and with a history of diabetic retinopathy at baseline experienced the highest incidence rate of retinopathy in both treatment arms.

Figure 9. Incidence Rate of first event of diabetic retinopathy complications between treatment arms by diabetic retinopathy at baseline and change in HbA1c at week 16 (reduction)




**Note:** The figure shows observed incidence rates for time to first EAC-confirmed event of diabetic retinopathy complications (vertical axis) for subgroups of subjects categorised by baseline diabetic retinopathy (yes, no, unknown/missing) and reduction in $HbA_{1c}$ (%-points) at week 16 (<0.5%-points, 0.5–1%-points, >1.5%-points), horizontal axes. Blue needles with pyramids are for semaglutide, grey needles with cubes are for placebo. Observed incidence rates per 100 PYR are calculated as 100 times the number of events divided by the total risk time. A subject's risk time is the time from randomisation until the subject's first EAC-confirmed event or censoring.

**Abbreviations:** EAC: event adjudication committee; PYR: patient years of risk time.

Source: Created by the reviewer

The *post hoc* analysis was based on a Cox proportional hazards model which included treatment, change in HbA1c at week 16, and 3 risk factors for diabetic retinopathy (HbA1c at baseline, retinopathy at baseline, and duration of diabetes at baseline) as independent variables. Table 13 presents the results of the *post hoc* analysis. The estimated hazard ratio for the time until first event of diabetic retinopathy complications associated with semaglutide in the *post hoc* analysis was 1.22 with an associated 95% confidence interval of (0.71, 2.09). The estimated hazard ratio associated with a 1%-point reduction in HbA1c at week 16 was 1.26 with 95% confidence interval of (1.03, 1.57). Based on these results, the Sponsor concluded that "a rapid decline in BG likely was the mechanism or contributed to the mechanisms underlying the development of diabetic retinopathy complications in those with a prior history of diabetic retinopathy"; and therefore, "the increased risk of diabetic retinopathy complication appeared to be mediated through the larger initial rapid reduction in HbA1c observed for semaglutide than for placebo".

Table 13. *Post hoc* Analysis for the Risk of Diabetic Retinopathy Complications

| **Sponsor's Post hoc Mediator Analysis** | **Hazard Ratio** (95% CI)<br>Semaglutide vs. Placebo<br>50/1648 29/1649 |
|---|---|
| Controlled direct effect of treatment | 1.22 (0.71, 2.09) |
| Effect of change in HbA1c at week 16 | 1.26 (1.03, 1.57) |

Source: Created by the reviewer

***Reviewer's comment:***

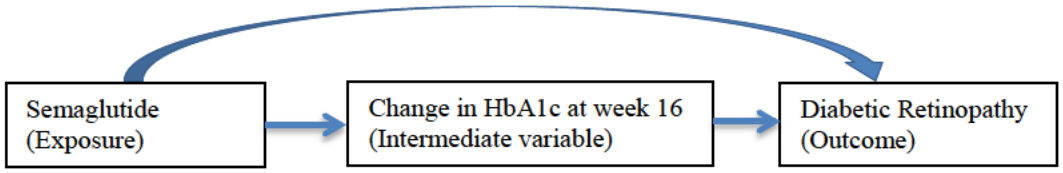
1) *The comparison of incidence rates of diabetic retinopathy (as shown in Figure 9) by 2 variables (diabetic retinopathy at baseline and change in HbA1c at week 16 from baseline) between the two treatment arms should be interpreted with caution. Because the variable of "change in HbA1c at week 16" is measured post-randomization, the baseline characteristics between the two treatment arms in subgroups defined by this post-randomization variable were not guaranteed to be balanced (Table 26 in Appendix presents baseline characteristics between the two treatment arms in subgroups by the post-randomization variable of "change in HbA1c at week 16 (reduction) for subjects with baseline retinopathy).Therefore, analyses comparing the two treatment arms might be biased due to possibly imbalanced baseline characteristics within subgroups defined by post-randomization characteristics .*

2) *For the post hoc analysis, we have concerns regarding the inclusion of the variable of "change in HbA1c at week 16" in the Cox proportional hazards model as an independent variable for the following reasons:*

   a. *This variable is measured post-randomization and is affected by (associated with) the treatment. Therefore, the results of the analysis might be biased if this variable is included as an independent variable in the Cox proportional hazard model.*

   b. *The Sponsor claimed that "a rapid decline in BG likely was the mechanism or contributed to the mechanism underlying the development of diabetic retinopathy". Based on this claim, the possible causal pathway from exposure to outcome is assumed as shown below in Figure 10. Controlling (i.e. adjust) for an intermediate variable (change in HbA1c at week 16) on a causal path from exposure to outcome might introduce overadjustment bias[2]. Thus, adjusting for the variable of "change in HbA1c at week 16 from baseline" as an independent variable in a Cox proportional hazard model is likely to bias the estimated hazard ratio of retinopathy associated with semaglutide towards the null (in other words, this analysis mutes the treatment effect).*

Figure 10. Causal Diagram for Overajustment Bias




3) *The results of these post hoc analyses should be interpreted as exploratory or hypothesis generating.*

### 3.1.5.4.1 Exploratory Analyses of Retinopathy Conducted by the Reviewer

To further explore the risk of retinopathy with semaglutide, we conducted the following exploratory analyses which are discussed in this section:

a) Descriptive summary of the characteristics of subjects who experienced an event of diabetic retinopathy complications before week 16.
b) Summary of the distribution of the time to first event of diabetic retinopathy complications by treatment arm.
c) Exploratory analysis to characterize possible subgroups with high risk of developing diabetic retinopathy complications.

**a) Characteristics of subjects who experienced an event of diabetic retinopathy complications before week 16.**

Because "change in HbA1c at week 16" was chosen as a marker for the initial rapid decline in BG in the Sponsor's *post hoc* analysis, we further investigated those subjects who experienced diabetic retinopathy complications before week 16 (shown in Table 14). There were 13 subjects (~16%; out of a total of 79 subjects with an event) who experienced diabetic retinopathy complications before week 16 (12 subjects with semaglutide; 1 subject with placebo). These events showed an early imbalance of retinopathy at week 16. Furthermore, among the 13 subjects with an event before week 16, 8 subjects (7 subjects with semaglutide; 1 subject with placebo) experienced the event before week 8. All of these 8 subjects had similar reductions in HbA1c at these two time points (week 8 and week 16) except for the subject on placebo (+0.5% change at week 8 and -0.6% change at week 16).

Table 14. HbA1c in Subjects who Experienced Diabetic Retinopathy Complications Before Week 16

| Time (Days) | Treatment | HbA1c (%) | | |
|---|---|---|---|---|
| | | at Baseline | change at week 8 | change at week 16 |
| 5 | Sema 1.0 | 10.4 | -3.1 | -3.9 |
| 6 | Sema 1.0 | 9.6 | -1.0 | -1.0 |
| 13 | Sema 1.0 | 7.8 | -1.2 | -1.3 |
| 15 | Sema 0.5 | 8.8 | -1.9 | -2.3 |
| 15 | Sema 0.5 | 10.6 | -3.1 | -3.7 |
| 16 | Sema 1.0 | 8.5 | -1.7 | -2.1 |
| 33 | Sema 1.0 | 11.6 | -2.8 | -4.4 |
| 37 | Placebo 0.5 | 10.8 | +0.5 | -0.6 |
| 60 | Sema 1.0 | 8.7 | -1.0 | -1.7 |
| 75 | Sema 1.0 | 8.4 | -1.2 | -1.4 |
| 77 | Sema 1.0 | 7.3 | -1.5 | -1.5 |
| 87 | Sema 0.5 | 7.8 | -1.1 | -1.0 |
| 92 | Sema 0.5 | 8.4 | -0.8 | +1.4 |

Source: Created by the reviewer

**b) Distribution of the time to first event of diabetic retinopathy complications by treatment arm.**

Of the 79 subjects with diabetic retinopathy complications, 43 (54%) subjects experienced the event within 1 year of randomization (29 with semaglutide; 14 with placebo), and 36 (46%) subjects experienced the event at least 1 year after randomization (21 with semaglutide; 15 with placebo). Table 15 shows a summary of the time to event of diabetic retinopathy complications by treatment based on FAS. The distribution of the time to event based on the on-treatment population was the same as the FAS population as is not discussed further.

Table 15. Time to Event of Diabetic Retinopathy Complications by Treatment

| **Time** (years) | **Semaglutide** N=50 | | **Placebo** N=29 | |
|---|---|---|---|---|
| | 0.5 mg | 1.0 mg | 0.5 mg | 1.0 mg |
| < 1 | 13 | 16 | 8 | 6 |
| 1-2 | 12 | 9 | 6 | 9 |

Source: Created by the reviewer

These two analyses raised some questions and concerns:

- Eight subjects experienced an event before week 8. It is a matter of clinical judgement whether a treatment effect may be associated with diabetic retinopathy complications within this short timeframe.

- Only 6 (~46%) out of 13 subjects who experienced an event before week 16 had a reduction in HbA1c larger than 1.5% (change ≤ -1.5%) at week 16. This result does not directly support the claim that the risk of diabetic retinopathy complications is mediated through a large initial rapid reduction in HbA1c.

- Approximately 58% of events in the semaglutide arm and 48% on placebo occurred within 1 year of randomization. It is unclear whether this is consistent with the proposed mechanism of an initial rapid reduction in HbA1c, which could be expected to result in a larger proportion of early retinopathies than was observed in the trial.

**c) Possible subgroups with high risk of developing diabetic retinopathy complications.**

This *post hoc* analysis was conducted (by the reviewer) to characterize possible subgroups with high risk of developing diabetic retinopathy complications. As shown in Table 12, approximately 84% of subjects with an event of diabetic retinopathy complications had diabetic retinopathy at baseline, compared to only 29% in the full trial population. Table 16 shows that subjects with a baseline history of retinopathy were more likely to experience diabetic retinopathy complications during the trial (8.2% of subjects on semaglutide, 5.2% on placebo) than subjects without a baseline history of retinopathy (0.7% on semaglutide, 0.4% on placebo).

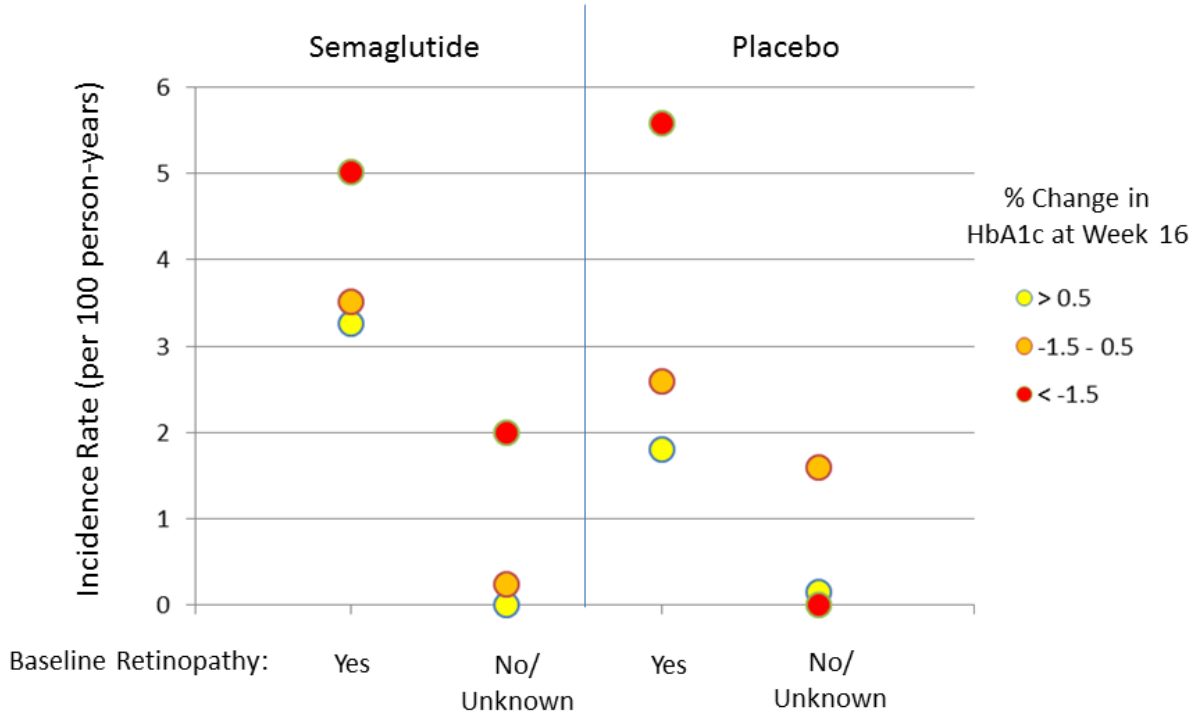
Table 16. Diabetic Retinopathy Complications by Retinopathy at Baseline

| Retinopathy at Baseline | **Semaglutide** N=1648 Events/N (%) | **Placebo** N=1649 Events/N (%) |
|---|---|---|
| Yes (N=969; 29%) | 42/510 (8.2%) | 24/459 (5.2%) |
| No/Unknown (N=2328; 71%) | 8/1138 (0.7%) | 5/1190 (0.4%) |

Source: Created by the reviewer

Figure 11 summarizes the incidence rate of diabetic retinopathy complications by baseline retinopathy, change in HbA1c at week 16, and treatment arm. Among subjects with baseline retinopathy, the highest incidence rate was observed in subjects with HbA1c reduction greater than 1.5% at week 16 in both treatment arms (5.02 per 100 PY on semaglutide and 5.58 per 100 PY on placebo). Note that the incidence rates between treatment arms on this figure should not be compared for the same reason mentioned on the reviewer's comments for the sponsor's *post hoc* analysis regarding the possible imbalanced baseline characteristics within subgroups defined by post-randomization characteristics.

Figure 11. Incidence rate of first event of diabetic retinopathy complications by diabetic retinopathy at baseline and change in HbA1c at week 16




Source: Created by the reviewer

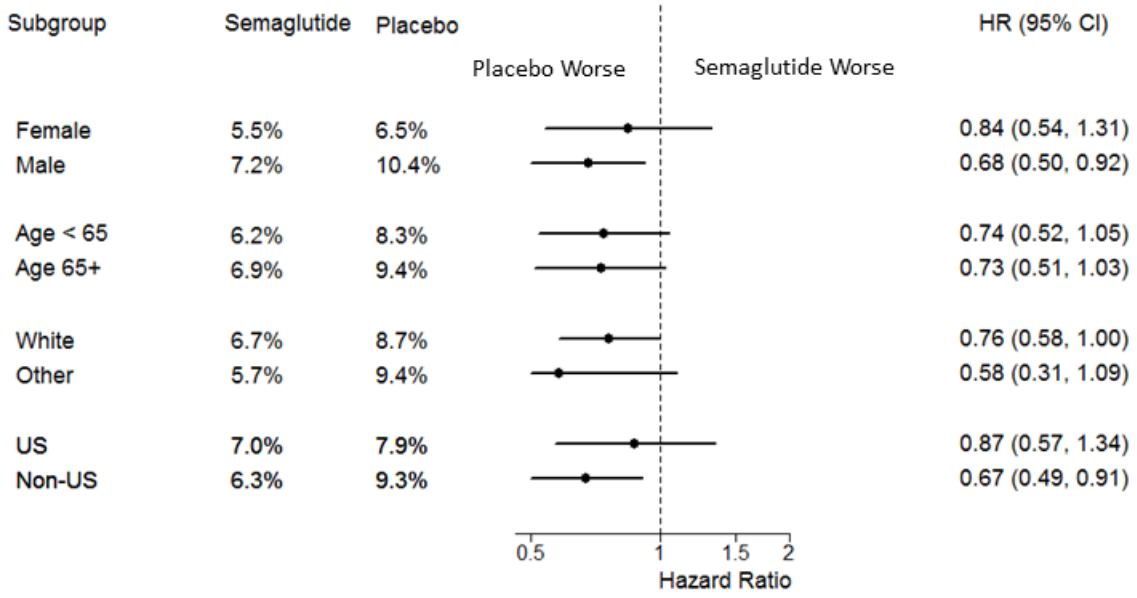
# 4. Findings in Special/Subgroup Populations

This section presents subgroup analyses for the primary MACE endpoint and the diabetic retinopathy complications endpoint. Analyses of subgroups were based upon a Cox proportional hazards model with a fixed treatment effect to estimate the hazard ratio and corresponding 95% confidence interval. All analyses were based on the ITT population (FAS) and its censoring rules. No adjustments for multiple comparisons were incorporated; therefore, the results of these subgroup analyses should be interpreted as exploratory purpose only.

## 4.1 Subgroups Analyses of MACE

The risk of MACE associated with semaglutide was evaluated within subgroups defined by gender, race, age, and country of randomization. Figure 12 summarizes the results of these subgroups analyses. The data showed no evidence of an increased risk of MACE associated with semaglutide in any of these subgroups.

Figure 12. Forest Plot of Hazard Ratio for MACE by Baseline Subgroups




Source: Created by the reviewer

## 4.2 Subgroup Analyses of Retinopathy

In the following paragraphs, the risk of diabetic retinopathy complications associated with semaglutide was evaluated within subgroups defined by age, gender, race, country of randomization, baseline HbA1c, duration of diabetics, and diabetic retinopathy at baseline.

### 4.2.1 Gender

Among 3297 randomized subjects, 61% were male and 39% were female. Among females, the estimated hazard ratio and 95% confidence interval were 1.38 (0.65, 2.92). Among males, the estimated hazard ratio of retinopathy associated with semaglutide and its corresponding 95% confidence interval were 1.97 (1.10, 3.53).

Table 17. Analysis of Diabetic Retinopathy Complications by Gender

| Gender | Semaglutide N=1648 Events/N (%) | Placebo N=1649 Events/N (%) | Hazard Ratio (95% CI) |
|---|---|---|---|
| Female (N=1295; 39%) | 16/635 (2.5%) | 12/660 (1.8%) | 1.38 (0.65, 2.92) |
| Male (N=2002; 61%) | 34/1013 (3.4%) | 17/989 (1.7%) | 1.97 (1.10, 3.53) |

Source: Created by the reviewer

### 4.2.2 Age

Approximately 52% of all randomized subjects were younger than 65 years old and 48% were 65 years old and older. The estimated hazard ratios and 95% confidence intervals for the risk of retinopathy associated with semaglutide were 1.74 (1.01, 3.02) for subjects aged less than 65 and 1.70 (0.74, 3.87) for subjects aged 65 and older.

Table 18. Analysis of Diabetic Retinopathy Complications by Age Group

| Age Group | Semaglutide N=1648 Events/N (%) | Placebo N=1649 Events/N (%) | Hazard Ratio (95% CI) |
|---|---|---|---|
| Age< 65 (N=1699; 52%) | 35/855 (4.1%) | 20/844 (2.4%) | 1.74 (1.01, 3.02) |
| Age≥ 65 (N=1598; 48%) | 15/793 (1.9%) | 9/805 (1.1%) | 1.70 (0.74, 3.87) |

Source: Created by the reviewer

### 4.2.3 Race

Approximately 83% of all 3297 randomized subjects were white. The other 17% were grouped into an “Other” race category. The estimated hazard ratios and 95% confidence intervals for the risk of retinopathy associated with semaglutide were 1.69 (1.03, 2.76) for white and 1.98 (0.58, 6.76) for other races.

Table 19. Analysis of Diabetic Retinopathy Complications by Race

| Race | Semaglutide N=1648 Events/N (%) | Placebo N=1649 Events/N (%) | Hazard Ratio (95% CI) |
|---|---|---|---|
| White (N=2736; 83%) | 43/1384 (3.1%) | 25/1352 (1.8%) | 1.69 (1.03, 2.76) |
| Other (N=561; 17%) | 7/264 (2.7%) | 4/297 (1.3%) | 1.98 (0.58, 6.76) |

Source: Created by the reviewer

### 4.2.4 Country of Randomization

Approximately 34% of the subjects were randomized in the United States. The estimated hazard ratios and 95% confidence intervals for the risk of retinopathy associated with semaglutide were 2.61 (0.93, 7.32) for the United States and 1.55 (0.93, 2.60) for the rest of the world.

Table 20. Analysis of Diabetic Retinopathy Complications by Country of Randomization

| Country | Semaglutide N=1648 Events/N (%) | Placebo N=1649 Events/N (%) | Hazard Ratio (95% CI) |
|---|---|---|---|
| US (N=1137; 34%) | 13/570 (2.3%) | 5/567 (0.9%) | 2.61 (0.93, 7.32) |
| Non-US (N=2160; 66 %) | 37/1078 (3.4%) | 24/1082 (2.2%) | 1.55 (0.93, 2.60) |

Source: Created by the reviewer

### 4.2.5 Baseline HbA1c

Approximately 56% of all randomized subjects had baseline HbA1c less than or equal to 8.5%. The estimated hazard ratios and 95% confidence intervals for the risk of retinopathy associated with semaglutide were 2.42 (1.16, 5.06) for subjects who had baseline HbA1c ≤ 8.5% and 1.37 (0.76, 2.48) for subjects who had baseline HbA1c > 8.5%.

Table 21. Analysis of Diabetic Retinopathy Complications by Baseline HbA1c

| Baseline HbA1c | Semaglutide N=1648 Events/N (%) | Placebo N=1649 Events/N (%) | Hazard Ratio (95% CI) |
|---|---|---|---|
| HbA1c ≤ 8.5% (N=1855; 56%) | 24/928 (2.6%) | 10/927 (1.1%) | 2.42 (1.16, 5.06) |
| HbA1c > 8.5% (N=1442; 44%) | 26/720 (3.6%) | 19/722 (2.6%) | 1.37 (0.76, 2.48) |

Source: Created by the reviewer

### 4.2.6 Diabetes Duration

Approximately 65% of randomized subjects had had diabetes for longer than 10 years at the time of randomization. The estimated hazard ratios and 95% confidence intervals for the risk of retinopathy associated with semaglutide were 3.01 (0.96, 9.46) for subjects who had had diabetes for less than or equal to 10 years and 1.50 (0.91, 2.47) for subjects who had had diabetes for more than 10 years.

Table 22. Analysis of Diabetic Retinopathy Complications by Diabetes Duration

| Diabetes Duration | Semaglutide N=1648 Events/N (%) | Placebo N=1649 Events/N (%) | Hazard Ratio (95% CI) |
|---|---|---|---|
| Diabetes ≤ 10 yrs (N=1145; 35%) | 11/546 (2.0%) | 4/599 (0.7%) | 3.01 (0.96, 9.46) |
| Diabetes > 10 yrs (N=2152; 65%) | 39/1102 (3.5%) | 25/1050 (2.4%) | 1.50 (0.91, 2.47) |

Source: Created by the reviewer

### 4.2.7 Diabetic Retinopathy at Baseline

The majority (~71%) of all randomized subjects had no or unknown status for diabetic retinopathy at baseline (as shown in Table 12). In comparison to subjects with no or unknown status of retinopathy at baseline, subjects with baseline retinopathy had higher percentage of having diabetic retinopathy complications (semaglutide: 0.7% vs. 8.2%; placebo: 0.4% vs. 5.2%). The estimated hazard ratios and 95% confidence intervals for the risk of diabetic retinopathy were 1.59 (0.96, 2.62) for subjects with retinopathy at baseline and 1.68 (0.55, 5.12) for subjects with no or unknown status of retinopathy at baseline.

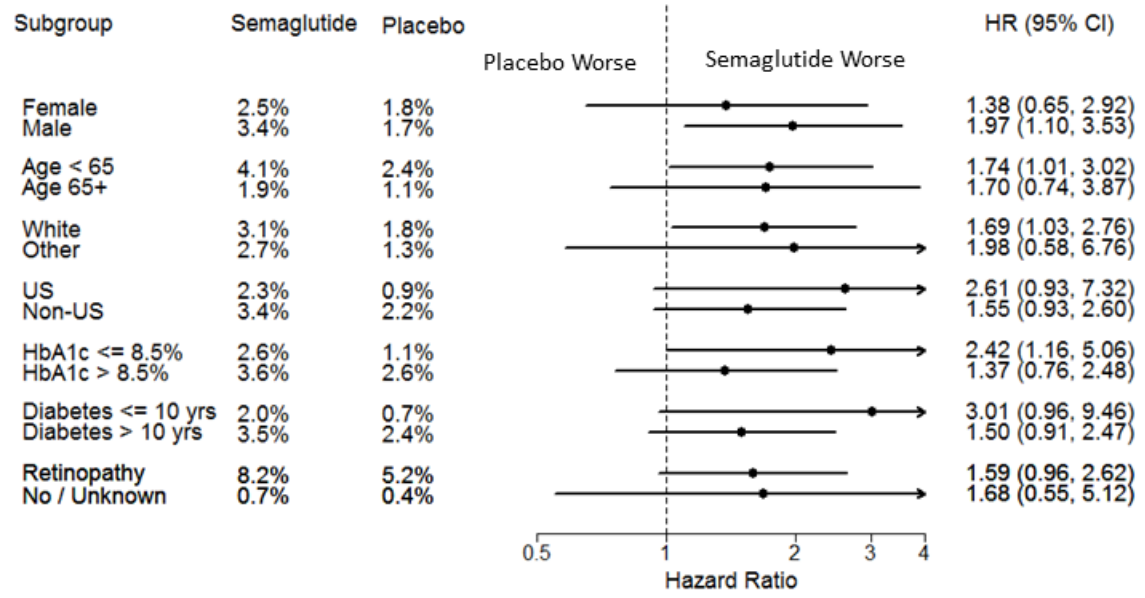
Table 23. Analysis of Diabetic Retinopathy Complications by Retinopathy at Baseline

| **Retinopathy at Baseline** | **Semaglutide** N=1648 Events/N (%) | **Placebo** N=1649 Events/N (%) | **Hazard Ratio (95% CI)** |
|---|---|---|---|
| Yes (N=969; 29%) | 42/510 (8.2%) | 24/459 (5.2%) | 1.59 (0.96, 2.62) |
| No/Unknown (N=2328; 71%) | 8/1138 (0.7%) | 5/1190 (0.4%) | 1.68 (0.55, 5.12) |

Source: Created by the reviewer

Figure 13 summarizes the results of these subgroups analyses. While the estimated hazard ratio for diabetic retinopathy complications associated with semaglutide was higher among some subgroups, the tests for interaction between subgroup and treatment were not statistically significant. The data showed consistently lower risk associated with placebo across all subgroups on the risk of diabetic retinopathy complications.

Figure 13. Forest Plot of Hazard Ratio for Diabetic Retinopathy Complications by Baseline Subgroups




Source: Created by the reviewer

# 5. Summary and Conclusions

## 5.1 Statistical Issues and Collective Evidence

SUSTAIN 6 was a multi-national, randomized, double-blind, and placebo-controlled cardiovascular outcomes trial designed to evaluate the cardiovascular safety of semaglutide. The primary CV endpoint was time from randomization to first EAC-adjudicated MACE (cardiovascular death including deaths with unknown cause, no-fatal MI, or non-fatal stroke).

This event-driven CVOT was designed to demonstrate that the hazard ratio of MACE associated with semaglutide relative to placebo is smaller than the risk margin of 1.8 in accordance with the FDA Diabetes Guidance for assessing cardiovascular safety. The pre-specified primary analysis used a Cox proportional hazards model with nine strata based on 3 variables (cardiovascular disease at baseline, insulin treatment at baseline, and renal impairment with GFR value at baseline) to estimate the hazard ratio of MACE associated with semaglutide.
There were 108 MACE observed among 1648 subjects randomized to semaglutide and 146 MACE observed among 1649 subjects randomized to placebo. The pre-specified stratified Cox proportional hazard model obtained an estimated hazard ratio of semaglutide vs. placebo of 0.74 with 95% confidence interval of (0.58, 0.95). The upper bound of this 95% confidence interval was below the risk margin of 1.8; and therefore met the pre-specified CV risk margin. Corresponding Kaplan-Meier curves showed that the observed probability of developing MACE was higher in the placebo arm throughout the trial. The results of the pre-specified secondary analyses of cardiovascular endpoints were consistent with the results of the pre-specified primary MACE endpoint shown in Table 24.

Subgroup analyses showed no evidence of an increased risk of MACE associated with semaglutide in subgroups defined by gender, age, race and country of randomization. Analyses results are provided in Section 4.1.

Table 24. Primary and Secondary Analyses of Cardiovascular Endpoints

| | **Semaglutide** N=1648 | **Placebo** N=1649 | **Hazard Ratio (95% CI)** |
|---|---|---|---|
| **Primary Analysis- MACE** | **108** | **146** | **0.74 (0.58, 0.95)** |
| **Secondary Analyses** | | | |
| Expanded CV outcome | 199 | 264 | 0.74 (0.62, 0.89) |
| Cardiovascular death | 44 | 46 | 0.98 (0.65, 1.48) |
| Non-fatal MI | 47 | 64 | 0.74 (0.51, 1.08) |
| Non-fatal Stroke | 27 | 44 | 0.61 (0.38, 0.99) |
| Revascularization | 83 | 126 | 0.65 (0.50, 0.86) |
| Hospitalization for Unstable Angina | 22 | 27 | 0.82 (0.47, 1.44) |
| Hospitalization for Heart Failure | 59 | 54 | 1.11 (0.77, 1.61) |
| All-Cause Death | 62 | 60 | 1.05 (0.74, 1.50) |
| MI (fatal + non-fatal) | 54 | 67 | 0.81 (0.57, 1.16) |
| Stroke (fatal + non-fatal) | 30 | 46 | 0.65 (0.41, 1.03) |
| MACE (on-treatment + 42 days)* | 88 | 124 | 0.73 (0.56, 0.96) |

*included all randomized subjects exposed to at least one dose of randomized treatment
Source: Created by the reviewer

The time to first event of diabetic retinopathy complication was pre-specified as a secondary endpoint. Of the 3297 randomized subjects in the trial, 79 subjects experienced a first event of diabetic retinopathy complications (50 with semaglutide; 29 with placebo). As shown in Table 25, the pre-specified Cox proportional hazard model obtained an estimated hazard ratio of semaglutide vs. placebo of 1.76 with an associated 95% confidence interval of (1.11, 2.78) indicating evidence of increased risk of diabetic retinopathy complications associated with semaglutide.

Among these 79 subjects, 43 (54%) subjects experienced an event within 1 year of randomization (29 with semaglutide; 14 with placebo). An early imbalance of events between treatment arms was observed at the time point of week 16 (12 events with semaglutide; 1 event with placebo). A *post hoc* analysis based on a Cox proportional hazards model with 5 independent variables was conducted by the Sponsor to further investigate the effect of semaglutide on the risk of retinopathy. This *post hoc* analysis resulted in an estimated hazard ratio of semaglutide relative to placebo of 1.22 with 95% confidence interval of (0.71, 2.09); a reduction of hazard ratio in comparison to the results of the pre-specified analysis. The estimated hazard ratio associated with a 1%-point reduction in HbA1c at week 16 was 1.26 with 95% confidence interval of (1.03, 1.57). Based on these results, the Sponsor concluded that the increased risk of diabetic retinopathy complication appeared to be mediated through the larger initial rapid reduction in HbA1c observed for semaglutide. However, the results of this analysis may have limitations and should be interpreted with caution due to the following reasons: 1) adjusting for the variable of "change in HbA1c at week 16 from baseline" as an independent variable in a Cox proportional hazard model is likely to bias the estimated hazard ratio of retinopathy associated with semaglutide towards the null (so-called overadjustment bias), and 2) the post hoc analysis is hypothesis generating and additional independent data may be needed to corroborate its findings.

Table 25. Analyses of Diabetic Retinopathy Complications

| | **HR (95% CI)** |
|---|---|
| | **Semaglutide vs. Placebo** |
| | 50/1648 29/1649 |
| **Pre-Specified Analysis** | **1.76 (1.11, 2.78)** |
| **Sponsor's *post hoc* analysis** | |
| Controlled direct effect of treatment | 1.22 (0.71, 2.09) |
| Effect of change in HbA1c at week 16 | 1.26 (1.02, 1.56) |

Source: Created by the reviewer

We conducted exploratory analyses to characterize possible subgroups with high risk of developing diabetic retinopathy complications. We found that subjects with a baseline history of retinopathy were more likely to experience retinopathy complications during the trial (8.2% of subjects on semaglutide, 5.2% on placebo) than subjects without a baseline history of retinopathy (0.7% on semaglutide, 0.4% on placebo). Our exploratory analyses also found that subjects with baseline retinopathy and more than 1.5% HbA1c reduction at week 16 had the highest risk of developing diabetic retinopathy complications in both treatment groups.

Subgroup analyses of diabetic retinopathy complications showed consistently lower risk associated with placebo across all subgroups. Details of these analyses results are provided in Section 4.2.

## 5.2 Conclusions and Recommendations

The Sponsor evaluated the cardiovascular safety of semaglutide through the cardiovascular outcomes trial SUSTAIN 6. The pre-specified Cox proportional hazards model obtained an estimated hazard ratio for the primary cardiovascular endpoint MACE (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) of 0.74 with an associated 95% confidence interval of (0.58, 0.95). The upper bound of this confidence interval was less than 1.8 and therefore met the hazard ratio risk margin set forth in the 2008 FDA Guidance on establishing cardiovascular safety of new antidiabetic products. The results of SUSTAIN 6 suggest that semaglutide is not associated with increased cardiovascular risk relative to placebo, both added to standard-of-care

The pre-specified Cox proportional hazards model to evaluate retinopathy showed evidence of increased risk of diabetic retinopathy complications associated with semaglutide (HR=1.76 with 95% confidence interval of (1.11, 2.78)). The Sponsor conducted a *post hoc* analysis that argued that the increased risk of diabetic retinopathy complications is mediated through the larger initial rapid reduction in HbA1c observed in semaglutide. However, this *post hoc* analysis has important limitations, such as potential overadjustment bias, that limit its interpretability beyond hypotheses generation.

Based on the Sponsor's and our *post hoc* analyses, the group of subjects with baseline retinopathy and more than 1.5% HbA1c reduction at week 16 might have a higher risk of developing diabetic retinopathy complications. Additional data are needed to assess whether a slower reduction in HbA1c among subjects with a history of retinopathy treated with semaglutide would result in a lower risk of diabetic retinopathy complications. One potential source to collect these data is a future dedicated clinical trial.

# 6. References


1. Food and Drug Administration. Guidance for industry: Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. December 2008. (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf)

2. Enrique F. Schisterman, Stephen R. Cole, and Robert W. Platt. Overadjustment Bias and Unnecessary Adjustment in Epidemiologic Studies. *Epidemiology*, 2009 July; 20(4): 488-495.

# 7. Appendix

## Assessment of Proportional Hazards

Figure 14. Assessment of Proportional Hazards Assumption: Schoenfeld Residual Plot (MACE)

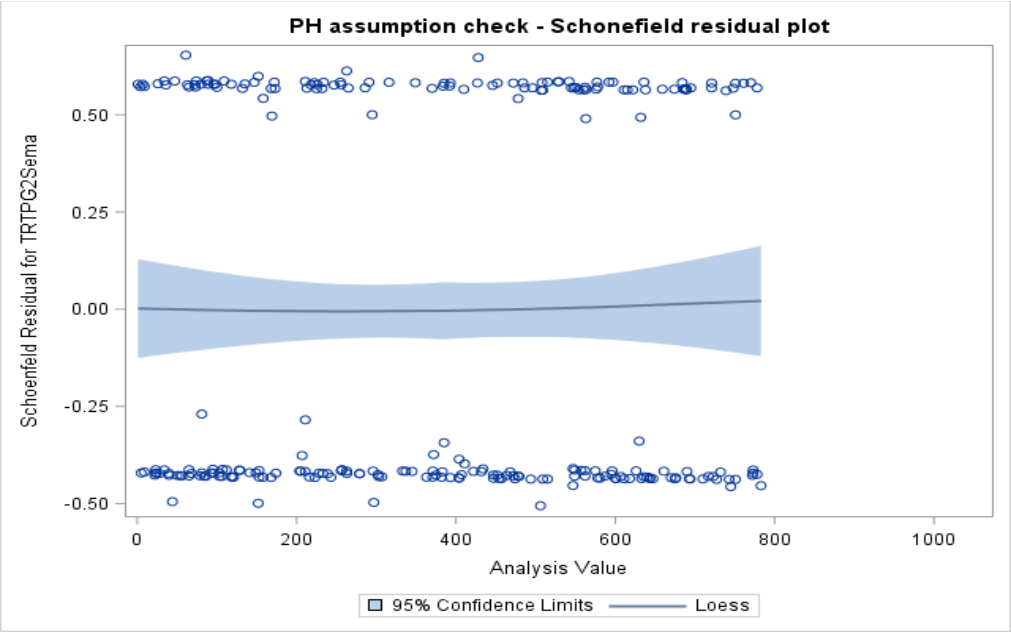



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Figure 15. Assessment of Proportional Hazards Assumption: Schoenfeld Residual Plot (Expanded MACE)

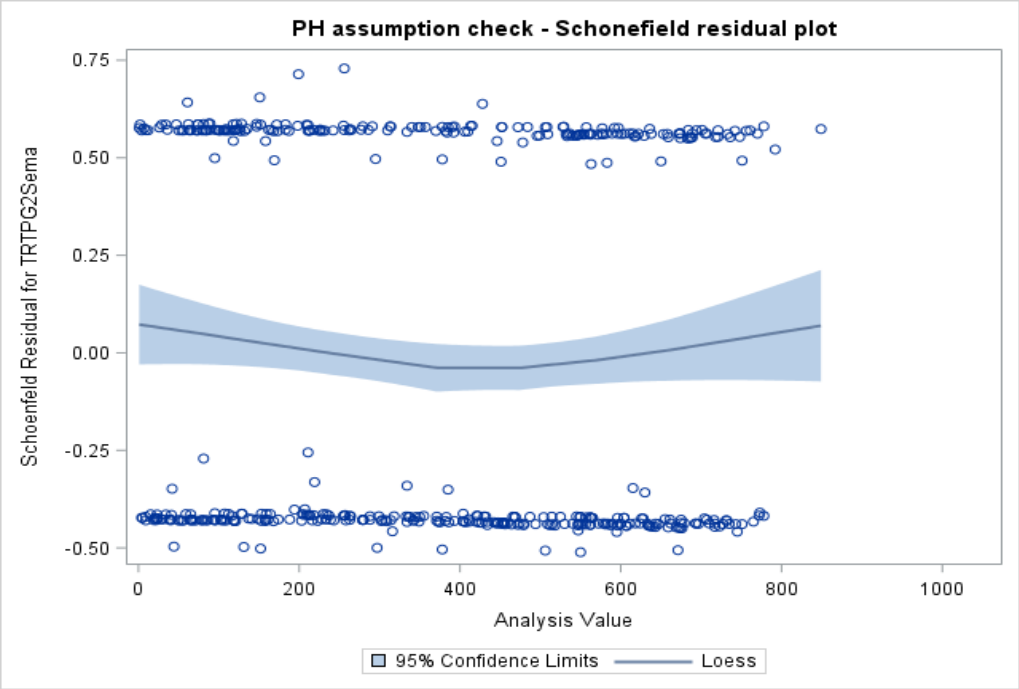


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Figure 16. Assessment of Proportional Hazards Assumption: Schoenfeld Residual Plot (Death)

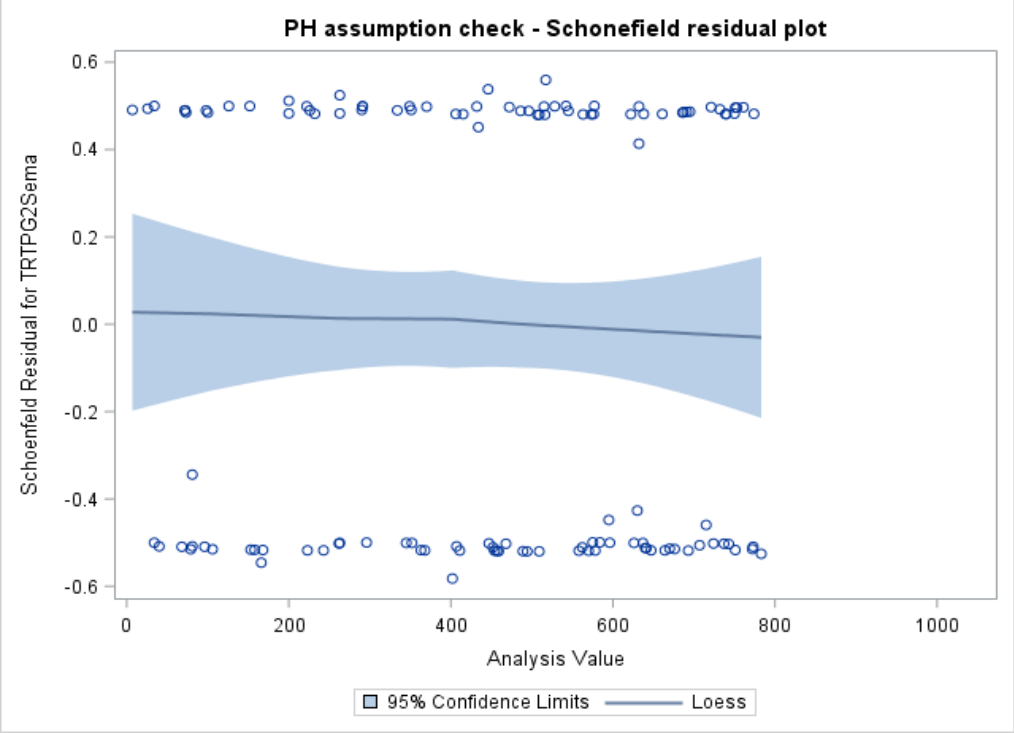


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Figure 17. Assessment of Proportional Hazards Assumption: Schoenfeld Residual Plot (Diabetic Retinopathy Complications)

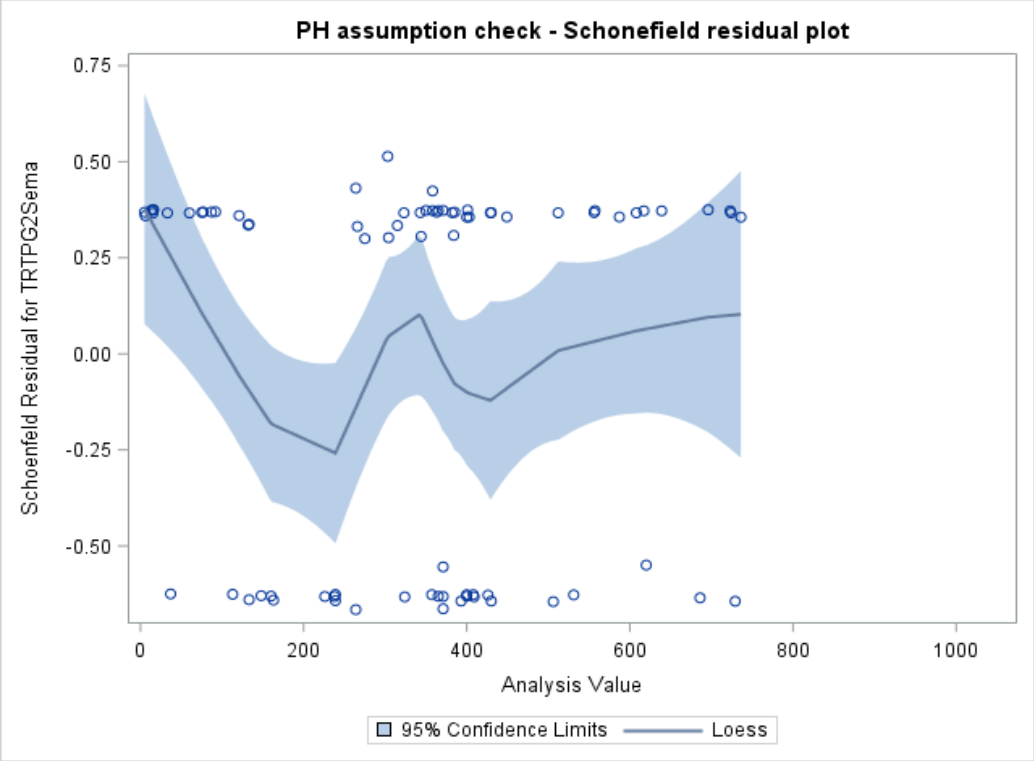


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Table 26. Baseline Characteristic of Subjects with Baseline Retinopathy by Change in HbA1c at Week 16

| Baseline Characteristics | % Change in HbA1c at week 16 (%) | | | | | |
|---|---|---|---|---|---|---|
| | > 0.5 | | -1.5 - 0.5 | | < -1.5 | |
| | **Semaglutide** (N=61) | **Placebo** (N=245) | **Semaglutide** (N=213) | **Placebo** (N=138) | **Semaglutide** (N=236) | **Placebo** (N=76) |
| Age, Mean ± SD | 64.8 ± 8.6 | 64.6 ± 7.7 | 65.6 ± 6.7 | 63.7 ± 7.4 | 63.6 ± 7.2 | 62.5 ± 7.1 |
| <65 | 49.2% | 51.8% | 45.4% | 58.0% | 62.7% | 67.1% |
| ≥65 | 50.8% | 48.2% | 54.5% | 42.0% | 37.3% | 32.9% |
| Sex | | | | | | |
| Female | 27.9% | 40.4% | 44.6% | 47.8% | 42.0% | 51.3% |
| Male | 72.1% | 59.6% | 55.4% | 52.2% | 58.0% | 48.7% |
| Race | | | | | | |
| White | 86.9% | 82.4% | 83.1% | 85.5% | 82.2% | 72.4% |
| Other | 13.1% | 17.6% | 16.9% | 14.5% | 17.8% | 27.6% |
| Country | | | | | | |
| US | 39.3% | 20.1% | 18.8% | 13.0% | 17.0% | 21.0% |
| Non-US | 60.7% | 79.6% | 81.2% | 87.0% | 83.0% | 79.0% |
| Insulin treatment at Baseline | | | | | | |
| Basal insulin | 29.5% | 40.0% | 26.3% | 37.0% | 33.5% | 29.0% |
| Premix insulin | 52.5% | 32.7% | 46.5% | 37.7% | 38.6% | 50.0% |
| None | 18.0% | 27.3% | 27.2% | 25.4% | 28.0% | 21.0% |
| Duration of Diabetes, Mean ± SD, yrs | 19.9 ± 9.3 | 16.2 ± 9.0 | 18.9 ± 8.9 | 17.1 ± 8.2 | 15.4 ± 7.5 | 16.0 ± 8.2 |
| Baseline HbA1c, Mean ± SD, % | 8.2 ± 0.9 | 8.4 ± 1.2 | 8.1 ± 1.0 | 9.1 ± 1.4 | 9.4 ± 1.3 | 10.6 ± 1.7 |

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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

| | |
|---|---|
| **NDA/BLA #:** | NDA 209637 |
| **Drug Name:** | Semaglutide Injection |
| **Indication(s):** | Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus (T2DM) |
| **Applicant:** | Novo Nordisk Inc. |
| **Date(s):** | Date submitted: December 5, 2016<br>Review due date: August 11, 2017<br>PDUFA due date: December 5, 2017 |
| **Review Priority:** | Standard |
| **Biometrics Division:** | Division of Biometrics II |
| **Statistical Reviewer:** | Jiwei He, Ph.D. |
| **Concurring Reviewers:** | Yun Wang, Ph.D. (Acting Team Leader) |
| **Medical Division:** | Metabolism and Endocrinology Products (DMEP) |
| **Clinical Team:** | Andreea Lungu, M.D.<br>William Chong, M.D. (Team Leader)<br>Jean-Marc Guettier, M.D. (Division Director) |
| **Project Manager:** | Peter Franks, M.S. |

**Keywords:** Type 2 diabetes, MMRM, Retrieved Dropout

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# 1. Executive Summary

Semaglutide is a Glucagon-like peptide-1 (GLP-1) receptor agonist (RA) developed by Novo Nordisk. It has 94% structural homology to native GLP-1, and is administered subcutaneously (s.c.) once weekly (OW) in two doses: 0.5 mg and 1.0 mg. Based on the results of change in HbA1c from baseline, the applicant claims semaglutide is effective in improving glycemic control in adults with Type 2 diabetes mellitus (T2DM). My review of the statistical evidence suggests both doses of semaglutide are superior to placebo and active comparators (sitagliptin, insulin glargine and exenatide extended release (ER)) in terms of change in HbA1c from baseline. This new drug application (NDA) is approvable from statistical point of view.

Five key efficacy phase 3 trials and a cardiovascular outcome trial (CVOT) were reviewed for this NDA submission (summarized in Table 1). The key efficacy trials include 2 placebo-controlled trials and 3 active-controlled trials. The primary efficacy endpoint was change in HbA1c from baseline in all the key efficacy trials, and change in body weight from baseline was a confirmatory secondary endpoint. Change in body weight at Week 104 and change in HbA1c at Week 30 for subjects on premix insulin at baseline and for subjects on SU monotherapy at baseline, were pre-specified as confirmatory secondary endpoints in the CVOT.

The pre-specified primary analysis was a mixed model for repeated measurements (MMRM) analysis using on-treatment data. MMRM rarely estimates a relevant causal effect in the presence of missing data. The applicant also performed multiple imputation based on data from retrieved dropouts followed by an analysis of covariance (ANCOVA) model (Section 3.2.2). The statistical reviewer thinks results from this analysis are more appropriate for labeling.

Both doses of semaglutide (0.5 mg and 1.0 mg) demonstrated superiority to placebo in terms of change in HbA1c from baseline, in a monotherapy trial as well as in a trial with basal insulin background therapy (Table 6). Both doses of semaglutide also demonstrated superiority to active comparators sitagliptin and insulin glargine for the HbA1c primary endpoint. Semaglutide 1.0 mg also demonstrated superiority to exenatide ER. Results from the subgroup analyses for the HbA1c primary endpoint suggest the treatment effect of semaglutide was consistent across different subgroups. In all the key efficacy trials, both doses of semaglutide also demonstrated superiority to placebo and the active comparators in terms of change in body weight from baseline. In the CVOT, both doses of semaglutide demonstrated superiority to placebo in terms of change in HbA1c and body weight at Week 104 as well as change in HbA1c at Week 30 for subjects on premix insulin at baseline and for subjects on SU monotherapy at baseline, although change in HbA1c at Week 104 was not a pre-specified secondary endpoint.

No major statistical issue was identified in this application. Please refer to Section 5.1 for more details.

# 2. Introduction

## *2.1 Overview*

### 2.1.1 Class and Indication

Semaglutide is a GLP-1 RA developed by Novo Nordisk. It has 94% structural homology to native GLP-1. It is structurally similar to liraglutide but modified to have a longer half-life, suitable for OW dosing. Novo Nordisk proposed semaglutide 0.5 mg and 1.0 mg s.c. OW for improving glycemic control in patients with T2D.

### 2.1.2 History of drug development

An end-of-phase 2 (EOP2) meeting was held on June 9, 2010, during which the Phase 3 development program was discussed. At that time, FDA agreed that data collected either after discontinuation of randomized treatment or addition of rescue medication can be excluded from the primary efficacy analysis. However, FDA's guidance on missing data has changed since then. In a Type C meeting on June 12, 2015, data format and standards for semaglutide NDA submission were discussed. A pre-NDA meeting was held on August 2, 2016. In the discussion about analysis plan, the sponsor agreed to include all collected primary endpoint data in an analysis and utilize a multiple imputation approach based on a retrieved dropout model (Section3.2.2).

### 2.1.3 Specific studies reviewed

Five key efficacy phase 3 trials and the efficacy secondary endpoints in a CVOT were reviewed for this NDA submission with a focus on the key efficacy trials. The CVOT had a safety primary objective. Please refer to Dr. Ya-Hui Hsueh's review for more details on the CVOT. Two local Japanese trials (trials 4091 and 4092) with a safety primary objective were not included in Section 14 of the proposed label and therefore were not covered in this review. The trial design for the 5 key efficacy trials and the CVOT was summarized in Table 1.

**Table 1** Summary of trial design of key efficacy trials

| Trial | Antidiabetic Background Medication[1] | Blinding[2] | Treatment Arms[3] | # of Subjects Randomized | Duration of Treatment/ weeks |
|---|---|---|---|---|---|
| 3623-SUSTAIN 1 | Monotherapy | DB | Sema 0.5mg OW<br>Sema 1.0mg OW<br>Placebo 0.5mg OW<br>Placebo 1.0mg OW | 129<br>130<br>65<br>64 | 30 |
| 3626-SUSTAIN 2 | Met, TZD or Met/TZD | DB, DD | Sema 0.5mg OW+Sitagliptin Placebo<br>Sema 1.0mg OW+Sitagliptin Placebo<br>Sitagliptin 100mg OD+0.5 mg Sema Placebo<br>Sitagliptin 100mg OD+1.0mg Sema Placebo | 410<br>410<br>205<br>206 | 56 |
| 3624-SUSTAIN 3 | 1-2 OADs (Met, TZD, SU) | OL | Sema 1.0mg OW<br>Exenatide ER 2.0mg OW | 406<br>407 | 56 |
| 3625-SUSTAIN 4 | Met or Met/SU, insulin naïve | OL | Sema 0.5mg OW<br>Sema 1.0mg OW<br>Insulin Glargine OD | 362<br>362<br>365 | 30 |
| 3627-SUSTAIN 5 | Basal insulin alone or in combination with Met | DB | Sema 0.5mg OW<br>Sema 1.0mg OW<br>Placebo 0.5mg OW<br>Placebo 1.0mg OW | 132<br>132<br>66<br>67 | 30 |
| 3744-SUSTAIN 6 (CVOT) | SU or (premix insulin with or without 2 OADs) | DB | Sema 0.5mg OW<br>Sema 1.0mg OW<br>Placebo 0.5mg OW<br>Placebo 1.0mg OW | 826<br>822<br>824<br>825 | 104 |

1. Met: metformin; SU, sulfonylurea; TZD: thiazolidinedione; OAD: oral antidiabetic drug
2. DB: double-blind; DD: double-dummy; OL: open-label
3. Sema: semaglutide; OW: once weekly; OD: once daily

### *2.2Data sources*

The data and final study report were submitted electronically. The submission was archived under the network path location <\\CDSESUB1\EVSPROD\NDA209637\209637.enx>. The information needed for this review was contained in Module 1 FDA Regional Information (cover letter, meeting correspondence, and labeling), Module 2.5 Clinical Overview, Module 2.7 Clinical Summary, and Module 5 Clinical Study Report.

## 3. Statistical evaluation

### *3.1Data and analysis quality*

This submission is in electronic common technical document (eCTD) format with xml backbone. The applicant submitted the datasets and annotated SAS code for all the primary and supportive analyses. Study datasets are provided as SAS XPORT transport files version 5. This review

covered datasets from 5 key Phase 3 efficacy studies and the efficacy secondary endpoints in the CVOT.

For the individual trials, both tabulation and analysis datasets were provided. The tabulation and analysis datasets are joinable by the unique record identifier (USUBJID). The SAS programs used to derive datasets for the efficacy endpoints and the SAS programs used for analyses on the primary and key secondary endpoints were provided. During the pre-NDA meeting, we requested additional analyses using multiple imputation based on retrieved dropouts. The SAS programs for these analyses were included in the integrated summary of efficacy (ISE).

The datasets are in good organization. Variables in study datasets are consistently named and used across trials, with clear description in the Define.pdf file. The reported analysis results are in good quality. The statistical reviewer was able to reproduce the applicant's results on the primary and key secondary efficacy endpoints using both the in-trial MMRM analysis and the retrieved dropout analysis.

## *3.2Evaluation of efficacy*

### 3.2.1 Study Design and Endpoints

Summary of trial design of the 5 key efficacy trials and the CVOT is given in Table 1. They were all randomized, parallel-group, multinational, multicenter trials, but differed in the diabetes background medication, comparators, and length of treatment periods. The trial populations for the key efficacy trials were adults with T2DM, and that for the CVOT was adults with T2DM and at high risk of cardiovascular (CV) events.

Trials 3623, 3627 and the CVOT were placebo-controlled, and Trials 3626, 3624, and 3625 were active-controlled. The placebo-controlled trials were double-blinded within dose groups (0.5 mg and 1.0 mg). No blinding of dose was performed. Double-blinding was also attained for the sitagliptin-controlled trial 3626 via a double dummy design. The insulin-controlled trial 3625 and the exenatide-controlled trial 3624 were both open-label. The applicant stated the open-label design was necessary due to the complexity of blinding insulin and the complexity of preparing a placebo version of exenatide ER.

**The primary efficacy endpoint** in the 5 key efficacy trials was change in HbA1c from baseline to the end of the planned treatment period. **The key secondary endpoint** in the 5 key efficacy trials was change in body weight from baseline to the end of the planned treatment period.

**The primary objective** in the placebo-controlled trials 3623 and 3627 was to demonstrate superiority of OW dosing of 2 dose levels of semaglutide vs placebo on glycemic control after 30 weeks of treatment. **The primary objective** in the active-controlled trials 3626, 3624 and 3625 was to compare the effect of OW dosing of semaglutide vs active comparator on glycemic

control. The secondary objectives in all the trials were to compare the effects of semaglutide on inducing and maintaining weight loss as well as other parameters of efficacy, safety and tolerability. The CVOT had a primary objective of studying the safety of semaglutide. Change in body weight at Week 104 and change in HbA1c at Week 30 for subjects on premix insulin at baseline and for subjects on SU monotherapy at baseline were pre-specified as confirmatory secondary efficacy endpoints in the CVOT.

### 3.2.2 Statistical Methodologies

**The efficacy analysis population** was full analysis set (FAS), which included all randomized subjects who had received at least one dose of randomized trial product.

**The pre-specified primary analysis** for continuous endpoints was an MMRM analysis using on-treatment data. It was based on all randomized and exposed patients using the on-treatment without rescue medication observation period. The model included treatment, country, stratification (if applicable) as fixed factors and baseline value as covariate, all nested within visit. An unstructured covariance matrix was assumed for measurements within the same subject. The applicant also performed an in-trial MMRM analysis. It used the same analysis model as the on-treatment MMRM, but included all data collected during trial regardless of treatment adherence or rescue status.

Following FDA's advice at the pre-NDA meeting, the applicant performed retrieved dropout analysis for the HbA1c and body weight endpoints. Retrieved dropouts were defined as subjects who had their HbA1c value at the primary endpoint visit assessed after the on-treatment observation period (> 7 days after last dose). Within each treatment arm, multiple imputation was performed for missing data based on measurements from retrieved dropouts in the same treatment arm. An ANCOVA model was fit to the complete datasets, containing the same covariates as the primary analysis.

**The study-wise type I error** was controlled for the primary and confirmatory secondary endpoints using a pre-specified hierarchical testing scheme. For the placebo-controlled key efficacy trials, superiority testing for change in HbA1c was performed. For the active-controlled key efficacy trials, testing of non-inferiority for change in HbA1c was performed before testing for superiority. The pre-specified non-inferiority margin was 0.3%. For the key efficacy trials with two semaglutide doses, semaglutide 1.0 mg was tested before semaglutide 0.5 mg within each endpoint. The order of testing differed slightly among different trials.

The pre-specified hierarchical testing procedure in the CVOT 3744 was:

1. Non-inferiority of semaglutide versus placebo for the safety primary endpoint
2. Superiority of semaglutide 1.0 mg versus placebo in change in body weight at week 104

3. Superiority of semaglutide 0.5 mg versus placebo in change in body weight at week 104
4. Superiority of semaglutide 1.0 mg versus placebo in change in HbA1c at week 30 for subjects on premix insulin at baseline
5. Superiority of semaglutide 0.5 mg versus placebo in change in HbA1c at week 30 for subjects on premix insulin at baseline
6. Superiority of semaglutide 1.0 mg versus placebo in change in HbA1c at week 30 for subjects on SU monotherapy at baseline
7. Superiority of semaglutide 0.5 mg versus placebo in change in HbA1c at week 30 for subjects on SU monotherapy at baseline

**Sample size calculation** for placebo-controlled key efficacy trials was based on the assumption of a true difference of -0.5% in HbA1c change between semaglutide and placebo and a standard deviation of 1.1% to give at least 90% power to conclude superiority. **Sample size calculation** for active-controlled key efficacy trials was based on a non-inferiority margin of 0.3% and the assumption of a true difference of 0 in HbA1C change between semaglutide and active control and a standard deviation of 1.1% to give at least 90% power to conclude non-inferiority. **Sample size calculation** for the CVOT was based on the assumption that the true hazard ratio was 1.0 for MACE between semaglutide and placebo to confirm the primary hypothesis of non-inferiority in cardiovascular risk with 90% power. The trial was to stop when 122 subjects had experienced an EAC-confirmed MACE event with a minimum requirement of 109 weeks of observation for each randomized subject.

### 3.2.3 Patient disposition, demographic and baseline characteristics (key efficacy trials)

Subject dispositions in the placebo-controlled key efficacy trials 3623 and 3627 and the active-controlled key efficacy trials 3626, 3624 and 3625 were given in Table 2 and Table 3 respectively. The amount of missing data in these trials was moderate (5 -10% in most trials). The sponsor attempted to collect data after treatment discontinuation or initiation of rescue therapy. This helped reduce the amount of missing data. The percent of retrieved dropouts was 3 - 13%.

**Table** 2 Summary of patient dispositions in placebo-controlled trials 3623 and 3627

| **Trial** | **3623** | | | | **3627** | | | |
|---|---|---|---|---|---|---|---|---|
| | Sema 0.5mg | Sema 1.0mg | Placebo 0.5mg | Placebo 1.0mg | Sema 0.5mg | Sema 1.0mg | Placeo 0.5mg | Placebo 1.0mg |
| **Randomized**, n | 129 | 130 | 65 | 64 | 132 | 132 | 66 | 67 |
| **Randomized and Treated (FAS)**, n(%) | 128 (99.2) | 130 (100) | 65 (100) | 64 (100) | 132 (100) | 131 (99.2) | 66 (100) | 67 (100) |
| **Completed Treatment**[1], n(%) | 111 (86.1) | 114 (87.7) | 57 (87.7) | 58 (90.6) | 118 (89.4) | 115 (87.8) | 59 (89.4) | 61 (91.0) |
| **Discontinued Treatment**[1], n(%) | 17 (13.3) | 16 (12.3) | 8 (12.3) | 6 (9.4) | 14 (10.6) | 16 (12.2) | 7 (10.6) | 6 (9.0) |
| Adverse event | 8 | 7 | 3 | 0 | 6 | 10 | 0 | 1 |
| Protocol violation | 4 | 2 | 0 | 1 | 1 | 0 | 2 | 0 |
| Pregnancy | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| Other | 5 | 7 | 4 | 5 | 6 | 6 | 5 | 5 |
| **Rescue medication during treatment**[1], n(%) | 6 (4.7) | 6 (4.6) | 14 (21.5) | 13 (20.3) | 3 (2.3) | 1 (0.8) | 12 (18.2) | 9 (13.4) |
| **Had HbA1c measurement at endpoint**[1], n(%) | 119 (93) | 121 (93.1) | 58 (89.2) | 58 (90.6) | 126 (95.5) | 124 (94.7) | 60 (90.9) | 64 (95.5) |
| **Missed HbA1c measurement at endpoint**[1], n(%) | 9 (7.0) | 9 (6.9) | 7 (10.8) | 6 (9.4) | 6 (4.5) | 7 (5.3) | 6 (9.1) | 3 (4.5) |
| **Retrieved dropouts**[1]**,** n(%) | 11 (8.6) | 12 (9.2) | 4 (6.2) | 2 (3.1) | 12 (9.1) | 15 (11.5) | 5 (7.6) | 8 (11.9) |

1. The number and % are based on the randomized and treated population

Source: Statistical reviewer's analysis

**Table 3** Summary of patient dispositions in active-controlled trials 3626, 3624 and 3625

| **Trial** | **3626** | | | | **3624** | | **3625** | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sema 0.5mg | Sema 1.0mg | Sitagliptin +0.5mg Placebo | Sitagliptin +1.0mg Placebo | Sema 1.0mg | Exenatide | Sema 0.5mg | Sema 1.0mg | Insulin Glargine |
| **Randomized**, n | 410 | 410 | 205 | 206 | 406 | 407 | 362 | 362 | 365 |
| **Randomized and Treated (FAS)**, n(%) | 409 (99.8) | 409 (99.8) | 203 (99.0) | 204 (99.0) | 404 (99.5) | 405 (99.5) | 362 (100) | 360 (99.4) | 360 (98.6) |
| **Completed Treatment**[1], n(%) | 356 (87.0) | 348 (85.1) | 182 (89.7) | 193 (94.6) | 322 (79.7) | 320 (79.0) | 313 (86.5) | 305 (84.7) | 334 (92.8) |
| **Discontinued Treatment**[1], n(%) | 53 (13.0) | 61 (14.9) | 21 (10.3) | 11 (5.4) | 82 (20.3) | 85 (21.0) | 49 (13.5) | 55 (15.3) | 26 (7.2) |
| Adverse event | 33 | 41 | 8 | 4 | 39 | 29 | 19 | 27 | 5 |
| Protocol violation | 4 | 4 | 1 | 5 | 15 | 21 | 12 | 13 | 2 |
| Pregnancy | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 |
| Other | 16 | 16 | 12 | 2 | 28 | 34 | 18 | 14 | 18 |
| **Rescue medication during treatment**[1], n(%) | 25 (6.1) | 10 (2.4) | 45 (22.2) | 40 (19.6) | 28 (6.9) | 48 (11.8) | 14 (3.9) | 9 (2.5) | 5 (1.4) |
| **Had HbA1c measurement at endpoint**[1], n(%) | 382 (93.4) | 387 (94.6) | 190 (93.6) | 194 (95.1) | 368 (91.1) | 359 (88.6) | 333 (92) | 337 (93.6) | 340 (94.4) |
| **Missed HbA1c measurement at endpoint**[1], n(%) | 27 (6.6) | 22 (5.4) | 13 (6.4) | 10 (4.9) | 36 (8.9) | 46 (11.4) | 29 (8) | 23 (6.4) | 20 (5.6) |
| **Retrieved dropouts**[1]**,** n(%) | 33 (8.1) | 47 (11.5) | 15 (7.4) | 8 (3.9) | 55 (13.6) | 51 (12.6) | 31 (8.6) | 48 (13.3) | 13 (3.6) |

1. The number and % are based on the randomized and treated population

Source: Statistical reviewer's analysis

Subject demographics in the placebo-controlled key efficacy trials 3623 and 3627 and the active-controlled key efficacy trials 3626, 3624 and 3625 were given in Table 4 and Table 5 respectively. The overall population was roughly balanced in sex and was predominantly white in all the trials. All the subjects in Trial 3626 were from non-US countries.

**Table 4** Summary of patient demographics in placebo-controlled trials 3623 and 3627

| **Trial** | **3623** | | | | **3627** | | | |
|---|---|---|---|---|---|---|---|---|
| | Sema 0.5mg | Sema 1.0mg | Placebo 0.5mg | Placebo 1.0mg | Sema 0.5mg | Sema 1.0mg | Placeo 0.5mg | Placebo 1 0mg |
| **Sex,** n(%) | | | | | | | | |
| Females | 69 (53.5) | 50 (38.5) | 28 (43.1) | 31 (48.4) | 58 (43.9) | 54 (40.9) | 30 (45.5) | 32 (47.8) |
| Males | 60 (46.5) | 80 (61.5) | 37 (56.9) | 33 (51.6) | 74 (56.1) | 78 (59.1) | 36 (54.6) | 35 (52.2) |
| **Age**, years | | | | | | | | |
| Mean (SD) | 54.7 (11.1) | 52.7 (11.9) | 54.6 (12.2) | 53.2 (9.7) | 59.1 (10.3) | 58.4 (9.0) | 59.5 (10.8) | 58.1 (11.0) |
| Range | 30 - 80 | 26 - 80 | 18 - 87 | 28 - 71 | 28 – 84 | 33 - 80 | 19 - 76 | 28 - 86 |
| < 65, n(%) | 102 (79.1) | 111 (85.4) | 49 (75.4) | 56 (87.5) | 93 (70.5) | 103 (78.0) | 38 (57.6) | 48 (71.6) |
| ≥ 65, n(%) | 27 (20.9) | 19 (14.6) | 16 (24.6) | 8 (12.5) | 39 (29.6) | 29 (22.0) | 28 (42.4) | 19 (28.4) |
| **Race**, n (%) | | | | | | | | |
| White | 83 (64.3) | 88 (67.7) | 37 (56.9) | 41 (64.1) | 108 (81.8) | 98 (74.2) | 53 (80.3) | 48 (71.6) |
| Black | 11 (8.5) | 11 (8.5) | 6 (9.2) | 3 (4.7) | 4 (3.0) | 10 (7.6) | 4 (6.1) | 4 (6.0) |
| Asian | 27 (20.9) | 25 (19.2) | 16 (24.6) | 16 (25.0) | 19 (14.4) | 23 (17.4) | 9 (13.6) | 15 (22.4) |
| Other | 8 (6.2) | 6 (4.6) | 6 (9.2) | 4 (6.3) | 1 (0.8) | 1 (0.8) | 0 (0.0) | 0 (0.0) |
| **Ethnicity,** n(%) | | | | | | | | |
| Hispanic | 34 (26.4) | 45 (34.6) | 15 (23.1) | 21 (32.8) | 15 (11.4) | 12 (9.1) | 13 (19.7) | 6 (9.0) |
| Not Hispanic | 95 (73.6) | 85 (65.4) | 50 (76.9) | 43 (67.2) | 117 (88.6) | 120 (90.9) | 53 (80.3) | 61 (91.0) |
| **Country,** n(%) | | | | | | | | |
| US | 41 (31.8) | 47 (36.2) | 16 (24.6) | 20 (31.3) | 60 (45.5) | 60 (45.5) | 30 (45.5) | 31 (46.3) |
| Not US | 88 (68.2) | 83 (63.9) | 49 (75.4) | 44 (68.8) | 72 (54.6) | 72 (54.6) | 36 (54.6) | 36 (53.7) |

Source: Statistical reviewer's analysis

**Table 5** Summary of patient demographics in active-controlled trials 3626, 3624 and 3625

| Trial | 3626 | | | | 3624 | | 3625 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sema 0.5mg | Sema 1.0mg | Sitagliptin +0.5mg Placebo | Sitagliptin+ 1.0mg Placebo | Sema 1.0mg | Exenatide | Sema 0.5mg | Sema 1.0mg | Insulin Glargine |
| **Sex,** n(%) | | | | | | | | | |
| Females | 202 (49.3) | 204 (49.8) | 101 (49.3) | 101 (49.0) | 185 (45.6) | 178 (43.7) | 165 (45.6) | 178 (49.2) | 166 (45.5) |
| Males | 208 (50.7) | 206 (50.2) | 104 (50.7) | 105 (51.0) | 221 (54.4) | 229 (56.3) | 197 (54.4) | 184 (50.8) | 199 (54.5) |
| **Age**, years | | | | | | | | | |
| Mean (SD) | 54.8 (10.1) | 56.0 (9.4) | 54.0 (10.3) | 55.1 (10.5) | 56.3 (10.2) | 56.6 (11.1) | 56.5 (10.3) | 56.7 (10.3) | 56.2 (10.6) |
| Range | 27 - 83 | 24 - 78 | 32 - 80 | 23 - 78 | 20 - 82 | 21 - 83 | 23 - 80 | 24 - 82 | 22 - 81 |
| < 65, n(%) | 334 (81.5) | 332 (81.0) | 170 (82.9) | 162 (78.6) | 318 (78.3) | 300 (73.7) | 279 (77.1) | 283 (78.2) | 285 (78.1) |
| ≥ 65, n(%) | 76 (18.5) | 78 (19.0) | 35 (17.1) | 44 (21.4) | 88 (21.7) | 107 (26.3) | 83 (22.9) | 79 (21.8) | 80 (21.9) |
| **Race**, n (%) | | | | | | | | | |
| White | 279 (68.1) | 280 (68.3) | 142 (69.3) | 140 (68.0) | 341 (84.0) | 340 (83.5) | 279 (77.1) | 280 (77.4) | 280 (76.7) |
| Black | 18 (4.4) | 24 (5.9) | 11 (5.4) | 8 (3.9) | 29 (7.1) | 30 (7.4) | 32 (8.8) | 35 (9.7) | 34 (9.3) |
| Asian | 107 (26.1) | 99 (24.2) | 50 (24.4) | 53 (25.7) | 8 (2.0) | 6 (1.5) | 42 (11.6) | 39 (10.8) | 38 (10.4) |
| Other | 6 (1.5) | 7 (1.7) | 2 (1.0) | 5 (2.4) | 5 (1.2) | 8 (2.0) | 4 (1.1) | 3 (0.8) | 6 (1.6) |
| NA | | | | | 23 (5.7) | 23 (5.7) | 5 (1.4) | 5 (1.4) | 7 (1.9) |
| **Ethnicity,** n(%) | | | | | | | | | |
| Hispanic | 69 (16.8) | 67 (16.3) | 38 (18.5) | 35 (17.0) | 91 (22.4) | 107 (26.3) | 61 (16.9) | 74 (20.4) | 78 (21.4) |
| Not Hispanic | 341 (83.2) | 343 (83.7) | 167 (81.5) | 171 (83.0) | 315 (77.6) | 300 (73.7) | 301 (83.2) | 288 (79.6) | 286 (78.4) |
| NA | | | | | | | 0 (0.0) | 0 (0.0) | 1 (0.3) |
| **Country,** n(%) | | | | | | | | | |
| US | | | | | 156 (38.4) | 159 (39.1) | 165 (45.6) | 164 (45.3) | 169 (46.3) |
| Not US | 410 (100) | 410 (100) | 205 (100) | 206 (100) | 250 (61.6) | 248 (60.9) | 197 (54.4) | 198 (54.7) | 196 (53.7) |

Source: Statistical reviewer's analysis

### 3.2.4 Results and Conclusions

The applicant's pre-specified primary analysis was on-treatment MMRM. It only used on-treatment data before the onset of rescue therapy and assumed missing data were missing at random (MAR). The in-trial MMRM analysis also assumed missing data were MAR. In both analyses, some off-treatment measurements at scheduled visits were replaced with on-treatment measurements taken at premature treatment discontinuation visits. Considering these problems, both approaches are not acceptable. Following FDA's advice at the pre-NDA meeting, the applicant performed retrieved dropout analysis for the primary and key secondary endpoints. In this analysis, missing data was imputed based on measurements from subjects who discontinued treatment but still had their measurements taken at the endpoint visit (retrieved dropouts) in each

treatment arm. We consider it a more appropriate way of handling missing data and based our conclusions on this analysis.

In all five key efficacy trials, superiority of semaglutide 0.5 mg and 1.0 mg versus placebo and the active comparators in terms of change in HbA1c from baseline was confirmed (Table 6). The conclusions from the applicant's pre-specified primary analysis (the on-treatment MMRM analysis), the in-trial MMRM analysis and the retrieved dropout analysis were consistent. Figure 1 showed the comparison of the results from the three analyses. It appears that the on-treatment MMRM analysis overestimated the treatment effect of semaglutide. Superiority of the two doses of semaglutide versus placebo or the active comparators in terms of change in body weight from baseline was also confirmed (Table 7).

I verified the applicant's results for changes in HbA1c and body weight in the CVOT using retrieved dropout analysis. The results were also shown in Table 6 and Table 7. Change in HbA1c from baseline to Week 30 for the subjects on premix insulin at baseline and for the subjects on SU monotherapy at baseline and change in body weight from baseline to Week 104 in the overall population were confirmatory secondary endpoints in the CVOT. Both doses of semaglutide demonstrated superiority to placebo in these endpoints.

One limitation of the retrieved dropout analysis is that due to the small number of retrieved dropouts the applicant had to use relatively simple imputation models without taking into consideration the time of discontinuing treatment. For the relatively small Trial 3623, a simpler imputation model was applied, where only the baseline measurements and measurements from the closest previous visit were used to impute the missing values. The imputation models may be subject to model mis-specification. We asked the applicant to investigate whether the time of discontinuing treatment was impactful. For Trials 3626, 3624, 3625 and 3627, the applicant extended the original imputation models with a categorical variable with two levels, representing early (prior to week 12) or late (after week 12) treatment discontinuation. Results from these analyses confirmed the results of the original retrieved dropout analysis (Table 14 of Appendix). For Trial 3623, the applicant performed a placebo-based multiple imputation analysis, where missing HbA11c values in the placebo arm were imputed based on the MAR assumption, and missing endpoint HbA1c values in the semaglutide arms were imputed based on the baseline HbA1c and the imputation model for placebo plus an error. This analysis resulted in slightly smaller treatment differences for semaglutide versus placebo than the original retrieved dropout analysis, but the conclusions remained unchanged (Table 14 of Appendix).

In the efficacy analyses, volume matching control groups were pooled for the placebo-controlled trials 3623 and 3627 and the sitagliptin-controlled trial 3626. The applicant later conducted additional analyses using volume matched control arms instead of a pooled control arm. The results were shown in Table 15 of Appendix. In trial 3623, the 1.0 mg placebo group showed a larger reduction of HbA1c from baseline compared to the 0.5 mg placebo group (-0.44 vs -

0.06%). Correspondingly, the estimated treatment difference for each semaglutide dose versus its volume matched placebo group was affected. The relative effect of high and low doses of semaglutide appeared to be reversed. Since conclusions from this trial remained unchanged (both doses of semaglutide achieved superiority to placebo), we do not consider the pooling approach problematic.

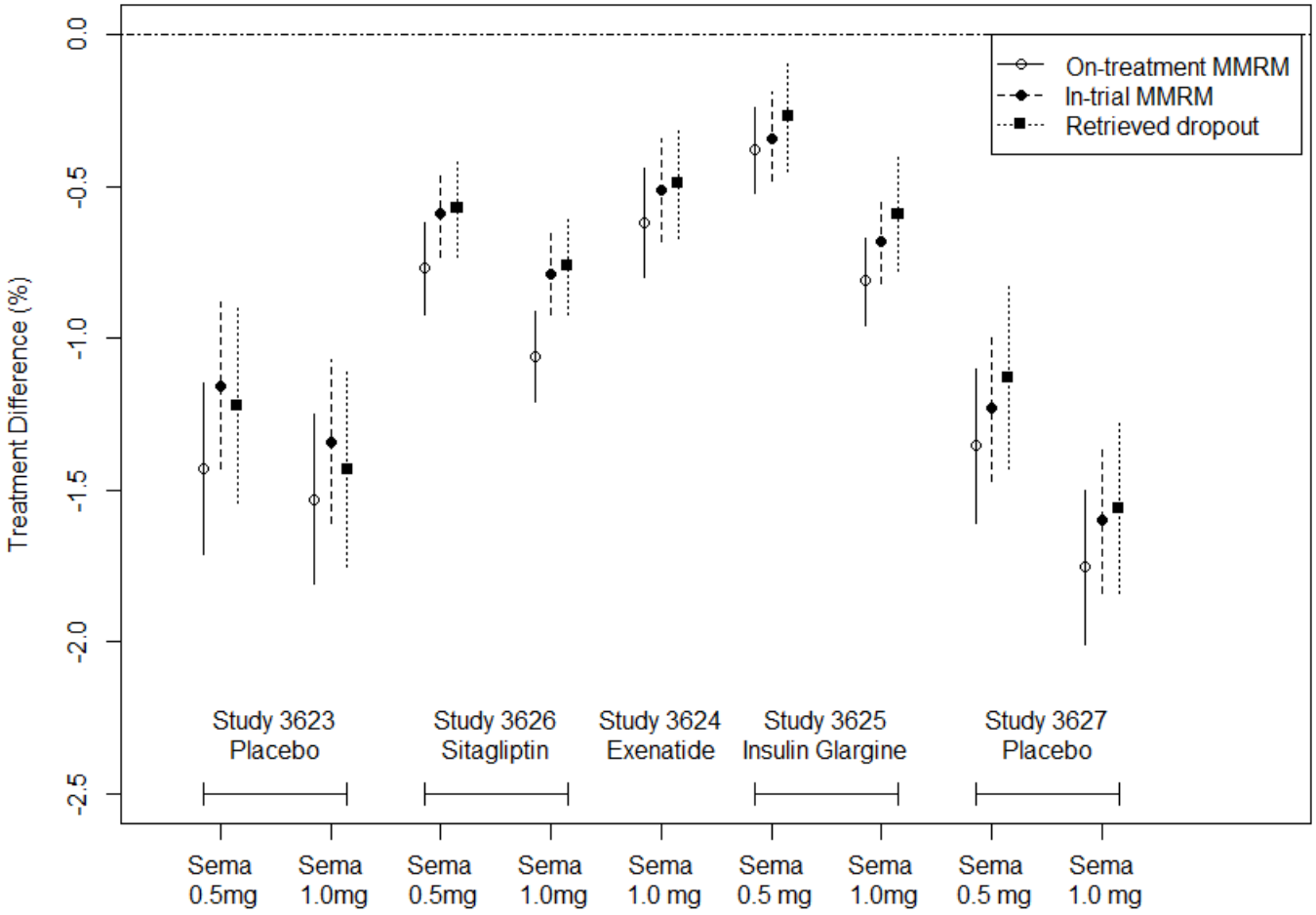
**Table 6** Change in HbA1c (%) from baseline to the end of treatment period using multiple imputation based on retrieved dropouts in FAS[1]

| Trial | Endpoint Visit/ Week | Treatment Arms | N | Baseline | Change from Baseline[2] | | Treatment Difference (Semaglutide-Comparator) | | | Achieving HbA1c<7% | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Mean | LS Mean | SE | LS Mean | 95% CI | P-value | n | (%) |
| 3623-SUSTAIN 1 | 30 | Sema 0.5mg | 128 | 8.09 | -1.37 | 0.11 | -1.22 | [-1.54; -0.90] | <.0001 | 93 | (73) |
| | | Sema 1.0mg | 130 | 8.12 | -1.57 | 0.11 | -1.43 | [-1.75; -1.11] | <.0001 | 91 | (70) |
| | | Placebo | 129 | 7.95 | -0.15 | 0.12 | | | | 36 | (28) |
| 3626-SUSTAIN 2 | 56 | Sema 0.5mg | 409 | 8.01 | -1.29 | 0.06 | -0.57 | [-0.73; -0.41] | <.0001 | 269 | (66) |
| | | Sema 1.0mg | 409 | 8.04 | -1.48 | 0.05 | -0.76 | [-0.91; -0.61] | <.0001 | 300 | (73) |
| | | Sitagliptin | 407 | 8.17 | -0.72 | 0.06 | | | | 165 | (40) |
| 3624-SUSTAIN 3 | 56 | Sema 1.0mg | 404 | 8.36 | -1.39 | 0.07 | -0.49 | [-0.67; -0.30] | <.0001 | 249 | (62) |
| | | Exenatide | 405 | 8.33 | -0.91 | 0.07 | | | | 163 | (40) |
| 3625-SUSTAIN 4 | 30 | Sema 0.5mg | 362 | 8.13 | -1.16 | 0.06 | -0.27 | [-0.45; -0.08] | 0.0047 | 200 | (55) |
| | | Sema 1.0mg | 360 | 8.25 | -1.48 | 0.06 | -0.59 | [-0.78; -0.40] | <.0001 | 237 | (66) |
| | | Insulin Glargine | 360 | 8.13 | -0.89 | 0.08 | | | | 144 | (40) |
| 3627-SUSTAIN 5 | 30 | Sema 0.5mg | 132 | 8.36 | -1.32 | 0.11 | -1.13 | [-1.43; -0.83] | <.0001 | 73 | (56) |
| | | Sema 1.0mg | 131 | 8.31 | -1.74 | 0.10 | -1.56 | [-1.84; -1.27] | <.0001 | 96 | (73) |
| | | Placebo | 133 | 8.42 | -0.19 | 0.11 | | | | 17 | (13) |
| 3744-SUSTAIN 6 (overall population)[3] | 104 | Sema 0.5mg | 826 | 8.67 | -1.05 | 0.05 | -0.68 | [-0.81; -0.55] | <.0001 | | |
| | | Sema 1.0mg | 822 | 8.73 | -1.37 | 0.05 | -1.00 | [-1.13; -0.87] | <.0001 | | |
| | | Placebo | 1649 | 8.70 | -0.37 | 0.04 | | | | | |
| 3744-SUSTAIN 6 (premix insulin subgroup) | 30 | Sema 0.5mg | 223 | 8.77 | -1.25 | 0.08 | -0.84 | [-1.04; -0.64] | <.0001 | | |
| | | Sema 1.0mg | 218 | 8.91 | -1.75 | 0.08 | -1.34 | [-1.54; -1.14] | <.0001 | | |
| | | Placebo | 426 | 8.90 | -0.41 | 0.06 | | | | | |
| 3744-SUSTAIN 6 (SU monotherapy subgroup) | 30 | Sema 0.5mg | 28 | 8.20 | -1.50 | 0.24 | -1.58 | [-2.14; -1.02] | <.0001 | | |
| | | Sema 1.0mg | 31 | 8.41 | -1.43 | 0.22 | -1.51 | [-2.04; -0.98] | <.0001 | | |
| | | Placebo | 64 | 8.39 | 0.08 | 0.16 | | | | | |

1. Control arms were pooled in studies 3623, 3626, 3627, 3744 in the analyses. Missing values at the end of trial were imputed based on retrieved dropouts. For the key efficacy trials, an ANCOVA model was fit including treatment, country as fixed factors, and baseline HbA1c as covariate. For trials 3625 and 3627, the model also included the stratification variable as a fixed factor. For the CVOT 3744 overall population, an ANCOVA model was fit containing treatment and the stratification variable as fixed factors, and baseline HbA1c as covariate. For the CVOT 3744 subgroups, the model included treatment by subgroup interaction.
2. The LS means were adjusted according to the distribution of baseline covariates.
3. Change in HbA1c from baseline to Week 104 in the overall population was not a pre-specified confirmatory secondary endpoint in Trial 3744.

Source: Statistical reviewer's analyses, verified applicant's results in Tables 6.9.1 of ISE and response to information request dated 25 May 2017, with negligible difference in the results for Trial 3744.

**Figure 1** Treatment difference of semaglutide minus comparator in terms of change in HbA1c (%) from baseline in the key efficacy trials




Source: Graph plotted by statistical reviewer

**Table 7** Change in body weight (kg) from baseline to the end of treatment period using multiple imputation based on retrieved dropouts in FAS1

| Trial | Endpoint Visit/ Week | Treatment Arms | N | Baseline | Change from Baseline[2] | | Treatment Difference (Semaglutide-Comparator) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Mean | LS Mean | SE | LS Mean | 95% CI | P-value |
| 3623-SUSTAIN 1 | 30 | Sema 0.5mg | 128 | 89.81 | -3.81 | 0.40 | -2.64 | [-3.82; -1.46] | <.0001 |
| | | Sema 1.0mg | 130 | 96.87 | -4.70 | 0.46 | -3.53 | [-4.82; -2.24] | <.0001 |
| | | Placebo | 129 | 89.05 | -1.17 | 0.45 | | | |
| 3626-SUSTAIN 2 | 56 | Sema 0.5mg | 409 | 89.93 | -4.19 | 0.26 | -2.51 | [-3.24; -1.79] | <.0001 |
| | | Sema 1.0mg | 409 | 89.21 | -5.47 | 0.25 | -3.80 | [-4.51; -3.09] | <.0001 |
| | | Sitagliptin | 407 | 89.29 | -1.67 | 0.26 | | | |
| 3624-SUSTAIN 3 | 56 | Sema 1.0mg | 404 | 96.21 | -4.82 | 0.27 | -2.86 | [-3.62; -2.09] | <.0001 |
| | | Exenatide | 405 | 95.37 | -1.97 | 0.28 | | | |
| 3625-SUSTAIN 4 | 30 | Sema 0.5mg | 362 | 93.73 | -3.15 | 0.25 | -4.09 | [-4.85; -3.33] | <.0001 |
| | | Sema 1.0mg | 360 | 94.00 | -4.66 | 0.25 | -5.60 | [-6.36; -4.84] | <.0001 |
| | | Insulin Glargine | 360 | 92.61 | 0.94 | 0.30 | | | |
| 3627-SUSTAIN 5 | 30 | Sema 0.5mg | 132 | 92.74 | -3.48 | 0.43 | -2.24 | [-3.40; -1.08] | 0.0001 |
| | | Sema 1.0mg | 131 | 92.49 | -5.96 | 0.39 | -4.72 | [-5.82; -3.61] | <.0001 |
| | | Placebo | 133 | 89.88 | -1.24 | 0.40 | | | |
| 3744-SUSTAIN 6 | 104 | Sema 0.5mg | 826 | 91.80 | -3.52 | 0.23 | -2.79 | [-3.34; -2.25] | <.0001 |
| | | Sema 1.0mg | 822 | 92.86 | -4.78 | 0.23 | -4.06 | [-4.60; -3.52] | <.0001 |
| | | Placebo | 1649 | 91.86 | -0.72 | 0.16 | | | |

1. Control arms were pooled in studies 3623, 3626, 3627, 3744 in the analyses. Missing values at the end of trial were imputed based on retrieved dropouts. An ANCOVA model was fit including treatment, country as fixed factors, and baseline body weight as covariate. For trials 3625 and 3627, the model also included the stratification variable as a fixed factor. For the CVOT 3744, an ANCOVA model was fit containing treatment and the stratification variable as fixed factors, and baseline body weight as covariate.
2. The LS means were adjusted according to the distribution of baseline covariates.

Source: Statistical reviewer's analyses, verified applicant's results in Tables 6.9.5 of ISE, with negligible difference in the results for Trial 3744.

### *3.3 Evaluation of safety*

Analyses on safety events were reviewed by Dr. Ya-Hui Hsueh from Division of Biometrics VII and Dr. Andreea Lungu from the Medical Division. Please refer to their respective reviews for details in safety analyses.

## 4. Findings in special/subgroup populations

### *4.1 Sex, Race, Age, and Geographic Region*

The factors considered for subgroup analyses include:

- Age (<65, ≥65)
- Sex
- Race

- Ethnicity
- Geographic Region (US, non-US)

For each key efficacy trial, I conducted subgroup analyses on HbA1c change using the same multiple imputation procedure and a similar ANCOVA model in the retrieved dropout analysis for overall populations, with additional covariates on the subgroups being analyzed and treatment-by-subgroup interactions. The estimates for treatment difference within subgroups and the p-value for subgroup by treatment interaction for each trial were presented in Table 8, Table 9, Table 10, Table 11 and Table 12 respectively.

In Trial 3623, the difference in treatment effect of semaglutide versus placebo between Hispanic and Non-Hispanic subjects was statistically significant for the two semaglutide doses (LS mean = 0.79%, SE= 0.34, numeric p-value = 0.02 for 0.5 mg semaglutide; LS mean = 0.67%, SE=0.33, numeric p-value = 0.04 for 1.0 mg semaglutide). The difference in treatment effect of 1.0 mg semaglutide versus placebo between White and non-White (LS mean = 0.71%, SE = 0.32, numeric p-value = 0.03).

In Trial 3625, the difference in treatment effect of 0.5 mg semaglutide versus insulin glargine between male and female was statistically significant (LS mean = 0.34%, SE = 0.16, numeric p-value = 0.03). The difference in treatment effect of 1.0 mg semaglutide versus placebo between < 65 age group and ≥ 65 age group was statistically significant (LS mean = -0.49%, SE = 0.19, numeric p-value = 0.01).

In Trials 3627, 3626 and 3624, no statistically significant difference in treatment effect between subgroups was found.

In general, the treatment effect of semaglutide was consistent in different subgroups. The significant differences found between subgroups were quantitative instead of qualitative. These results should be viewed with caution due to the lack of adjustment for multiplicity.

**Table 8** Subgroup analysis on HbA1c (%) change from baseline in FAS (Trial 3623)

| | N (Sema 0.5 mg, Sema 1.0 mg, Placebo ) | Treatment Difference Sema 0.5 mg - Placebo [95% CI] | | P-value[1] | Treatment Difference Sema 1.0 mg - Placebo [95% CI] | | P-value[1] |
|---|---|---|---|---|---|---|---|
| **Sex** | | | | 0.23 | | | 0.22 |
| Male | 60, 80, 70 | -1.38 | [-1.81; -0.95] | | -1.61 | [-2.01; -1.21] | |
| Female | 68, 50, 59 | -1.02 | [-1.47; -0.57] | | -1.23 | [-1.71; -0.74] | |
| **Age** | | | | 0.61 | | | 0.20 |
| <65 | 102, 111, 105 | -1.26 | [-1.62; -0.91] | | -1.52 | [-1.86; -1.17] | |
| ≥65 | 26, 19, 24 | -1.06 | [-1.76; -0.35] | | -0.98 | [-1.73; -0.23] | |
| **Race** | | | | 0.17 | | | 0.03 |
| White | 83, 88, 78 | -1.05 | [-1.45; -0.66] | | -1.17 | [-1.55; -0.79] | |
| Non-White | 45, 42, 51 | -1.49 | [-1.99; -0.98] | | -1.88 | [-2.39; -1.36] | |
| **Ethnicity** | | | | 0.02 | | | 0.04 |
| Hispanic | 34, 45, 36 | -0.65 | [-1.24; -0.05] | | -0.97 | [-1.54; -0.41] | |
| Non-Hispanic | 94, 85, 93 | -1.44 | [-1.80; -1.08] | | -1.65 | [-2.01; -1.28] | |
| **Country** | | | | 0.97 | | | 0.30 |
| US | 41, 47, 36 | -1.20 | [-1.55; -0.86] | | -1.55 | [-1.91; -1.19] | |
| Non-US | 87, 83, 93 | -1.22 | [-1.88; -0.56] | | -1.17 | [-1.80; -0.54] | |

1. F-test for subgroup by treatment interaction

Source: Statistical reviewer's analysis

**Table 9** Subgroup analysis on HbA1c (%) change from baseline in FAS (Trial 3627)

| | N (Sema 0.5 mg, Sema 1.0 mg, Placebo ) | Treatment Difference Sema 0.5 mg - Placebo [95% CI] | | P-value[1] | Treatment Difference Sema 1.0 mg - Placebo [95% CI] | | P-value[1] |
|---|---|---|---|---|---|---|---|
| **Sex** | | | | 0.67 | | | 0.85 |
| Male | 74, 77, 71 | -1.07 | [-1.49; -0.64] | | -1.52 | [-1.91; -1.13] | |
| Female | 58, 54, 62 | -1.20 | [-1.64; -0.76] | | -1.58 | [-2.00; -1.15] | |
| **Age** | | | | 0.38 | | | 0.52 |
| <65 | 93, 102, 86 | -1.23 | [-1.59; -0.88] | | -1.64 | [-1.98; -1.31] | |
| ≥65 | 39, 29, 47 | -0.94 | [-1.50; -0.38] | | -1.43 | [-1.98; -0.87] | |
| **Race** | | | | 0.58 | | | 0.21 |
| White | 108, 98, 101 | -1.08 | [-1.43; -0.73] | | -1.45 | [-1.78; -1.12] | |
| Non-White | 24, 33, 32 | -1.28 | [-1.88; -0.67] | | -1.88 | [-2.45; -1.31] | |
| **Ethnicity** | | | | 0.68 | | | 0.39 |
| Hispanic | 15, 12, 19 | -0.95 | [-1.87; -0.04] | | -1.17 | [-2.11; -0.24] | |
| Non-Hispanic | 117, 119, 114 | -1.16 | [-1.47; -0.84] | | -1.60 | [-1.90; -1.31] | |
| **Country** | | | | 0.70 | | | 0.50 |
| US | 60, 59, 61 | -1.17 | [-1.56; -0.79] | | -1.64 | [-2.01; -1.28] | |
| Non-US | 72, 72, 72 | -1.07 | [-1.52; -0.59] | | -1.45 | [-1.89; -0.99] | |

1. F-test for subgroup by treatment interaction

Source: Statistical reviewer's analysis

**Table 10** Subgroup analysis on HbA1c (%) change from baseline in FAS (Trial 3626)

| | N (Sema 0.5 mg, Sema 1.0 mg, Sitagliptin ) | Treatment Difference Sema 0.5 mg - Sitagliptin [95% CI] | | | P-value[1] | Treatment Difference Sema 1.0 mg - Sitagliptin [95% CI] | | | P-value[1] |
|---|---|---|---|---|---|---|---|---|---|
| **Sex** | | | | | 0.77 | | | | 0.45 |
| Male | 207, 205, 208 | -0.55 | [-0.76; | -0.34] | | -0.71 | [-0.91; | -0.50] | |
| Female | 202, 204, 199 | -0.59 | [-0.81; | -0.37] | | -0.82 | [-1.04; | -0.60] | |
| **Age** | | | | | 0.26 | | | | 0.28 |
| <65 | 333, 332, 328 | -0.61 | [0.09; | -0.78] | | -0.80 | 0.09 | -0.97 | |
| ≥65 | 76, 77, 79 | -0.39 | [0.18; | -0.74] | | -0.60 | 0.17 | -0.94 | |
| **Race** | | | | | 0.78 | | | | 0.90 |
| White | 279, 279, 281 | -0.55 | [-0.74; | -0.37] | | -0.75 | [-0.94; | -0.57] | |
| Non-White | 130, 130, 126 | -0.60 | [-0.87; | -0.33] | | -0.77 | [-1.04; | -0.51] | |
| **Ethnicity** | | | | | 0.36 | | | | 0.67 |
| Hispanic | 69, 67, 73 | -0.72 | [-1.07; | -0.37] | | -0.83 | [-1.18; | -0.48] | |
| Non-Hispanic | 340, 342, 334 | -0.54 | [-0.71; | -0.37] | | -0.75 | [-0.91; | -0.58] | |

1. F-test for subgroup by treatment interaction
2. All the subjects in this trial were from non-USA countries

Source: Statistical reviewer's analysis

**Table 11** Subgroup analysis on HbA1c (%) change from baseline in FAS (Trial 3624)

| | N (Sema 1.0 mg, Exenatide) | Treatment Difference Sema 0.5 mg - Exenatide [95% CI] | | | P-value[1] |
|---|---|---|---|---|---|
| **Sex** | | | | | 0.24 |
| Male | 219, 228 | -0.38 | [-0.64; | -0.13] | |
| Female | 185, 177 | -0.60 | [-0.87; | -0.33] | |
| **Age** | | | | | 0.95 |
| <65 | 316, 298 | -0.49 | [-0.71; | -0.28] | |
| ≥65 | 88, 107 | -0.48 | [-0.84; | -0.11] | |
| **Race** | | | | | 0.84 |
| White | 341, 338 | -0.49 | [-0.70; | -0.29] | |
| Non-White | 63, 67 | -0.44 | [-0.90; | 0.02] | |
| **Ethnicity** | | | | | 0.59 |
| Hispanic | 91, 106 | -0.58 | [-0.94; | -0.21] | |
| Non-Hispanic | 313, 299 | -0.46 | [-0.68; | -0.25] | |
| **Country** | | | | | 0.45 |
| US | 155, 158 | -0.56 | [-0.79; | -0.33] | |
| Non-US | 249, 247 | -0.41 | [-0.72; | -0.10] | |

1. F-test for subgroup by treatment interaction

Source: Statistical reviewer's analysis

**Table 12** Subgroup analysis on HbA1c (%) change from baseline in FAS (Trial 3625)

| | N (Sema 0.5 mg, Sema 1.0 mg, Insulin Glargine ) | Treatment Difference Sema 0.5 mg – Insulin Glargine [95% CI] | P-value[1] | Treatment Difference Sema 1.0 mg – Insulin Glargine [95% CI] | P-value[1] |
|---|---|---|---|---|---|
| **Sex** | | | 0.03 | | 0.38 |
| Male | 197, 182, 195 | -0.11 [-0.36; 0.14] | | -0.53 [-0.79; -0.28] | |
| Female | 165, 178, 165 | -0.45 [-0.69; -0.22] | | -0.67 [-0.91; -0.44] | |
| **Age** | | | 0.76 | | 0.01 |
| <65 | 279, 281, 281 | -0.28 [0.10; -0.48] | | -0.70 [0.10; -0.91] | |
| ≥65 | 83, 79, 79 | -0.22 [0.17; -0.56] | | -0.21 [0.18; -0.56] | |
| **Race** | | | 0.53 | | 0.60 |
| White | 279, 279, 276 | -0.30 [-0.49; -0.10] | | -0.62 [-0.81; -0.42] | |
| Non-White | 83, 81, 84 | -0.17 [-0.54; 0.20] | | -0.51 [-0.90; -0.13] | |
| **Ethnicity** | | | 0.27 | | 0.41 |
| Hispanic | 61, 74, 78 | -0.43 [-0.80; -0.05] | | -0.71 [-1.08; -0.34] | |
| Non-Hispanic | 301, 286, 282 | -0.21 [-0.40; -0.01] | | -0.55 [-0.75; -0.35] | |
| **Country** | | | 0.70 | | 0.12 |
| US | 165, 162, 168 | -0.30 [-0.52; -0.08] | | -0.71 [-0.94; -0.49] | |
| Non-US | 197, 198, 192 | -0.23 [-0.50; 0.03] | | -0.47 [-0.73; -0.20] | |

1. F-test for subgroup by treatment interaction

Source: Statistical reviewer's analysis

# 5. Summary and conclusions

## *5.1Statistical Issues*

Statistical issues identified in this application are as follows. Overall, these issues are not major and will not change our efficacy conclusion.

- The amount of missing data was moderate (5-10%) in the 5 key efficacy trials. The pre-specified primary analysis using on-treatment MMRM relies on the MAR assumption which is questionable. Following FDA's advice at the pre-NDA meeting, the applicant performed retrieved dropout analysis for the HbA1c and body weight endpoints. We consider it a more appropriate way of handling missing data and based our conclusions on this analysis.

- The insulin-controlled Trial 3625 and the exenatide-controlled Trial 3624 were both open-label. The applicant stated the open-label design was necessary due to the complexity of blinding insulin and the complexity of preparing a placebo version of exenatide ER. It was not an optimal study design, since bias could be introduced.

- Trials 3623, 3627 and 3626 were double-blinded to treatment but not to dose. In the analyses for these studies, the applicant pooled the two controls arms corresponding to high and low doses of semaglutide. They later conducted additional analyses using

volume matched control arms instead of a pooled control arm. Conclusions from these analyses were consistent. Therefore, we do not think the pooling approach is problematic.

## *5.2 Collective Evidence*

The primary efficacy endpoint was change in HbA1c from baseline in all the key efficacy trials. Both doses of semaglutide (0.5 mg and 1.0 mg) demonstrated superiority to placebo for the primary endpoint, in the monotherapy Trial 3623 as well as Trial 3627 with basal insulin background therapy. Both doses of semaglutide also demonstrated superiority to active comparators sitagliptin and insulin glargine for the primary endpoint. Semaglutide 1.0 mg demonstrated superiority to exenatide ER. Results from the subgroup analyses for the HbA1c endpoint suggest the treatment effect of semaglutide was consistent across different subgroups.

In all the key efficacy trials, both doses of semaglutide also demonstrated superiority to placebo and the active comparators in terms of change in body weight from baseline. In the CVOT, both doses of semaglutide demonstrated superiority to placebo in terms of change in HbA1c and body weight at Week 104 as well as change in HbA1c at Week 30 for subjects on premix insulin at baseline and for subjects on SU monotherapy at baseline, although change in HbA1c at Week 104 was not a pre-specified secondary endpoint.

## *5.3 Conclusions and Recommendations*

My review on efficacy supports the claim of using semaglutide for improving glycemic control in adults with T2DM. This NDA is approvable from statistical point of view.

## *5.4 Labeling recommendations*

Section 14 of the proposed product label contains results from the 5 key efficacy trials and the CVOT. The results for HbA1c and body weight endpoints as well as fasting plasma glucose were based on [redacted] (b) (4). It is recommended that they be replaced with results from the retrieved dropout analysis, which is a more appropriate way of dealing with missing data.

Change in HbA1c at Week 104 was not a pre-specified secondary endpoint in the CVOT 3744. Change in body weight at Week 104 and change in HbA1c at Week 30 for subjects on premix insulin at baseline and for subjects on SU monotherapy at baseline, were pre-specified as confirmatory secondary endpoints in the CVOT. The two dose matched placebo arms were pooled in the analyses. The results in the label should be made consistent with the protocol.

# Appendices

**Table 13** Change in HbA1c (%) from baseline to the end of treatment period using in-trial MMRM analysis in FAS[1]

| Trial | Treatment Arms | N | Baseline | Change from Baseline[2] | | Treatment Difference (Semaglutide - Comparator) | | |
|---|---|---|---|---|---|---|---|---|
| | | | Mean | LS Mean | SE | LS Mean | 95% CI | P-value |
| 3623-SUSTAIN 1 | Sema 0.5mg | 128 | 8.09 | -1.52 | 0.10 | -1.16 | [-1.43; -0.88] | <.0001 |
| | Sema 1.0mg | 130 | 8.12 | -1.71 | 0.10 | -1.34 | [-1.61; -1.07] | <.0001 |
| | Placebo | 129 | 7.95 | -0.36 | 0.10 | | | |
| 3626-SUSTAIN 2 | Sema 0.5mg | 409 | 8.01 | -1.37 | 0.05 | -0.59 | [-0.73; -0.45] | <.0001 |
| | Sema 1.0mg | 409 | 8.04 | -1.56 | 0.05 | -0.79 | [-0.92; -0.65] | <.0001 |
| | Sitagliptin | 407 | 8.17 | -0.78 | 0.05 | | | |
| 3624-SUSTAIN 3 | Sema 1.0mg | 404 | 8.36 | -1.63 | 0.07 | -0.51 | [-0.68; -0.34] | <.0001 |
| | Exenatide | 405 | 8.33 | -1.12 | 0.07 | | | |
| 3625-SUSTAIN 4 | Sema 0.5mg | 362 | 8.13 | -1.28 | 0.06 | -0.34 | [-0.48; -0.19] | <.0001 |
| | Sema 1.0mg | 360 | 8.25 | -1.63 | 0.06 | -0.68 | [-0.82; -0.54] | <.0001 |
| | Insulin Glargine | 360 | 8.13 | -0.95 | 0.06 | | | |
| 3627-SUSTAIN 5 | Sema 0.5mg | 132 | 8.36 | -1.38 | 0.11 | -1.23 | [-1.47; -0.98] | <.0001 |
| | Sema 1.0mg | 131 | 8.31 | -1.75 | 0.11 | -1.60 | [-1.84; -1.35] | <.0001 |
| | Placebo | 133 | 8.42 | -0.15 | 0.11 | | | |

1. Control arms were pooled in studies 3623, 3626, 3627 in the analyses. An MMRM model was fit to all in-trial observations including treatment, country as fixed factors, and baseline body weight as covariate. For trials 3625 and 3627, the model also included the stratification variable as a fixed factor.
2. The LS means were adjusted according to the distribution of baseline covariates.

Source: Statistical reviewer's analyses, verified applicant's results in Table 14.2.6 of CSR of Trial 3623, CSR of Trial 3627, Table 14.2.8 of CSR of Trial 3626, CSR of Trial 3524, CSR of Trial 3625.

**Table 14** Additional sensitivity analyses for change in HbA1c (%) from baseline to the end of treatment period[1]

| Trial | Treatment Arms | N | Baseline | Change from Baseline[2] | | Treatment Difference (Semaglutide - Comparator) | | |
|---|---|---|---|---|---|---|---|---|
| | | | Mean | LS Mean | SE | LS Mean | 95% CI | P-value |
| 3623-SUSTAIN 1 | Sema 0.5mg | 128 | 8.09 | -1.32 | 0.10 | -1.05 | [-1.33 ; -0.77] | <.0001 |
| | Sema 1.0mg | 130 | 8.12 | -1.55 | 0.10 | -1.28 | [-1.56 ; -1.00] | <.0001 |
| | Placebo | 129 | 7.95 | -0.27 | 0.10 | | | |
| 3626-SUSTAIN 2 | Sema 0.5mg | 409 | 8.01 | -1.28 | 0.06 | -0.55 | [-0.71 ; -0.40] | <.0001 |
| | Sema 1.0mg | 409 | 8.04 | -1.47 | 0.05 | -0.75 | [-0.90 ; -0.59] | <.0001 |
| | Sitagliptin | 407 | 8.17 | -0.72 | 0.06 | | | |
| 3624-SUSTAIN 3 | Sema 1.0mg | 404 | 8.36 | -1.39 | 0.07 | -0.50 | [-0.68 ; -0.31] | <.0001 |
| | Exenatide | 405 | 8.33 | -0.89 | 0.07 | | | |
| 3625-SUSTAIN 4 | Sema 0.5mg | 362 | 8.13 | -1.15 | 0.06 | -0.26 | [-0.47 ; -0.05] | 0.0142 |
| | Sema 1.0mg | 360 | 8.25 | -1.46 | 0.06 | -0.57 | [-0.79 ; -0.36] | <.0001 |
| | Insulin Glargine | 360 | 8.13 | -0.89 | 0.09 | | | |
| 3627-SUSTAIN 5 | Sema 0.5mg | 132 | 8.36 | -1.33 | 0.13 | -1.12 | [-1.46 ; -0.78] | <.0001 |
| | Sema 1.0mg | 131 | 8.31 | -1.74 | 0.10 | -1.52 | [-1.83 ; -1.21] | <.0001 |
| | Placebo | 133 | 8.42 | -0.21 | 0.12 | | | |

1. Control arms were pooled in studies 3623, 3626, 3627 in the analyses. For Trial 3623, a placebo-based multiple imputation analysis was performed. For Trials 3626, 3624 and 3627, retrieved

dropout analysis was performed including timing of treatment discontinuation before or after Week 12 as an additional factor in the imputation model compared to the original retrieved dropout analysis.

2. The LS means were adjusted according to the distribution of baseline covariates.

Source: Applicant's response to information request dated 21 February 2017

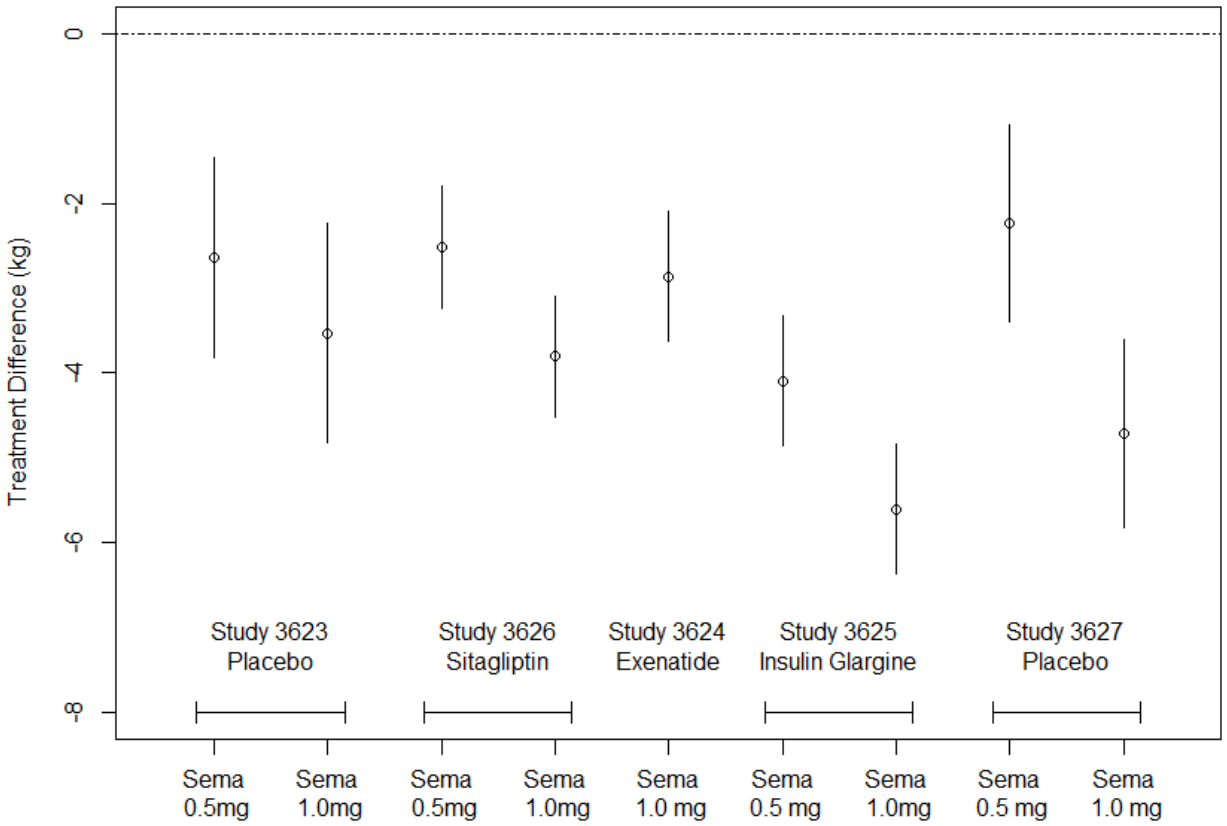
**Table 15** Change in HbA1c (%) from baseline to the end of treatment period using in-trial MMRM analysis and volume matched control arms[1]

| Trial | Treatment Arms | N | Baseline | Change from Baseline[2] | | Treatment Difference (Semaglutide - volume matched control) | | |
|---|---|---|---|---|---|---|---|---|
| | | | Mean | LS Mean | SE | LS Mean | 95% CI | P-value |
| 3623-SUSTAIN 1 | Sema 0.5mg | 128 | 8.09 | -1.40 | 0.10 | -1.35 | [-1.68 ; -1.01] | <.0001 |
| | Sema 1.0mg | 130 | 8.12 | -1.59 | 0.10 | -1.15 | [-1.49 ; -0.82] | <.0001 |
| | Placebo 0.5mg | 65 | 7.98 | -0.06 | 0.14 | | | |
| | Placebo 1.0mg | 64 | 7.93 | -0.44 | 0.14 | | | |
| 3626-SUSTAIN 2 | Sema 0.5mg | 409 | 8.01 | -1.32 | 0.05 | -0.59 | [-0.76 ; -0.42] | <.0001 |
| | Sema 1.0mg | 409 | 8.04 | -1.51 | 0.05 | -0.78 | [-0.95 ; -0.61] | <.0001 |
| | Sitagliptin (0.5mg) | 203 | 8.17 | -0.72 | 0.07 | | | |
| | Sitagliptin (1.0mg) | 204 | 8.17 | -0.73 | 0.07 | | | |
| 3627-SUSTAIN 5 | Sema 0.5mg | 132 | 8.36 | -1.38 | 0.09 | -1.24 | [-1.55 ; -0.94] | <.0001 |
| | Sema 1.0mg | 131 | 8.31 | -1.75 | 0.09 | -1.58 | [-1.88 ; -1.28] | <.0001 |
| | Placebo 0.5mg | 66 | 8.53 | -0.13 | 0.13 | | | |
| | Placebo 1.0mg | 67 | 8.31 | -0.17 | 0.13 | | | |

1. Volume matched control arms were used in the analyses. An MMRM model was fit to all in-trial observations including treatment, country as fixed factors, and baseline body weight as covariate. For trials 3625 and 3627, the model also included the stratification variable as a fixed factor.
2. The LS means were adjusted according to the distribution of baseline covariates.

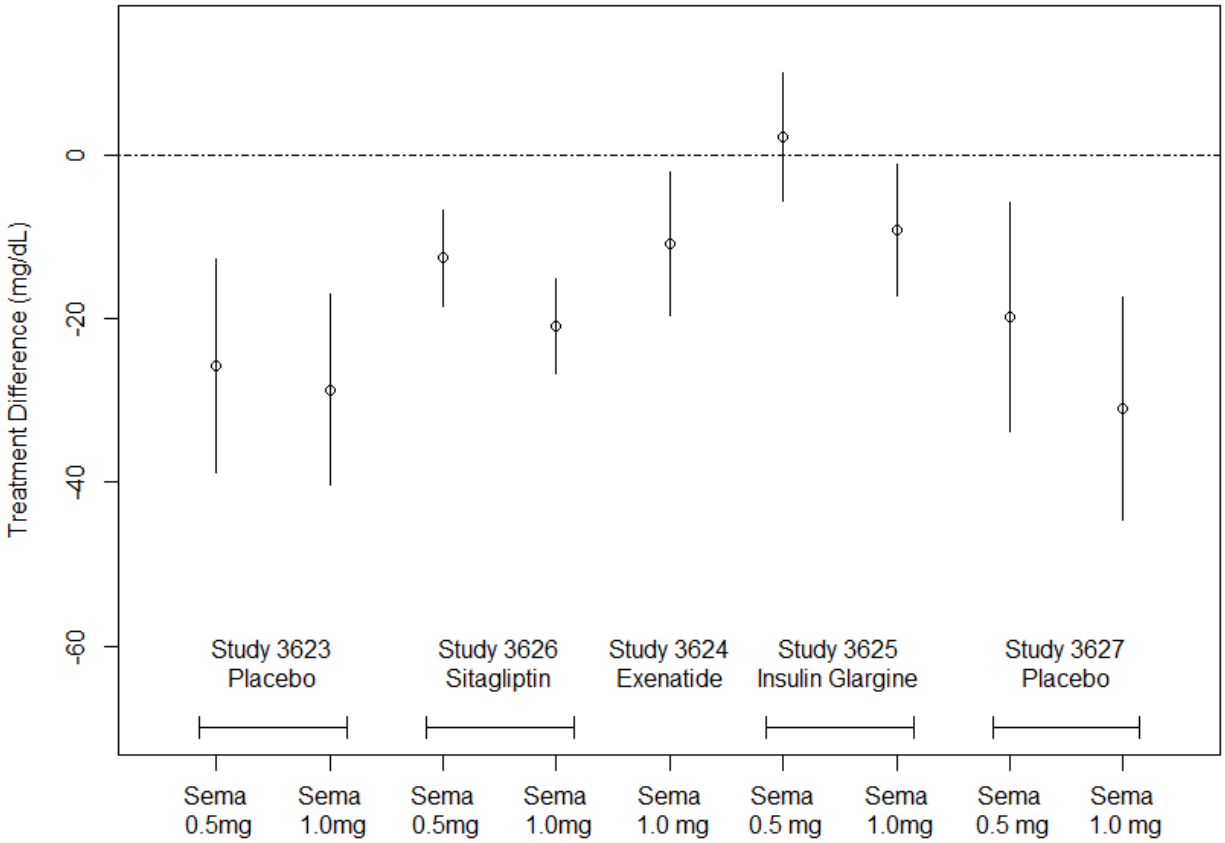
Source: Applicant's response to information request dated 21 February 2017

**Figure 2** Treatment difference of semaglutide minus comparator in terms of change in body weight (kg) from baseline in the key efficacy trials (retrieved dropout analysis)




Source: Graph plotted by statistical reviewer based on applicant's results in Tables 6.9.5 of ISE

**Figure 3** Treatment difference of semaglutide minus comparator in terms of change in fasting plasma glucose (mg/dL) from baseline in the key efficacy trials (retrieved dropout analysis)




Source: Graph plotted by statistical reviewer based on applicant's results in Tables 6.9.4 of ISE

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JIWEI HE
08/11/2017

YUN WANG
08/11/2017

# STATISTICAL REVIEW AND EVALUATION
## FILING REVIEW OF AN NDA/BLA

| | |
|---|---|
| **NDA/BLA #:** | NDA 209637 |
| **Related IND #:** | IND 79754 |
| **Product Name:** | semaglutide (0.5 mg and 1.0 mg s.c. OW) |
| **Indication(s):** | To improve glycemic control in patients with T2DM [redacted] (b) (4) |
| **Applicant:** | Novo Nordisk |
| **Dates:** | Date submitted: 12/05/2016<br>PDUFA due date: 12/05/2017<br>Review due date: 08/02/2017 |
| **Review Priority:** | Standard |
| **Biometrics Division:** | II |
| **Statistical Reviewer:** | Jiwei He, PhD |
| **Concurring Reviewers:** | Yun Wang, PhD |
| **Medical Division:** | DMEP |
| **Clinical Team:** | Andreea Lungu, MD |
| **Project Manager:** | Martin White, MS |

## 1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

[*Note to reviewer: In this section provide a summary of the clinical trials that will be reviewed in your statistical assessment of the NDA/BLA. See Table 1 below for an example summary of the trials. Additional information to consider including in this section would be a discussion regarding the ability of the submitted trials to support the sponsor's proposed labeling claims and a discussion of trials that will not be reviewed and why.*]

**Table 1: Summary of Trials to be Assessed in the Statistical Review**

| Trial ID | Design* | Background Therapy | Treatment/ Sample Size† | Endpoint/Analysis | Preliminary Findings‡ |
|---|---|---|---|---|---|
| 3623-SUSTAIN 1 | R, DB, PG, PC, MC (30 wks) | Monotherapy in Drug-naive subjects with T2D | Sema 0.5mg/129<br>Sema 1.0mg/130<br>Placeo 0.5mg/65<br>Placebo 1.0mg/64 | Primary: change in HbA1c from baseline<br>Key Secondary: Change in body weight | Superiority to placebo was achieved for both doses:<br>-1.16 [-1.43 ; -0.88]<br>-1.34 [-1.61 ; -1.07] |
| 3626-SUSTAIN 2 | R, DB, DD, AC, PG, MC (56 wks) | Add-on to metformin and/or TZD in subjects with T2D | Sema 0.5mg/410<br>Sema 1.0mg/410<br>Sitagliptin 100 mg OD+0.5 mg Placebo/205 | Primary: change in HbA1c from baseline<br>Key Secondary: Change in body | Superiority to sitagliptin was achieved for both doses:<br>-0.59 [-0.73 ; -0.45] |

| | | | | | |
|---|---|---|---|---|---|
| | | | Sitagliptin 100 mg OD+1.0mg Placebo/206 | weight | -0.79 [-0.92 ; -0.65] |
| 3624-SUSTAIN 3 | R, OL, AC, PG, MC (56 wks) | Add-on to 1-2 OADs in subjects with T2D | Sema 1.0mg/406 Exenatide ER 2.0mg OW/407 | Primary: change in HbA1c from baseline Key Secondary: Change in body weight | Superiority to exenatide was achieved: -0.51 [-0.68 ; -0.34] |
| 3625-SUSTAIN 4 | R, OL, AC, PG, MC (30 wks) | Add-on to metformin with/without sulphonylurea in insulin naive subjects with T2D | Sema 0.5mg/362 Sema 1.0mg/362 Insulin Glargine OD/365 | Primary: change in HbA1c from baseline Key Secondary: Change in body weight | Superiority to insulin glargine was achieved for both doses: -0.34 [-0.48 ; -0.19] -0.68 [-0.82 ; -0.54] |
| 3627-SUSTAIN 5 | R, DB, PG, PC, MC (30 wks) | Add-on to basal insulin alone or in combination with metforminin subjects with T2D | Sema 0.5mg/132 Sema 1.0mg/132 Placebo 0.5mg/66 Placebo 1.0mg/67 | Primary: change in HbA1c from baseline Key Secondary: Change in body weight | Superiority to placebo was achieved for both doses: -1.23 [-1.47 ; -0.98] -1.60 [-1.84 ; -1.35] |
| 3744-SUSTAIN 6 | R, DB, PG, PC, MC (long term) | Add-on to standard-of-care in T2D subjects at high risk of CV events | Sema 0.5mg/826 Sema 1.0mg/822 Placebo 0.5mg/824 Placebo 1.0mg/825 | Primary: time from randomization to the first occurrence of 3-composite MACE Key secondary: Change in body weight; change in HbA1c in subgroups | Noninferiority to placebo was achieved: Estimate for HR=0.74[0.58; 0.95] |

* MC: multi-center, R: randomized, DB: double-blind, OL: open-label, PG: parallel group, PC: placebo controlled, AC: active controlled, DD: double-dummy

† Control arms were pooled in studies 3623, 3626, 3627 for efficacy analyses. Pooled semaglutide arms were compared with pooled placebo arms in the primary endpoint in study 3744.

‡ Except for Study 3744, estimated using in-trial MMRM analysis including all data collected regardless of treatment discontinuation or initiation of rescue medication. The pre-specified primary analysis is an on-treatment MMRM analysis that is not recommended. The treatment effects from the in-trial MMRM analysis were smaller than those from the on-treatment MMRM analysis in all the key efficacy trials. The HR in Study 3744 was estimated using a stratified Cox proportional hazards model using all randomized subjects during in-trail period.

Note: Two Phase 3 studies (4091 and 4092) were conducted solely in Japan and had safety primary objective. I do not plan to include them in my review.

# 2. Assessment of Protocols and Study Reports

[*Note to reviewer: The following section should be addressed based upon review of the protocol(s) and the study report submitted for each trial referenced in Table 1 above. The reviewer is encouraged to provide details in the "Response/Comments" column of Table 2.*]

**Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)**

| Content Parameter | Response/Comments |
|---|---|
| Designs utilized are appropriate for the indications requested. | Yes |

| | |
|---|---|
| Endpoints and methods of analysis are specified in the protocols/statistical analysis plans. | Yes |
| Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available. | No interim analyses |
| Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations). | Yes |
| Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate. | At the pre-NDA meeting, FDA requested additional analyses using multiple imputation for missing data based on a retrieved dropout model. The sponsor provided the results in ISE and the SAS code in ISS.<br>We would also like to request additional analyses for the CVOT Study 3744. |

# 3. Electronic Data Assessment

[*Note to Reviewer: The following section is meant to document the details as they pertain to the electronic data submitted in the application.*]

**Table 3: Information Regarding the Data**

| Content Parameter | Response/Comments |
|---|---|
| Dataset location | \\CDSESUB1\EVSPROD\NDA209637\209637.enx |
| Were analysis datasets provided? | Yes |
| Dataset structure (e.g., SDTM or ADaM) | Both SDTM and ADaM |
| Are the define files sufficiently detailed? | Yes |
| List the dataset(s) that contains the primary endpoint(s) | adlb.xpt (HbA1c), advs.xpt (body weight)<br>adtte.xpt for the CVOT study |
| Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? * | Yes |
| Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale. | No |
| Safety data are organized to permit analyses across clinical trials in the NDA/BLA. | Yes |

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

# 4. Filing Issues

[*Note to Reviewer: This information is needed or essential to be able to review the application.*]

**Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):**

| Content Parameter | Yes | No | NA | Comments |
|---|---|---|---|---|
| Index is sufficient to locate necessary reports, tables, data, etc. | * | | | |
| ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.) | * | | | For efficacy, data were not pooled due to the difference in comparators and background medication across trials. |
| Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated. | * | | | |
| Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors). | * | | | |
| Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements | * | | | |

**IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?**
Yes

# 5. Comments to be Conveyed to the Applicant

[*Note to Reviewer: In this section provide all comments that should be conveyed to the sponsor. Section 5.1 "Refuse-to-File Information Requests" should be based upon deficiencies identified in Section 4 of the Filing Review. Section 5.2 "Information Requests/Review Issues" should be used to request any additional information that would facilitate the review or to note any review issues identified by the time of filing that are meant to be conveyed to the sponsor. All comments in this section should be written in such a way that they can be copied by the project management staff.*]

## *5.1. Refuse-to-File Issues*

NA

## *5.2. Information Requests/Review Issues*

1. To justify the assumption that the volume of placebo is not impactful, please compare each semaglutide dose to its matching placebo dose using in trial MMRM for the primary endpoint in the placebo-controlled and sitagliptin-controlled studies (3623, 3626, 3627) where the control arms were pooled in analyses.

2. We acknowledge the additional imputation analyses based on retrieved dropouts you did according to FDA's request at the pre-NDA meeting. Please conduct exploratory analyses to investigate whether the time of discontinuing treatment is impactful for the change in HbA1c from baseline.

   For Study 3623 where imputation based on retrieved dropouts cannot be performed, we suggest the following approach: impute missing endpoint HbA1c measurements in the placebo arm based on the missing at random assumption. Impute missing endpoint HbA1c measurements in the semaglutide arms based on the baseline HbA1c and the imputation model for placebo plus an error. In the placebo-controlled study, the imputation should consider a washout of any semaglutide effect for those subjects known or believed to have discontinued protocol therapy who did not have HbA1c measurement at the endpoint. Intermediate measurements in the semaglutide arms should not be included in the imputation model.

3. In regards to how you address missing data in the CVOT Study 3744, we refer you to the FDA statistical presentation at the June 28th 2016 Advisory Committee for Empagliflozin. The presentation describes how FDA used follow-up data from retrieved drop-outs to model the missing follow-up. Please provide an additional analysis based on that with clearly annotated SAS code.

4. We notice that you did some data reallocation (reallocating measurements at unscheduled visits to scheduled visits). For each key efficacy trial, please provide a list of subjects who had data reallocation to the end-of-study visit for HbA1c and the details about the reallocation procedure.

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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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JIWEI HE
01/24/2017

YUN WANG
01/25/2017