CENTER FOR DRUG EVALUATION AND RESEARCH

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<u>STATISTICAL REVIEW(S)</u>

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 214012
Drug Name:	ALN-PCSSC, Inclisiran
Indication:	Treatment of [REDACTED (b) (4)]
Studies:	Carcinogenicity Studies in Rats for 104 weeks and in Mice for 26 weeks
Applicant:	Study Sponsor:
	The Medicines Company
	7170 Frederick Banting, 2nd Floor
	St. Laurent (Québec) H4S 2A1
	Canada
	Rat Study Testing Facility: [REDACTED (b) (4)]
	Mouse Study Testing Facility: [REDACTED (b) (4)]
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Keywords:	Carcinogenicity, Dose response

Table of Contents

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 determine the carcinogenic potential of the test item, ALN-PCSSC, a PCSK9 inhibitor, administered once every 28 days with subcutaneous injection during the dosing period to Sprague-Dawley rats over a 2-year period, and to TgRasH2 hemizygous mice for 25 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 three treated groups, and two vehicle control groups. Two hundred and seventy-five Sprague-Dawley rats of each sex were assigned randomly in size of 55 rats per group. The dose levels for the three treated groups were 40, 95, and 250 mg/kg/day for both male and female rats. In this review these dose groups were referred to as the low (Group 3), mid (Group 4), and high (Group 5) dose groups, respectively. The rats in the vehicle control groups were treated with the reference item, 0.9 % Sodium Chloride for Injection USP (Saline), 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 Toxicity Animals		Test Material	Dosage Level (mg/kg/day)	
	Male	Female		Male	Female
1	55	55	Vehicle control	0	0
2	55	55	Vehicle control	0	0
3	55	55	ALN-PCSSC Low	40	40
4	55	55	ALN-PCSSC Mid	95	95
5	55	55	ALN-PCSSC High	250	250

Mortality checks were recorded concomitantly with the cage-side clinical sign observations during all phases of the study. Cage-side clinical signs (ill health, behavioral changes, etc.) were recorded twice daily throughout the study. A detailed clinical examination was performed on each animal prior to animal assignment, during the week prior to initiation of dosing and weekly thereafter, including up to one day prior to initiation of dosing and prior to necropsy. From Week 26 onwards, all animals were examined for the presence of palpable masses weekly during the detailed examination. The site, size and appearance of these masses were recorded when first detected and, following this initial description, the presence or disappearance of these masses was monitored. Death and observed clinical signs were individually recorded.

The study duration was intended to be 104 weeks, but all groups were terminated differentially prior to Week 100 as per below when their numbers reached ≤ 15 animals in accordance with the comments and recommendations received from the FDA's Center for Drug Evaluation and

Research in correspondence to the Sponsor dated February 5, 2018. Early termination of surviving animals in each group was as follows:
- Group 4 females at Week 86
- Group 5 females at Week 88
- Group 1, 2 and 3 females at Week 90
- Group 5 males at Week 94
- Group 3 males at Week 95
- All remaining study animals, i.e., Groups 1, 2 and 4 males at Week 99.

Animals surviving to scheduled termination were euthanized following an overnight period without food and subjected to a macroscopic examination. For all animals, necropsy consisted of an external macroscopic examination, including identification of all clinically-recorded lesions, as well as a detailed internal examination. Necropsies performed during regular working hours were performed under the supervision of a veterinary pathologist. A similar proportion of animals from each group and gender, as appropriate, were euthanized on any one day. Where possible, the order of necropsy for each prosection group started with a control animal (Groups 1 or 2). Histopathological examination was performed by the Study Pathologist, on the tissues identified under the tissue preservation section from all Main study animals.

2.1.   Sponsor's analyses

2.1.1.   Survival analysis

In the sponsor's report, the end of the experimental period was defined as specified in Table 2. The survival function of each group was estimated using the Kaplan-Meier product-limit method applied on daily intervals. Any animal with accidental injury that causes its death were censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day. The Kaplan-Meier estimates of the survival distribution function was computed using SAS/STAT module and graphs were produced and presented in the main study report.

Table 2. Subsets of groups and considered end of experimental period submitted to statistical comparisons

Subset	Sex	List of Groups	Considered End of Experimental Period
A – First Phase	Male	1 and 2	Day 687
B – Second Phase	Male	1, 2, 3, 4 and 5	Day 655
C – Second Phase	Male	1, 2, 3 and 4	Day 663
D – Second Phase	Male	1, 2 and 4	Day 687
E – First Phase	Female	1 and 2	Day 622
F – Second Phase	Female	1, 2, 3, 4 and 5	Day 595
G – Second Phase	Female	1, 2, 3 and 5	Day 611
H – Second Phase	Female	1, 2 and 3	Day 622

The statistical analysis of the mortality data was performed in two separate phases. In the first phase, the analysis consisted in comparing the dual reference item treated groups together in

order to determine the control group (labeled hereafter as Group 0) to use in the second phase. In the second phase, the analysis consisted in comparing the considered control Group 0 with the test item treated groups. Considering early group terminations, the statistical comparisons were performed independently for each subset of groups as described in Table 2. The survival distribution functions of the dual control groups were first compared using a Peto two-sided test and considering the end of the experimental period as study day 687 for males and 622 for females.

First Phase
For the first statistical analysis phase, a Peto two-sided test was conducted in order to compare the survival curves of the dual control groups. Since the survival curves of the two control groups were not found to be significantly different for both sexes ($p > 0.05$), then the two reference item treated groups were pooled into a single control group (labeled hereafter as Group 0) which was used in the analysis undertaken in the second phase.

Second Phase
For the second statistical analysis phase, the log-rank test including the considered control Group 0 and the considered test item treated groups was performed in order to assess the significance of the overall group effect on mortality data.

Sponsor's findings:

The sponsor's report showed that the numbers of rats surviving to their terminal necropsy were 13 (24%), 14 (25%), 15 (27%), 14 (25%), and 15 (27%), in Groups 1, 2, 3, 4, and 5 for male rats, respectively, and 19 (35%), 19 (35%), 15 (27%), 15 (27%), and 15 (27%), for female rats respectively. In the sponsor's analysis, no significant difference of surviving curves was observed between dual controls groups for both sexes ($p > 0.05$). Therefore, the dual control groups were combined as Group 0 for the comparison of the test item treated groups with the control. Considering the early group terminations, the group comparison was performed using different subset of groups according to different considered end of experimental period (see Table 2). No significant group differences were observed in any cases ($p > 0.05$).

Comment: According to the sponsor's report, three (3) out of the 396 early decedents were considered to have died accidentally during the course of the study. Animal No. 2538 (Control) died due to trauma, while Nos. 5552 and 5553 (250 mg/kg/month) died due to bin flooding following a sipper malfunction. As such, these deaths were considered unrelated to the test item and were censored in the estimation. However, based on the tumor data that the sponsor submitted, all animals had either the Natural Death (DTHSACST = 1) or the Terminal Sacrifice (DTHSACST = 2), and there were no animals categorized as Accidental Death (DTHSACST = 4). The animal No. 2538, 5552, and 5553 were all categorized as Natural Death (DTHSACST = 1).

2.1.2.   Tumor data analysis

In the sponsor's analysis, the statistical evaluation of tumor data was limited to non–metastatic tumors. Unless specified otherwise as described below, the statistical evaluation was restricted to

neoplastic lesions found in the study plan-required tissues/sites for which it was planned to microscopically examine all animals. Furthermore, the death time of all animals that die after the end of the experimental period was considered to be the first day following the experimental period.

In general, a separate statistical analysis was conducted for each dataset containing the findings of each tumor type listed under a study plan-required tissue/site. However, as usually recommended by study pathologists, the findings of tumors of the same type tabulated under "Skin & Subcutis" and under "Injection site(s)" were combined, and the resulting combinations along with the findings of the distinct tumors were listed under a new site denoted by "Skin Tissues (Combination)". Similarly, the findings of tumors of the same type tabulated under the study plan-required "Skeletal Muscle (thigh)" and under non-study plan listed "Skeletal Muscle", were combined together, and the resulting combinations along with the findings of the distinct tumors were listed under a new denotation "Skeletal Muscle Tissues (Combination)". In addition, the findings of tumors of the same type tabulated under the study plan-required "Femur with marrow", "Sternum with marrow" and under non-study plan listed bone tissues were combined together, and the resulting combinations along with the findings of the distinct tumors were listed under a new site denoted by "Bone Tissues (Combination)". The statistical analysis of all tumors and tumor combinations listed under these three new sites was based on all animals. Furthermore, hemangioma and hemangiosarcomas were combined across each study plan required tissue/site and each non study plan-listed tissue/site under which they appear. The resulting combination was listed under a site denoted respectively by "Hemangioma, all sites" and "Hemangiosarcoma, all sites". The statistical evaluation of the hemangiomas and hemangiosarcomas was done separately for each study plan-required tissue/site as well as for the combination of sites.

Neoplastic lesions found under "Skin Tissues (Combination)", clitoral gland, mammary gland, preputial gland, salivary gland, and zymbal gland, were considered observable through palpation and, consequently, were categorized a priori as clinically palpable neoplasms. Therefore, these lesions were analyzed in a "mortality independent (or observable)" context according to Peto's onset rate method [Peto *et al*., 1980]. More precisely, the time of first palpation was used as the estimate of the tumor onset time for each palpable lesion detected/identified during the experimental period. The death time was used as the onset time for a lesion categorized as palpable and not detected in-vivo during the experimental period (i.e. when an animal dies preterminally and the lesion was found ex-vivo or when the lesion was first detected during the terminal sacrifice period).

The statistical analysis involving the onset rate method was based on all animals having the required tissues/sites examined by palpation during the in-life experimental period. When an analysis had to be performed on a combination of neoplastic findings that were all categorized as palpable, then the earliest onset time among the related findings was used in the analysis. When an analysis had to be performed on a combination of neoplastic findings including both palpable and non-palpable lesions, then the animal death time was used for the analysis and the findings of this combination were analyzed using the "mortality dependent" method described hereafter for non-palpable tumors.

Tumors categorized as non-palpable were analyzed using the "mortality dependent" method. In this context, each neoplastic finding was classified as the cause of death (designated by the study pathologist as definitely or probably fatal) or not the cause of death (designated by the study pathologist as definitely or probably incidental or undetermined). However, all nonpalpable neoplasms found in an animal were automatically classified as incidental if the animal died after the experimental period. In the case of a combination of neoplastic findings, if an animal had at least one of the related tumors classified as fatal, then the neoplastic finding defined by this combination was classified as fatal for that animal. Otherwise, it was classified as incidental.

Neoplastic findings classified as fatal and incidental were processed using the death rate method and the prevalence method, respectively. The processing of incidental tumors was done by creating a single separate interval for the time period following the experimental period (terminal sacrifice period) and by dividing the experimental period into the following fixed intervals (FDA's draft Guidance for industry, 2001): weeks 1-52, weeks 53-78, weeks 79-92, and over week 92. Using the derived outcomes from the processing of both fatal and incidental tumors, a test statistic was built to perform a global survival-adjusted trend test (Peto's test) on tumor data observed in a "mortality dependent" context (Peto et al., 1980).

For each dataset within each sex, the statistical analysis of the tumor rates was performed in two separate phases. In the first phase, the dual reference item treated groups were compared together in order to determine the subsequent control group (labeled hereafter as Group 0). In the second phase, the considered control Group 0 was compared with the test item treated groups. Considering early group terminations, the statistical comparisons were performed independently for each subset of groups as described in Table 2.

First Phase
For the first statistical analysis phase, the Peto's two-sided test was used to compare the dual control groups together. Since both the tumor occurrence rates and the survival curves corresponding to the two control groups were not found to be significantly different ($p > 0.05$), then the two reference item treated groups were pooled together to form a single control group (labeled hereafter as Group 0) which defined the reference item treated group in the analysis undertaken in the second phase.

Second Phase
For the second statistical analysis phase, the significance of an overall linear dose-related increase in tumor occurrence rates across the considered control Group 0 and test item treated groups was evaluated using Peto's survival-adjusted one-tailed trend test. The dose level scores were used to perform the overall trend test. Furthermore, the considered control Group 0 was compared to each of the test item treated groups. These pairwise comparisons were implemented using Peto's upper-tailed trend test in order to assess if the tumor rate in each test item treated group was significantly higher than the Group 0. When performing a pairwise comparison, only the data corresponding to the two compared groups was submitted to the statistical analysis.

As mentioned by Lin (Lin, 1997), the discrete permutation distribution was used to compute the corresponding p-value for each statistical test performed on a dataset with 10 or less tumor occurrences. Please note that the trend test and the pairwise comparison are the same test when

there are only two groups to compare and so, the *p*-value result is reported as pairwise comparison in such a case.

Adjustment for multiple testing:

In the sponsor's report, all overall trend tests and the pairwise comparison tests with a *p*-value ≤ 0.05 were identified but are discussed according to the tumor prevalence classification (common or rare) and the recommendations of Lin and Rahman (Lin and Rahman, 1998). As per their recommendations, the alpha levels to declare significant overall trend test or pairwise group comparisons are specified in the following table. A tumor type is classified as rare if the background rate is less than or equal to 1 percent.

One-Sided Test	Tumor Prevalence	
	Common	Rare
Overall Trend Test	0.005	0.025
Pairwise Comparison	0.01	0.05

Lin K.K. and Rahman M.A. (1998), Overall false positive rates in tests for linear trend in tumor incidence in animal carcinogenicity studies of new drugs. J. of Biopharm. Stat., 8(1), 1-15.

Sponsor's findings:

In the sponsor's report, for all analyzed tumors or combination of tumors, no significant difference was observed between dual control groups for males and females ($p > 0.05$). Therefore, for all subsequent tests, the dual control groups were combined as a unique control (identified as Group 0).

When including all test item treated groups and the designated control for males and when considering the end of the experimental period as study day 655 (Subset B), the trend test for Fibroma+Fibrosarcoma is not considered significant according to the recommendation of Lin and Rahman regardless the tumor prevalence classification, since the *p*-value is greater than 0.025. In addition, as per the recommendation, the trend test and the pairwise comparison for Fibroma (B) are considered significant only if this tumor is considered as being rare.

When including all test item treated groups and the designated control for females and when considering the end of the experimental period as study day 595 (Subset F), for the trend tests related to Subset F, only the combination of tumors "Carcino.+Adeno. Aris.+Fibroad." and the "Fibroadenoma (B)" in "Mammary Gland" are considered significant as per the recommendation of Lin and Rahman regardless the tumor prevalence classification ($p \leq 0.005$). Also, for pairwise group comparisons, there were significant group differences between Group 0 and Groups 4 and 5 for "Fibroadenoma (B)" in "Mammary Gland" and between Group 0 and Group 5 for the combination "Carcino.+Adeno. Aris.+Fibroad." in "Mammary Gland" ($p \leq 0.01$). The differences between the Groups 0 and 4 for "Adenocarcinoma (M)" and the combination "Carcino.+Adeno. Aris.+Fibroad." in "Mammary Gland" should be considered significant only if these tumors are classified as rare.

When including only Groups 0, 3 and 4 for males and considering the end of the experimental period as study day 663 (Subset C), the trend test was significant for "Lymphoma (M)" in "Hemolymphoreticular System" only if this tumor is classified as rare as per Lin and Rahman recommendation.

When including only Groups 0, 3 and 5 for females and considering the end of the experimental period as study day 611 (Subset G), as per Lin and Rahman recommendation, the trend test for "Adenoma, C Cell (B)" in "Thyroids" is not considered significant. Also, the trend test and the Groups 0 vs 5 difference for the combination of "Adeno.+Carcino. C Cell" in "Thyroids" should be considered significant only if the tumor combination is considered rare. However, the trend test and the Groups 0 vs 5 difference for the tumor combination of "Carcino.+Adeno. Aris.+Fibroad." and for the "Fibroadenoma (B)" in "Mammary Gland" are significant whatever the tumor classification.

There was no pairwise group comparison with a *p*-value ≤ 0.05 for males when including only Groups 0 and 4 and considering the end of the experimental period as study day 687 (Subset D), and for females when including only Groups 0 and 3 and considering the end of the experimental period as study day 622 (Subset H).

No other statistically significant findings were noted for male and female rats in the sponsor's report.

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 (two control groups, and low, mid, and high dose group) were estimated using the Kaplan-Meier product limit method. The dose response relationship was tested across the combined control group, and low, mid, and high dose groups 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 the combined control group, and low, mid, and high dose groups 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 13 (24%), 14 (25%), 15 (27%), 14 (25%), and 15 (27%), in Groups 1, 2, 3, 4, and 5 for male rats, respectively, and 19 (35%), 19 (35%), 15 (27%), 15 (27%), and 15 (27%), for female rats respectively. The reviewer's analysis did not show any statistically significant dose response relationships or pairwise comparisons in mortality for both male and female rats.

2.2.2.   Tumor data analysis

The tumor data were analyzed for dose response relationships across the combined control group, and low, mid, and high dose groups, and pairwise comparisons of each of the three treated groups against the combined control group, 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 α=0.01 for common tumors and α=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.

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 3.

Table 3. 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	Vehicle 0 mg 1	0 mg 2	Vehicle (C12) 0 mg (1+2) P - Trend	Low (L) 40 mg P-L vs C12	Mid (M) 95 mg P-M vs C12	High (H) 250 mg P-H vs C12
Male							
Hemolymphoreticular System	Lymphoma (M)	1/55	0/55	1/110 (62) 0.4669	0/55 (26) 1.0000	4/55 (30) 0.0374 @	0/55 (27) 1.0000
Mammary Gland	Fibroadenoma (B)	1/55	2/55	3/110 (63) 0.0276 @	2/55 (27) 0.4741	0/55 (29) 1.0000	5/55 (29) 0.0617
Female							
Mammary Gland	Fibroadenoma (B)	22/55	27/55	49/110 (75) 0.0046 $	29/55 (39) 0.2215	29/55 (38) 0.1643	35/55 (40) 0.0081 $
Skin & Subcutis	Keratoacanthoma (B)/ Carcinoma, Squamous Cell (M)/ Papilloma, Squamous Cell (B)	0/55	0/55	0/110 (50) 0.0462 @	1/55 (24) 0.3243	0/55 (20) NC	2/55 (22) 0.0904
Thyroids	Adenoma, C Cell (B)/ Carcinoma, C Cell (M)	5/55	4/55	9/110 (54) 0.0390 @	2/55 (25) 0.9232	3/55 (22) 0.7429	8/55 (25) 0.1075

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

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

$ = 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;

Based on the criteria of adjustment for multiple testing discussed above, a statistically significant positive dose response relationship was noted in fibroadenoma of mammary gland in female rats (p-value = 0.0046), with a corresponding statistically significant increase in the high dose group when comparing to the vehicle control group (p-value = 0.0081), regardless its tumor classification (rare or common). No other statistically significant tumor findings were noted in the reviewer's analysis for both male and female rats.

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, one reference item (control) group, and one positive control group. Each group comprised 25 animals per sex. The dose levels for the three treated groups were starting with 300, 600 and 1500 mg/kg body weight/day. In this review the three dose groups were referred to as the low (Group 2), mid (Group 3), and high (Group 4) dose groups, respectively. The mice in the control group were treated with the reference item (0.9% sodium chloride), and handled for the same duration and in the same manner as the treated groups. The mice in the positive control group received a single intraperitoneal dose of N-Methyl-N-Nitrosurea (MNU) on Day 1 at 75 mg/kg.

Table 4: Experimental Design in Mouse Study

Group No.	No. of Toxicity Animals		Test Material	Dosage Level (mg/kg/day)	
	Male	Female		Male	Female
1	25	25	Control	0	0
2	25	25	Inclisiran Low	300	300
3	25	25	Inclisiran Mid	600	600
4	25	25	Inclisiran High	1500	1500
5	25	25	Positive control	0	0

Throughout the study, animals were observed for general health/mortality and moribundity twice daily, once in the morning and once in the afternoon. Animals were not removed from cage during observation, unless necessary for identification or confirmation of possible findings. The animals were removed from the cage and a detailed clinical observation was performed weekly, beginning Day -1. The presence of palpable masses was observed during the detailed examination. The site, size and appearance of these masses were recorded when first detected and, following this initial description, the presence or disappearance of these masses was monitored. A necropsy was conducted for main study animals that died on study, and specified tissues were saved. Main study animals surviving until scheduled euthanasia underwent exsanguination from the abdominal aorta after isoflurane anesthesia and blood sample collection. When possible, the animals were euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, were necropsied throughout the days. Main study animals were subjected to a complete necropsy examination, which included evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

3.1.   Sponsor's analyses

3.1.1.   Survival analysis

In the sponsor's report, the survival function of each group was estimated using the Kaplan-Meier product-limit method applied on daily intervals and graphs were produced. Any animal with accidental injury that caused its death or its unscheduled sacrifice, or still alive at the day following the last day of the experimental period was censored in the estimation. The log-rank

test was applied to the five groups in order to assess the significance of the overall group effect on mortality data. If this test was found to be significant, then the significance of a dose-related trend in mortality across the control group (Group 1) and the three Test Item treated groups (Groups 2, 3, and 4) was evaluated using Peto's two-sided test. Furthermore, the control group (Group 1) was compared to the positive control group (Group 5) and to each of Groups 2, 3, and 4 using Peto's two-sided test. Each statistical test was conducted at the 5% significance level.

Sponsor's findings:

The sponsor's analysis showed that the numbers of mice surviving to their terminal necropsy were 25 (100%), 24 (96%), 24 (96%), 25 (100%), and 6 (24%) in Groups1, 2, 3, 4, and 5 for male mice, respectively, and 24 (96%), 24 (96%), 25 (100%), 23 (92%), and 1 (4%) for female mice, respectively. The sponsor's report showed that compared to the saline control group (Group 1), the subcutaneous injection of inclisiran once monthly at doses up to 1500 mg/kg/occasion for 26 weeks had no effect on the survivability during the course of this study.

3.1.2.   Tumor data analysis

In the sponsor's analysis, the statistical evaluation of tumor data was done separately for each sex and was limited to subcutis and hemolymphoreticular tissue using all study animals, to all non-secondary neoplastic lesions found in Study Plan-required tissues/sites, and to the combination of hemangiosarcoma findings across whole body, harderian gland adenoma and adenocarcinoma in males only, and lung bronchioalveolar adenoma and bronchioalveolar carcinoma. For each dataset of interest within each sex, the significance of an overall linear dose-related increase in tumor incidence rate across Groups 1, 2, 3, and 4 was evaluated using Cochran-Armitage's one-sided exact test. Furthermore, Group 1 was compared to each of Groups 2, 3, 4, and 5. These pairwise comparisons were implemented using Fisher's exact one-sided test in order to check if the tumor incidence rate in each of Groups 2, 3, 4, and 5 was significantly higher than the tumor incidence rate in Group 1. Each statistical test was conducted at the 5% significance level.

Multiple testing adjustment:

No multiple testing adjustment was described in the sponsor's report.

Sponsor's findings:

In the sponsor's analysis, there were no neoplastic changes attributed to the subcutaneous injection of inclisiran to hemizygous TgRasH2 mice once every 28 days for up to 25 weeks at doses up to 1500 mg/kg/occasion. For both sexes, there were no statistically significant increases in any tumor incidence related to inclisiran.

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. 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

Reviewer's findings:

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 25 (100%), 24 (96%), 24 (96%), 25 (100%), and 6 (24%) in Groups1, 2, 3, 4, and 5 for male mice, respectively, and 24 (96%), 24 (96%), 25 (100%), 23 (92%), and 1 (4%) for female mice, respectively. No statistically significant findings in mortality was noted in both male and female mice data.

3.2.2. Tumor data analysis

The tumor rates and the p-values of the tested tumor types are given in Tables 4A and Table 4B in the appendix, for male and female mice, respectively.

Reviewer's findings:

The reviewer's analysis showed no statistically significant dose response relationship or pairwise comparisons in the treated groups when compared to the vehicle control group for both male and female mice.

3.3.   Review of the SEND data

According to the "Guidance for Industry - Providing Regulatory Submissions in Electronic Format - Standardized Study Data" (2014), the SEND data was required for this mice study as its study start date is 4/3/2018.

The following steps were used by the reviewer to review the SEND data.
1. examined the tumor related SEND domains (MI, DS, DM, EX, and TX),
2. reviewed the nSDRG submitted with the SEND data,
3. created a tumor dataset based on the SEND data using the same format as the FDA standard tumor data format,
4. compared this SEND based tumor data (SEND tumor.xpt) with the original tumor data (tumor.xpt) submitted by the sponsor in the FDA standard tumor data format,
5. identified the discrepancies or inconsistencies between the SEND_tumor.xpt and tumor.xpt, and consequently
6. identified the corresponding issues in the SEND data or the tumor.xpt.

The reviewer provided the following comments about the tumor data submitted by the sponsor.

> *Comment 1: Animal #3001 was marked as "FOUND DEAD" in the DS domain, which means DTHSACST = 1 (Natural death or moribund sacrifice). However, this animal was marked as DTHSACST = 4 (Accidental death) in the tumor.xpt. No explanation about this discrepancy was provided in the nSDRG.*

Comment 2: There is an MISPEC = "GUT-ASSOCIATED LYMPHOID TISSUE" in the MI domain, whereas the corresponding organ name in the tumor.xpt is "galt". No explanation about this discrepancy was provided in the nSDRG.

Comment 3: Tumor.xpt has an organ "site, injection" with ORGANEXM = 3 for all animals, whereas no "MISTAT = NOT DONE" and no neoplastic tumor was found for this organ in the MI domain. No explanation about this discrepancy was provided in the nSDRG.

Comment 4: According to SENDIGv3.1, "neoplastic findings must be populated using the NEOPLASM (CDISC Controlled Terminology list) controlled list" (page 102), and "When MIORRES contains a tumor finding, the corresponding term from NEOPLASM should be used to populate MISTRESC" (page 105). However, as listed in Table 5 below, some tumor findings in the MI domain were not populated using the NEOPLASM for the variable MISTRESC. No explanation about this issue was provided in the nSDRG.

Table 5 List of Tumor Findings in MI.xpt not Populated Using the NEOPLASM for MISTRESC

MISTRESC	Frequency
Adenocarcinoma, malignant with metastasis	1
Bronchioloalveolar carcinoma, malignant with metastasis	1
Bronchioloalveolar carcinoma, malignant without metastasis	4
Deciduoma, malignant, malignant without metastasis	1
Fibrosarcoma, malignant with metastasis	1
Hemangiosarcoma, malignant with metastasis	1
Hemangiosarcoma, malignant without metastasis	28
Lymphoma, malignant, malignant with metastasis	44
Squamous cell carcinoma, malignant with metastasis	2
Squamous cell carcinoma, malignant without metastasis	8
Thymoma, benign, benign	1
Thymoma, malignant, malignant without metastasis	5

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 determine the carcinogenic potential of the test item, ALN-PCSSC, a PCSK9 inhibitor, administered once every 28 days with subcutaneous injection during the dosing period to Sprague-Dawley rats over a 2-year period, and to TgRasH2 hemizygous mice for 25 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 three treated groups, and two vehicle control groups. Two hundred and seventy-five Sprague-Dawley rats of each sex were assigned randomly in size of 55

rats per group. The dose levels for the three treated groups were 40, 95, and 250 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 13 (24%), 14 (25%), 15 (27%), 14 (25%), and 15 (27%), in Groups 1, 2, 3, 4, and 5 for male rats, respectively, and 19 (35%), 19 (35%), 15 (27%), 15 (27%), and 15 (27%), for female rats respectively. The reviewer's analysis did not show any statistically significant dose response relationships or pairwise comparisons in mortality for both male and female rats.

A statistically significant positive dose response relationship was noted in fibroadenoma of mammary gland in female rats (p-value = 0.0046), with a corresponding statistically significant increase in the high dose group when comparing to the vehicle control group (p-value = 0.0081), regardless its tumor classification (rare or common). No other statistically significant tumor findings were noted in the reviewer's analysis 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, one reference item (control) group, and one positive control group. Each group comprised 25 animals per sex. The dose levels for the three treated groups were starting with 300, 600 and 1500 mg/kg body weight/day.

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 25 (100%), 24 (96%), 24 (96%), 25 (100%), and 6 (24%) in Groups1, 2, 3, 4, and 5 for male mice, respectively, and 24 (96%), 24 (96%), 25 (100%), 23 (92%), and 1 (4%) for female mice, respectively. No statistically significant findings in mortality was noted in both male and female mice data.

The reviewer's analysis showed no statistically significant dose response relationship or pairwise comparisons in the treated groups when compared to the vehicle control group for both male and female mice.

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Hepei Chen.
Mathematical Statistician

</div>

Concur: Karl Lin, Ph.D.
                 Team Leader, DBVI

Cc: Archival NDA 214012
Dr. Elena Braithwaite

5. Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

Week / Type of Death	Vehicle Control 1 No. of Death	Cum %	Vehicle Control 2 No. of Death	Cum %	40 mg/kg/day Low No. of Death	Cum %	95 mg/kg/day Mid No. of Death	Cum %	250 mg/kg/day High No. of Death	Cum %
0 - 52	4	7.27	3	5.45	4	7.27	4	7.27	3	5.45
53 - 78	13	30.91	12	27.27	18	40.00	18	40.00	17	36.36
79 - 91	14	56.36	15	54.55	11	60.00	10	58.18	16	65.45
92 - 99	11	76.36	11	74.55	7	72.73	9	74.55	4	72.73
Terminal sacrifice	13	23.64	14	25.45	15	27.27	14	25.45	15	27.27
Total	55		55		55		55		55	

Test	All Dose Groups	Control 1+2 vs. Low	Control 1+2 vs. Mid	Control 1+2 vs. High
Dose-Response (Likelihood Ratio)	0.3941	0.3091	0.7912	0.2651
Homogeneity (Log-Rank)	0.6565	0.2965	0.7878	0.2526

All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 1B: Intercurrent Mortality Rate in Female Rats

Week / Type of Death	Vehicle Control 1 No. of Death	Cum %	Vehicle Control 2 No. of Death	Cum %	40 mg/kg/day Low No. of Death	Cum %	95 mg/kg/day Mid No. of Death	Cum %	250 mg/kg/day High No. of Death	Cum %
0 - 52	2	3.64	3	5.45	4	7.27	5	9.09	5	9.09
53 - 78	18	36.36	15	32.73	18	40.00	27	58.18	23	50.91
79 - 91	16	65.45	18	65.45	18	72.73	8	72.73	12	72.73
Terminal sacrifice	19	34.55	19	34.55	15	27.27	15	27.27	15	27.27
Total	55		55		55		55		55	

Test	All Dose Groups	Control 1+2 vs. Low	Control 1+2 vs. Mid	Control 1+2 vs. High
Dose-Response (Likelihood Ratio)	0.0810	0.3998	0.0398	0.1051
Homogeneity (Log-Rank)	0.1083	0.3869	0.0315	0.0919

All Cum. % Cumulative Percentage except for Terminal sacrifice;

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

Organ name	Tumor name	Vehicle 0 mg	Vehicle 0 mg	Vehicle (C12) 0 mg (1+2)	Low (L) 40 mg	Mid (M) 95 mg	High (H) 250 mg
		1	2	P - Trend	P-L vs C12	P-M vs C12	P-H vs C12
Adrenal Glands	Adenoma, Adrenocortical (B)	0/55	0/55	0/110 (62)	0/55 (26)	1/55 (29)	0/55 (27)
				0.3889	NC	0.3187	NC
	Carcinoma, Adrenocortical (M)	0/55	2/55	2/110 (63)	0/55 (26)	0/55 (29)	0/55 (27)
				1.0000	1.0000	1.0000	1.0000
	Adenoma, Adrenocortical (B)/ Carcinoma, Adrenocortical (M)	0/55	2/55	2/110 (63)	0/55 (26)	1/55 (29)	0/55 (27)
				0.7770	1.0000	0.6838	1.0000
	Pheochromocytoma (B)	2/55	4/55	6/110 (63)	2/55 (27)	4/55 (30)	0/55 (27)
				0.9241	0.7573	0.4098	1.0000
	Pheochromocytoma (M)	1/55	1/55	2/110 (62)	3/55 (27)	0/55 (29)	1/55 (28)
				0.6199	0.1614	1.0000	0.6781
	Pheochromocytoma (B)/ Pheochromocytoma (M)	3/55	5/55	8/110 (64)	5/55 (28)	4/55 (30)	1/55 (28)
				0.9141	0.3522	0.5743	0.9683
Bone	Osteosarcoma (M)	1/55	1/55	2/110 (63)	0/55 (26)	0/55 (29)	1/55 (27)
				0.4710	1.0000	1.0000	0.6620
Brain	Astrocytoma (M)	0/55	2/55	2/110 (62)	0/55 (26)	2/55 (29)	0/55 (27)
				0.6834	1.0000	0.3809	1.0000
	Granular Cell Tumor (B)	0/55	0/55	0/110 (62)	0/55 (26)	1/55 (29)	0/55 (27)
				0.3889	NC	0.3187	NC
	Oligodendroglioma (M)	2/55	1/55	3/110 (63)	1/55 (27)	0/55 (29)	0/55 (27)
				0.9672	0.7669	1.0000	1.0000
Heart	Mesothelioma, Atriocaval (M)	0/55	0/55	0/110 (62)	1/55 (27)	0/55 (29)	0/55 (27)
				0.5724	0.3034	NC	NC
	Schwannoma, Endocardial (M)	1/55	0/55	1/110 (62)	0/55 (26)	0/55 (29)	1/55 (28)
				0.3500	1.0000	1.0000	0.5278
Hemolymphoreticular System	Lymphoma (M)	1/55	0/55	1/110 (62)	0/55 (26)	4/55 (30)	0/55 (27)
				0.4669	1.0000	0.0374	1.0000
	Sarcoma, Histiocytic (M)	1/55	2/55	3/110 (63)	1/55 (27)	3/55 (30)	1/55 (28)
				0.5209	0.7669	0.2943	0.7771

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

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

Organ name	Tumor name	Vehicle 0 mg 1	Vehicle 0 mg 2	Vehicle (C12) 0 mg (1+2) P - Trend	Low (L) 40 mg P-L vs C12	Mid (M) 95 mg P-M vs C12	High (H) 250 mg P-H vs C12
Injection Site(S)	Fibroma (B)	1/55	2/55	3/110 (62) 0.6515	1/55 (27) 0.7715	0/55 (29) 1.0000	1/55 (28) 0.7817
	Fibrosarcoma, Pleomorphic (M)	0/55	0/55	0/110 (62) 0.1875	0/55 (26) NC	0/55 (29) NC	1/55 (27) 0.3034
	Fibroma (B)/ Fibrosarcoma, Pleomorphic (M)	1/55	2/55	3/110 (62) 0.3317	1/55 (27) 0.7715	0/55 (29) 1.0000	2/55 (28) 0.4974
Kidneys	Sarcoma (M)	0/55	0/55	0/110 (62) 0.3889	0/55 (26) NC	1/55 (29) 0.3187	0/55 (27) NC
Liver	Adenoma, Hepatocellular (B)	0/55	0/55	0/110 (62) 0.1875	0/55 (26) NC	0/55 (29) NC	1/55 (27) 0.3034
	Carcinoma, Hepatocellular (M)	0/55	0/55	0/110 (62) 0.3931	0/55 (26) NC	1/55 (30) 0.3261	0/55 (27) NC
	Adenoma, Hepatocellular (B)/ Carcinoma, Hepatocellular (M)	0/55	0/55	0/110 (62) 0.1112	0/55 (26) NC	1/55 (30) 0.3261	1/55 (27) 0.3034
Lungs With Bronchi	Carcinoma, Bronchioloal. (M)	0/55	0/55	0/110 (62) 0.5724	1/55 (27) 0.3034	0/55 (29) NC	0/55 (27) NC
Mammary Gland	Fibroadenoma (B)	1/55	2/55	3/110 (63) 0.0276	2/55 (27) 0.4741	0/55 (29) 1.0000	5/55 (29) 0.0617
Pancreas	Adenoma, Acinar-Islet Cell (B)	0/55	0/55	0/110 (62) 0.5724	1/55 (27) 0.3034	0/55 (29) NC	0/55 (27) NC
	Adenoma, Islet Cell (B)	2/55	4/55	6/110 (64) 0.5309	6/55 (28) 0.1090	3/55 (30) 0.5952	3/55 (28) 0.5553
	Carcinoma, Islet Cell (M)	2/55	4/55	6/110 (64) 0.8191	3/55 (27) 0.5342	3/55 (30) 0.5952	1/55 (27) 0.9232
	Adenoma, Islet Cell (B)/ Carcinoma, Islet Cell (M)	4/55	8/55	12/110 (66) 0.7667	9/55 (29) 0.1317	6/55 (31) 0.5475	4/55 (29) 0.7920
Parathyroids	Adenoma (B)	1/55	0/55	1/110 (62) 0.3409	0/55 (26) 1.0000	0/55 (29) 1.0000	1/55 (27) 0.5171
Pituitary Gland	Adenoma (B)	45/55	43/55	88/110 (99) 0.5834	35/55 (43) 0.9267	33/55 (45) 0.9944	43/55 (49) 0.6896
	Carcinoma (M)	0/55	0/55	0/110 (62) 0.3889	0/55 (26) NC	1/55 (29) 0.3187	0/55 (27) NC
	Adenoma (B)/ Carcinoma (M)	45/55	43/55	88/110 (99) 0.5721	35/55 (43) 0.9267	34/55 (45) 0.9878	43/55 (49) 0.6896

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

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

Organ name	Tumor name	Vehicle 0 mg 1	0 mg 2	Vehicle (C12) 0 mg (1+2) P - Trend	Low (L) 40 mg P-L vs C12	Mid (M) 95 mg P-M vs C12	High (H) 250 mg P-H vs C12
Preputial Glands	Papilloma, Squamous Cell (B)	0/55	0/55	0/110 (62) 0.1140	0/55 (26) NC	1/55 (29) 0.3187	1/55 (28) 0.3111
Prostate Gland	Adenocarcinoma (M)	1/55	0/55	1/110 (63) 0.3479	0/55 (26) 1.0000	0/55 (29) 1.0000	1/55 (28) 0.5231
Skin & Subcutis	Adenoma, Sebaceous (B)	1/55	0/55	1/110 (62) 0.8189	1/55 (27) 0.5171	0/55 (29) 1.0000	0/55 (27) 1.0000
	Basal Cell Tumor (B)	0/55	3/55	3/110 (62) 0.5962	0/55 (26) 1.0000	0/55 (29) 1.0000	1/55 (27) 0.7715
	Fibroma (B)	1/55	3/55	4/110 (63) 0.1288	2/55 (27) 0.5861	1/55 (29) 0.8571	4/55 (29) 0.2137
	Fibrosarcoma (M)	4/55	3/55	7/110 (64) 0.4146	0/55 (26) 1.0000	2/55 (30) 0.8493	3/55 (28) 0.6400
	Fibroma (B)/Fibrosarcoma (M)	5/55	6/55	11/110 (66) 0.1725	2/55 (27) 0.9409	3/55 (30) 0.8816	7/55 (30) 0.3053
	Hemangioma (B)	0/55	0/55	0/110 (62) 0.3889	0/55 (26) NC	1/55 (29) 0.3187	0/55 (27) NC
	Hemangiosarcoma (M)	0/55	1/55	1/110 (62) 1.0000	0/55 (26) 1.0000	0/55 (29) 1.0000	0/55 (27) 1.0000
	Hemangioma (B)/ Hemangiosarcoma (M)	0/55	1/55	1/110 (62) 0.6282	0/55 (26) 1.0000	1/55 (29) 0.5382	0/55 (27) 1.0000
	Keratoacanthoma (B)	0/55	1/55	1/110 (62) 0.6327	1/55 (27) 0.5171	2/55 (30) 0.2471	0/55 (27) 1.0000
	Carcinoma, Squamous Cell (M)	0/55	1/55	1/110 (62) 0.3500	0/55 (26) 1.0000	0/55 (29) 1.0000	1/55 (28) 0.5278
	Keratoacanthoma (B)/ Carcinoma, Squamous Cell (M)/P	1/55	4/55	5/110 (64) 0.5110	1/55 (27) 0.8875	2/55 (30) 0.7196	2/55 (29) 0.7049
	Lipoma (B)	2/55	0/55	2/110 (62) 0.5147	1/55 (27) 0.6670	0/55 (29) 1.0000	1/55 (27) 0.6670
	Papilloma, Squamous Cell (B)	1/55	2/55	3/110 (64) 0.6007	0/55 (26) 1.0000	0/55 (29) 1.0000	1/55 (28) 0.7726
	Sarcoma (M)	2/55	2/55	4/110 (63) 0.6461	1/55 (27) 0.8401	2/55 (30) 0.6342	1/55 (27) 0.8401
	Tumor, Hair Follicle (B)	0/55	0/55	0/110 (62) 0.3931	0/55 (26) NC	1/55 (30) 0.3261	0/55 (27) NC

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

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

Organ name	Tumor name	Vehicle 0 mg 1	Vehicle 0 mg 2	Vehicle (C12) 0 mg (1+2) P - Trend	Low (L) 40 mg P-L vs C12	Mid (M) 95 mg P-M vs C12	High (H) 250 mg P-H vs C12
Testes	Hemangioma (B)	0/55	0/55	0/110 (62) 0.3889	0/55 (26) NC	1/55 (29) 0.3187	0/55 (27) NC
	Leydig Cell Tumor (B)	1/55	0/55	1/110 (62) 1.0000	0/55 (26) 1.0000	0/55 (29) 1.0000	0/55 (27) 1.0000
Thymus	Schwannoma (M)	0/55	1/55	1/110 (62) 1.0000	0/55 (26) 1.0000	0/55 (29) 1.0000	0/55 (27) 1.0000
	Thymoma (M)	0/55	1/55	1/110 (62) 0.6333	0/55 (26) 1.0000	1/55 (30) 0.5483	0/55 (27) 1.0000
Thyroids	Adenoma, C Cell (B)	4/55	4/55	8/110 (65) 0.3048	5/55 (28) 0.3418	4/55 (31) 0.5858	5/55 (29) 0.3659
	Carcinoma, C Cell (M)	3/55	5/55	8/110 (64) 0.3428	1/55 (27) 0.9649	2/55 (29) 0.8824	4/55 (28) 0.5271
	Adenoma, C Cell (B)/ Carcinoma, C Cell (M)	7/55	8/55	15/110 (67) 0.2132	6/55 (28) 0.6384	6/55 (31) 0.7228	9/55 (30) 0.2880
	Adenoma, Follicular Cell (B)	1/55	3/55	4/110 (63) 0.7290	2/55 (27) 0.5861	1/55 (29) 0.8571	1/55 (27) 0.8401
	Carcinoma, Follicular Cell (M)	0/55	1/55	1/110 (62) 0.4475	3/55 (27) 0.0815	1/55 (29) 0.5382	1/55 (28) 0.5278
	Adenoma, Follicular Cell (B)/ Carcinoma, Follicular Cell (M)	1/55	4/55	5/110 (63) 0.6511	5/55 (28) 0.1507	2/55 (29) 0.7119	2/55 (28) 0.6966
Zymbals Glands	Carcinoma (M)	0/55	1/55	1/110 (63) 0.3479	0/55 (26) 1.0000	0/55 (29) 1.0000	1/55 (28) 0.5231

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

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

		Vehicle		Vehicle (C12)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	40 mg	95 mg	250 mg
Organ name	Tumor name	1	2	P - Trend	P-L vs C12	P-M vs C12	P-H vs C12
Adrenal Glands	Adenoma, Adrenocortical (B)	1/55	0/55	1/110 (50)	1/55 (24)	1/55 (20)	1/55 (21)
				0.2876	0.5465	0.4928	0.5070
	Carcinoma, Adrenocortical (M)	0/55	0/55	0/110 (50)	0/55 (24)	0/55 (20)	1/55 (21)
				0.1826	NC	NC	0.2958
	Adenoma, Adrenocortical (B)/ Carcinoma, Adrenocortical (M)	1/55	0/55	1/110 (50)	1/55 (24)	1/55 (20)	2/55 (22)
				0.1108	0.5465	0.4928	0.2195
	Pheochromocytoma (B)	0/55	0/55	0/110 (50)	0/55 (24)	1/55 (20)	0/55 (21)
				0.3565	NC	0.2857	NC
	Pheochromocytoma (M)	1/55	0/55	1/110 (50)	0/55 (24)	0/55 (20)	0/55 (21)
				1.0000	1.0000	1.0000	1.0000
	Pheochromocytoma (B)/ Pheochromocytoma (M)	1/55	0/55	1/110 (50)	0/55 (24)	1/55 (20)	0/55 (21)
				0.5879	1.0000	0.4928	1.0000
	Pheochromocytoma, Complex (M)	1/55	0/55	1/110 (50)	0/55 (24)	0/55 (20)	0/55 (21)
				1.0000	1.0000	1.0000	1.0000
	Pheochromocytoma (M)/ Pheochromocytoma, Complex (M)	2/55	0/55	2/110 (51)	0/55 (24)	0/55 (20)	0/55 (21)
				1.0000	1.0000	1.0000	1.0000
	Pheochromocytoma (B)/ Pheochromocytoma (M)/ Pheochromocytoma, Complex (M)	2/55	0/55	2/110 (51)	0/55 (24)	1/55 (20)	0/55 (21)
				0.7416	1.0000	0.6356	1.0000
Brain	Astrocytoma (M)	0/55	0/55	0/110 (50)	0/55 (24)	1/55 (21)	0/55 (21)
				0.3621	NC	0.2958	NC
	Granular Cell Tumor (B)	0/55	1/55	1/110 (50)	0/55 (24)	0/55 (20)	0/55 (21)
				1.0000	1.0000	1.0000	1.0000
Eyes	Leiomyoma (B)	0/55	0/55	0/110 (50)	0/55 (24)	0/55 (20)	1/55 (22)
				0.1897	NC	NC	0.3056
	Schwannoma (M)	0/55	0/55	0/110 (50)	1/55 (24)	0/55 (20)	0/55 (21)
				0.5652	0.3243	NC	NC
Heart	Mesothelioma, Atriocaval (M)	0/55	0/55	0/110 (50)	1/55 (24)	0/55 (20)	0/55 (21)
				0.5652	0.3243	NC	NC
Hemolymphoretic ular System	Lymphoma (M)	0/55	1/55	1/110 (50)	1/55 (24)	0/55 (20)	2/55 (22)
				0.1227	0.5465	1.0000	0.2195
	Sarcoma, Histiocytic (M)	0/55	0/55	0/110 (50)	2/55 (25)	0/55 (20)	0/55 (21)
				0.6289	0.1081	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;
NA = Not calculable.

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

Organ name	Tumor name	Vehicle 0 mg 1	0 mg 2	Vehicle (C12) 0 mg (1+2) P - Trend	Low (L) 40 mg P-L vs C12	Mid (M) 95 mg P-M vs C12	High (H) 250 mg P-H vs C12
Kidneys	Adenoma, Renal Tubule (B)	0/55	0/55	0/110 (50) 0.5652	1/55 (24) 0.3243	0/55 (20) NC	0/55 (21) NC
	Carcinoma, Renal Tubule (M)	1/55	0/55	1/110 (50) 0.8131	1/55 (24) 0.5465	0/55 (20) 1.0000	0/55 (21) 1.0000
	Adenoma, Renal Tubule (B)/ Carcinoma, Renal Tubule (M)	1/55	0/55	1/110 (50) 0.8018	2/55 (25) 0.2562	0/55 (20) 1.0000	0/55 (21) 1.0000
Liver	Adenoma, Hepatocellular (B)	0/55	0/55	0/110 (50) 0.3621	0/55 (24) NC	1/55 (21) 0.2958	0/55 (21) NC
Mammary Gland	Adenocarcinoma (M)	14/55	13/55	27/110 (64) 0.2454	16/55 (32) 0.3053	16/55 (29) 0.1739	15/55 (30) 0.3123
	Adenoma (B)	2/55	2/55	4/110 (52) 0.2511	3/55 (26) 0.4293	3/55 (22) 0.3432	3/55 (23) 0.3654
	Adenocarcinoma Ar. In Fib. (M)	4/55	6/55	10/110 (55) 0.7721	6/55 (27) 0.4374	2/55 (21) 0.9049	3/55 (23) 0.8104
	Adenoma (B)/ Adenocarcinoma (M)/ Adenocarcinoma Ar. In Fib. (M)	17/55	17/55	34/110 (67) 0.2724	21/55 (35) 0.2484	19/55 (31) 0.2252	18/55 (31) 0.3243
	Carcinoma, Adenosquamous (M)	0/55	0/55	0/110 (50) 0.5652	1/55 (24) 0.3243	0/55 (20) NC	0/55 (21) NC
	Carcinosarcoma (M)	0/55	0/55	0/110 (50) 0.5652	1/55 (24) 0.3243	0/55 (20) NC	0/55 (21) NC
	Fibroadenoma (B)	22/55	27/55	49/110 (75) 0.0046	29/55 (39) 0.2215	29/55 (38) 0.1643	35/55 (40) 0.0081
Mesentery	Lipoma (B)	0/55	1/55	1/110 (50) 1.0000	0/55 (24) 1.0000	0/55 (20) 1.0000	0/55 (21) 1.0000
Ovaries	Granulosa Cell Tumor (M)	0/55	0/55	0/110 (50) 0.5652	1/55 (24) 0.3243	0/55 (20) NC	0/55 (21) NC
	Tumor, Sex Cord Stromal (B)	1/55	1/55	2/110 (51) 0.4584	0/55 (24) 1.0000	0/55 (20) 1.0000	1/55 (21) 0.6508
Pancreas	Adenoma, Islet Cell (B)	0/55	0/55	0/110 (50) 0.5652	1/55 (24) 0.3243	0/55 (20) NC	0/55 (21) NC
	Carcinoma, Islet Cell (M)	0/55	1/55	1/110 (50) 0.2876	1/55 (24) 0.5465	1/55 (20) 0.4928	1/55 (21) 0.5070
	Adenoma, Islet Cell (B)/ Carcinoma, Islet Cell (M)	0/55	1/55	1/110 (50) 0.3482	2/55 (25) 0.2562	1/55 (20) 0.4928	1/55 (21) 0.5070

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

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

Organ name	Tumor name	Vehicle 0 mg 1	0 mg 2	Vehicle (C12) 0 mg (1+2) P - Trend	Low (L) 40 mg P-L vs C12	Mid (M) 95 mg P-M vs C12	High (H) 250 mg P-H vs C12
Parathyroids	Adenoma (B)	1/55	0/55	1/110 (50) 1.0000	0/55 (24) 1.0000	0/55 (20) 1.0000	0/55 (21) 1.0000
Pituitary Gland	Adenoma (B)	51/55	47/55	98/110 (102) 0.9758	48/55 (51) 0.8319	43/55 (48) 0.9695	40/55 (46) 0.9895
	Carcinoma (M)	1/55	2/55	3/110 (52) 0.2650	1/55 (24) 0.7890	2/55 (21) 0.4485	2/55 (22) 0.4689
	Adenoma (B)/Carcinoma (M)	52/55	49/55	101/110 (104) 0.9641	49/55 (52) 0.9042	45/55 (49) 0.9653	42/55 (47) 0.9884
Skeletal Muscle	Fibroma (B)	0/55	0/55	0/110 (50) 0.1826	0/55 (24) NC	0/55 (20) NC	1/55 (21) 0.2958
Skin & Subcutis	Carcinoma, Sebaceous Cell (M)	1/55	0/55	1/110 (50) 1.0000	0/55 (24) 1.0000	0/55 (20) 1.0000	0/55 (21) 1.0000
	Fibroma (B)	1/55	3/55	4/110 (52) 0.9741	2/55 (25) 0.6401	0/55 (20) 1.0000	0/55 (21) 1.0000
	Fibrosarcoma (M)	0/55	1/55	1/110 (50) 0.1093	1/55 (25) 0.5586	1/55 (20) 0.4928	2/55 (22) 0.2195
	Fibroma (B)/Fibrosarcoma (M)	1/55	4/55	5/110 (53) 0.5632	3/55 (26) 0.5264	1/55 (20) 0.8651	2/55 (22) 0.6679
	Fibrosarcoma, Pleomorphic (M)	1/55	0/55	1/110 (51) 1.0000	0/55 (24) 1.0000	0/55 (20) 1.0000	0/55 (21) 1.0000
	Fibroma (B)/Fibrosarcoma (M)/ Fibrosarcoma, Pleomorphic (M)	2/55	4/55	6/110 (53) 0.6490	3/55 (26) 0.6231	1/55 (20) 0.9054	2/55 (22) 0.7465
	Keratoacanthoma (B)	0/55	0/55	0/110 (50) 0.1897	0/55 (24) NC	0/55 (20) NC	1/55 (22) 0.3056
	Carcinoma, Squamous Cell (M)	0/55	0/55	0/110 (50) 0.1826	0/55 (24) NC	0/55 (20) NC	1/55 (21) 0.2958
	Papilloma, Squamous Cell (B)	0/55	0/55	0/110 (50) 0.5652	1/55 (24) 0.3243	0/55 (20) NC	0/55 (21) NC
	Keratoacanthoma (B)/ Carcinoma, Squamous Cell (M)/ Papilloma, Squamous Cell (B)	0/55	0/55	0/110 (50) 0.0462	1/55 (24) 0.3243	0/55 (20) NC	2/55 (22) 0.0904
	Lipoma (B)	0/55	0/55	0/110 (50) 0.3565	0/55 (24) NC	1/55 (20) 0.2857	0/55 (21) NC
	Sarcoma (M)	1/55	2/55	3/110 (52) 0.3590	2/55 (25) 0.5259	0/55 (20) 1.0000	2/55 (22) 0.4689
Spinal Cord, Cervical	Granular Cell Tumor (M)	0/55	0/55	0/110 (50) 0.1897	0/55 (24) NC	0/55 (20) NC	1/55 (22) 0.3056

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

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

Organ name	Tumor name	Vehicle 0 mg 1	Vehicle 0 mg 2	Vehicle (C12) 0 mg (1+2) P - Trend	Low (L) 40 mg P-L vs C12	Mid (M) 95 mg P-M vs C12	High (H) 250 mg P-H vs C12
Thyroids	Adenoma, C Cell (B)	5/55	4/55	9/110 (54) 0.0636	1/55 (24) 0.9810	2/55 (21) 0.8779	7/55 (24) 0.1684
	Carcinoma, C Cell (M)	0/55	0/55	0/110 (50) 0.1499	1/55 (24) 0.3243	1/55 (20) 0.2857	1/55 (22) 0.3056
	Adenoma, C Cell (B)/ Carcinoma, C Cell (M)	5/55	4/55	9/110 (54) 0.0390	2/55 (25) 0.9232	3/55 (22) 0.7429	8/55 (25) 0.1075
	Adenoma, Follicular Cell (B)	0/55	0/55	0/110 (50) 0.1732	1/55 (25) 0.3333	0/55 (20) NC	1/55 (21) 0.2958
	Carcinoma, Follicular Cell (M)	0/55	0/55	0/110 (50) 0.3565	0/55 (24) NC	1/55 (20) 0.2857	0/55 (21) NC
	Adenoma, Follicular Cell (B)/ Carcinoma, Follicular Cell (M)	0/55	0/55	0/110 (50) 0.1411	1/55 (25) 0.3333	1/55 (20) 0.2857	1/55 (21) 0.2958
Uterus	Adenocarcinoma, Endomet. (M)	0/55	1/55	1/110 (50) 1.0000	0/55 (24) 1.0000	0/55 (20) 1.0000	0/55 (21) 1.0000
	Polyp(S), Endomet. Stromal (B)	4/55	4/55	8/110 (53) 0.8277	3/55 (26) 0.7761	0/55 (20) 1.0000	2/55 (23) 0.8728
	Adenocarcinoma, Endomet. (M)/ Polyp(S), Endomet. Stromal (B)	4/55	4/55	8/110 (53) 0.8277	3/55 (26) 0.7761	0/55 (20) 1.0000	2/55 (23) 0.8728
	Sarcoma, Endomet. Stroma (M)	1/55	0/55	1/110 (51) 0.5840	0/55 (24) 1.0000	1/55 (20) 0.4869	0/55 (21) 1.0000
	Adenocarcinoma, Endomet. (M)/ Polyp(S), Endomet. Stromal (B)/ Sarcoma, Endomet. Stroma (M)	5/55	4/55	9/110 (54) 0.8488	3/55 (26) 0.8239	1/55 (20) 0.9667	2/55 (23) 0.9033
	Carcinoma, Squamous Cell (M)	0/55	0/55	0/110 (50) 0.1826	0/55 (24) NC	0/55 (20) NC	1/55 (21) 0.2958
	Leiomyoma (B)	0/55	0/55	0/110 (50) 0.5652	1/55 (24) 0.3243	0/55 (20) NC	0/55 (21) NC
	Leiomyosarcoma (M)	0/55	0/55	0/110 (50) 0.5652	1/55 (24) 0.3243	0/55 (20) NC	0/55 (21) NC
	Leiomyoma (B)/ Leiomyosarcoma (M)	0/55	0/55	0/110 (50) 0.6289	2/55 (25) 0.1081	0/55 (20) NC	0/55 (21) NC
	Polyp(S) (B)	0/55	0/55	0/110 (50) 0.1826	0/55 (24) NC	0/55 (20) NC	1/55 (21) 0.2958
	Tumor, Granular Cell (B)	0/55	0/55	0/110 (50) 0.5652	1/55 (24) 0.3243	0/55 (20) NC	0/55 (21) NC
Vagina	Leiomyosarcoma (M)	0/55	0/55	0/110 (50) 0.3565	0/55 (24) NC	1/55 (20) 0.2857	0/55 (21) NC

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

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

Organ name	Tumor name	Vehicle 0 mg 1	0 mg 2	Vehicle (C12) 0 mg (1+2) P - Trend	Low (L) 40 mg P-L vs C12	Mid (M) 95 mg P-M vs C12	High (H) 250 mg P-H vs C12
Zymbals Glands	Carcinoma (M)	1/55	0/55	1/110 (50) 0.3447	0/55 (24) 1.0000	0/55 (20) 1.0000	1/55 (22) 0.5207

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

NA = Not calculable.

Table 3A: Intercurrent Mortality Rate in Male Mice

Week / Type of Death	Vehicle control No. of Death	Vehicle control Cum %	Low No. of Death	Low Cum %	Mid No. of Death	Mid Cum %	High No. of Death	High Cum %	Positive Control No. of Death	Positive Control Cum %
0 - 13									3	12.00
14 - 27			1	4.00					16	76.00
Accidental Death					1	4.00				
Terminal sacrifice	25	100.00	24	96.00	24	96.00	25	100.00	6	24.00
Total	25		25		25		25		25	

Test	All Dose Groups	Vehicle control vs. Low	Vehicle control vs. Mid	Vehicle control vs. High
Dose-Response (Likelihood Ratio)	0.5585	0.2390	NC	NC
Homogeneity (Log-Rank)	0.3978	0.3173	NC	NC

All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 3B: Intercurrent Mortality Rate in Female Mice

Week / Type of Death	Vehicle control No. of Death	Vehicle control Cum %	Low No. of Death	Low Cum %	Mid No. of Death	Mid Cum %	High No. of Death	High Cum %	Positive Control No. of Death	Positive Control Cum %
0 - 13									4	16.00
14 - 27	1	4.00	1	4.00			2	8.00	20	96.00
Terminal sacrifice	24	96.00	24	96.00	25	100.00	23	92.00	1	4.00
Total	25		25		25		25		25	

Test	All Dose Groups	Vehicle control vs. Low	Vehicle control vs. Mid	Vehicle control vs. High
Dose-Response (Likelihood Ratio)	0.4139	0.9885	0.2390	0.5362
Homogeneity (Log-Rank)	0.5462	0.9885	0.3173	0.5396

All Cum. % Cumulative Percentage except for Terminal sacrifice;

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

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 300 mg P - VC vs. L	Mid (M) 600 mg P - VC vs. M	High (H) 1500 mg P - VC vs. H	Positive (PC) 0 mg P - VC vs. PC
Body Cavity, Nasal	Hemangiosarcoma	0/25 (25) 0.2525	0/25 (25) NC	0/25 (24) NC	1/25 (25) 0.5000	1/25 (14) 0.3590
	Squamous Cell Carcinoma	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	1/25 (13) 0.3421
Bone Marrow	Hemangioma	0/25 (25) 0.7475	1/25 (25) 0.5000	0/25 (24) NC	0/25 (25) NC	0/25 (13) NC
	Hemangiosarcoma	1/25 (25) 0.4432	0/25 (25) 1.0000	0/25 (24) 1.0000	1/25 (25) 0.7551	0/25 (13) 1.0000
	Hemangioma/Hemangiosarcoma	1/25 (25) 0.4482	1/25 (25) 0.2449	0/25 (24) 0.4898	1/25 (25) 0.2449	0/25 (13) 0.6579
Gland, Harderian	Adenocarcinoma	0/25 (25) 0.7475	0/25 (25) NC	1/25 (24) 0.4898	0/25 (25) NC	0/25 (13) NC
	Adenoma	0/25 (25) 0.8093	2/25 (25) 0.2449	0/25 (24) NC	0/25 (25) NC	2/25 (13) 0.1110
	Adenocarcinoma/Adenoma	0/25 (25) 0.6436	2/25 (25) 0.2449	1/25 (24) 0.4898	0/25 (25) NC	2/25 (13) 0.8890
Gland, Preputial	Hemangioma	1/25 (25) 0.8093	0/25 (25) 1.0000	1/25 (24) 0.7449	0/25 (25) 1.0000	1/24 (13) 0.5733
	Hemangiosarcoma	0/25 (25) 0.6238	1/25 (25) 0.5000	1/25 (24) 0.4898	0/25 (25) NC	0/24 (13) NC
	Hemangioma/Hemangiosarcoma	1/25 (25) 0.7308	1/25 (25) 0.2449	2/25 (24) 0.4844	0/25 (25) 0.5000	1/24 (13) 0.4267
Hemolymphoretic ular Tissue	Lymphoma, Malignant	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	19/25 (22) 0.0000 $
Kidney	Adenoma	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	2/25 (13) 0.1110
Liver	Hepatocellular Adenoma	1/25 (25) 0.8093	0/25 (25) 1.0000	1/25 (24) 0.7449	0/25 (25) 1.0000	0/25 (13) 1.0000

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

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

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 300 mg P - VC vs. L	Mid (M) 600 mg P - VC vs. M	High (H) 1500 mg P - VC vs. H	Positive (PC) 0 mg P - VC vs. PC
Lung	Bronchioloalveolar Adenoma	3/25 (25) 0.6056	1/25 (25) 0.9451	1/25 (24) 0.9403	2/25 (25) 0.8257	2/25 (13) 0.5665
	Bronchioloalveolar Carcinoma	0/25 (25) 0.7475	1/25 (25) 0.5000	0/25 (24) NC	0/25 (25) NC	0/25 (13) NC
	Bronchioloalveolar Adenoma/ Bronchioloalveolar Carcinoma	3/25 (25) 0.6009	2/25 (25) 0.5000	1/25 (24) 0.6798	2/25 (25) 0.5000	2/25 (13) 0.4335
	Hemangiosarcoma	0/25 (25) 0.7475	1/25 (25) 0.5000	0/25 (24) NC	0/25 (25) NC	0/25 (13) NC
Skin	Papilloma	1/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	11/25 (16) 0.0000
Small Intestine, Duodenum	Adenoma	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	1/25 (14) 0.3590
Small Intestine, Jejunum	Adenocarcinoma	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	1/25 (14) 0.3590
Spleen	Hemangiosarcoma	0/25 (25) 0.2812	3/25 (25) 0.1173	1/25 (24) 0.4898	2/25 (25) 0.2449	1/25 (13) 0.3421
Stomach	Adenocarcinoma	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	2/25 (15) 0.1346
	Adenoma	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	1/25 (13) 0.3421
	Adenocarcinoma/Adenoma	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	3/25 (15) 0.9539
	Papilloma	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	19/25 (21) 0.0000 $
	Squamous Cell Carcinoma	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	4/25 (15) 0.0149 $
Thymus	Thymoma, Benign	0/24 (24) 0.7551	1/25 (25) 0.5102	0/25 (24) NC	0/25 (25) NC	0/25 (13) NC

& X/YY (ZZ): 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

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 300 mg P - VC vs. L	Mid (M) 600 mg P - VC vs. M	High (H) 1500 mg P - VC vs. H	Positive (PC) 0 mg P - VC vs. PC
Body Cavity, Nasal	Hemangiosarcoma	1/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	0/25 (23) 1.0000	0/25 (9) 1.0000
Gland, Harderian	Adenoma	0/25 (25) 0.3007	1/25 (24) 0.4898	2/25 (25) 0.2449	1/25 (23) 0.4792	2/25 (10) 0.0756
Gland, Mammary	Adenocarcinoma	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	0/25 (23) NC	1/23 (9) 0.2647
Gland, Salivary, Mandibular	Hemangiosarcoma	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	0/25 (23) NC	1/25 (10) 0.2857
Gland, Zymbals	Squamous Cell Carcinoma	0/25 (25) 0.7423	1/25 (24) 0.4898	0/25 (25) NC	0/25 (23) NC	0/25 (9) NC
Hemolymphoretic ular Tissue	Lymphoma, Malignant	1/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	0/25 (23) 1.0000	24/25 (24) 0.0000
Kidney	Hemangiosarcoma	1/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	0/25 (23) 1.0000	0/25 (9) 1.0000
Lung	Bronchioloalveolar Adenoma	0/25 (25) 0.3139	1/25 (24) 0.4898	2/25 (25) 0.2449	1/25 (24) 0.4898	0/25 (9) NC
	Bronchioloalveolar Carcinoma	0/25 (25) 0.7191	2/25 (25) 0.2449	1/25 (25) 0.5000	0/25 (23) NC	1/25 (9) 0.2647
	Bronchioloalveolar Adenoma/ Bronchioloalveolar Carcinoma	0/25 (25) 0.5091	3/25 (25) 0.1173	3/25 (25) 0.1173	1/25 (24) 0.4898	1/25 (9) 0.7353
Ovary	Hemangioma	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	0/25 (23) NC	1/25 (10) 0.2857
	Hemangiosarcoma	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	0/25 (23) NC	1/25 (9) 0.2647
	Hemangioma/Hemangiosarcoma	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	0/25 (23) NC	2/25 (10) 0.9244
Skin	Fibrosarcoma	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	0/25 (23) NC	1/25 (10) 0.2857
	Hemangiosarcoma	0/25 (25) 0.7423	1/25 (24) 0.4898	0/25 (25) NC	0/25 (23) NC	0/25 (9) NC
	Papilloma	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	0/25 (23) NC	7/25 (14) 0.0002 $
	Squamous Cell Carcinoma	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	0/25 (23) NC	2/25 (10) 0.0756

& X/YY (ZZ): 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	Vehicle (VC) 0 mg P - Trend	Low (L) 300 mg P - VC vs. L	Mid (M) 600 mg P - VC vs. M	High (H) 1500 mg P - VC vs. H	Positive (PC) 0 mg P - VC vs. PC
Spleen	Hemangiosarcoma	3/25 (25)	0/25 (24)	3/25 (25)	2/25 (24)	0/25 (9)
		0.5114	1.0000	0.6664	0.8129	1.0000
Stomach	Papilloma	0/25 (25)	0/25 (24)	0/25 (25)	0/25 (23)	20/25 (21)
		NC	NC	NC	NC	0.0000 $
	Squamous Cell Carcinoma	0/25 (25)	0/25 (24)	0/25 (25)	0/25 (23)	2/25 (9)
		NC	NC	NC	NC	0.0642
Thymus	Thymoma, Malignant	2/25 (25)	1/25 (24)	1/25 (25)	1/25 (23)	0/25 (9)
		0.6960	0.8752	0.8827	0.8670	1.0000
Uterus	Deciduoma, Malignant	0/25 (25)	1/25 (24)	0/25 (25)	0/25 (23)	0/25 (9)
		0.7423	0.4898	NC	NC	NC
	Endometrial Stromal Polyp	1/25 (25)	1/25 (24)	0/25 (25)	0/25 (23)	0/25 (9)
		0.9356	0.7449	1.0000	1.0000	1.0000
	Hemangioma	0/25 (25)	0/25 (24)	0/25 (25)	0/25 (23)	1/25 (9)
		NC	NC	NC	NC	0.2647
Vagina	Hemangiosarcoma	0/25 (25)	0/24 (23)	0/25 (25)	0/25 (23)	1/25 (10)
		NC	NC	NC	NC	0.2857

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

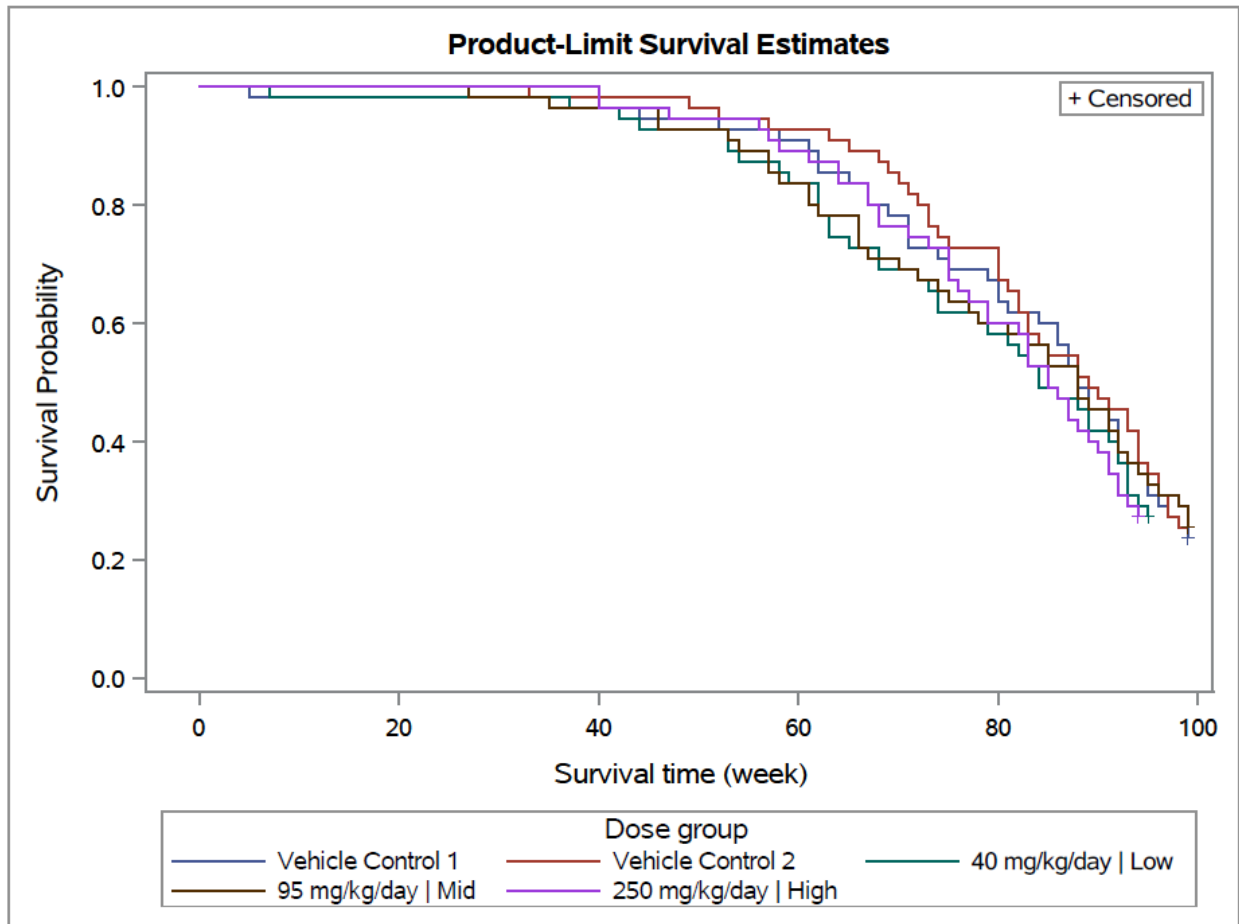**Figure 1A: Kaplan-Meier Survival Functions for Male Rats**

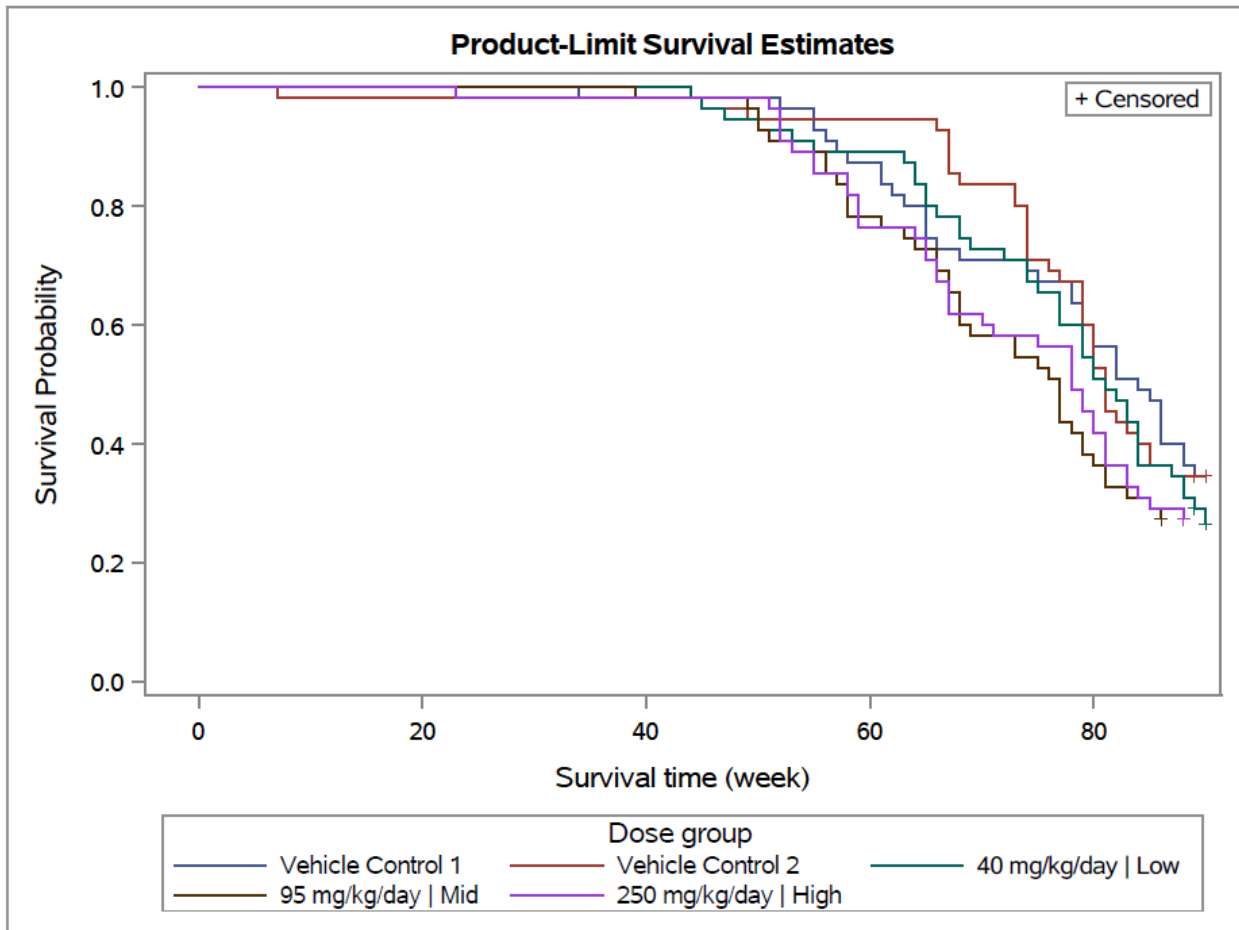**Figure 1B: Kaplan-Meier Survival Functions for Female Rats**

Product-Limit Survival Estimates

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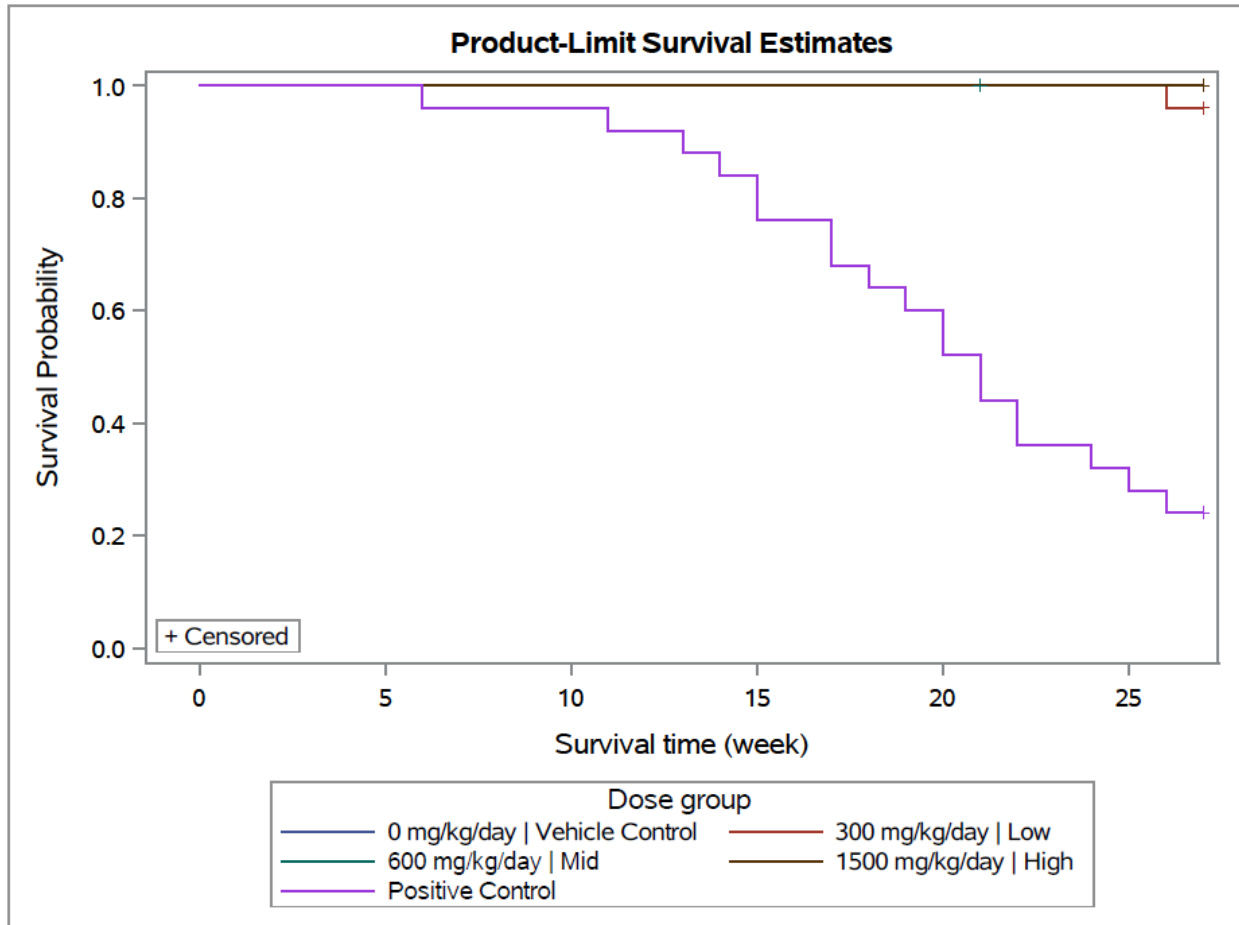
Figure 2B: Kaplan-Meier Survival Functions for Female Mice

Product-Limit Survival Estimates
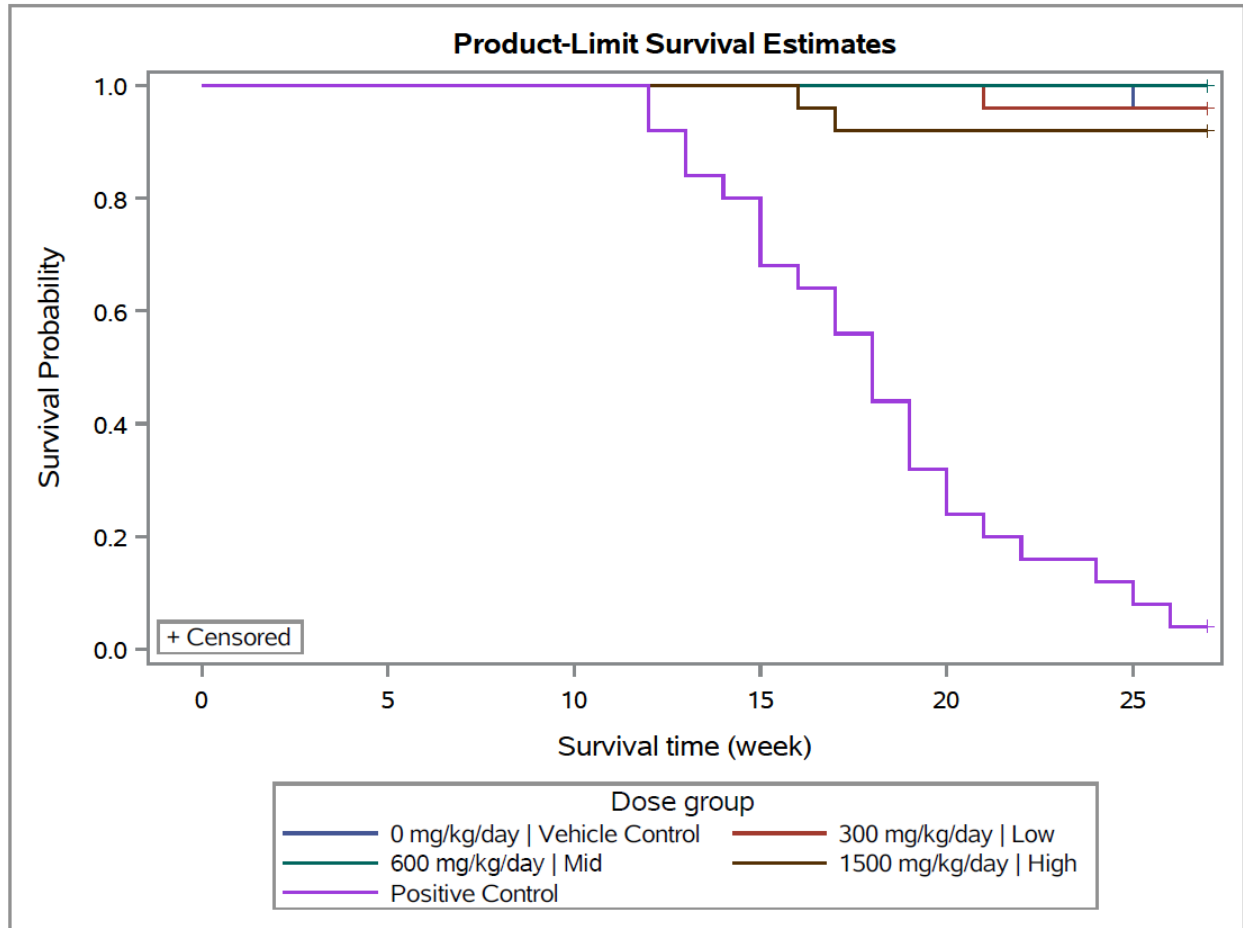
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HEPEI CHEN
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KARL K LIN
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Concur with review.

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 214012
Supplement #:	Original
Drug Name:	Inclisiran
Indication(s):	Adults with primary hyperlipidemia to reduce LDL-C
Applicant:	The Medicines Company
Date(s):	Submitted: 12/23/2019
	Filing: 2/21/2020
	Review Due: 10/1/2020
	PDUFA: 12/23/2020
Review Priority:	Standard
Biometrics Division:	DBII
Statistical Reviewer:	Jennifer Clark, PhD
Concurring Reviewers:	Feng Li, PhD
	Mark Rothmann, PhD
Medical Division:	Division of Diabetes, Lipid disorders, and Obesity.
Clinical Team:	Clinical Efficacy: Eileen Craig, MD
	Clinical Safety: Iffat Chowdhury, MD
	Clinical TL: John Sharretts, MD
Project Manager:	Kati Johnson

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

The applicant, The Medicines Company, submitted three safety and efficacy studies for inclisiran injection in patients with heterozygous familial hypercholesterolemia (HeFH), atherosclerotic cardiovascular disease (ASCVD), and ASCVD risk equivalents. The proposed indication is for inclisiran to be "an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical ASCVD, who require additional lowering of low-density lipoprotein cholesterol (LDL-C)."

The three studies, ORION-9, ORION-10, and ORION-11, were similarly designed with primary differences being in the randomized study population. The same endpoints and analysis methods were specified for each of these studies. Results for the primary percent change in LDL-C at Day 510 are shown in Table 1. These results are in line with the applicant's results. Minor differences from the sponsor results (within 1%) are observed and primarily due to differences in the multiple imputation pattern.

Table 1: Treatment Effect (95% confidence interval) for % Change in LDL-C at Day 510

ORION-9	ORION-10	ORION-11
-47.89 (-53.52, -42.26)	-52.34 (-55.74, -48.95)	-49.80 (-53.03, -46.57)

There were no major statistical issues found in the review of this submission. Minor issues regarding redundancy with some of the pre-specified endpoints (section 3.1.4) can be resolved through judicious labeling. Collectively, these studies showed evidence of a large and robust treatment effect (section 3.1.4) for the study populations. Based on these findings, we recommend approval for the requested indication.

2 INTRODUCTION

On 23 December 2019, The Medicines Company submitted an original NDA for approval of inclisiran injection for lowering of LDL-C in adults with HeFH or clinical ASCVD. Treatment with inclisiran involves a twice-a-year dosing schedule with a single use prefilled syringe (300 mg inclisiran sodium in 1 (b)(4) mL aqueous solution containing 284 mg of inclisiran) administered by a healthcare professional.

2.1 Overview

Inclisiran is a double-stranded small interfering ribonucleic acid (siRNA) that inhibits the production of PCSK9. Early phase I and II study data indicated maximum reductions in PCSK9 and LDL-C levels are observed within 30 to 60 days after injection. Most of the PCSK9 reduction occurred within 7 days, and LDL-C reduction within 14 days. According to the applicant, while effects were persistent over the dosing period, they returned to baseline from peak effects at a linear rate of ~2% per month.

The applicant complied with all the statistical comments conveyed during the IND stage of this submission. The efficacy estimand and the associated pre-specified primary analyses are in-line with current recommendations that are given by the division for similar products. They completed three Phase III studies with nearly identical designs over an 18-month treatment observation period and are currently running a cardiovascular outcomes (CVOT) study enrolling 15,000 ASCVD patients. This statistical review assesses the three completed Phase III studies, but not the CVOT study which is not a part of the submission.

High-level information regarding the three studies is seen in Table 2. The main difference between the three studies is in the study population and regions where the study sites were located. ORION-9 had clinical sites in North America, Europe, and South Africa; ORION-10 had sites only in North America; ORION-11 had sites in Europe and South Africa. Study populations included heterozygous familial hypercholesterolemia (HeFH) (ORION-9), ASCVD and elevated LDL-C (ORION-10), and ASCVD or ASCVD-risk equivalents (ORION-11). All three studies were multi-center, randomized, double-blind, parallel group, placebo-controlled with the same pre-specified primary and secondary endpoints.

Table 2: Efficacy Studies Reviewed in this Submission

Trial ID	Trt, Sample Size	Population	Primary Endpoints	Secondary Endpoints
ORION-9	Inclisiran, N=241 Placebo, N=240	HeFH and elevated LDL-C	1) % change in LDL-C from baseline to Day 510	1) Absolute change in LDL-C from baseline to Day 510 2) Time-adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540
ORION-10	Inclisiran, N=781	ASCVD and elevated LDL-C	2) Time-adjusted	

ORION-11	Placebo, N=778	ASCVD or ASCVD-risk equivalents and elevated LDL-C	% change in LDL-C from baseline after Day 90 and up to Day 540	3) % change from baseline to Day 510 in PCSK9, total cholesterol, APO-B, and non-HDL-C
	Inclisiran, N=810			
	Placebo, N=805			

Overall, follow-up for the endpoints was done well. Given the large sample sizes and treatment effects, results were robust. There were no major statistical issues in the review of this submission. Minor issues regarding redundancy in primary and secondary endpoints, as well as subgroups for the treatment effect by baseline LDL status will be addressed in this review.

2.2 Data Sources

Material for this statistical review, including the data and clinical study report (CSR) were submitted electronically under the network path location <\\cdsesub1\evsprod\NDA214012\0001 >. The information necessary for this review was contained in Module 1 (Cover Letters, Previous Correspondence, Labeling) and Module 5 (Clinical Study Report, Protocol, Amendments, Statistical Analysis Plan, Data, and Data Dictionary).

Small differences in FDA results vs. the applicant's results has to do with minor differences in how the imputation was run. Overall differences were typically less than one and did not change the overall interpretation or significance of the results.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Efficacy analyses were similarly pre-specified for all three studies. Methods were generally the same for the same endpoints. Discussions for this section will consider the analogous study design, methods, and endpoints jointly with comments indicating differences for individual studies.

3.1.1 Study Design and Endpoints

ORION-9, ORION-10, and ORION-11 were all confirmatory Phase III, placebo-controlled, double-blind, randomized studies with an 18-month placebo-controlled treatment phase. A dose of 300 mg of inclisiran, or matching placebo, was given using the same dosing regimen and visit schedules. Subjects were on a background of maximally tolerated statin therapy with or without other LDL-C lowering agents before randomization. Randomization was 1:1, stratified by current use of statins or other lipid-modifying therapies. In ORION-9 and ORION-11, patients were also stratified by country; ORION-10 was only conducted in sites within the U.S.A. Figure 1 shows an applicant created schematic of the study design used for all the studies.

Figure 1: Applicant Diagram of the Study Design
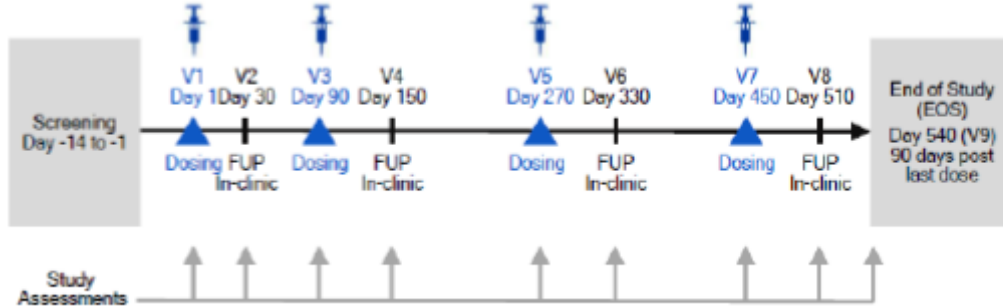
Chief differences between the studies have to do with inclusion criteria for the different study populations and underlying conditions leading to elevated LDL-C.

- ORION-9: HeFH and elevated LDL-C, despite receiving the maximally tolerated dose of statin therapy
- ORION-10: ASCVD and elevated LDL-C, despite receiving the maximally tolerated dose of statin therapy
- ORION-11: ASCVD and ASCVD risk equivalents defined as type 2 diabetes, familial hypercholesterolemia, or 10-year risk of 20% or greater of having a CV event assessed by Framingham Risk Score or equivalent and elevated LDL-C, despite receiving the maximally tolerated dose of statin therapy.

Endpoints

LDL-C was used for many of the pre-specified endpoints. These endpoints used a reflexive LDL-C approach wherein calculated LDL-C was used unless it was <40 mg/dL or triglycerides were >400 mg/dL, or calculated LDL-C was missing. In such cases, directly measured (ultracentrifugation) LDL-C was used if available. Two co-primary endpoints were pre-specified using reflexive LDL-C in these studies:

- Percentage change from baseline to Day 510
- Time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540

The first percent change endpoint is meant to show long-term efficacy with little to no attenuation. The second time-adjusted percent change is meant to show an integrated effect on LDL-C over time. Essentially, this second endpoint is a linear combination of the treatment effect at days 150, 270, 300, 340, and 510. The first endpoint is just the treatment effect at day 510. There is some redundancy between these two endpoints, but differences in interpretation, although subtle, do lend to a stronger validation of a prolonged and meaningful treatment effect. While similar results between these two endpoints would give a more detailed understanding of the treatment effect and further assurance of a meaningful benefit for patients, it is unclear if having both results would add any additional benefit for prescribers over only having results for one of the endpoints.

8

The co-primary endpoints used a sequential testing procedure, testing percentage change at Day 510 first at a 2-sided level of alpha=0.05. While a sequential testing procedure does not typically conform to how co-primary endpoints normally control for type I error, alpha levels are controlled and the correlation along with the nested nature of these two endpoints make this a non-issue. Type I error was controlled at a 2-sided significance level of alpha=0.05 through the Hochberg procedure for key secondary endpoints.

- Absolute change in LDL-C from baseline to Day 510
- Time-adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540
- Percentage change from baseline to Day 510 in:
  - PCSK9
  - Total Cholesterol
  - Apolipoprotein B (Apo-B)
  - Non-HDL-C

3.1.2 Statistical Methodologies

All primary analyses were conducted on the ITT Population which was pre-specified to be all subjects randomized into the study. Treatment classification was based on the randomized treatment group. All follow-up data, regardless of treatment status, were used for the primary analysis.

For the primary percent change in LDL-C endpoint, an analysis of covariance (ANCOVA) model was specified which included fixed effects for treatment group and baseline LDL-C. Missing values were imputed for LDL-C using a modified control-based multiple imputation model with 100 imputed datasets. Once the missing LDL-C values were imputed, the change or percent change for the endpoint was calculated using the imputed values. For the modified control-based MI, missing data were imputed based on the following underlying assumptions for different groups of patients:

- Placebo patients: missing at random (MAR)
- Inclisiran patients completing all 4 doses and have data for Day 540 (completers): MAR, imputation was based on baseline values and observed efficacy measurements from the inclisiran group at Day 510
- Remaining Inclisiran patients: missing not at random (MNAR), control-based multiple imputation with imputations based on baseline values of the efficacy measurement, and observed values at Day 510 from the placebo group

The time adjusted percent change in LDL-C endpoints were analyzed using a mixed effects model for repeated measures (MMRM) approach. A control-based pattern-mixture model (PMM) for imputing missing data was used with 100 datasets. The model included fixed effects for treatment, visit, baseline, and an interaction between treatment and visit. This was different from the modified control-based MI used in the ANCOVA analysis as no inclisiran patients were imputed MAR. A linear combination of the estimated means after (not including) Day 90 and up to Day 540 was used to estimate the treatment effect.

9

Analyses for pre-specified key secondary endpoints used a MMRM approach with fixed effects for treatment, visit (Days 90, 150, 270, 330, 450, and 510), baseline, and an interaction between treatment and visit. For time adjusted percent change analyses, data up to and including Day 90 was excluded from the model. A control-based PMM, similar to what was specified for time-adjusted percent change in LDL-C, was specified for the analysis for secondary endpoints. Statin use was used in the imputation model for all secondary endpoints except PCSK9 which had convergence problems when this was in the model.

A tipping point analysis was run by the applicant to test the robustness of the treatment effect. Given the low amount of missing data (Table 8) and the consistently large treatment effect in for all the pre-specified endpoints across all three studies (Table 10 - Table 15), sensitivity analyses will show little differences unless underlying assumptions were varied drastically.

3.1.3   Patient Disposition, Demographic and Baseline Characteristics

Overall, patients were balanced between study arms for all three studies. Most patients were white, Non-Hispanic, and on statins at baseline. Differences between patients enrolled in ORION-9 can be seen in the lower proportion of diabetes and higher LDL-C when compared to ORION-10 and 11. Such differences are expected given the different patient populations. Table 4, Table 5, and Table 6 show demographics for ORION-9, 10, and 11, respectively. Follow-up was done well with most patients completing the visit at Day 540 to be considered completers. Many were on treatment at the time of completion. Of those who did not complete, many withdrew consent, more in the placebo arm for all studies than those randomized to inclisiran. Of those who broke the protocol and initiated a PCSK9, all were in the placebo arm (Table 3).

Table 3: Disposition

	ORION-9		ORION-10		ORION-11	
	Inclisiran	Placebo	Inclisiran	Placebo	Inclisiran	Placebo
Screened	617		2329		2381	
Randomized	242	240	781	780	810	801
Completed	235 (97.11%)	231 (96.25%)	721 (92.32%)	694 (88.97%)	772 (95.31%)	770 (95.42%)
On Treatment	229	229	689	665	732	735
Off Treatment	6	2	32	29	40	35
Non-Completion	7 (2.89%)	9 (3.75%)	60 (7.68%)	86 (11.03%)	38 (4.69%)	37 (4.58%)
Adverse Event	0	0	8	5	4	0
Physician Decision	0	0	1	0	1	1
Other	5	1	5	3	0	1
Withdrew Consent	0	4	24	34	13	17
Lost to follow-up	1	2	10	24	6	3
Death	1	1	12	11	14	15
Initiated PCSK9	0	1	0	9	0	0

None of the deaths were considered to be due to study drug. These were balanced between the inclisiran and placebo arms with a pooled total of 27 in each arm. The most common cause of

death in all three studies were cardiac disorders, these were generally balanced between the arms. While imputation is not the most realistic way to handle missing data for these patients, since deaths were minimal, balanced among treatment arms, and not considered to be related to study treatment, any affect the imputation has would be cancelled out in the treatment effect. Any impact that the imputation has on the treatment effect would be minimal and would favor the placebo arm given the conservative imputation methods used.

Table 4: ORION-9 Baseline Demographics and Characteristics

Characteristic	Category	Inclisiran N=242	Placebo N=240
Sex	Male	112 (46.3%)	115 (47.9%)
	Female	130 (53.7%)	125 (52.1%)
Race	White	226 (93.4%)	227 (94.6%)
	Black	8 (3.3%)	7 (2.9%)
	Other	8 (3.3%)	6 (2.5%)
Ethnicity	Hispanic	7 (2.9%)	8 (3.3%)
	Non-Hispanic	235 (97.1%)	232 (96.7%)
BMI	Normal	64 (26.4%)	57 (23.8%)
	Overweight	89 (36.8%)	103 (42.9%)
	Obese	89 (36.8%)	80 (33.3%)
Region	N America	45 (18.6%)	43 (17.9%)
	Europe	109 (45.0%)	108 (45.0%)
	S Africa	88 (36.4%)	89 (37.1%)
Diabetes	Yes	20 (8.3%)	28 (11.7%)
	No	222 (91.7%)	212 (88.3%)
Statin Use	Yes	227 (93.8%)	225 (93.8%)
	No	15 (6.2%)	15 (6.3%)
Renal	Normal	173 (71.5%)	166 (69.2%)
	Mild	53 (21.9%)	60 (25.0%)
	Moderate	16 (6.6%)	14 (5.8%)
GFR	30 to 60	17 (7.0%)	20 (8.3%)
	60 to 90	131 (54.1%)	138 (57.5%)
	at least 90	94 (38.8%)	82 (34.2%)
Phenotype	FH	207 (85.5%)	200 (83.3%)
	Non-FH	35 (14.5%)	40 (16.7%)

11

Age	N	242	240
	Mean (SD)	54.4 (12.5)	55.0 (11.8)
	Median (Min, Max)	56.0 (22.0, 79.0)	56.0 (21.0, 80.0)
Height	N	242	240
	Mean (SD)	169.8 (11.1)	170.5 (10.1)
	Median (Min, Max)	169.0 (147.0, 199.0)	169.0 (149.0, 199.0)
Weight	N	242	240
	Mean (SD)	83.7 (18.6)	84.2 (18.3)
	Median (Min, Max)	83.0 (41.0, 136.0)	80.0 (47.0, 139.0)
LDL	N	242	240
	Mean (SD)	151.4 (50.3)	154.7 (58.1)
	Median (Min, Max)	139.0 (69.0, 322.0)	138.0 (57.0, 460.0)
PCSK9	N	241	240
	Mean (SD)	452.2 (131.2)	429.1 (135.3)
	Median (Min, Max)	448.4 (125.2, 1004.2)	413.5 (137.1, 1155.7)
APoB	N	241	240
	Mean (SD)	123.8 (33.2)	124.5 (34.8)
	Median (Min, Max)	118.0 (66.0, 254.0)	116.0 (64.0, 304.0)
Cholesterol	N	242	240
	Mean (SD)	230.0 (54.6)	232.4 (62.8)
	Median (Min, Max)	218.5 (140.0, 410.0)	214.0 (119.0, 540.0)
Non-HDL	N	242	240
	Mean (SD)	178.5 (55.4)	181.5 (62.5)
	Median (Min, Max)	167.5 (86.0, 374.0)	158.0 (85.0, 505.0)

Table 5: ORION-10 Baseline Demographics and Characteristics

		Inclisiran N=781	Placebo N=780
Characteristic	Category		
Sex	Male	535 (68.5%)	548 (70.3%)
	Female	246 (31.5%)	232 (29.7%)

12

Race	White	653 (83.6%)	685 (87.8%)
	Black	110 (14.1%)	87 (11.2%)
	Other	18 (2.3%)	8 (1.0%)
Ethnicity	Hispanic	108 (13.8%)	104 (13.3%)
	Non-Hispanic	673 (86.2%)	676 (86.7%)
BMI	Missing	0 (0.0%)	1 (0.1%)
	Normal	85 (10.9%)	75 (9.6%)
	Overweight	267 (34.2%)	274 (35.1%)
	Obese	429 (54.9%)	430 (55.1%)
Diabetes	Yes	371 (47.5%)	331 (42.4%)
	No	410 (52.5%)	449 (57.6%)
Statin Use	Yes	717 (91.8%)	717 (91.9%)
	No	64 (8.2%)	63 (8.1%)
Renal	Missing	0 (0.0%)	1 (0.1%)
	Normal	395 (50.6%)	410 (52.6%)
	Mild	269 (34.4%)	260 (33.3%)
	Moderate	113 (14.5%)	107 (13.7%)
	Severe	4 (0.5%)	2 (0.3%)
GFR	15 to 30	10 (1.3%)	7 (0.9%)
	30 to 60	170 (21.8%)	169 (21.7%)
	60 to 90	422 (54.0%)	414 (53.1%)
	at least 90	179 (22.9%)	190 (24.4%)
Age	N	781	780
	Mean (SD)	66.4 (8.9)	65.7 (8.9)
	Median (Min, Max)	67.0 (35.0, 90.0)	66.0 (39.0, 89.0)
Height	N	781	780
	Mean (SD)	171.0 (10.6)	171.3 (10.1)
	Median (Min, Max)	172.7 (124.0, 197.4)	172.7 (135.8, 205.7)
Weight	N	781	779
	Mean (SD)	92.2 (19.6)	93.6 (21.6)
	Median (Min, Max)	91.0 (47.0, 187.0)	91.0 (31.0, 192.0)
LDL	N	781	780

13

	Mean (SD)	104.5 (39.6)	104.8 (37.0)
	Median (Min, Max)	94.0 (33.0, 466.0)	95.0 (40.0, 329.0)
PCSK9	N	776	779
	Mean (SD)	422.1 (176.9)	414.9 (145.7)
	Median (Min, Max)	405.2 (153.8, 3814.3)	394.9 (105.9, 2415.5)
APoB	N	777	779
	Mean (SD)	94.1 (25.6)	94.6 (25.1)
	Median (Min, Max)	89.0 (39.0, 287.0)	90.0 (48.0, 234.0)
Cholesterol	N	781	780
	Mean (SD)	180.6 (46.1)	180.6 (43.6)
	Median (Min, Max)	170.0 (70.0, 552.0)	171.5 (108.0, 461.0)
Non-HDL	N	781	780
	Mean (SD)	134.0 (44.5)	134.7 (43.5)
	Median (Min, Max)	122.0 (49.0, 496.0)	124.0 (68.0, 431.0)

Table 6: ORION-11 Baseline Demographics and Characteristics

Characteristic	Category	Inclisiran N=810	Placebo N=807
Sex	Male	579 (71.5%)	581 (72.0%)
	Female	231 (28.5%)	226 (28.0%)
Race	White	791 (97.7%)	796 (98.6%)
	Black	12 (1.5%)	8 (1.0%)
	Other	7 (0.9%)	3 (0.4%)
Ethnicity	Hispanic	5 (0.6%)	4 (0.5%)
	NonHispanic	805 (99.4%)	803 (99.5%)
Region	Europe	750 (92.6%)	746 (92.4%)
	S Africa	60 (7.4%)	61 (7.6%)
BMI	Missing	0 (0.0%)	1 (0.1%)
	Normal	120 (14.8%)	106 (13.1%)

14

Characteristic	Category	Inclisiran N=810	Placebo N=807
	Overweight	350 (43.2%)	315 (39.0%)
	Obese	340 (42.0%)	385 (47.7%)
Diabetes	Yes	296 (36.5%)	272 (33.7%)
	No	514 (63.5%)	535 (66.3%)
Statin Use	Yes	777 (95.9%)	778 (96.4%)
	No	33 (4.1%)	29 (3.6%)
Renal	Missing	0 (0.0%)	1 (0.1%)
	Normal	428 (52.8%)	444 (55.0%)
	Mild	315 (38.9%)	280 (34.7%)
	Moderate	67 (8.3%)	81 (10.0%)
	Severe	0 (0.0%)	1 (0.1%)
GFR	15 to 30	1 (0.1%)	2 (0.2%)
	30 to 60	108 (13.3%)	98 (12.1%)
	60 to 90	459 (56.7%)	482 (59.7%)
	at least 90	242 (29.9%)	225 (27.9%)
Age	N	810	807
	Mean (SD)	64.8 (8.3)	64.8 (8.7)
	Median (Min, Max)	66.0 (20.0, 88.0)	65.0 (34.0, 87.0)
Height	N	810	806
	Mean (SD)	169.7 (9.4)	169.8 (9.2)
	Median (Min, Max)	170.5 (131.0, 203.0)	170.0 (131.0, 197.5)
Weight	N	810	806
	Mean (SD)	85.8 (16.2)	87.6 (18.2)
	Median (Min, Max)	84.0 (46.0, 185.0)	86.0 (45.0, 187.0)
LDL	N	810	807
	Mean (SD)	107.1 (41.8)	103.7 (36.4)

Characteristic	Category	Inclisiran N=810	Placebo N=807
	Median (Min, Max)	97.0 (32.0, 556.0)	96.0 (41.0, 335.0)
PCSK9	N	809	803
	Mean (SD)	354.9 (98.9)	352.7 (97.4)
	Median (Min, Max)	345.9 (133.7, 737.4)	340.5 (127.2, 711.7)
APoB	N	810	806
	Mean (SD)	97.1 (28.0)	95.1 (25.2)
	Median (Min, Max)	92.0 (50.0, 335.0)	91.0 (48.0, 231.0)
Cholesterol	N	810	807
	Mean (SD)	187.3 (48.2)	183.3 (42.8)
	Median (Min, Max)	177.0 (100.0, 659.0)	175.0 (95.0, 425.0)
Non-HDL	N	810	807
	Mean (SD)	137.6 (46.9)	133.9 (41.0)
	Median (Min, Max)	126.0 (50.0, 570.0)	126.0 (63.0, 375.0)

3.1.4 Results and Conclusions

3.1.4.1 Missing Data

It should be noted that those considered to be completers for disposition in Table 3 may not necessarily have an LDL-C measurement at day 510 for the primary analysis. Those missing day 510 measurements are shown in Table 8. Missing measurements were imputed for the primary analysis results in Table 10 according to the methodology described in section 3.1.2. Differences in the number missing vs. the number of completers in Table 3 are shown in Table 7. The number of patients which had measurements missing for each of the secondary endpoints at Day 510 is shown in Table 9.

Table 7: Disposition completers by number of missing/observed at Day 510

	ORION-9				ORION-10				ORION-11			
	Inclisiran		Placebo		Inclisiran		Placebo		Inclisiran		Placebo	
Disp. completer Day 510	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Missing	0	11	1	10	56	34	80	34	33	53	32	36

16

Observed	7	224	8	221	4	687	6	660	5	719	5	734

*Disposition completer is defined as someone who completed a day 540 visit

Table 8: Observed and Missing observations for LDL-C at Day 510

	ORION-9		ORION-10		ORION-11	
	Inclisiran	Placebo	Inclisiran	Placebo	Inclisiran	Placebo
	N=242	N=240	N=781	N=780	N=810	N=807
Observed	231	229	691	666	724	739
	95.45%	95.42%	88.48%	85.38%	89.38	91.57
Missing	7	11	66	114	52	68
	2.89%	4.58%	8.45%	14.62%	6.42%	8.43%
Missing, completed on Inclisiran	4	.	24	.	34	.
	1.65%	.	3.07%	.	4.20%	.

Table 9: Missing observations at Day 510 for secondary endpoints

	ORION-9		ORION-10		ORION-11	
	Inclisiran	Placebo	Inclisiran	Placebo	Inclisiran	Placebo
	N=242	N=240	N=781	N=780	N=810	N=807
ApoB	11 (4.53%)	13 (5.42%)	110 (14.1%)	96 (12.3%)	74 (9.1%)	80 (9.9%)
Total Cholesterol	11 (4.53%)	12 (5%)	108 (13.8%)	96 (12.3%)	75 (9.3%)	79 (9.8%)
Non-HDL Cholesterol	11 (4.53%)	12 (5%)	108 (13.8%)	96 (12.3%)	75 (9.3%)	79 (9.8%)
PCSK9	13 (5.35%)	13 (5.42%)	111 (14.2%)	97 (12.4%)	75 (9.3%)	81 (10.0%)

3.1.4.2   Primary Endpoint Results for % change in LDL

Results for both the percent change and time-adjusted percent change in LDL were in line with the applicant's results and showed consistency in treatment effect. Given the similarity in the results of these two endpoints, and the nuanced differences in interpretation that may not be well-understood by the general community of prescribers, it may be better to only include one of these endpoints for labeling. The time adjusted endpoint shows consistency of the treatment effect, which is important to establish given the 6-month window between treatment administration. The effect at Day 510 shows durability of the treatment effect over time. With low rates of missing data, a figure of LDL over time (Figure 2) would be easier to interpret durability of treatment effect. The disadvantage to this is that there is no longer hypothesis test results for those who prefer a more rigorous methodology.

While both consistency and durability are important to establish given the length of time between treatment visits, results from both may not provide additional information that would be useful for prescribers. The time adjusted endpoint provides a rigorous framework in which consistency

17

of a treatment effect can be put into a hypothesis test. As long as there is little to no missing data, a plot of the change in LDL-C over the course of the treatment period may provide support for consistency that would be more readily understood by those who are not familiar with the time adjusted methodology and associated interpretation. Given that follow-up was generally well-done with low missing data and results for the time-adjusted analyses were significant, such plots could be useful for these studies.

Table 10: Primary endpoint results, % LDL-C

Study			Inclisiran	Placebo
ORION-9	% Change LDL at Day 510	Change from Baseline	-39.68 (-43.72, -35.63)	8.22 (4.27,12.16)
		Treatment Effect	-47.89 (-53.52, -42.26)	
	Time-Adjusted % Change in LDL	Change from Baseline	-38.08 (-41.03, -35.14)	6.22 (3.26, 9.17)
		Treatment Effect	-44.3 (-48.58, -40.12)	
ORION-10	% Change LDL at Day 510	Change from Baseline	-51.36 (-53.82, -48.90)	0.98 (-1.47,3.43)
		Treatment Effect	-52.34 (-55.74, -48.95)	
	Time-Adjusted % Change in LDL	Change from Baseline	-51.34 (-53.08, -49.61)	2.51 (0.78,4.25)
		Treatment Effect	-53.86 (-56.30, -51.41)	
ORION-11	% Change LDL at Day 510	Change from Baseline	-45.82 (-48.18, -43.46)	3.98 (1.71,6.25)
		Treatment Effect	-49.80 (-53.03, -46.57)	
	Time-Adjusted % Change in LDL	Change from Baseline	-45.80 (-47.50, -44.11)	3.33 (1.62,5.04)
		Treatment Effect	-49.13 (-51.54, -46.73)	

Figure 2: Percent Change in LDL Over Time

ORION 10

ORION 11
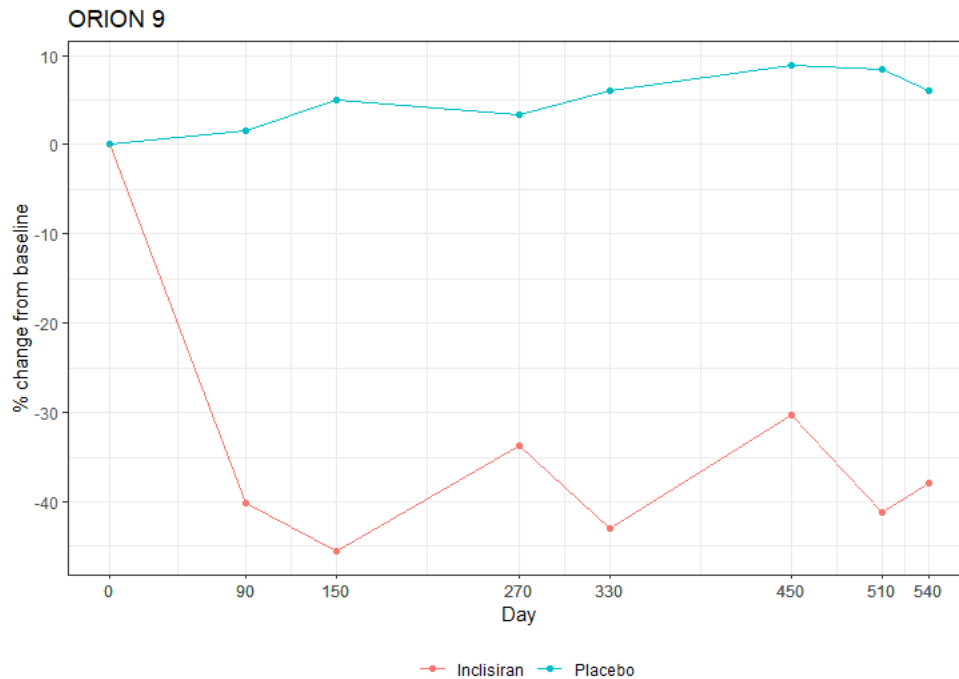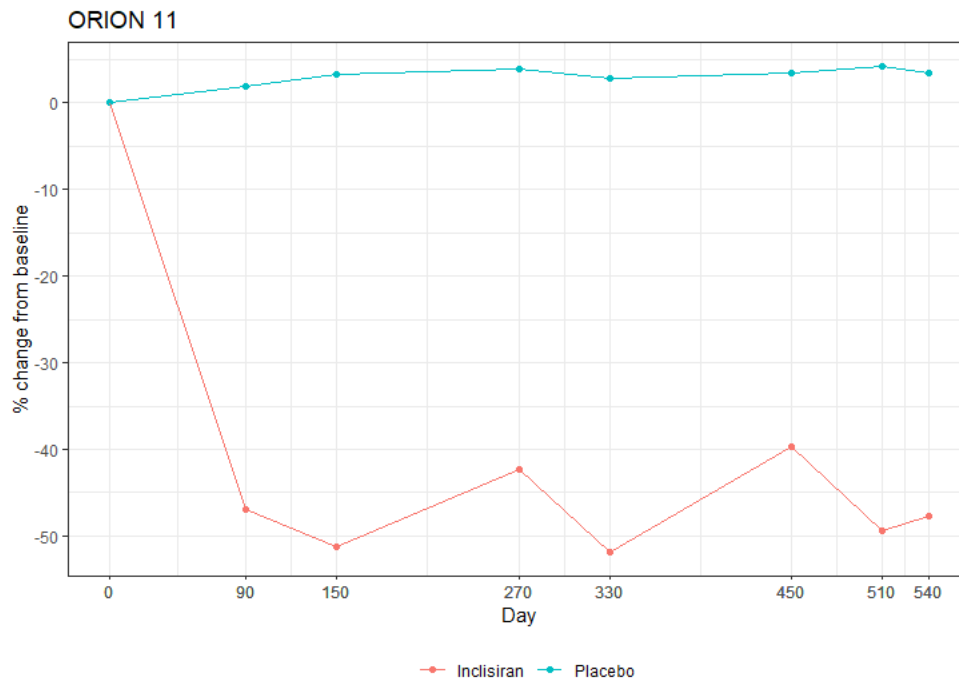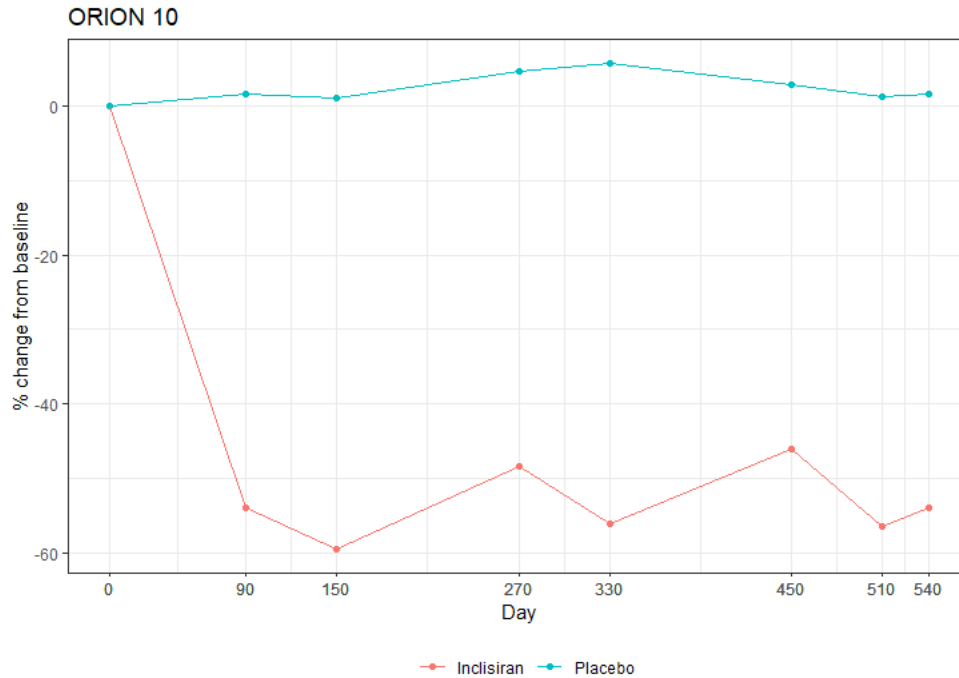
3.1.4.3 Secondary Endpoint Results
Absolute change in LDL-C
Secondary endpoint results for absolute change in LDL at Day 510 also show a similarly large treatment effect as percent change. Given that these results are based on the same LDL-C

19

measurements, but on a different scale, it may be redundant to include both this and the percent chance in LDL-C for labeling purposes.

Table 11: Results for Absolute change in LDL-C

Study			Inclisiran	Placebo
ORION-9	Abs Change LDL at Day 510	Change from Baseline	-58.75 (-64.63, -52.87)	9.8 (3.98, 15.61)
		Treatment Effect	-68.55 (-76.79, -60.31)	
	Time-Adjusted Abs Change in LDL	Change from Baseline	-56.58 (-60.98, -52.17)	6.17 (1.72, 10.62)
		Treatment Effect	-62.74 (-69.01, -56.48)	
ORION-10	Abs Change LDL at Day 510	Change from Baseline	-54.11 (-56.53, -51.70)	-2.11 (-4.53,0.31)
		Treatment Effect	-52.00 (-55.34, -48.67)	
	Time-Adjusted Abs Change in LDL	Change from Baseline	-53.73 (-55.49, -51.98)	-0.39 (-2.14,1.36)
		Treatment Effect	-53.34 (-55.82, -50.86)	
ORION-11	Abs Change LDL at Day 510	Change from Baseline	-50.80 (-53.02, -48.57)	0.82 (-1.41,3.05)
		Treatment Effect	-51.62 (-54.75, -48.48)	
	Time-Adjusted Abs Change in LDL	Change from Baseline	-48.61 (-50.34, -46.87)	0.30 (-1.44,2.04)
		Treatment Effect	-48.91 (-51.36, -46.45)	

Percentage Change in PCSK9 at Day 510

Percentage change in PCSK9 indicated a large effect when compared to placebo. While this change is important to measure in the context of a clinical trial and ascertaining that the treatment is working along the pathway under which it was developed, it is unclear if the treatment effect on PCSK9 will give additional benefit to prescribers. Lowering PCSK9 is meant to have a downstream effect of lowering LDL-C, which these results, combined with the primary endpoint results, indicate that it does. Given that prescribers already know the effects on LDL-C, it may not be beneficial to include further details on PCSK9 lowering.

Table 12: % Change in PCSK9 at Day 510

Study		Inclisiran	Placebo
ORION-9	Change from Baseline	-59.63 (-63.54, -55.73)	17.61 (13.79, 21.43)
	Treatment Effect	-77.24 (-82.68, -71.80)	
ORION-10	Change from Baseline	-69.78 (-73.88, -65.67)	13.52 (9.28, 17.77)
	Treatment Effect	-83.30 (-89.25, -77.34)	
ORION-11	Change from Baseline	-63.63 (-65.53, -61.72)	15.65 (13.73, 17.56)
	Treatment Effect	-79.27 (-81.97, -76.58)	

Percentage Change in Total Cholesterol at Day 510

Percentage change in total cholesterol showed a consistently large treatment effect when compared to placebo.

20

Table 13: % Change in Total Cholesterol at Day 510

Study		Inclisiran	Placebo
ORION-9	Change from Baseline	-25.10 (-27.89, -22.31)	6.64 (3.92, 9.35)
	Treatment Effect	-31.74 (-35.61, -27.86)	
ORION-10	Change from Baseline	-33.56 (-35.09, -32.03)	-0.42 (-1.95, 1.11)
	Treatment Effect	-33.13 (-35.30, -30.97)	
ORION-11	Change from Baseline	-28.00 (-29.40, -26.60)	1.79 (0.38, 3.21)
	Treatment Effect	-29.79 (-31.78, -27.81)	

Percentage Change in Apo-B at Day 510

Percentage change in Apo-B showed a consistently large treatment effect across all three studies when compared to placebo.

Table 14: % Change in Apo-B at Day 510

Study		Inclisiran	Placebo
ORION-9	Change from Baseline	-32.88 (-35.94, -29.81)	3.10 (0.28, 5.91)
	Treatment Effect	-35.97 (-40.03, -31.92)	
ORION-10	Change from Baseline	-44.81 (-46.52, -43.10)	-1.72 (-3.46, 0.02)
	Treatment Effect	-43.09 (-45.50, -40.67)	
ORION-11	Change from Baseline	-38.15 (-39.76, -36.54)	0.79 (-0.82, 2.41)
	Treatment Effect	-38.94 (-41.21, -36.67)	

Percentage Change in Non-HDL at Day 510

Percentage change in non-HDL cholesterol showed a consistently large treatment effect across all three studies when compared to placebo.

Table 15: % Change in Non-HDL Cholesterol at Day 510

Study		Inclisiran	Placebo
ORION-9	Change from Baseline	-34.75 (-38.39, -31.11)	7.56 (4.04, 11.09)
	Treatment Effect	-42.31 (-47.35, -37.28)	
ORION-10	Change from Baseline	-47.41 (-49.44, -45.38)	-0.05 (-2.08, 1.99)
	Treatment Effect	-47.36 (-50.25, -44.47)	
ORION-11	Change from Baseline	-41.16 (-43.09, -39.24)	2.15 (0.22, 4.09)
	Treatment Effect	-43.32 (-46.04, -40.60)	

3.2   Evaluation of Safety

Overall, safety was balanced between the two treatment arms with slightly fewer patients on inclisiran reporting a series adverse event (AE) compared to placebo. The most common treatment emergent AE was diabetes (11.4% placebo vs. 11.6% inclisiran). Injection site reactions had the biggest difference of adverse events with 0.1% placebo patients and 3.1% inclisiran patients. There were no major safety issues found in the three studies.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Sample estimates for the treatment effect of percent change in LDL-C at Day 510 were generally similar for subgroups and in line with the primary endpoint results for each study (Figure 3, Figure 4, Figure 5). Estimates were obtained using the same MI ANCOVA model as discussed in section 3.1.2 for the primary analysis based on 100 imputed datasets. All subgroups showed a treatment effect trending favorably for inclisiran.

There were some random highs and random lows in sample estimates of subgroup treatment effects due to small sample size and large variability for some subgroups. Therefore, we also derive shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. We used the same flat prior to derive shrinkage estimates for all subgroups. The Bayesian hierarchical model assumptions are:

For $i = 1, 2\ldots$ Y_i represents the observed sample estimate of treatment effect in a subgroup level i, assume $Y_i \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variance for sample estimates
- $\mu_i \sim N(\mu, \tau^2)$
- $\mu \sim N(0, 100)$, $1/\tau^2 \sim Gamma(0.001, 0.001)$

Results from both the sample and shrinkage estimates of the treatment effects for the subgroups are presented for each of the three studies in Figure 3, Figure 4, Figure 5. Sample and shrinkage estimates are generally consistent with each other and in line with the overall treatment effect.

Figure 3: ORION-9 Subgroup Results

ORION-9: Subgroup Analyses, Inclisiran vs. Placebo

■ Sample ■ Shrinkage

Subgroup	Category	HR Sample	HR Shrinkage
Age	65 or Less	-48.74	-48.11
	Over 65	-45.14	-47.39
Ethnicity	Hispanic	-44.59	-47.23
	NonHispanic	-48.01	-47.86
LDL Quartiles	Quartile 1	-65.33	-58.84
	Quartile 2	-40.75	-43.42
	Quartile 3	-46.63	-47.1
	Quartile 4	-38.84	-42.18
Race	Black	-64.6	-49.8
	Other	-51.35	-48.61
	White	-47.16	-47.71
Region	Europe	-46.83	-47.69
	N America	-44.41	-47.5
	S Africa	-50.89	-48.23
Sex	Female	-46.14	-47.51
	Male	-49.92	-48.3

Figure 4: ORION-10 Subgroup Results

ORION-10: Subgroup Analyses, Inclisiran vs. Placebo

■ Sample ■ Shrinkage

Subgroup	Category	HR Sample	HR Shrinkage
Age	65 or Less	-52.83	-52.46
	Over 65	-52.01	-52.28
Ethnicity	Hispanic	-39.55	-42.52
	NonHispanic	-54.39	-53.91
LDL Quartiles	Quartile 1	-64.39	-62.36
	Quartile 2	-54.79	-54.35
	Quartile 3	-46.56	-47.42
	Quartile 4	-42.97	-44.36
Race	Black	-44.49	-49.88
	Other	-43.74	-50.67
	White	-53.86	-52.96
Sex	Female	-53.44	-52.63
	Male	-52.04	-52.35

23

Figure 5: ORION-11 Subgroup Results

ORION-11: Subgroup Analyses, Inclisiran vs. Placebo

Subgroup	Category	HR Sample	HR Shrinkage
Age	65 or Less	-51.62	-50.27
	Over 65	-47.76	-49.16
Ethnicity	Hispanic	-9.4	-38.55
	NonHispanic	-50.03	-49.89
LDL Quartiles	Quartile 1	-59.24	-57.64
	Quartile 2	-53.45	-52.79
	Quartile 3	-46.95	-47.37
	Quartile 4	-38.67	-40.46
Race	Black	-48.34	-49.51
	Other	-46.27	-49.41
	White	-49.76	-49.71
Region	Europe	-49.06	-49.52
	S Africa	-58.89	-52.51
Sex	Female	-49.92	-49.81
	Male	-49.75	-49.78

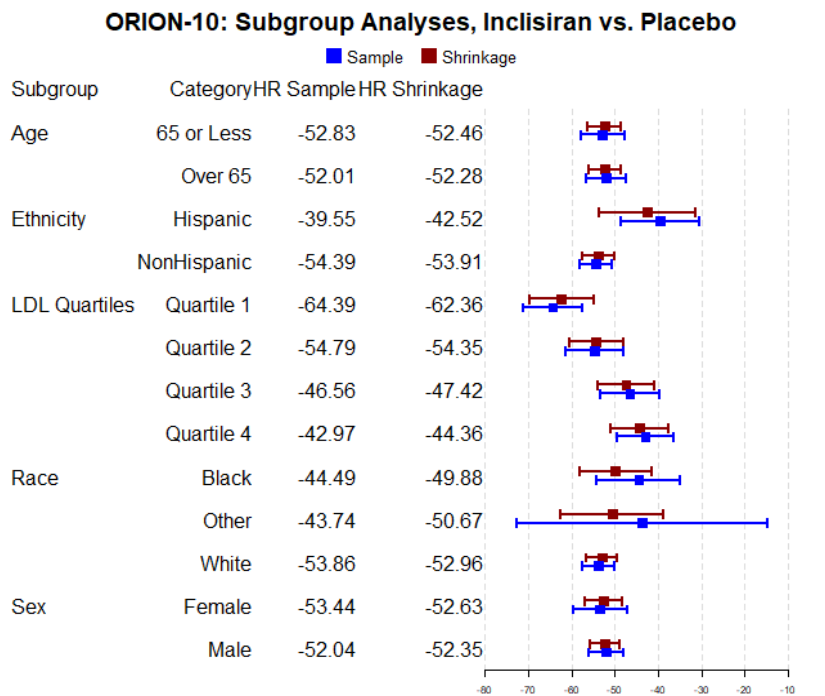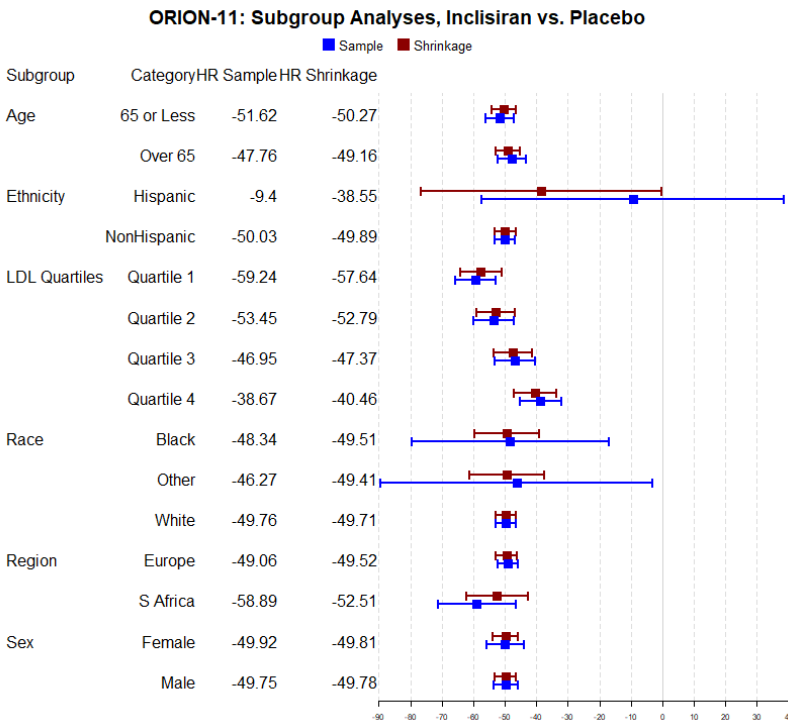## 4.2 Baseline LDL-C Subgroups

There was a trend in all three studies where those with lower baseline LDL-C in the lowest quartile seemed to have a stronger treatment effect than those with higher LDL-C at baseline (Table 16). Figure 6 shows results by baseline LDL-C for all three studies with vertical lines drawn at the baseline LDL-C quartiles. Simple linear lines of best fit were drawn in to show general trend for each treatment group. However, given the results seen in Table 16, nonparametric curves which relax linearity assumptions were also drawn in to better see how trends between the arms may change over the LDL-C spectrum and quartiles.

The few patients with very low baseline LDL-C tended to be more likely to have an increased percent LDL-C in both ORION-10 and 11, although that is not typical for most patients within the first quartile. The trends seen in the placebo arm tended to be similar, but with improved LDL-C percent change in the inclisiran group, which is indicative of a treatment effect. The treatment effect may be somewhat attenuated at higher baseline levels of LDL-C.

Results for ORION-9, which had a HeFH population, trended a little differently from the other two studies. The inclisiran group didn't have patients in the lowest quartile with a large percentage gain in LDL-C, although there were some in the placebo arm. Patients in ORION-9 had a higher median baseline LDL-C, and patients in the first quartile of this study tended to have a higher baseline LDL-C which may also attribute to the differences between the studies in

24

the lowest quartile. Thus, we see a larger treatment effect in the lowest quartile, which is much stronger than in the other two studies when compared to the other quartiles. This effect could be due to the higher LDL-C levels seen in this patient population. Figure 6 and Table 16 indicate treatment effect for this population may be somewhat different than those in the other studies, although baseline levels make it difficult to determine if it's because the population is different or because the LDL-C levels tended to be higher. Overall, though, all study participants in all three studies tended to do better on inclisiran than on placebo at all baseline LDL-C levels.

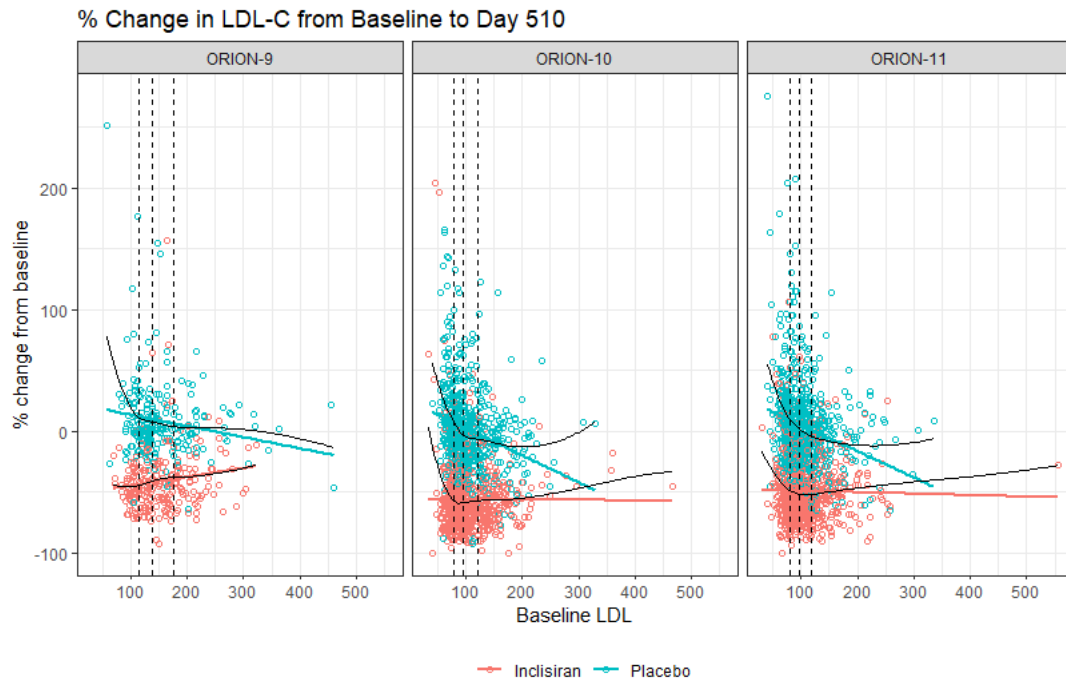**Figure 6: % Change in LDL-C by baseline LDL-C**

Table 16: % Change in LDL-C (Change from baseline and treatment effect) by Baseline LDL-C Quartiles

		Inclisiran	Placebo
ORION-9	Quartile 1	-46.33 (4.82)	19 (4.97)
		-65.33 (-76.49, -54.17)	
	Quartile 2	-37.91 (4.69)	2.84 (4)
		-40.75 (-52.22, -29.28)	
	Quartile 3	-37.4 (3.95)	9.23 (4.03)
		-46.63 (-57.69, -35.57)	
	Quartile 4	-35.83 (5.46)	3.01 (6.02)
		-38.84 (-50.02, -27.66)	
ORION-10	Quartile 1	-49.44 (2.89)	14.94 (2.9)
		-64.39 (-71.34, -57.43)	
	Quartile 2	-54.59 (2.48)	0.2 (2.53)
		-54.79 (-61.39, -48.18)	

	Quartile 3	-51.18 (2.55)	-4.61 (2.4)
		-46.56 (-53.32, -39.81)	
	Quartile 4	-50.12 (3.27)	-7.14 (3.33)
		-42.97 (-49.65, -36.3)	
	Quartile 1	-45.87 (2.7)	13.37 (2.55)
		-59.24 (-65.64, -52.84)	
	Quartile 2	-47.21 (2.34)	6.24 (2.41)
ORION-11		-53.45 (-59.86, -47.04)	
	Quartile 3	-48.17 (2.39)	-1.22 (2.24)
		-46.95 (-53.34, -40.56)	
	Quartile 4	-42.33 (3.03)	-3.66 (2.96)
		-38.67 (-45.13, -32.21)	

5   SUMMARY AND CONCLUSIONS

5.1   Statistical Issues

There were no major statistical issues that would impact or change the overall conclusions. Minor issues that were in all three studies included redundancy in the endpoints. This, however, does not impact significance of the endpoints and can be surmounted with careful thought into what is most useful to communicate to prescribers through labeling. We defer to the clinical team to determine which endpoints are useful and well understood by prescribers.

5.2   Collective Evidence

Follow-up for all three studies was generally well done which led to low levels for missing data (Table 7). Large treatment effects observed in each study (Section 3.1.4) combined with low amounts of missing data led to robust efficacy results. Results did not tip except under highly implausible scenarios.

5.3   Conclusions and Recommendations

The collective evidence from the submitted data from three safety and efficacy studies provide strong evidence of a treatment effect in the study populations. We recommend approval for the proposed indication based on these findings.

5.4   Labeling Recommendations

26

Although all primary and key secondary endpoints were considered statistically significant, due to a high amount of redundancy between some of these endpoints we do not recommend that all go into the label. The sponsor has included only results for ▨▨▨▨▨▨▨▨▨▨▨▨ (b) (4) ▨▨▨▨▨▨ percent change in LDL-C, percent change in total cholesterol, percent change in non-HDL-C, and percent change in Apo B at Day 510 in the proposed label. We support the clinical recommendation ▨▨▨▨▨▨▨▨▨▨▨▨▨▨▨▨▨▨ (b) (4) of plots of observed LDL-C over the treatment period, similar to Figure 2.

27

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I concur