CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 204-042
Drug Name:	JNJ-28431754-ZAE
Applicant:	Sponosor: Janssen Research & Development, a division of Janssen Pharmaceutica N.V. B-2340 Beerse, Belgium Test Facility: Drug Safety Sciences, Beerse site Turnhoutseweg 30 B-2340 Beerse, Belgium
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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. The purpose of rat study was to assess the carcinogenic potential of JNJ-28431754-ZAE, an SGLT2 inhibitor for the potential treatment of Type II diabetes, when administered orally via gavage to male and female SPF Sprague-Dawley rats at daily doses of 10, 30 or 100 mg eq./kg body weight/day (mg eq./kg/day) during 2 years. A vehicle group [aqueous solution containing 0.5% w/v Methocel (Hydroxypropyl Methylcellulose)] and three treated groups were included. The purpose of the mouse study was to assess the carcinogenic potential of JNJ-28431754-ZAE following daily oral gavage administration for up to two years in CD-1 mice. Three treatment groups of 65 male and 65 female Crl:CD1®(Icr) mice were administered the test article at respective dose levels of 10, 30, or 100 mg/kg/day. One additional group of 65 animals/sex served as the control and received the vehicle, 0.5% (w/v) hypromellose in deionized water. The vehicle or test article was administered to all groups via oral gavage, once daily for 104 consecutive weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Alavi.

2. Rat Study

Two separate experiments were conducted, one in males and one in females. Male and female SPF Sprague-Dawley rats were assigned to 4 groups (65/sex/group) and received one control or at a dose level of 10, 30, or 100 mg eq./kg/day to male and female rats. The following table contains the information about the study design:

	Identitynumber(computernumber)ofrats	
Dosagegroups (color code)	Males	Females
V: Vehicle (blue) Dosage: 0 mg eq./kg/day Concentration: 0 mg eq./ml Volume: 5 ml/kg/day	1 - 65	401 - 465
L : Low (red) Dosage: 10 mg eq./kg/day Concentration: 2 mg eq./ml Volume: 5 ml/kg/day	101 - 165	501 - 565
M : Medium (yellow) Dosage: 30 mg eq./kg/day Concentration: 6 mg eq./ml Volume: 5 ml/kg/day	201 - 265	601 - 665
H : High (green) Dosage: 100 mg eq./kg/day Concentration: 20 mg eq./ml Volume: 5 ml/kg/day	301 - 365	701 - 765

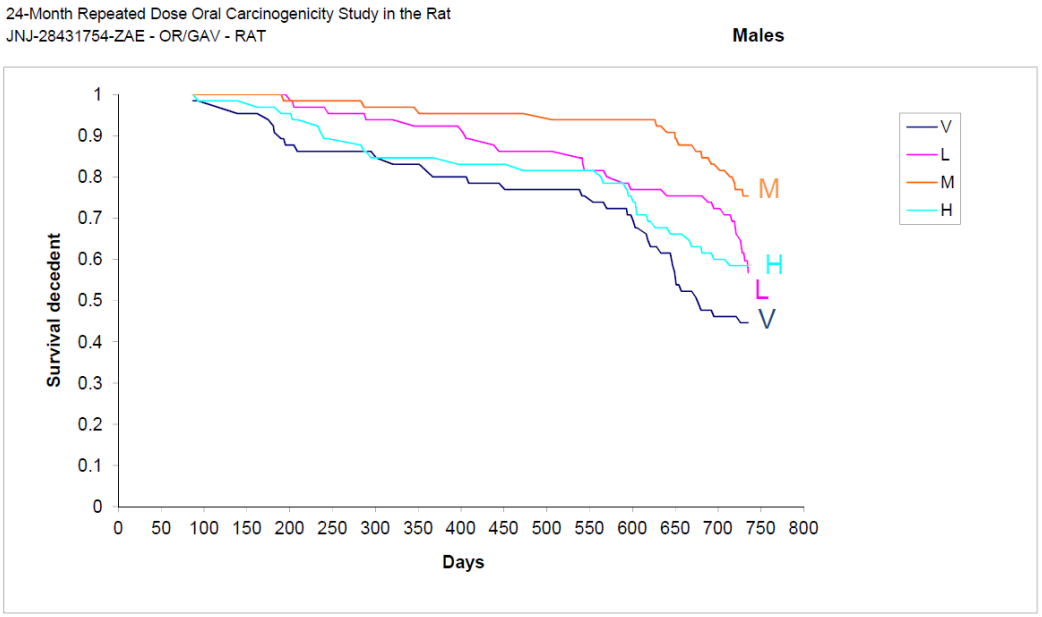
All animals were observed at least once a day for signs of ill health, abnormal behavior or unusual appearance, occurrence of untoward clinical effects and manifestations of toxic and pharmacological response, moribund state and mortality. Special attention was paid to development of palpable masses: the time of onset, location, dimensions, appearance and progression of each visible or palpable mass were recorded after clinical palpation. Therefore an extensive examination was performed on a weekly basis, to discover new masses and to give them a score. The discovered masses were checked and scored daily.

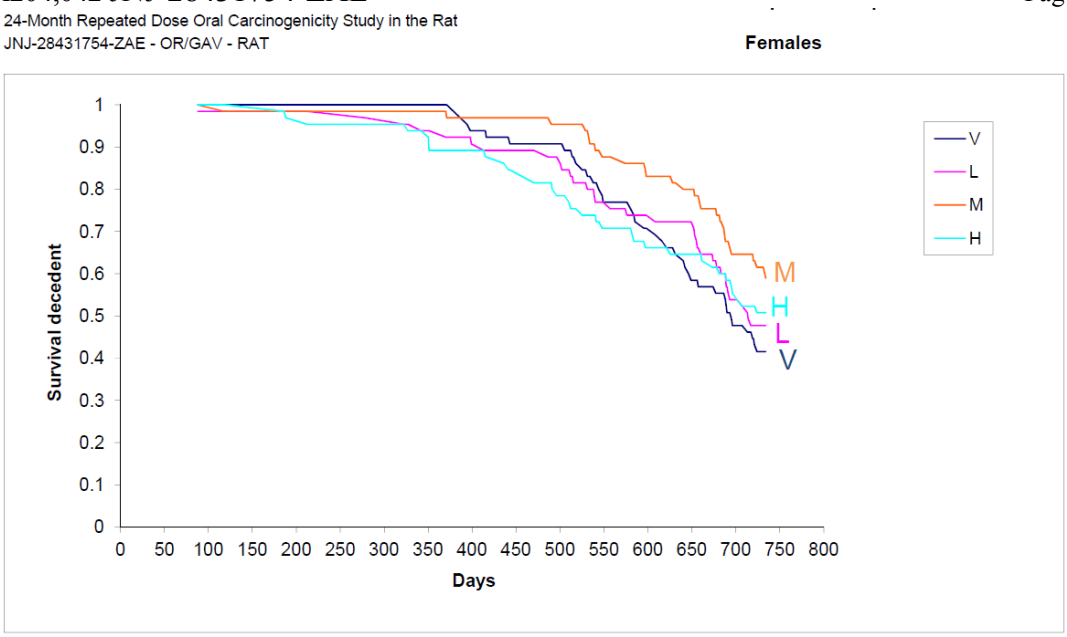
2.1. Sponsor's analyses

2.1.1. Survival analysis

Non-stratified mortality tables were analyzed using the Cochran-Armitage trend test. Stratified mortality tables were analyzed using two different tests for heterogeneity, i.e. the Logrank test as well as the generalized test according to Wilcoxon-Gehan. Kaplan-Meier Curves were plotted to show survival distribution function versus time (study day on test) for each group. All tests were conducted at a minimum risk level of 5%.

Sponsor's findings: Repeated oral administration of JNJ-28431754-ZAE to male and female rats at 10, 30 or 100 mg/kg body weight/day for two years did not have a negative impact on the overall survival, but survival seemed increased in all test article dosed animals. This was somewhat more pronounced in males and statistically significant in male animals dosed at 30 mg eq./kg/day while lowest survival was observed in vehicle animals (29/65 and 27/65 survivors in males and females, respectively).





2.1.2. Tumor data analysis

Tumor incidences were analyzed using the two (positive and negative) one-sided Fisher Exact tests comparing group incidences between vehicle group and treated groups with Bonferroni-Holm correction at the 5% risk level. Statistical analysis was done on the number of animals with individual or combined tumors, with benign or malignant status, from a specific tissue or a group of tissues.
The presence of a positive dose related trend across observed dose levels was tested using Peto's prevalence, death rate and onset-rate analyses for incidental, fatal or mortality independent tumors respectively. The trend analysis was carried out comparing treated animals against the vehicle group. Peto's prevalence method depends on the partitioning of the study time period into intervals in order to eliminate biases caused by inter-current mortality differences. Peto's ad-hoc method for interval selection based on the total incidence of all tumors was employed.
When a tumor was fatal for some animals and incidental for other animals, data for incidental and fatal tumors were analyzed separately by the prevalence and death rate methods and the results from the different methods were then combined by simply adding together the separate observed frequencies, expected frequencies and the variances, to yield an overall result. When the total number of tumor occurrence across treatment groups is small, the approximation may not be stable and/or reliable. When the total number of tumor bearing animals in all treatment groups was 8 or less the "exact" permutation trend test was used to test for the positive trend.
All tests were performed at a significance level of five percent or less.
All statistical methods used were:
1. Fisher test using 1-sided analysis.
2. Peto's prevalence, death rate and onset-rate analyses for incidental, fatal or mortality independent tumors, respectively.

Sponsor's findings: In male rats dosed at 100 mg eq./kg/day, the combined incidence of hepatocellular tumors and hepatocellular carcinoma showed a positive trend and fell above the study site historical control data (HCD) (see table below). This increase is not considered toxicologically relevant in the absence of

other relevant (pre-neoplastic) liver changes such as increased foci of cellular alteration. In females, there was even a decrease in foci of cellular alteration, both basophilic and eosinophilic, at 100 mg eq./kg/day.
Lymphoma:
In females at 100 mg eq./kg/day, a positive trend was noted for malignant lymphoma. The incidence was above the study site HCD (see table below), ut was within the historical control range of other test facilities e.g., (b) (4) (maximum lymphoma incidence of 10 % in females). This higher incidence in females only was not considered toxicologically relevant.
Histiocytic sarcoma:
In both sexes dosed at 10 and in males dosed at 100 mg eq./kg/day, the incidence of histiocytic sarcoma fell slightly outside the study site HCD (see table below). This was considered incidental and not toxicologically relevant, based on the lack of a dose-related effect. Peto-analysis showed no positive trend (both sexes). This tumor type is commonly encountered in rats

	Males					Females				
Dose group	V	L	M	H	HCD	V	L	M	H	HCD
Liver	65	65	65	65		65	65	65	65	
Hepatocellular tumor	3	3	2	9	7/65	0	1	1	1	4/65
Adenoma hepatocellular	2	3	2	5	6/65	0	1	1	1	4/65
Carcinoma hepatocellular	1	0	0	4	2/65	0	0	0	0	1/65
Foci of cellular alt basophilic	38	41	49	40		53	47	41	32	
Foci of cellular alt eosinophilic	26	21	22	21		22	15	17	9	
Haemolymphoreticular system										
Histiocytic sarcoma	1	5	3	4	3/65	0	2	1	1	1/65
Lymphoma malignant	3	2	1	3	2/65	0	1	1	3	1/65

HCD: Beerse HCD; maximum incidence in control or vehicle group

Lab – Max HCD	**J&J**		(b) (4)		(b) (4)		(b) (4)	
Sex	M	F	M	F	M	F	M	F
Adenoma hepatocellular	6/65	4/65	3/60	3/65	4/50	3/60	4/60	8/60
Carcinoma hepatocellular	2/65	1/65	2/60	1/65	3/50	1/60	4/60	1/60
Haemolymphoreticular system								
Histiocytic sarcoma	3/65	1/65	3/60	6/60	4/60	3/50	3/50	4/130
Lymphoma malignant	2/65	1/65	3/60	1/60	4/60	5/70	4/70	5/50

Max HCD: maximum incidence in control or vehicle group of respective lab

Mammarygland:
In mid and high dose females there was a lower incidence of mammary gland tumors; this was considered to be related to the lower body weight.

	Males				Females			
Dose groups	**V**	**L**	**M**	**H**	**V**	**L**	**M**	**H**
Pheochrom. (B+ M)	**4**	**4**	**7**	**28**	**2**	**1**	**3**	**7**
Terminal rats	3	3	6	23	2		3	4
Pre-terminal: 1st day	*617*	*720*	*691*	*594*		*716*		*624*
Leydig cell tumor	**1**	**8**	**20**	**24**				
Terminal rats		8	17	20				
Pre-terminal: 1st day	*648*		*673*	*562*				

Animal No. (males)	**301**	**306**	**310**	**314**	**321**	**322**	**332**	**333**	**351**	**355**	**364**
Group Symbol	H	H	H	H	H	H	H	H	H	H	H
Days on test	T	T	T	T	T	T	604	T	T	680	T
KIDNEY											
Adenoma (B)/carcinoma (N)	B	B	B	N	B	B	B	B+N	B	N	N
ADRENAL MEDULLA											
Hyperplasia				1		3		3		4	
Pheochromocytoma	B	B	B		B	B			B		B
TESTES – Leydig cell											
Hyperplasia			1	2	2	3	2	2			1
Adenoma (B)			B		B	B	B	B	B	B	

2.2. Reviewer's analyses

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

2.2.1. Survival analysis

The survival distributions of animals in four treatment groups (three treated groups and one control group) were

tested by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested using the Cox test (Cox, 1972). The inter-current mortality data are given in Tables 1A and 1B in the appendix in males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for males and females, respectively. Results for the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for males and females, respectively.

Reviewer's findings: The test results showed no statistically significant dose-response relationship in mortality in either sex across all treatment groups. The tests showed statistically significant difference in survival between medium dose group and the control group in both males and females, between low dose group and the control group in males. Also the tests showed statistically significant pair-wise differences between medium dose group and the control group in survival in both males and females. There were some differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.

2.2.2. Tumor data analysis

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

As suggested by the reviewing pharmacologist Dr. Alavi, this reviewer did the analysis of all the combinations of all organ/tumors described in the table below:

Combining Tumors for Statistical Analysis †					
Tissue	**Tumor types [a]**	**Rat**		**Mouse**	
All sites	Hemangiomas + hemangiosarcomas	♂	♀	♂	♀
All sites	Mesotheliomas	♂	♀	♂	♀
All sites	Leukemias	♂		♂	♀
All sites	Lymphomas	♂	♀	♂	♀
All bone [b]	Chondromas + osteosarcomas + osteomas	♂	♀	♂	♀
Common sites	Lipomas + liposarcomas	♂	♀	♂	♀
Adrenals	Cortical adenomas + carcinomas				♀
Adrenals	Benign + malignant pheochromocytomas				♀
Alimentary tract (upper) [c]	Adenomas + carcinomas [c]			♂	
Alimentary tract (lower) [d]	Adenomas + carcinomas [d]			♂	
Alimentary tract (all) [e]	Adenomas + carcinomas [e]			♂	
Duodenum	Leiomyomas + leiomyosarcomas		♀		
Harderian gland	Adenomas + adenocarcinomas			♂	
Injection site	Fibromas + fibrosarcomas			♂	
Injection site	Fibromas + fibrosarcomas + sarcomas + rhabdomyosarcomas			♂	
Kidney	Tubular cell adenomas + carcinomas	♂		♂	
Liver	Hepatocellular adenomas + carcinomas	♂		♂	
Lung	Bronchio-alveolar adenomas + carcinomas			♂	
Mammary	Adenomas + carcinomas		♀		
Mammary	Fibroadenomas + fibrocarcinomas		♀		
Mammary gland	Adenomas + adenocarcinomas + adenoacanthomas				♀
Oral cavity + tongue	Squamous cell papillomas + carcinomas	♂	♀	♂	♀
Pancreas	Islet cell adenomas + mixed acinar/islet cell adenomas	♂			
Pancreas	Mixed acinar/islet cell adenomas + acinar cell adenomas	♂			
Pituitary	Anterior lobe adenomas + carcinomas	♂	♀	♂	♀
Skin and subcutis	Basal cell adenomas + carcinomas	♂			
Skin and subcutis	Squamous cell papillomas + carcinomas + keratoacanthomas	♂	♀	♂	
Skin and subcutis	Sarcomas (not specified) + fibrosarcomas + liposarcomas + rhabdomyosarcomas				♀
Testis	Interstitial cell adenomas + mesotheliomas + rete testis adenomas + sex cord stromal tumors	♂		♂	
Thoracic cavity	Hibernomas (benign + malignant)	♂	♀		
Thymus	Thymomas (benign + malignant)	♂			
Thyroid	C-cell adenomas + carcinomas	♂	♀	♂	♀

Thyroid	Follicular cell adenomas + carcinomas	♂	♀	♂	♀
Uterus	Stromal polyps + sarcomas		♀		
Uterus	Stromal polyps + endometrial stromal sarcomas				♀
Uterus	Adenomas + adenocarcinomas		♀		
Uterus	Schwannomas (benign + malignant)				♀
Uterus	Leiomyomas + leiomyosarcomas				♀
Uterus + vagina	Uterus stromal neoplasms + vaginal stromal neoplasms		♀		♀

† Tumor combinations by sex (not combined across sexes or across species)
[a] Include separate analyses for individual tumor types
[b] For example bone, cranium, femur, etc.
[c] Stomach, duodenum, jejunum
[d] Colon, cecum
[e] Stomach, duodenum, jejunum, colon, cecum

Multiple testing adjustment: Adjustment for the multiple dose response relationship testing was done using the criteria developed by Lin and Rahman (1998). The criteria recommend the use of a significance level α=0.025 for rare tumors and α=0.005 for common tumors for a submission with two species for 2-year rodent studies, and a significance level α=0.05 for rare tumors and α=0.01 for common tumors for a submission with only one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the overall spontaneous tumor rate is less than 1%. The adjustment for multiple pair-wise comparisons was done using the criteria developed by Haseman (1983) that recommends the use of a significance level α=0.05 for rare tumors and α=0.01 for common tumors, in order to keep the overall false-positive rate at the nominal level of approximately 10%. It should be noted that the recommended test levels by Lin and Rahman for the adjustment of multiple testing were originally based on the result of a simulation and an empirical study using the Peto method for dose response relationship analysis. However, some later simulation results by Rahman and Lin (2008) indicate that the criteria apply equally well to the analysis using the poly-3 test.

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 in either tests for dose response relationship and/or pair-wise comparisons between control and each of individual treated groups. In the following table, p-values in red show significant findings based on the above proposed levels of significance and numbers with brackets are survival-adjusted group sizes.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pair-wise Comparisons

	Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Male										
	ADRENAL GLANDS	Pheochromocytoma ben	4	4	7	26	0.000	0.741	0.466	0.000
			[44]	[53]	[60]	[50]	.	.	.	.
	ADRENALS	B+M_PHEOCHROMOCYTOMA	4	4	7	28	0.000	0.741	0.466	0.000
			[44]	[53]	[60]	[50]	.	.	.	.
	KIDNEYS	Adenoma renal tubule	0	0	1	8	0.000	.	0.577	0.004
			[44]	[53]	[60]	[49]	.	.	.	.
		Carcinoma renal tubu	0	0	1	5	0.001	.	0.573	0.037
			[44]	[53]	[59]	[49]	.	.	.	.
		T_CELL_ADENOMAS+CARC	0	0	2	12	0.000	.	0.331	0.000
			[44]	[53]	[60]	[49]	.	.	.	.
	LIVER	ADENOMA+CARCINOMA	3	3	2	10	0.003	0.745	0.896	0.054
			[44]	[53]	[59]	[49]	.	.	.	.
		Carcinoma hepatocell	1	0	0	4	0.012	.	.	0.216
			[44]	[53]	[59]	[49]	.	.	.	.
	TESTES	Adenoma interstitial	1	8	20	24	0.000	0.030	0.000	0.000
			[44]	[53]	[60]	[50]	.	.	.	.

	Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Female										
	ADRENAL GLANDS	Pheochromocytoma ben	2	1	3	7	0.008	0.883	0.565	0.079
			[48]	[49]	[55]	[48]	.	.	.	.
	HEMOLYMPHORETIC	Lymphoma malignant	0	1	1	3	0.044	0.505	0.539	0.129
			[48]	[49]	[56]	[50]	.	.	.	.
	KIDNEY	T_CELL_ADENOMA+CARCI	0	0	0	8	0.000	.	.	0.003
			[48]	[49]	[55]	[48]	.	.	.	.
	KIDNEYS	Adenoma renal tubule	0	0	0	7	0.000	.	.	0.006
			[48]	[49]	[55]	[48]	.	.	.	.

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, the positive dose-response relationships in the incidences of renal tubule adenoma and combined tubular adenomas and carcinomas in kidneys in both males and females, pheochromocytoma and combined benign and malignant

pheochromocytomas in adrenal glands, renal tubule carcinoma in kidneys, combined adenomas and carcinomas in liver and interstitial adenoma in testes in males were considered to be statistically significant.

In both males and females, the pair-wise comparison of renal tubule adenoma and combined tubule adenomas and carcinomas in kidneys between high dose group and the control were considered to be statistically significant for increased tumor incidence.

In males only, also based on the criteria of Haseman, the pair-wise comparison of pheochromocytoma and combined benign and malignant pheochromocytomas in adrenal glands, renal tubule carcinoma in kidneys and interstitial adenoma in testes between the high dose group and the control were considered to be statistically significant for increased tumor incidence. In addition, the pair-wise comparison of interstitial adenoma in testes between the medium dose group and the control was considered to be statistically significant for increased tumor incidence.

3. Mouse Study

The objective of this study was to evaluate the oncogenic potential of JNJ-28431754-ZAE (the hemi-hydrate salt form of JNJ-28431754) following daily oral gavage administration for up to two years in CD-1 mice. Three treatment groups of 65 male and 65 female Crl:CD1®(Icr) mice were administered the test article at respective dose levels of 10, 30, or 100 mg/kg/day. One additional group of 65 animals/sex served as the control and received the vehicle, 0.5% (w/v) hypromellose in deionized water. The vehicle or test article was administered to all groups via oral gavage, once daily for 104 consecutive weeks (with the exception of 2 dose groups) at a dose volume of 10 mL/kg. Females given 30 mg/kg/day were dosed for 101 consecutive weeks and males given 100 mg/kg/day were dosed for 103 consecutive weeks. Additionally, one group of 20 animals/sex served as the control toxicokinetic (TK) animals and three groups of 39 animals/sex/group served as the treated TK animals and received the vehicle or test article in the same manner as the main study groups at respective dose levels of 0, 10, 30, or 100 mg/kg/day.
Observations for morbidity, mortality, injury, and the availability of food and water were conducted twice daily for all animals. Observations for clinical signs and masses were conducted weekly. Body weights were measured and recorded weekly for the first 14 weeks, every two weeks until Week 28, and every four weeks thereafter. Food consumption was measured and recorded weekly for the first 14 weeks, every two weeks until Week 28, and every four weeks thereafter. Ophthalmoscopic examinations were conducted for main study animals predose, at 12 months and prior to the terminal necropsy. Blood samples for clinical pathology evaluations were collected from designated animals at terminal necropsy or animals euthanized *in extremis*. The TK parameters were determined for the test article and the M5 and M7 glucuronide metabolites of the parent compound (JNJ-28431754) from concentration-time data in the test species. At study termination, necropsy examinations were performed, organ weights were recorded, and tissues were microscopically examined.

The summary table of the study design given the following table:

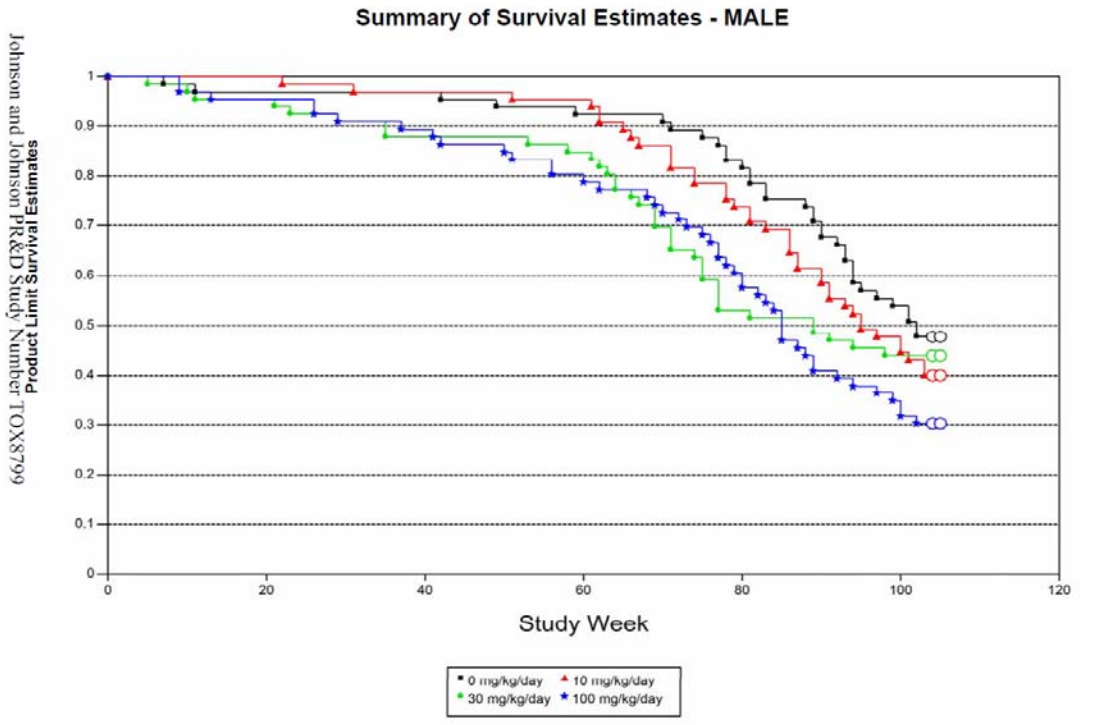
Group	Dose (mg/kg)	Dose volume (mL/kg)	Number of animals	
			Male	Female
MAIN STUDY				
1	0	10	65	65
2	10	10	65	65
3	30	10	65	65
4	100	10	65	65
TOXICOKINETICS				
5	0	10	18+2*	18+2*
6	10	10	36+3*	36+3*
7	30	10	36+3*	36+3*
8	100	10	36+3*	36+3*
* - additional animals included as possible replacements				

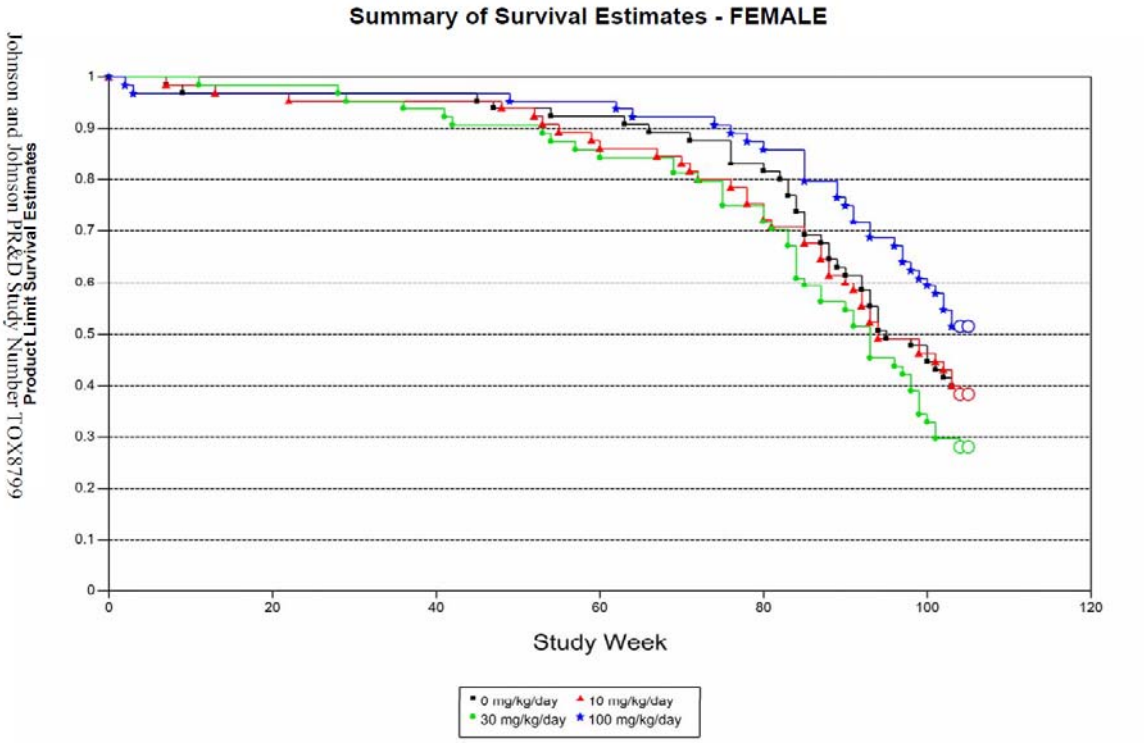
3.1. Sponsor's analyses

3.1.1. Survival analysis

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

Sponsor's findings: No test article-related mortality was noted for males or females at any JNJ-28431754-ZAE dose level. Females given 30 mg/kg/day were dosed for 101 weeks and males given 100 mg/kg/day were dosed for 103 weeks due to survival falling to 20 animals/sex or below.





3.1.2. Tumor data analysis

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

Sponsor's findings: In conclusion, administration of JNJ-28431754 to male and female mice did not result in an increased number of neoplastic lesions when administered by oral gavage at doses up to 100 mg/kg/day for up to two years. Neoplasms in this study were of the type typically seen in this strain and age of mouse. Some tumors were present in only the treated animals; these tumors were still within the incidence range of historical control data (b) (4) Historical Control Neoplastic Data, CD-1 Mouse, (b) (4) 2 Year Studies, 10/99 to 10/09.) Any differences in tumor incidence between control and JNJ-28431754-treated animals were small and not interpreted as biologically significant.

3.2. Reviewer's analyses

To verify sponsor's analyses and to perform the additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses.

3.2.1. Survival analysis

The inter-current mortality data are given in Tables 4A and 4B in the appendix for all four groups of males and females, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for all four groups of males and females, respectively. Results for the tests for dose response relationship and homogeneity of survivals, are given in Tables 5A and 5B in the appendix in males and females, respectively.

Reviewer's findings: The test results showed a statistically significant dose-response relationship in mortality in females across all treatment groups. The tests showed a statistically significant difference in survival between high dose group and the control group in males. Also the tests showed a statistically significant pair-wise difference between high dose group and the control group in survivals in both males and females. There were some differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.

3.2.2. Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and pair-wise comparisons of the control group and treated groups are given in Table 6A and 6B in the appendix in males and females, respectively.

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 either tests for dose response relationship and/or pair-wise comparisons between control and each of individual treated groups. In the following table, p-values in red show significant findings based on the above proposed levels of significance and numbers with brackets are survival-adjusted group sizes.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pair-wise Comparisons

			0 mg	10 mg	30 mg	100 mg				
			Cont	Low	Med	High	P_Value	P_Value	P_Value	P_Value
	Organ Name	Tumor Name	N=65	N=65	N=64	N=44	Dos Resp	C vs. L	C vs. M	C vs. H
Female										
	LUNG	BRON_ADENOMA+CARCINO	12	9	6	14	0.048	0.810	0.939	0.176
			[49]	[47]	[43]	[39]	.	.	.	.
		lymph node, ing LYMPHOMA	0	6	0	0	0.944	0.013	.	.
			[47]	[47]	[41]	[38]	.	.	.	.
		SEX-CORD/STROMAL TUM	2	3	0	5	0.047	0.490	1.000	0.139
			[47]	[46]	[41]	[38]	.	.	.	.

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, there is no statistically significant dose-response relationship in any tested single tumor type in male mouse study. In females only, also based on the criteria of Haseman, the pair-wise comparison of lymphoma in lung between the low dose group and the control was considered to be statistically significant for increased tumor incidence.

4. Evaluation of validity of the designs of the male mouse experiment

As has been noted, the tumor data analyses from male mouse study showed no statistically significant dose-response relationship or pair-wise difference in incidence rate in any tested single tumor type. Before drawing any conclusion regarding the carcinogenic or non-carcinogenic potential of the drug in male mice, it is important to look into the following two issues, pointed out in the paper by Haseman (1984).

(i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?
(ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group. The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman (1985) did an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3Fl mice conducted at the National Toxicology Program (NTP). It was found that, on the average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics-6, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals or 20 to 30 animals still alive in the high dose group, between weeks 80-90, would be consider as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward (1981), suggested that" to be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted based on the toxicity endpoints approach that the high dose should be close to the maximum tolerated dose (MTD). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met.

(i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."

(ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the Minocycline HCl in female mouse carcinogenicity study in the light of the above guidelines.

4.1. Male Mouse Study

The following is the summary of survival data of mice in the high dose groups in males:

Percentage of survival in the high dose group at the end of Weeks 52 and 79

	Percentage of survival	
	End of 52 weeks	End of 79 weeks
Male	84.73%	64.06%

Based on the survival criterion Haseman proposed, it could be concluded that there were enough mice in both males and females that were exposed to the high dose for a sufficient amount of time.

The following table shows the percent difference in mean body weight gain of treated groups when compared with the concurrent combined control, defined as

$$\text{Percent difference} = \frac{(\text{Final BW} - \text{Baseline BW})_{\text{Treated}} - (\text{Final BW} - \text{Baseline BW})_{\text{Control}}}{(\text{Final BW} - \text{Baseline BW})_{\text{Control}}} \times 100$$

Percent Difference in Mean body Weight Gain from Control

Male Control		
10 mg	30 mg	100 mg
-6	-10	-7.3

Therefore, relative to the control, there was a less than 10% in body weight loss in high dose group in male mice.

The mortality rates at the end of the experiment were as follows:

Mortality Rates at the End of the Experiment

	Cont	10 mg	30 mg	100 mg
Male	52.31%	60.0%	55.38%	68.75%

This shows that the morality rate of in the high dose group in males is 16.44% higher than the control. Based on the survival criterion Haseman proposed, it could be concluded that there were enough animals exposed to the high dose for a sufficient amount of time for male experiments. It could be concluded that the high doses used in the males and females were over MTD based on mortality increase criterion and close to MTD based on loss in body weight gain criterion. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

5. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. The purpose of the rat study was to assess the carcinogenic potential of JNJ-28431754-ZAE, an SGLT2 inhibitor for the potential treatment of Type II diabetes, when administered orally via gavage to male and female SPF Sprague-Dawley rats at daily doses of 10, 30 or 100 mg eq./kg body weight/day (mg eq./kg/day) during 2 years. The purpose of the mice study was to assess the carcinogenic potential of JNJ-28431754-ZAE following daily oral gavage administration for up to two years in CD-1 mice.

Rat Study: Two separate experiments were conducted, one in males and one in females. Male and female SPF Sprague-Dawley rats were assigned to 4 groups (65/sex/group) and received one control or at a dose level of 10, 30, or 100 mg eq./kg/day to male and female rats. The test results showed no statistically significant dose-response relationship in mortality in either sex across all treatment groups. The tests showed a statistically significant pair-wise difference in survival between medium dose group and the control group in both males and females, between low dose group and the control group in males. Also the tests showed a statistically significant pair-wise difference between medium dose group and the control group in survivals in both males and females.

The tests showed the positive dose-response relationships in the incidence of renal tubule adenoma and combined tubular adenomas and carcinomas in kidneys in both males and females, pheochromocytoma and combined benign and malignant pheochromocytomas in adrenal glands, renal tubule carcinoma in kidneys, combined adenomas and carcinomas in liver and interstitial adenoma in testes in males were considered to be statistically significant.

In both males and females, the pair-wise comparison of renal tubule adenoma and combined tubule adenomas and carcinomas in kidneys between high dose group and the control were considered to be statistically significant for increased tumor incidence.

In males only, also based on the criteria of Haseman, the pair-wise comparison of pheochromocytoma and combined benign and malignant pheochromocytomas in adrenal glands, renal tubule carcinoma in kidneys and interstitial adenoma in testes between the high dose group and the control were considered to be statistically significant for increased tumor incidence. In addition, the pair-wise comparison of interstitial

adenoma in testes between the medium dose group and the control was considered to be statistically significant for increased tumor incidence.

Mouse Study: The objective of this study was to evaluate the oncogenic potential of JNJ-28431754-ZAE (the hemi-hydrate salt form of JNJ-28431754) following daily oral gavage administration for up to two years in CD-1 mice. Three treatment groups of 65 male and 65 female Crl:CD1®(Icr) mice were administered the test article at respective dose levels of 10, 30, or 100 mg/kg/day. One additional group of 65 animals/sex served as the control and received the vehicle, 0.5% (w/v) hypromellose in deionized water. The vehicle or test article was administered to all groups via oral gavage, once daily for 104 consecutive weeks. Females given 30 mg/kg/day were dosed for 101 consecutive weeks and males given 100 mg/kg/day were dosed for 103 consecutive weeks.

The test results showed a statistically significant dose-response relationship in mortality in females across all treatment groups. The tests showed a statistically significant pair-wise difference in survival between high dose group and the control group in males. Also the tests showed a statistically significant pair-wise difference between high dose group and the control group in survivals in both males and females.

The tests showed the pair-wise comparison of lymphoma in lung between the low dose group and the control to be statistically significant for increased tumor incidence in females only. As having been noted, the tumor data analyses from male mouse study showed no statistically significant dose-response relationship in any tested single tumor type. Based on the survival criterion Haseman proposed, it could be concluded that there were enough animals exposed to the high dose for a sufficient amount of time for male experiments. It could be concluded that the high doses used in the males and females were over MTD based on mortality increase criterion and close to MTD based on loss in body weight gain criterion. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

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6. Appendix

Table 1A: Intercurrent Mortality Rate
Male Rats

Week	CONTROL NO.OF DEATH	PERCENT	10mg NO.OF DEATH	PERCENT	30mg NO.OF DEATH	PERCENT	100mg NO.OF DEATH	PERCENT
0-52	11	16.9%	5	7.7%	3	4.6%	10	15.4%
53-78	5	24.6%	7	18.5%	1	6.2%	2	18.5%
79-92	9	38.5%	4	24.6%	2	9.2%	10	33.9%
93-103	11	55.4%	9	38.5%	9	23.1%	5	41.5%
Term. Sac.	29	100.0%	40	100.0%	50	100.0%	38	100.0%

Table 1B: Intercurrent Mortality Rate
Female Rats

Week	CONTROL NO.OF DEATH	PERCENT	10mg NO.OF DEATH	PERCENT	30mg NO.OF DEATH	PERCENT	100mg NO.OF DEATH	PERCENT
0-52	.	.	4	6.2%	1	1.5%	7	10.8%
53-78	13	20.0%	11	23.1%	6	10.8%	11	27.7%
79-92	12	38.5%	3	27.7%	6	20.0%	5	35.4%
93-103	13	58.5%	16	52.3%	12	38.5%	9	49.2%
Term. Sac.	27	100.0%	31	100.0%	40	100.0%	33	100.0%

Table 2A: Intercurrent Mortality Comparison
Male Rats

Test	P-Value (across four groups)	P-Value (control vs low)	P-Value (control vs medium)	P-Value (control vs high)
Dose Response	0.6314	0.0456	0.0005	0.1443
Homogeneity	0.0016	0.0570	<.0001	0.1374

Table 2B: Intercurrent Mortality Comparison
Female Rats

Test	P-Value (across four groups)	P-Value (control vs low)	P-Value (control vs medium)	P-Value (control vs high)
Dose Response	0.6048	0.4672	0.0173	0.3863
Homogeneity	0.1794	0.5339	0.0233	0.5166

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

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ADRENAL GLANDS		(65)	(64)	(64)	(65)	.	.	.	.
	Adenoma cortical, single, with	2	1	1	0	0.945	0.910	0.925	1.000
		[44]	[53]	[59]	[49]	.	.	.	.
	Pheochromocytoma benign, singl	4	4	7	26	0.000	0.741	0.466	0.000
		[44]	[53]	[60]	[50]	.	.	.	.
	Pheochromocytoma malignant, si	0	0	1	2	0.062	.	0.573	0.275
		[44]	[53]	[59]	[49]	.	.	.	.
ADRENALS		(65)	(65)	(65)	(65)	.	.	.	.
	B+M_PHEOCHROMOCYTOMAS	4	4	7	28	0.000	0.741	0.466	0.000
		[44]	[53]	[60]	[50]	.	.	.	.
ALL_SITES		(65)	(65)	(65)	(65)	.	.	.	.
	HEMANGIOMAS	0	2	4	1	0.526	0.296	0.103	0.527
		[44]	[53]	[59]	[49]	.	.	.	.
	HEMANGIOMAS+HEMANGIOSARCOMAS	0	3	4	2	0.382	0.159	0.103	0.275
		[44]	[53]	[59]	[49]	.	.	.	.
	HEMANGIOSARCOMAS	0	1	0	1	0.319	0.546	.	0.527
		[44]	[53]	[59]	[49]	.	.	.	.
	MESOTHELIOMAS	1	0	0	1	0.422	1.000	1.000	0.779
		[44]	[53]	[59]	[49]	.	.	.	.
BONE, STIFLE		(65)	(65)	(64)	(65)	.	.	.	.
	Osteofibroma	1	0	0	0	1.000	1.000	1.000	1.000
		[44]	[53]	[59]	[49]	.	.	.	.
BRAIN		(65)	(65)	(65)	(65)	.	.	.	.
	Astrocytoma benign, single	0	1	2	0	0.649	0.546	0.331	.
		[44]	[53]	[60]	[49]	.	.	.	.
	Astrocytoma malignant	2	0	0	0	1.000	1.000	1.000	1.000
		[44]	[53]	[59]	[49]	.	.	.	.
	Granular cell tumor benign, si	0	0	0	1	0.239	.	.	0.527
		[44]	[53]	[59]	[49]	.	.	.	.
	Hemangioma, single, meninges,	0	1	0	0	0.785	0.546	.	.
		[44]	[53]	[59]	[49]	.	.	.	.
HEART		(65)	(65)	(65)	(64)	.	.	.	.
	Schwannoma benign, base	1	1	0	0	0.955	0.797	1.000	1.000
		[44]	[53]	[59]	[49]	.	.	.	.
HEMOLYMPHORETIC		(65)	(65)	(65)	(65)	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

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

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
HEMOLYMPHORETIC	Lymphoma malignant	3	2	1	3	0.379	0.865	0.966	0.700
		[46]	[54]	[59]	[50]	.	.	.	.
	Sarcoma histiocytic	1	5	3	4	0.265	0.145	0.424	0.208
		[45]	[53]	[60]	[49]	.	.	.	.
KIDNEYS		(65)	(65)	(64)	(65)	.	.	.	.
	Adenoma renal tubule, single,	0	0	1	8	0.000	.	0.577	0.004
		[44]	[53]	[60]	[49]	.	.	.	.
	Carcinoma renal tubule, single	0	0	1	5	0.001	.	0.573	0.037
		[44]	[53]	[59]	[49]	.	.	.	.
	Carcinoma transitional cell, i	0	0	0	1	0.239	.	.	0.527
		[44]	[53]	[59]	[49]	.	.	.	.
	Mesenchymal cell tumor benign,	0	0	0	1	0.239	.	.	0.527
		[44]	[53]	[59]	[49]	.	.	.	.
	T_CELL_ADENOMAS+CARCINOMAS	0	0	2	12	0.000	.	0.331	0.000
		[44]	[53]	[60]	[49]	.	.	.	.
LIVER		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA+CARCINOMA	3	3	2	10	0.003	0.745	0.896	0.054
		[44]	[53]	[59]	[49]	.	.	.	.
	Adenoma hepatocellular, single	2	3	2	5	0.108	0.588	0.793	0.264
		[44]	[53]	[59]	[49]	.	.	.	.
	Adenoma hepatocholangiocellula	0	0	0	1	0.239	.	.	0.527
		[44]	[53]	[59]	[49]	.	.	.	.
	Carcinoma hepatocellular, sing	1	0	0	4	0.012	1.000	1.000	0.216
		[44]	[53]	[59]	[49]	.	.	.	.
LYMPH N MESENTE		(65)	(65)	(64)	(64)	.	.	.	.
	Hemangioma, multiple	0	1	3	1	0.381	0.546	0.184	0.527
		[44]	[53]	[59]	[49]	.	.	.	.
MAMMARY GLAND(S		(65)	(65)	(65)	(65)	.	.	.	.
	Adenocarcinoma arising in fibr	0	0	1	0	0.527	.	0.573	.
		[44]	[53]	[59]	[49]	.	.	.	.
	Adenocarcinoma, single	0	1	0	0	0.785	0.546	.	.
		[44]	[53]	[59]	[49]	.	.	.	.
	Fibroadenoma, fibromatous, wit	0	0	1	1	0.195	.	0.573	0.527
		[44]	[53]	[59]	[49]	.	.	.	.
MAMMARY_GLAND		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOCARCINOMA	0	1	1	0	0.653	0.546	0.573	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

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

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
MAMMARY_GLAND	ADENOCARCINOMA	[44]	[53]	[59]	[49]	.	.	.	.
PANCREAS		(64)	(65)	(65)	(64)	.	.	.	.
	Adenoma acinar cell, single, s	0	1	0	0	0.785	0.546	.	.
		[44]	[53]	[59]	[49]	.	.	.	.
	Adenoma islet cell, single, sm	9	4	7	6	0.627	0.983	0.926	0.905
		[45]	[53]	[60]	[49]	.	.	.	.
	Carcinoma islet cell, single,	0	1	0	0	0.785	0.546	.	.
		[44]	[53]	[59]	[49]	.	.	.	.
PARATHYROID GLA		(64)	(63)	(64)	(60)	.	.	.	.
	Adenoma, unilateral	0	1	1	0	0.653	0.546	0.573	.
		[44]	[53]	[59]	[49]	.	.	.	.
PITUITARY GLAND		(63)	(65)	(65)	(65)	.	.	.	.
	Adenoma	23	20	18	18	0.777	0.928	0.982	0.931
		[48]	[56]	[60]	[51]	.	.	.	.
	Adenoma pars intermedia, singl	0	0	1	0	0.527	.	0.573	.
		[44]	[53]	[59]	[49]	.	.	.	.
PREPUTIAL GLAND		(56)	(62)	(63)	(57)	.	.	.	.
	Carcinoma squamous cell, singl	0	0	0	1	0.239	.	.	0.527
		[44]	[53]	[59]	[49]	.	.	.	.
PROSTATE		(65)	(65)	(64)	(65)	.	.	.	.
	Adenocarcinoma, invasive; with	2	1	0	0	0.991	0.913	1.000	1.000
		[44]	[54]	[59]	[49]	.	.	.	.
SKIN		(65)	(65)	(65)	(65)	.	.	.	.
	Adenoma sebaceous cell, single	1	0	0	0	1.000	1.000	1.000	1.000
		[44]	[53]	[59]	[49]	.	.	.	.
	Carcinoma squamous cell, kerat	2	0	0	1	0.557	1.000	1.000	0.890
		[46]	[53]	[59]	[49]	.	.	.	.
	KERATOACANTHOMAS+SQUAMOUS_CELL	4	1	3	2	0.658	0.981	0.875	0.912
		[46]	[53]	[60]	[49]	.	.	.	.
	Keratoacanthoma	1	1	2	0	0.808	0.797	0.616	1.000
		[44]	[53]	[60]	[49]	.	.	.	.
	Papilloma squamous cell, singl	1	0	1	1	0.400	1.000	0.820	0.779
		[44]	[53]	[59]	[49]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

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

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
SKIN	Tumor basal cell benign, singl	2	0	0	0	1.000	1.000	1.000	1.000
		[44]	[53]	[59]	[49]	.	.	.	.
SMALL INT. JEJU		(64)	(64)	(57)	(63)	.	.	.	.
SPLEEN		(65)	(65)	(64)	(64)	.	.	.	.
	Hemangioma, single	0	0	1	0	0.527	.	0.573	.
		[44]	[53]	[59]	[49]	.	.	.	.
TESTES		(65)	(65)	(64)	(65)	.	.	.	.
	Adenoma interstitial cell, sin	1	8	20	24	0.000	0.030	0.000	0.000
		[44]	[53]	[60]	[50]	.	.	.	.
	Sarcoma not otherwise specifie	0	0	1	0	0.529	.	0.577	.
		[44]	[53]	[60]	[49]	.	.	.	.
THYMUS		(54)	(56)	(59)	(52)	.	.	.	.
	Thymoma malignant, epithelial,	1	0	0	0	1.000	1.000	1.000	1.000
		[44]	[53]	[59]	[49]	.	.	.	.
THYROID GLANDS		(64)	(65)	(64)	(65)	.	.	.	.
	Adenoma C-cell, single	8	8	4	7	0.597	0.766	0.982	0.786
		[44]	[54]	[59]	[49]	.	.	.	.
	Adenoma follicular cell, singl	1	0	3	2	0.194	1.000	0.427	0.541
		[44]	[53]	[59]	[49]	.	.	.	.
	Carcinoma C-cell, single	0	0	1	0	0.527	.	0.573	.
		[44]	[53]	[59]	[49]	.	.	.	.
THYROID_GLAND		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA+CARCINOMA	8	8	5	7	0.607	0.766	0.961	0.786
		[44]	[54]	[59]	[49]	.	.	.	.
TONGUE		(63)	(65)	(64)	(65)	.	.	.	.
URINARY BLADDER		(64)	(65)	(64)	(65)	.	.	.	.
	Carcinoma transitional cell, s	0	0	0	1	0.239	.	.	0.527
		[44]	[53]	[59]	[49]	.	.	.	.
	Papilloma transitional cell, e	0	0	0	1	0.239	.	.	0.527
		[44]	[53]	[59]	[49]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

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

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ADRENAL GLANDS		(65)	(63)	(62)	(64)	.	.	.	.
	Adenoma cortical, single	5	2	3	4	0.413	0.950	0.909	0.746
		[48]	[50]	[56]	[47]	.	.	.	.
	Pheochromocytoma benign, singl	2	1	3	7	0.008	0.883	0.565	0.079
		[48]	[49]	[55]	[48]	.	.	.	.
ALL_SITES		(65)	(65)	(65)	(65)	.	.	.	.
	HEMANGIOMAS	1	1	1	1	0.503	0.753	0.780	0.742
		[49]	[49]	[55]	[47]	.	.	.	.
	HEMANGIOMAS+HEMANGIOSARCOMAS	1	1	2	1	0.488	0.753	0.550	0.742
		[49]	[49]	[56]	[47]	.	.	.	.
	HEMANGIOSARCOMAS	0	0	1	0	0.513	.	0.534	.
		[48]	[49]	[55]	[47]	.	.	.	.
BONE, STIFLE		(64)	(64)	(65)	(64)	.	.	.	.
BRAIN		(65)	(65)	(65)	(64)	.	.	.	.
	Astrocytoma benign, single	1	0	0	0	1.000	1.000	1.000	1.000
		[49]	[49]	[55]	[47]	.	.	.	.
	Astrocytoma malignant, multifo	0	2	0	0	0.823	0.258	.	.
		[48]	[50]	[55]	[47]	.	.	.	.
	Oligodendroglioma malignant, w	0	0	0	1	0.240	.	.	0.500
		[48]	[49]	[55]	[48]	.	.	.	.
CERVIX		(64)	(65)	(65)	(65)	.	.	.	.
	Hemangioma, cavernous, single	0	0	0	1	0.236	.	.	0.495
		[48]	[49]	[55]	[47]	.	.	.	.
	Polyp endometrial stromal, sin	0	0	0	1	0.236	.	.	0.495
		[48]	[49]	[55]	[47]	.	.	.	.
	Tumor granular cell benign	5	5	6	5	0.481	0.643	0.596	0.616
		[48]	[49]	[55]	[47]	.	.	.	.
CLITORAL GLAND(		(59)	(58)	(60)	(60)	.	.	.	.
	Carcinoma squamous cell, singl	0	0	1	1	0.186	.	0.534	0.495
		[48]	[49]	[55]	[47]	.	.	.	.
HEART		(65)	(63)	(65)	(65)	.	.	.	.
HEMOLYMPHORETIC		(65)	(65)	(65)	(65)	.	.	.	.
	Leukemia granulocytic, neutrop	0	0	1	0	0.515	.	0.539	.
		[48]	[49]	[56]	[47]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Rats

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
HEMOLYMPHORETIC	Lymphoma malignant	0	1	1	3	0.044	0.505	0.539	0.129
		[48]	[49]	[56]	[50]	.	.	.	.
	Sarcoma histiocytic	0	2	1	1	0.410	0.258	0.539	0.495
		[48]	[50]	[56]	[47]	.	.	.	.
KIDNEY		(65)	(65)	(65)	(65)	.	.	.	.
	T_CELL_ADENOMA+CARCINOMA	0	0	0	8	0.000	.	.	0.003
		[48]	[49]	[55]	[48]	.	.	.	.
KIDNEYS		(65)	(64)	(65)	(65)	.	.	.	.
	Adenoma renal tubule, basophil	0	0	0	7	0.000	.	.	0.006
		[48]	[49]	[55]	[48]	.	.	.	.
	Carcinoma renal tubule	0	0	0	2	0.055	.	.	0.242
		[48]	[49]	[55]	[47]	.	.	.	.
	Liposarcoma, single	0	0	1	0	0.513	.	0.534	.
		[48]	[49]	[55]	[47]	.	.	.	.
LIVER		(65)	(63)	(65)	(65)	.	.	.	.
	Adenoma hepatocellular, single	0	1	1	1	0.292	0.505	0.539	0.495
		[48]	[49]	[56]	[47]	.	.	.	.
	Hemangioma, single	1	0	0	0	1.000	1.000	1.000	1.000
		[49]	[49]	[55]	[47]	.	.	.	.
LYMPH N MESENTE		(62)	(63)	(65)	(64)	.	.	.	.
	Hemangioma, single	0	1	0	0	0.759	0.505	.	.
		[48]	[49]	[55]	[47]	.	.	.	.
MAMMARY GLAND(S		(65)	(65)	(65)	(64)	.	.	.	.
	Adenocarcinoma arising in fibr	4	3	2	1	0.912	0.782	0.918	0.967
		[50]	[50]	[55]	[47]	.	.	.	.
	Adenocarcinoma, multiple, with	19	16	10	11	0.907	0.776	0.991	0.950
		[53]	[52]	[56]	[48]	.	.	.	.
	Adenoma, single, small	2	0	0	2	0.235	1.000	1.000	0.676
		[49]	[49]	[55]	[47]	.	.	.	.
	Fibroadenoma, fibromatous, sin	35	33	21	24	0.941	0.763	1.000	0.973
		[54]	[55]	[59]	[50]	.	.	.	.
MAMMARY_GLAND		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA+ADENOCARCINOMA	22	17	12	12	0.933	0.856	0.992	0.972
		[54]	[52]	[56]	[48]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Rats

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
NOSE		(65)	(64)	(64)	(62)	.	.	.	.
	Adenoma, vomeronasal lumen	0	0	1	0	0.513	.	0.534	.
		[48]	[49]	[55]	[47]	.	.	.	.
OVARIES		(64)	(63)	(63)	(65)	.	.	.	.
	Cystadenocarcinoma, invasive	1	0	0	0	1.000	1.000	1.000	1.000
		[48]	[49]	[55]	[47]	.	.	.	.
	Luteoma benign, single	0	1	0	0	0.760	0.510	.	.
		[48]	[50]	[55]	[47]	.	.	.	.
PANCREAS		(65)	(63)	(64)	(64)	.	.	.	.
	ADENOMA+CARCINOMA	3	2	1	2	0.589	0.819	0.954	0.806
		[49]	[49]	[55]	[47]	.	.	.	.
	Adenoma islet cell, single	3	1	1	2	0.504	0.941	0.954	0.806
		[49]	[49]	[55]	[47]	.	.	.	.
	Carcinoma islet cell, single	0	1	0	0	0.759	0.505	.	.
		[48]	[49]	[55]	[47]	.	.	.	.
PARATHYROID GLA		(59)	(63)	(62)	(60)	.	.	.	.
	Adenoma, single, small	0	1	0	0	0.759	0.505	.	.
		[48]	[49]	[55]	[47]	.	.	.	.
PITUITARY GLAND		(65)	(65)	(65)	(64)	.	.	.	.
	Adenoma	39	40	36	40	0.191	0.500	0.848	0.272
		[57]	[57]	[59]	[53]	.	.	.	.
	Adenoma pars intermedia, small	0	0	1	0	0.513	.	0.534	.
		[48]	[49]	[55]	[47]	.	.	.	.
	Carcinoma not otherwise specif	1	2	0	1	0.617	0.500	1.000	0.747
		[49]	[49]	[55]	[48]	.	.	.	.
SKIN		(62)	(62)	(64)	(63)	.	.	.	.
	Carcinoma squamous cell, kerat	1	0	2	0	0.689	1.000	0.558	1.000
		[48]	[49]	[56]	[47]	.	.	.	.
SMALL INT. JEJU		(59)	(60)	(62)	(64)	.	.	.	.
	Leiomyoma, single	0	3	0	0	0.900	0.125	.	.
		[48]	[49]	[55]	[47]	.	.	.	.
SPLEEN		(65)	(63)	(64)	(64)	.	.	.	.
STOMACH		(65)	(64)	(64)	(64)	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Rats

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
STOMACH	Papilloma squamous cell, singl	0	0	0	1	0.236	.	.	0.495
		[48]	[49]	[55]	[47]	.	.	.	.
THYMUS		(54)	(57)	(59)	(54)	.	.	.	.
	THYMOMA	0	1	0	1	0.303	0.505	.	0.495
		[48]	[49]	[55]	[47]	.	.	.	.
	Thymoma benign, epithelial, si	0	0	0	1	0.236	.	.	0.495
		[48]	[49]	[55]	[47]	.	.	.	.
	Thymoma malignant, epithelial,	0	1	0	0	0.759	0.505	.	.
		[48]	[49]	[55]	[47]	.	.	.	.
THYROID		(65)	(65)	(65)	(65)	.	.	.	.
	ADENOMA+CARCINOMA	2	0	2	1	0.539	1.000	0.734	0.871
		[49]	[49]	[55]	[47]	.	.	.	.
THYROID GLANDS		(64)	(65)	(64)	(63)	.	.	.	.
	Adenoma C-cell, single	3	7	2	7	0.147	0.159	0.853	0.150
		[49]	[49]	[55]	[48]	.	.	.	.
	Adenoma follicular cell, singl	1	0	1	1	0.384	1.000	0.780	0.742
		[49]	[49]	[55]	[47]	.	.	.	.
	Carcinoma follicular cell, sin	1	0	1	0	0.764	1.000	0.785	1.000
		[48]	[49]	[55]	[47]	.	.	.	.
TONGUE		(64)	(65)	(65)	(62)	.	.	.	.
	Hemangiosarcoma, single	0	0	1	0	0.513	.	0.534	.
		[48]	[49]	[55]	[47]	.	.	.	.
URINARY BLADDER		(64)	(63)	(64)	(65)	.	.	.	.
	Papilloma transitional cell, e	0	1	0	3	0.029	0.505	.	0.117
		[48]	[49]	[55]	[47]	.	.	.	.
UTERUS		(64)	(64)	(64)	(65)	.	.	.	.
	Adenocarcinoma endometrial, in	0	1	0	0	0.759	0.505	.	.
		[48]	[49]	[55]	[47]	.	.	.	.
	Hemangioma, single	0	0	1	0	0.513	.	0.534	.
		[48]	[49]	[55]	[47]	.	.	.	.
	Leiomyoma, single	0	0	0	1	0.236	.	.	0.495
		[48]	[49]	[55]	[47]	.	.	.	.
	Polyp endometrial stromal, uni	4	6	4	6	0.271	0.396	0.714	0.344
		[49]	[51]	[56]	[47]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Rats

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
VAGINA		(64)	(65)	(64)	(65)	.	.	.	.
	Hemangiosarcoma, single	0	0	1	0	0.513	.	0.534	.
		[48]	[49]	[55]	[47]	.	.	.	.
	Tumor granular cell benign, si	6	13	9	9	0.427	0.068	0.392	0.258
		[49]	[50]	[56]	[47]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 4A: Intercurrent Mortality Rate
Male Mice

Week	CONTROL NO.OF DEATH	PERCENT	10mg NO.OF DEATH	PERCENT	30mg NO.OF DEATH	PERCENT	100mg NO.OF DEATH	PERCENT
0-52	4	6.2%	3	4.6%	8	12.3%	10	15.6%
53-78	7	16.9%	13	24.6%	23	47.7%	13	35.9%
79-92	11	33.9%	13	44.6%	4	53.9%	15	59.4%
93-103	12	52.3%	10	60.0%	2	56.9%	6	68.8%
Term. Sac.	31	100.0%	26	100.0%	29	100.0%	20	100.0%

Table 4B: Intercurrent Mortality Rate
Female Mice

Week	CONTROL NO.OF DEATH	PERCENT	10mg NO.OF DEATH	PERCENT	30mg NO.OF DEATH	PERCENT	100mg NO.OF DEATH	PERCENT
0-52	4	6.2%	5	7.7%	6	9.4%	1	2.3%
53-78	7	16.9%	11	24.6%	10	25.0%	3	9.1%
79-92	16	41.5%	13	44.6%	15	48.4%	5	20.5%
93-103	12	60.0%	10	60.0%	14	70.3%	8	38.6%
Term. Sac.	26	100.0%	26	100.0%	19	100.0%	27	100.0%

Table 5A: Intercurrent Mortality Comparison
Male Mice

Test	P-Value (across four groups)	P-Value (control vs low)	P-Value (control vs medium)	P-Value (control vs high)
Dose Response	0.0586	0.4188	0.3185	0.0422
Homogeneity	0.1102	0.3048	0.1774	0.0128

Table 5B: Intercurrent Mortality Comparison
Female Mice

Test	P-Value (across four groups)	P-Value (control vs low)	P-Value (control vs medium)	P-Value (control vs high)
Dose Response	0.0428	0.8922	0.2401	0.0693
Homogeneity	0.0063	0.8615	0.2016	0.0118

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=64	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ALL_SITES		(65)	(65)	(65)	(64)	.	.	.	.
	HEMANGIOMAS+HEMANGIOSARCOMAS	5	6	5	5	0.392	0.456	0.481	0.464
		[50]	[47]	[40]	[39]	.	.	.	.
	LEUKEMIAS	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMAS	2	5	2	1	0.807	0.186	0.595	0.817
		[51]	[47]	[40]	[38]	.	.	.	.
LIVER		(65)	(65)	(65)	(64)	.	.	.	.
	HEP_ADENOMA+CARCINOMA	16	5	6	5	0.924	0.997	0.984	0.990
		[51]	[46]	[41]	[38]	.	.	.	.
LUNG		(65)	(65)	(65)	(64)	.	.	.	.
	BRON_ADENOMA+CARCINOMA	22	14	7	9	0.951	0.943	0.998	0.985
		[52]	[48]	[41]	[39]	.	.	.	.
adrenal glands		(65)	(65)	(65)	(64)	.	.	.	.
	ADENOMA, SUBCAPSULAR CELL	0	3	0	2	0.232	0.110	.	0.188
		[49]	[46]	[40]	[38]	.	.	.	.
	HEMANGIOSARCOMA	0	1	0	0	0.717	0.484	.	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	0	1	1	0	0.568	0.484	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	PHEOCHROMOCYTOMA	2	0	0	1	0.527	1.000	1.000	0.826
		[49]	[46]	[40]	[38]	.	.	.	.
bone marrow, fe		(65)	(65)	(65)	(64)	.	.	.	.
	HEMANGIOSARCOMA	0	0	1	1	0.149	.	0.449	0.437
		[49]	[46]	[40]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	3	0	1	0.644	0.278	1.000	0.680
		[50]	[46]	[40]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	0	1	0.220	.	.	0.437
		[49]	[46]	[40]	[38]	.	.	.	.
bone marrow, st		(65)	(65)	(65)	(64)	.	.	.	.
	HEMANGIOSARCOMA	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=64	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
bone marrow, st	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	3	0	1	0.644	0.278	1.000	0.680
		[50]	[46]	[40]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	0	1	0.220	.	.	0.437
		[49]	[46]	[40]	[38]	.	.	.	.
bone marrow, ti		(65)	(65)	(65)	(64)	.	.	.	.
	HEMANGIOSARCOMA	0	0	0	1	0.220	.	.	0.437
		[49]	[46]	[40]	[38]	.	.	.	.
bone, femur		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	0	1	0	0.697	1.000	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
bone, sternum		(65)	(65)	(65)	(64)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOLA	1	0	0	0	1.000	1.000	1.000	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	2	1	1	0	0.891	0.859	0.829	1.000
		[51]	[46]	[40]	[38]	.	.	.	.
brain		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	0	1	0	0.697	1.000	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
	MENINGIOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
cavity, abdomin		(65)	(65)	(65)	(64)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOLA	1	0	0	0	1.000	1.000	1.000	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
	HEMANGIOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	4	1	0	0.910	0.156	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size
Numbers are the tumor bearing animals

Table 6A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=64	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
cavity, abdomin	SARCOMA, HISTIOCYTIC	[50]	[46]	[40]	[38]	.	.	.	.
	SCHWANNOMA	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
cavity, thoraci		(65)	(65)	(65)	(64)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOLA	1	0	0	0	1.000	1.000	1.000	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	4	1	0	0.910	0.156	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
coagulating gla		(65)	(65)	(65)	(64)	.	.	.	.
	ADENOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	3	1	0	0.875	0.278	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
ears		(65)	(65)	(65)	(64)	.	.	.	.
	LYMPHOMA	0	1	0	0	0.717	0.484	.	.
		[49]	[46]	[40]	[38]	.	.	.	.
epididymides		(65)	(65)	(65)	(64)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOLA	1	0	0	0	1.000	1.000	1.000	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	3	1	0	0.875	0.278	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
esophagus		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	0	1	0	0	0.717	0.484	.	.
		[49]	[46]	[40]	[38]	.	.	.	.
eyes		(65)	(65)	(65)	(64)	.	.	.	.
	LYMPHOMA	1	1	0	0	0.919	0.731	1.000	1.000
		[50]	[46]	[40]	[38]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons

Male Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=64	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
gallbladder		(65)	(65)	(65)	(64)	.	.	.	.
	ADENOMA	0	0	0	1	0.220	.	.	0.437
		[49]	[46]	[40]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	0	4	1	0	0.842	0.051	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
harderian gland		(65)	(65)	(65)	(64)	.	.	.	.
	ADENOMA	6	10	8	5	0.662	0.170	0.227	0.578
		[50]	[47]	[40]	[39]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	2	1	0	0.828	0.468	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	0	1	0.220	.	.	0.437
		[49]	[46]	[40]	[38]	.	.	.	.
heart		(65)	(65)	(65)	(64)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOLA	1	0	0	0	1.000	1.000	1.000	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
	HEMANGIOSARCOMA	0	1	1	0	0.568	0.484	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	2	1	1	0	0.891	0.859	0.829	1.000
		[51]	[46]	[40]	[38]	.	.	.	.
joint, tibiofem		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
kidneys		(65)	(65)	(65)	(64)	.	.	.	.
	ADENOMA, TUBULAR CELL	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	2	4	2	0	0.934	0.291	0.595	1.000
		[51]	[46]	[40]	[38]	.	.	.	.
lacrimal glands		(65)	(65)	(65)	(64)	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animal

Table 6A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=64	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
lacrimal glands	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	2	1	0	0.828	0.468	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
large intestine		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	0	1	1	0	0.568	0.484	0.449	.
		1	2	1	0	0.828	0.468	0.694	1.000
		[49]	[46]	[40]	[38]	.	.	.	.
		[50]	[46]	[40]	[38]	.	.	.	.
larynx		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	0	1	1	0	0.568	0.484	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
liver		(65)	(65)	(65)	(64)	.	.	.	.
	ADENOMA, HEPATOCELLULAR	9	4	3	4	0.723	0.946	0.962	0.895
		[51]	[46]	[40]	[38]	.	.	.	.
	CARCINOMA, HEPATOCELLULAR	7	1	3	1	0.932	0.996	0.908	0.992
		[50]	[46]	[40]	[38]	.	.	.	.
	CARCINOMA, UNDIFFERENTIATED	0	1	0	0	0.717	0.484	.	.
		[49]	[46]	[40]	[38]	.	.	.	.
	HEMANGIOSARCOMA	3	4	3	2	0.637	0.453	0.550	0.723
		[50]	[46]	[40]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	2	2	1	0.505	0.468	0.416	0.680
		[50]	[46]	[40]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	0	1	0.220	.	.	0.437
		[49]	[46]	[40]	[38]	.	.	.	.
lung		(65)	(65)	(65)	(64)	.	.	.	.
	ADENOMA, BRONCHIOLAR ALVEOLAR	16	12	6	7	0.919	0.806	0.984	0.956
		[51]	[47]	[41]	[39]	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOLA	7	4	1	3	0.758	0.865	0.993	0.887
		[51]	[46]	[40]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=64	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
lung	LEUKEMIA, GRANULOCYTIC	[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	2	3	2	0	0.910	0.451	0.595	1.000
		[51]	[46]	[40]	[38]	.	.	.	.
lymph node, ili		(65)	(65)	(65)	(64)	.	.	.	.
	LYMPHOMA	0	1	0	0	0.717	0.484	.	.
		[49]	[46]	[40]	[38]	.	.	.	.
lymph node, ing		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	0	1	0	0.697	1.000	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
lymph node, man		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	5	1	0	0.933	0.089	0.694	1.000
		[50]	[47]	[40]	[38]	.	.	.	.
lymph node, med		(65)	(65)	(65)	(64)	.	.	.	.
	LYMPHOMA	1	1	0	0	0.919	0.731	1.000	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
lymph node, mes		(65)	(65)	(65)	(64)	.	.	.	.
	HEMANGIOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
	HEMANGIOSARCOMA	0	0	0	1	0.220	.	.	0.437
		[49]	[46]	[40]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	5	1	0	0.933	0.089	0.694	1.000
		[50]	[47]	[40]	[38]	.	.	.	.
lymph node, tra		(65)	(65)	(65)	(64)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOLA	1	0	0	0	1.000	1.000	1.000	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
mammary gland		(65)	(65)	(65)	(64)	.	.	.	.
	ADENOCARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[50]	[46]	[40]	[38]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=64	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
mesentery/perit		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
multicentric ne		(65)	(65)	(65)	(64)	.	.	.	.
	HEMANGIOMA	1	0	1	0	0.697	1.000	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
	HEMANGIOSARCOMA	4	6	4	5	0.312	0.331	0.512	0.344
		[50]	[47]	[40]	[39]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	2	5	2	1	0.807	0.186	0.595	0.817
		[51]	[47]	[40]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	1	0	0	2	0.121	1.000	1.000	0.397
		[50]	[46]	[40]	[38]	.	.	.	.
nerve, sciatic		(65)	(65)	(65)	(64)	.	.	.	.
	LYMPHOMA	1	2	1	0	0.828	0.468	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
nose, level a		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
nose, level b		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	0	1	0	0.697	1.000	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
nose, level c		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	0	1	0	0.697	1.000	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
nose, level d		(65)	(65)	(65)	(64)	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=64	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
nose, level d	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	0	1	0	0.697	1.000	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
pancreas		(65)	(65)	(65)	(64)	.	.	.	.
	HEMANGIOSARCOMA	0	1	0	0	0.717	0.484	.	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	0	3	2	0	0.769	0.110	0.199	.
		[49]	[46]	[40]	[38]	.	.	.	.
penis and surro		(65)	(65)	(65)	(64)	.	.	.	.
	HEMANGIOMA	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	0	1	1	0	0.568	0.484	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
peyers patch		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	3	1	0	0.875	0.278	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
pharynx		(65)	(65)	(65)	(64)	.	.	.	.
	LYMPHOMA	0	1	0	0	0.717	0.484	.	.
		[49]	[46]	[40]	[38]	.	.	.	.
pituitary gland		(65)	(65)	(65)	(64)	.	.	.	.
	ADENOMA, PARS DISTALIS	1	0	0	0	1.000	1.000	1.000	1.000
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
preputial gland		(65)	(65)	(65)	(64)	.	.	.	.
	LYMPHOMA	0	3	1	0	0.775	0.110	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
prostate gland		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=64	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
prostate gland	LEUKEMIA, GRANULOCYTIC	[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	3	1	0	0.875	0.278	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
salivary gland,		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	0	1	0	0	0.717	0.484	.	.
		1	2	1	0	0.828	0.468	0.694	1.000
			3	1	0	0.875	0.278	0.694	1.000
		[49]	[46]	[40]	[38]	.	.	.	.
		[50]	[46]	[40]	[38]	.	.	.	.
seminal vesicle		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	4	1	0	0.910	0.156	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
skeletal muscle		(65)	(65)	(65)	(64)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOLA	1	0	0	0	1.000	1.000	1.000	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
	HEMANGIOSARCOMA	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	0	2	1	0	0.675	0.232	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
skin		(65)	(65)	(65)	(64)	.	.	.	.
	LYMPHOMA	0	1	0	0	0.717	0.484	.	.
		[49]	[46]	[40]	[38]	.	.	.	.
	PAPILLOMA, SQUAMOUS CELL	0	0	1	0	0.454	.	0.456	.
		[49]	[46]	[41]	[38]	.	.	.	.
skin, subcutis		(65)	(65)	(65)	(64)	.	.	.	.
	HEMANGIOSARCOMA	0	1	0	1	0.267	0.484	.	0.437
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	2	1	0	0.828	0.468	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
	SARCOMA, UNDIFFERENTIATED	0	0	1	1	0.149	.	0.449	0.437
		[49]	[46]	[40]	[38]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=64	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
small intestine		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	0	1	1	0	0.568	0.484	0.449	.
			2	1	0	0.675	0.232	0.449	.
		1	1	1	0	0.778	0.731	0.694	1.000
		[49]	[46]	[40]	[38]	.	.	.	.
		[50]	[46]	[40]	[38]	.	.	.	.
spleen		(65)	(65)	(65)	(64)	.	.	.	.
	HEMANGIOSARCOMA	1	1	0	3	0.067	0.737	1.000	0.227
		[49]	[46]	[40]	[39]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	4	1	1	0.684	0.162	0.694	0.680
		[50]	[47]	[40]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	0	1	0.220	.	.	0.437
		[49]	[46]	[40]	[38]	.	.	.	.
stomach, glandu		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	3	1	0	0.875	0.278	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
stomach, nongla		(65)	(65)	(65)	(64)	.	.	.	.
	CARCINOMA, SQUAMOUS CELL	0	1	0	0	0.717	0.484	.	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	0	1	0	0	0.717	0.484	.	.
		[49]	[46]	[40]	[38]	.	.	.	.
	PAPILLOMA, SQUAMOUS CELL	0	1	0	0	0.717	0.484	.	.
		[49]	[46]	[40]	[38]	.	.	.	.
testes		(65)	(65)	(65)	(64)	.	.	.	.
	ADENOMA, INTERSTITIAL CELL	0	4	0	2	0.314	0.054	.	0.188
		[49]	[47]	[40]	[38]	.	.	.	.
	HEMANGIOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	2	0	0	0.912	0.468	1.000	1.000

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=64	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
testes	LYMPHOMA	[50]	[46]	[40]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	0	1	0.220	.	.	0.437
		[49]	[46]	[40]	[38]	.	.	.	.
thymus gland		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	4	1	0	0.909	0.162	0.694	1.000
		[50]	[47]	[40]	[38]	.	.	.	.
thyroid gland		(65)	(65)	(65)	(64)	.	.	.	.
	CARCINOMA, FOLLICULAR CELL	0	0	0	1	0.220	.	.	0.437
		[49]	[46]	[40]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	2	0	0	0.912	0.468	1.000	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
tongue		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	0	2	0	0	0.770	0.232	.	.
		[49]	[46]	[40]	[38]	.	.	.	.
trachea		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	0	1	0	0	0.717	0.484	.	.
		[49]	[46]	[40]	[38]	.	.	.	.
ureters		(65)	(65)	(65)	(64)	.	.	.	.
	LYMPHOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
urinary bladder		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	4	1	0	0.910	0.156	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.
	MESENCHYMAL TUMOR	2	0	0	0	1.000	1.000	1.000	1.000
		[49]	[46]	[40]	[38]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons

Male Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=65	100 mg High N=64	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
zymbal`s gland		(65)	(65)	(65)	(64)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	0	0	1	0	0.451	.	0.449	.
		[49]	[46]	[40]	[38]	.	.	.	.
	LYMPHOMA	1	1	1	0	0.778	0.731	0.694	1.000
		[50]	[46]	[40]	[38]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=64	100 mg High N=44	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ALL_BONE		(65)	(65)	(64)	(44)	.	.	.	.
	LEIOMYOMAS+LEIOMYOSARCOMAS	0	1	0	1	0.279	0.489	.	0.454
		[47]	[45]	[41]	[39]	.	.	.	.
ALL_SITES		(65)	(65)	(64)	(44)	.	.	.	.
	HEMANGIOMAS+HEMANGIOSARCOMAS	3	9	6	6	0.281	0.055	0.191	0.150
		[48]	[47]	[43]	[39]	.	.	.	.
	LEUKEMIAS	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMAS	15	21	17	13	0.599	0.167	0.334	0.489
		[50]	[51]	[47]	[40]	.	.	.	.
LUNG		(65)	(65)	(64)	(44)	.	.	.	.
	BRON_ADENOMA+CARCINOMA	12	9	6	14	0.048	0.810	0.939	0.176
		[49]	[47]	[43]	[39]	.	.	.	.
MAMMARY_GLAND		(65)	(65)	(64)	(44)	.	.	.	.
	ADENOMA+ADENOCARCINOMA+ADENOAC	2	1	0	1	0.620	0.867	1.000	0.831
		[48]	[45]	[41]	[38]	.	.	.	.
SKIN_SUBCUTIS		(65)	(65)	(64)	(44)	.	.	.	.
	SARCOMA+FIBROSARCOMA+LIPSARCOM	2	1	0	2	0.308	0.867	1.000	0.610
		[48]	[45]	[41]	[39]	.	.	.	.
THYROID		(65)	(65)	(64)	(44)	.	.	.	.
	FOLLICULAR_CELL_ADENOMA+CARCIN	1	0	1	0	0.712	1.000	0.718	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
UTERUS_CERVIX		(65)	(65)	(64)	(44)	.	.	.	.
	LEIOMYOMAS+LEIOMYOSARCOMAS	2	1	4	3	0.192	0.871	0.286	0.411
		[47]	[45]	[42]	[39]	.	.	.	.
	STROMAL_POLYP+SARCOMA	9	7	12	9	0.215	0.752	0.255	0.365
		[49]	[46]	[46]	[38]	.	.	.	.
adrenal glands		(65)	(65)	(64)	(44)	.	.	.	.
	ADENOMA, SUBCAPSULAR CELL	0	1	2	2	0.103	0.489	0.214	0.197
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	2	4	3	3	0.342	0.329	0.447	0.389
		[48]	[47]	[43]	[38]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=64	100 mg High N=44	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
adrenal glands	PHEOCHROMOCYTOMA	0	2	1	0	0.687	0.237	0.466	.
		[47]	[45]	[41]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
bone		(65)	(65)	(64)	(44)	.	.	.	.
	OSTEOSARCOMA	0	1	0	0	0.725	0.489	.	.
		[47]	[45]	[41]	[38]	.	.	.	.
bone marrow, fe		(65)	(65)	(64)	(44)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	3	6	5	3	0.587	0.232	0.309	0.558
		[48]	[47]	[44]	[39]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
bone marrow, st		(65)	(65)	(64)	(44)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	3	6	5	3	0.587	0.232	0.309	0.558
		[48]	[47]	[44]	[39]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
bone, femur		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	0	3	1	0	0.786	0.117	0.472	.
		[47]	[46]	[42]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
bone, sternum		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	3	3	4	1	0.795	0.641	0.438	0.908
		[48]	[46]	[43]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
bone, vertebra		(65)	(65)	(64)	(44)	.	.	.	.
	OSTEOMA	0	0	0	1	0.227	.	.	0.454
		[47]	[45]	[41]	[39]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=64	100 mg High N=44	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
brain		(65)	(65)	(64)	(44)	.	.	.	.
	CARCINOMA, PARS DISTALIS	0	1	0	0	0.727	0.495	.	.
		[47]	[46]	[41]	[38]	.	.	.	.
	LYMPHOMA	0	2	0	1	0.384	0.237	.	0.447
		[47]	[45]	[41]	[38]	.	.	.	.
cavity, abdomin		(65)	(65)	(64)	(44)	.	.	.	.
	HEMANGIOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	5	10	8	5	0.633	0.130	0.221	0.509
		[48]	[48]	[44]	[40]	.	.	.	.
	NEUROENDOCRINE TUMOR	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	2	1	1	0	0.901	0.867	0.848	1.000
		[48]	[45]	[41]	[38]	.	.	.	.
cavity, thoraci		(65)	(65)	(64)	(44)	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOLA	0	1	0	0	0.727	0.495	.	.
		[47]	[46]	[41]	[38]	.	.	.	.
	LYMPHOMA	8	10	9	4	0.873	0.379	0.422	0.873
		[49]	[48]	[45]	[39]	.	.	.	.
	SARCOMA, HISTIOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
clitoral glands		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	3	3	5	2	0.604	0.651	0.297	0.748
		[48]	[47]	[43]	[39]	.	.	.	.
ears		(65)	(65)	(64)	(44)	.	.	.	.
	HEMANGIOMA	0	0	0	1	0.222	.	.	0.447
		[47]	[45]	[41]	[38]	.	.	.	.
esophagus		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	0	0	1	0	0.462	.	0.466	.
		[47]	[45]	[41]	[38]	.	.	.	.
eyes		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	0	1	2	1	0.266	0.489	0.220	0.447
		[47]	[45]	[42]	[38]	.	.	.	.
eyes, optic ner		(65)	(65)	(64)	(44)	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=64	100 mg High N=44	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
eyes, optic ner	LYMPHOMA	0	1	0	1	0.273	0.495	.	0.447
		[47]	[46]	[41]	[38]	.	.	.	.
gallbladder		(65)	(65)	(64)	(44)	.	.	.	.
	ITO CELL TUMOR	0	0	0	1	0.222	.	.	0.447
		[47]	[45]	[41]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	3	5	2	2	0.726	0.357	0.783	0.756
		[47]	[47]	[42]	[39]	.	.	.	.
	SARCOMA, HISTIOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
harderian gland		(65)	(65)	(64)	(44)	.	.	.	.
	ADENOMA	3	3	1	4	0.202	0.641	0.924	0.381
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	4	4	2	1	0.899	0.643	0.865	0.951
		[48]	[48]	[42]	[38]	.	.	.	.
heart		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	9	10	7	7	0.572	0.480	0.721	0.626
		[49]	[48]	[44]	[39]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	1	0.156	.	0.472	0.447
		[47]	[45]	[42]	[38]	.	.	.	.
joint, tibiofem		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	0	4	1	0	0.849	0.059	0.472	.
		[47]	[47]	[42]	[38]	.	.	.	.
kidneys		(65)	(65)	(64)	(44)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	8	12	10	7	0.610	0.242	0.321	0.552
		[49]	[50]	[45]	[40]	.	.	.	.
	SARCOMA, HISTIOCYTIC	1	0	2	0	0.638	1.000	0.457	1.000
		[47]	[45]	[42]	[38]	.	.	.	.
lacrimal glands		(65)	(65)	(64)	(44)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	8	8	6	3	0.916	0.590	0.742	0.942

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=64	100 mg High N=44	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
lacrimal glands	LYMPHOMA	[49]	[48]	[44]	[39]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
large intestine		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	1	0	0	0	1.000	1.000	1.000	1.000
				1	0	0.712	1.000	0.718	1.000
		4	2	1	1	0.858	0.893	0.963	0.953
		[47]	[45]	[41]	[38]	.	.	.	.
			[46]	[42]	[38]	.	.	.	.
larynx		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	2	4	2	1	0.778	0.318	0.640	0.831
		[48]	[46]	[42]	[38]	.	.	.	.
liver		(65)	(65)	(64)	(44)	.	.	.	.
	ADENOMA, HEPATOCELLULAR	2	2	1	1	0.685	0.675	0.857	0.836
		[47]	[45]	[42]	[38]	.	.	.	.
	CHOLANGIOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	HEMANGIOMA	0	0	0	1	0.222	.	.	0.447
		[47]	[45]	[41]	[38]	.	.	.	.
	HEMANGIOSARCOMA	2	2	3	2	0.414	0.675	0.446	0.608
		[47]	[45]	[42]	[38]	.	.	.	.
	ITO CELL TUMOR	0	0	0	1	0.222	.	.	0.447
		[47]	[45]	[41]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	9	13	10	6	0.801	0.235	0.398	0.745
		[50]	[50]	[45]	[40]	.	.	.	.
	SARCOMA, HISTIOCYTIC	2	1	3	1	0.572	0.867	0.447	0.831
		[48]	[45]	[43]	[38]	.	.	.	.
lung		(65)	(65)	(64)	(44)	.	.	.	.
	ADENOCARCINOMA	0	0	0	1	0.222	.	.	0.447
		[47]	[45]	[41]	[38]	.	.	.	.
	ADENOMA, BRONCHIOLAR ALVEOLAR	11	7	3	12	0.067	0.877	0.990	0.261
		[49]	[46]	[41]	[39]	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOLA	1	2	3	2	0.297	0.492	0.275	0.420
		[47]	[46]	[43]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=64	100 mg High N=44	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
lung	LEUKEMIA, GRANULOCYTIC	[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	12	10	11	8	0.633	0.749	0.574	0.760
		[50]	[49]	[45]	[40]	.	.	.	.
	OSTEOSARCOMA	0	0	0	2	0.050	.	.	0.203
		[47]	[45]	[41]	[39]	.	.	.	.
	SARCOMA, HISTIOCYTIC	2	0	1	0	0.864	1.000	0.853	1.000
		[48]	[45]	[42]	[38]	.	.	.	.
	SARCOMA, STROMAL	0	1	0	0	0.727	0.495	.	.
		[47]	[46]	[41]	[38]	.	.	.	.
lymph node, hep		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	1	3	1	0	0.885	0.300	0.718	1.000
		[47]	[46]	[41]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	2	0	1	0	0.861	1.000	0.848	1.000
		[48]	[45]	[41]	[38]	.	.	.	.
lymph node, ili		(65)	(65)	(64)	(44)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	2	4	1	0	0.960	0.328	0.857	1.000
		[47]	[46]	[42]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.462	.	0.466	.
		[47]	[45]	[41]	[38]	.	.	.	.
lymph node, ing		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	0	6	0	0	0.944	0.013	.	.
		[47]	[47]	[41]	[38]	.	.	.	.
lymph node, man		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	10	12	8	5	0.892	0.426	0.702	0.891
		[49]	[50]	[44]	[39]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
lymph node, med		(65)	(65)	(64)	(44)	.	.	.	.
	ADENOCARCINOMA	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
	CARCINOMA, BRONCHIOLAR ALVEOLA	0	1	0	0	0.727	0.495	.	.
		[47]	[46]	[41]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=64	100 mg High N=44	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
lymph node, med	LYMPHOMA	1	3	1	1	0.627	0.300	0.718	0.697
		[47]	[46]	[41]	[38]	.	.	.	.
lymph node, mes		(65)	(65)	(64)	(44)	.	.	.	.
	HEMANGIOSARCOMA	0	0	0	1	0.222	.	.	0.447
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	9	14	10	7	0.715	0.185	0.417	0.626
		[49]	[50]	[45]	[39]	.	.	.	.
	SARCOMA, HISTIOCYTIC	1	0	1	0	0.715	1.000	0.724	1.000
		[47]	[45]	[42]	[38]	.	.	.	.
lymph node, ren		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	2	7	1	1	0.899	0.079	0.853	0.831
		[48]	[48]	[42]	[38]	.	.	.	.
mammary gland		(65)	(65)	(64)	(44)	.	.	.	.
	ADENOACANTHOMA	2	0	0	0	1.000	1.000	1.000	1.000
		[48]	[45]	[41]	[38]	.	.	.	.
	ADENOCARCINOMA	0	0	0	1	0.222	.	.	0.447
		[47]	[45]	[41]	[38]	.	.	.	.
	ADENOMA	0	1	0	0	0.725	0.489	.	.
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	4	8	5	2	0.878	0.178	0.444	0.844
		[48]	[48]	[44]	[39]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
mesentery/perit		(65)	(65)	(64)	(44)	.	.	.	.
	HEMANGIOMA	0	1	0	0	0.727	0.495	.	.
		[47]	[46]	[41]	[38]	.	.	.	.
	LYMPHOMA	1	1	1	0	0.790	0.742	0.718	1.000
		[48]	[46]	[42]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
	SARCOMA, STROMAL	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
multicentric ne		(65)	(65)	(64)	(44)	.	.	.	.
	HEMANGIOMA	0	2	2	2	0.164	0.242	0.220	0.197
		[47]	[46]	[42]	[38]	.	.	.	.
	HEMANGIOSARCOMA	3	7	4	4	0.449	0.141	0.425	0.370

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=64	100 mg High N=44	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
multicentric ne	HEMANGIOSARCOMA	[48]	[46]	[42]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	14	16	13	9	0.805	0.414	0.578	0.798
		[50]	[50]	[46]	[40]	.	.	.	.
	SARCOMA, HISTIOCYTIC	4	1	3	1	0.782	0.967	0.735	0.951
		[48]	[45]	[43]	[38]	.	.	.	.
nerve, sciatic		(65)	(65)	(64)	(44)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	3	5	2	4	0.329	0.345	0.775	0.384
		[48]	[47]	[42]	[39]	.	.	.	.
nose, level a		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	1	1	0	0	0.923	0.736	1.000	1.000
		[48]	[45]	[41]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
nose, level b		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	1	0	1	2	0.131	1.000	0.718	0.422
		[48]	[45]	[42]	[39]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
nose, level c		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	2	0	2	1	0.473	1.000	0.640	0.831
		[48]	[45]	[42]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
nose, level d		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	1	1	2	0	0.741	0.736	0.450	1.000
		[48]	[45]	[42]	[38]	.	.	.	.
ovaries		(65)	(65)	(64)	(44)	.	.	.	.
	ADENOCARCINOMA	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
	CYSTADENOMA	3	4	1	1	0.865	0.476	0.920	0.908
		[48]	[46]	[41]	[38]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=64	100 mg High N=44	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ovaries	HEMANGIOMA	0	0	2	0	0.453	.	0.220	.
		[47]	[45]	[42]	[38]	.	.	.	.
	HEMANGIOSARCOMA	2	0	0	0	1.000	1.000	1.000	1.000
		[48]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	7	11	9	5	0.746	0.232	0.304	0.692
		[49]	[50]	[44]	[39]	.	.	.	.
	SARCOMA, HISTIOCYTIC	2	1	1	1	0.607	0.867	0.853	0.831
		[48]	[45]	[42]	[38]	.	.	.	.
	SARCOMA, STROMAL	0	1	0	0	0.727	0.495	.	.
		[47]	[46]	[41]	[38]	.	.	.	.
	SEX-CORD/STROMAL TUMOR	2	3	0	5	0.047	0.490	1.000	0.139
		[47]	[46]	[41]	[38]	.	.	.	.
pancreas		(65)	(65)	(64)	(44)	.	.	.	.
	ADENOMA, ISLET CELL	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	10	10	8	5	0.860	0.579	0.685	0.892
		[50]	[49]	[44]	[40]	.	.	.	.
	SARCOMA, HISTIOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
parathyroid gla		(65)	(65)	(64)	(44)	.	.	.	.
	ADENOMA	0	0	1	0	0.462	.	0.466	.
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	0	1	0	0	0.725	0.489	.	.
		[47]	[45]	[41]	[38]	.	.	.	.
peyers patch		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	7	7	5	6	0.455	0.597	0.751	0.575
		[48]	[47]	[42]	[39]	.	.	.	.
pharynx		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	0	1	0	1	0.273	0.489	.	0.447
		[47]	[45]	[41]	[38]	.	.	.	.
pituitary gland		(65)	(65)	(64)	(44)	.	.	.	.
	ADENOMA, PARS DISTALIS	4	1	1	0	0.983	0.969	0.961	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	CARCINOMA, PARS DISTALIS	0	1	0	0	0.727	0.495	.	.
		[47]	[46]	[41]	[38]	.	.	.	.
	LYMPHOMA	0	1	1	1	0.249	0.489	0.472	0.447

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=64	100 mg High N=44	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
pituitary gland	LYMPHOMA	[47]	[45]	[42]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
salivary gland,		(65)	(65)	(64)	(44)	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	2	2	2	1	0.653	0.675	0.640	0.831
		3	4	4	2	0.646	0.488	0.438	0.739
		4	3	5	1	0.853	0.765	0.431	0.951
		[48]	[46]	[42]	[38]	.	.	.	.
			[47]	[43]	[38]	.	.	.	.
		[49]	[47]	[44]	[39]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
skeletal muscle		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	2	4	4	2	0.569	0.329	0.287	0.610
		[48]	[47]	[43]	[39]	.	.	.	.
	OSTEOSARCOMA	0	0	0	1	0.227	.	.	0.454
		[47]	[45]	[41]	[39]	.	.	.	.
	SARCOMA, HISTIOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
skin		(65)	(65)	(64)	(44)	.	.	.	.
	CARCINOMA, BASAL CELL	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	2	3	2	2	0.487	0.490	0.640	0.610
		[48]	[47]	[42]	[39]	.	.	.	.
skin, subcutis		(65)	(65)	(64)	(44)	.	.	.	.
	FIBROSARCOMA	2	0	0	1	0.538	1.000	1.000	0.837
		[48]	[45]	[41]	[39]	.	.	.	.
	HEMANGIOSARCOMA	0	2	0	0	0.780	0.242	.	.
		[47]	[46]	[41]	[38]	.	.	.	.
	LIPOSARCOMA	0	1	0	0	0.725	0.489	.	.
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	3	0	4	0	0.860	1.000	0.438	1.000
		[48]	[45]	[43]	[38]	.	.	.	.
	OSTEOSARCOMA	0	0	1	1	0.160	.	0.472	0.454
		[47]	[45]	[42]	[39]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=64	100 mg High N=44	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
skin, subcutis	SARCOMA, UNDIFFERENTIATED	0	0	0	1	0.222	.	.	0.447
		[47]	[45]	[41]	[38]	.	.	.	.
small intestine		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	4	2	3	1	0.825	0.888	0.724	0.951
				4	1	0.821	0.883	0.579	0.951
			6	4	1	0.929	0.357	0.579	0.951
		[48]	[45]	[43]	[38]	.	.	.	.
			[46]	[42]	[38]	.	.	.	.
			[47]	[43]	[38]	.	.	.	.
spinal cord, ce		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	0	0	0	1	0.222	.	.	0.447
		[47]	[45]	[41]	[38]	.	.	.	.
spinal cord, lu		(65)	(65)	(64)	(44)	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
spleen		(65)	(65)	(64)	(44)	.	.	.	.
	HEMANGIOSARCOMA	0	3	1	0	0.786	0.113	0.466	.
		[47]	[45]	[41]	[38]	.	.	.	.
	LEUKEMIA, GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	11	13	9	9	0.568	0.430	0.705	0.597
		[49]	[50]	[45]	[40]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
stomach, glandu		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	5	5	4	4	0.508	0.630	0.699	0.643
		[48]	[48]	[43]	[39]	.	.	.	.
stomach, nongla		(65)	(65)	(64)	(44)	.	.	.	.
	CARCINOMA, SQUAMOUS CELL	0	0	1	0	0.462	.	0.466	.
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	0	2	0	1	0.382	0.242	.	0.447
		[47]	[46]	[41]	[38]	.	.	.	.
	PAPILLOMA, SQUAMOUS CELL	0	1	0	1	0.273	0.489	.	0.447
		[47]	[45]	[41]	[38]	.	.	.	.
	SARCOMA, STROMAL	0	0	1	0	0.465	.	0.472	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=64	100 mg High N=44	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
stomach, nongla	SARCOMA, STROMAL	[47]	[45]	[42]	[38]	.	.	.	.
thymus gland		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	9	12	7	7	0.659	0.294	0.705	0.630
		[50]	[49]	[44]	[40]	.	.	.	.
	SARCOMA, HISTIOCYTIC	1	1	1	0	0.795	0.742	0.724	1.000
		[47]	[45]	[42]	[38]	.	.	.	.
thyroid gland		(65)	(65)	(64)	(44)	.	.	.	.
	ADENOMA, FOLLICULAR CELL	0	0	1	0	0.462	.	0.466	.
		[47]	[45]	[41]	[38]	.	.	.	.
	CARCINOMA, FOLLICULAR CELL	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	5	7	5	1	0.960	0.380	0.573	0.974
		[48]	[48]	[44]	[38]	.	.	.	.
tongue		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	5	3	2	1	0.920	0.852	0.921	0.974
		[48]	[46]	[42]	[38]	.	.	.	.
trachea		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	0	2	3	1	0.417	0.237	0.105	0.447
		[47]	[45]	[43]	[38]	.	.	.	.
ureters		(65)	(65)	(64)	(44)	.	.	.	.
	LYMPHOMA	0	1	0	0	0.725	0.489	.	.
		[47]	[45]	[41]	[38]	.	.	.	.
urinary bladder		(65)	(65)	(64)	(44)	.	.	.	.
	ADENOCARCINOMA	0	1	0	0	0.725	0.489	.	.
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	5	10	4	5	0.595	0.140	0.699	0.492
		[48]	[49]	[43]	[39]	.	.	.	.
	MESENCHYMAL TUMOR	0	1	0	1	0.273	0.489	.	0.447
		[47]	[45]	[41]	[38]	.	.	.	.
	POLYP	0	0	1	0	0.462	.	0.466	.
		[47]	[45]	[41]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
uterus with cer		(65)	(65)	(64)	(44)	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 6B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice

Organ Name	Tumor Name	0 mg Cont N=65	10 mg Low N=65	30 mg Med N=64	100 mg High N=44	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
uterus with cer	ADENOCARCINOMA	1	1	1	2	0.204	0.742	0.724	0.420
		[47]	[45]	[42]	[38]	.	.	.	.
	CARCINOMA, SQUAMOUS CELL	0	1	0	0	0.725	0.489	.	.
		[47]	[45]	[41]	[38]	.	.	.	.
	GRANULAR CELL TUMOR	0	0	2	0	0.453	.	0.220	.
		[47]	[45]	[42]	[38]	.	.	.	.
	HEMANGIOMA	0	1	0	0	0.727	0.495	.	.
		[47]	[46]	[41]	[38]	.	.	.	.
	HEMANGIOSARCOMA	1	1	0	0	0.926	0.742	1.000	1.000
		[47]	[45]	[41]	[38]	.	.	.	.
	LEIOMYOMA	2	1	3	2	0.344	0.871	0.446	0.618
		[47]	[45]	[42]	[39]	.	.	.	.
	LEIOMYOSARCOMA	0	0	1	1	0.156	.	0.466	0.447
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	6	10	7	6	0.542	0.194	0.416	0.470
		[49]	[48]	[44]	[40]	.	.	.	.
	POLYP, GLANDULAR	1	1	1	0	0.791	0.747	0.718	1.000
		[47]	[46]	[41]	[38]	.	.	.	.
	POLYP, STROMAL	6	7	9	8	0.163	0.467	0.242	0.219
		[48]	[46]	[45]	[38]	.	.	.	.
	SARCOMA, HISTIOCYTIC	3	0	3	1	0.609	1.000	0.608	0.908
		[48]	[45]	[43]	[38]	.	.	.	.
	SARCOMA, STROMAL	5	2	2	1	0.899	0.941	0.925	0.975
		[47]	[46]	[42]	[38]	.	.	.	.
vagina		(65)	(65)	(64)	(44)	.	.	.	.
	ADENOCARCINOMA	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
	HEMANGIOSARCOMA	0	0	0	1	0.222	.	.	0.447
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	2	4	5	2	0.576	0.329	0.174	0.610
		[48]	[47]	[43]	[39]	.	.	.	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0.465	.	0.472	.
		[47]	[45]	[42]	[38]	.	.	.	.
zymbal`s gland		(65)	(65)	(64)	(44)	.	.	.	.
	CARCINOMA, ZYMBALS GLAND	0	0	1	0	0.462	.	0.466	.
		[47]	[45]	[41]	[38]	.	.	.	.
	LYMPHOMA	2	6	3	2	0.671	0.134	0.447	0.599
		[48]	[48]	[43]	[38]	.	.	.	.

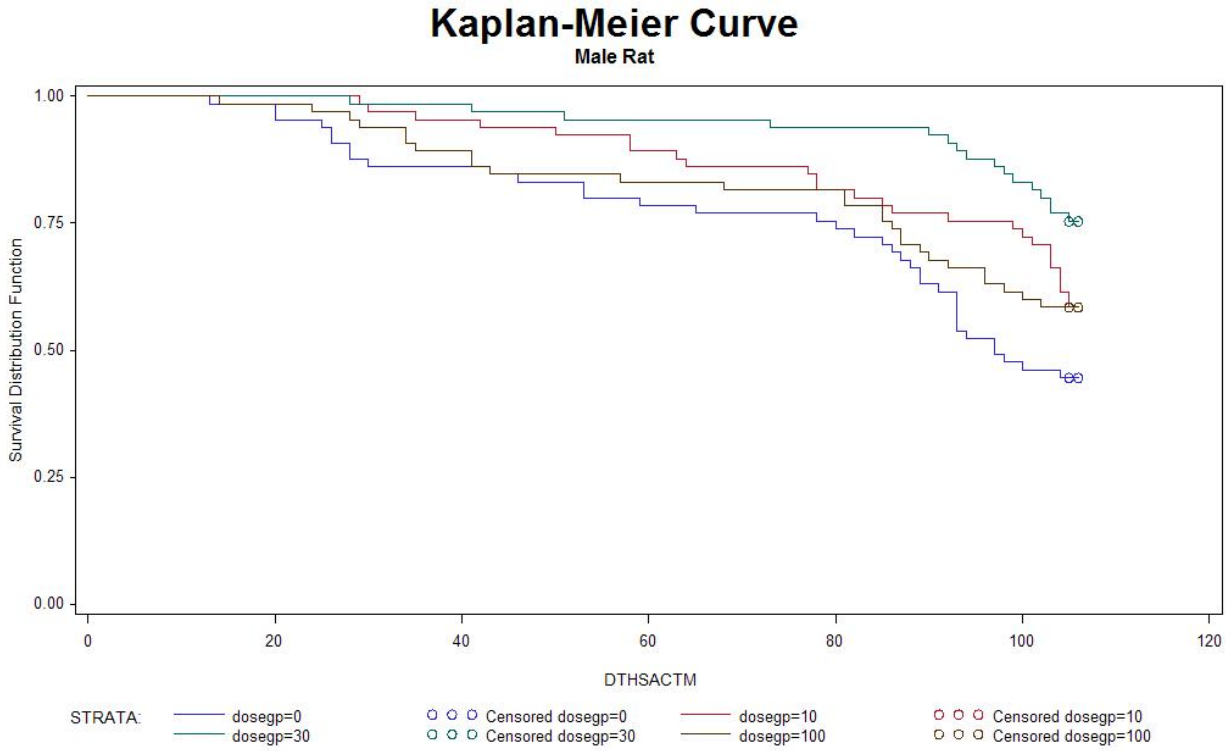
Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

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

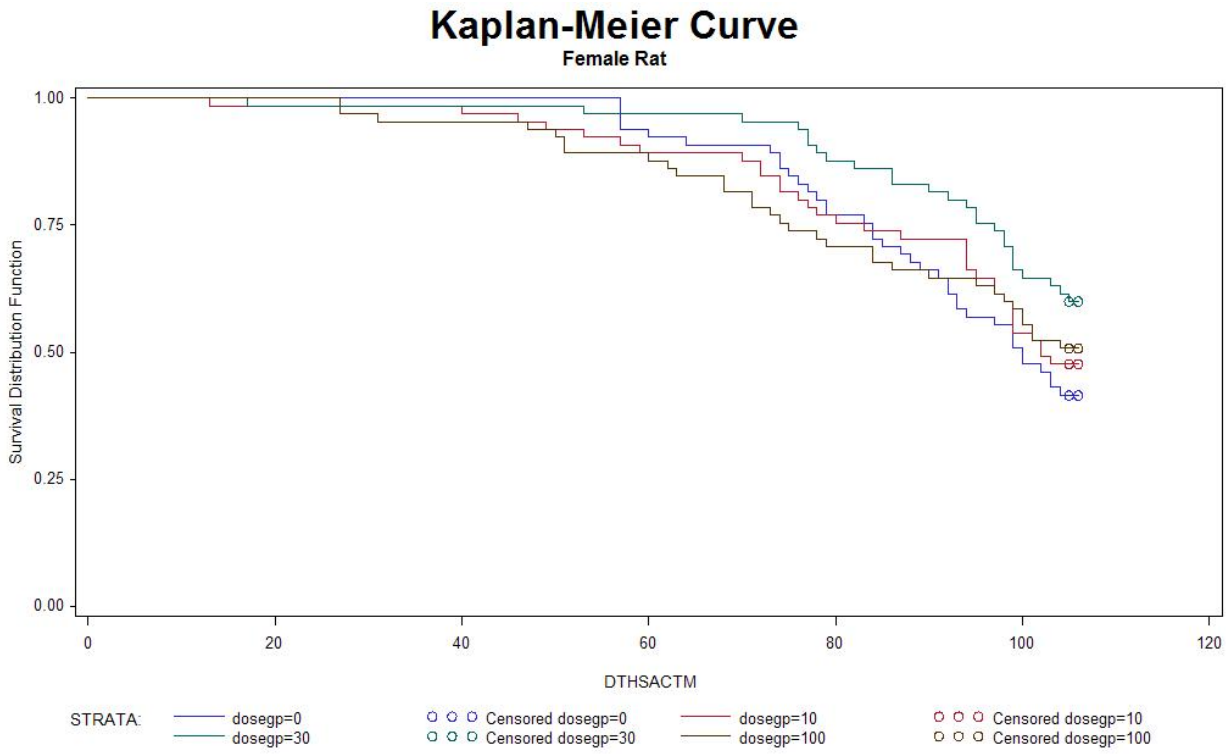
Male Rats



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

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

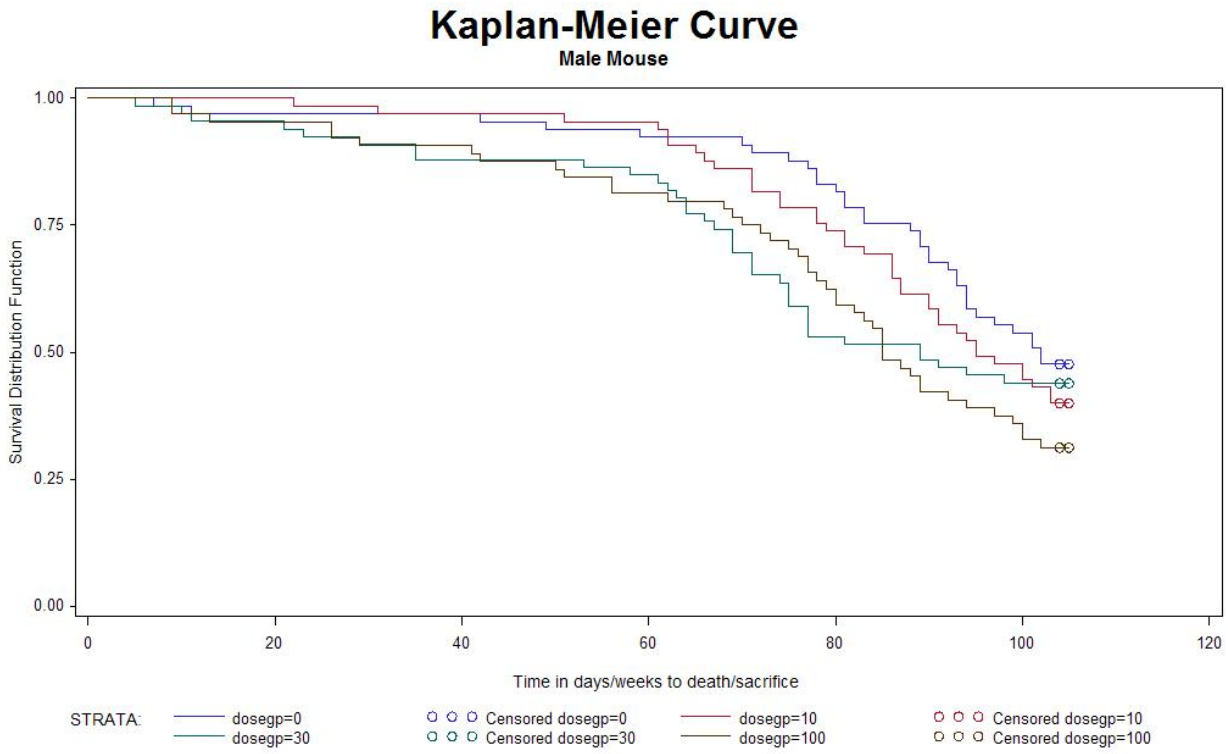
Female Rats



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

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

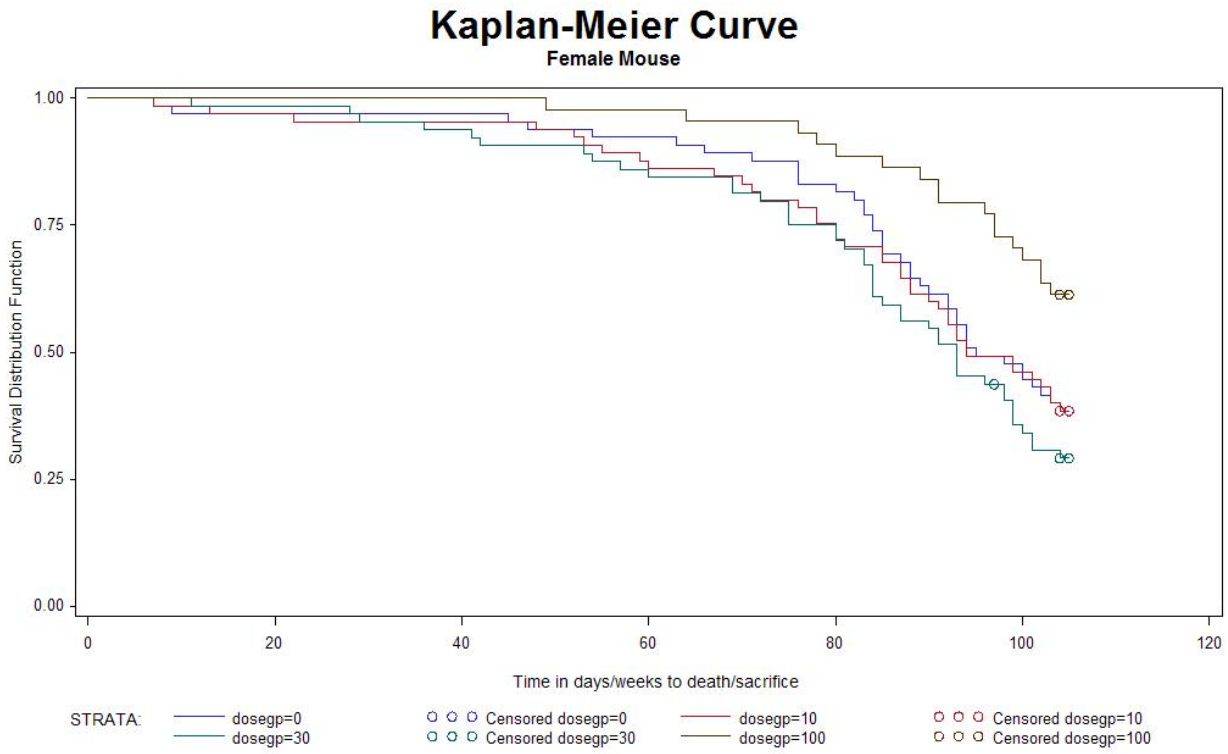
Male Mice



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

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

Female Mice



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

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/s/

MIN MIN
03/20/2013

KARL K LIN
03/21/2013
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 204042/0000
Supplement #:	NA
Drug Name:	Canagliflozin (proposed tradename INVOCANA)
Indication(s):	Treatment of patients with type 2 diabetes mellitus
Applicant:	Janssen Research & Development, LLC
Date(s):	May 31, 2012
Review Priority:	Standard (10-month)
Biometrics Division:	Division of Biometrics 2 (HFD-715)
Statistical Reviewer:	Wei Liu, Ph.D.
Concurring Reviewers:	J. Todd Sahlroot, Ph.D. (Deputy Director)
Medical Division:	Metabolism and Endocrinological Products (HFD-510, DMEP)
Clinical Team:	Hyon Kwon, PharmD, MPH
	Jean-Marc Guettier, M.D. (Team Leader)
Project Manager:	

Keywords: NDA review, clinical studies

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

The applicant seeks the indication of canagliflozin (proposed tradename INVOKANA) tablets for the treatment of patients with type 2 diabetes mellitus.

Confirmation of efficacy:
All superiority comparisons of canagliflozin 300 mg and 100 mg doses vs placebo in HbA1c change from baseline, the primary efficacy endpoint, were significant in all studies. The results were based on LOCF as the primary method for accounting for missing data. Analyses using MMRM were consistent with the primary results with LOCF.

The primary efficacy findings by the Agency are shown in Table 1.

Table 1. Primary Efficacy Results (HbA1c) for Canagliflozin (300 mg and 100 mg) in Patients with Type 2 Diabetes (Phase 3 Studies) (mITT/LOCF)

Study (Weeks)	Treatment arm	n	Baseline Mean ± SE	LSMean change ± SE	Canaglifozin minus control (95% CI)	p-value
Monotherapy						
DIA3005 (26) Main study	Cana 300 mg Cana 100 mg Placebo	193 191 189	8.01 ± 0.07 8.06 ± 0.07 7.97 ± 0.07	-1.03 ± 0.06 -0.77 ± 0.06 0.14 ± 0.06	-1.16 (-1.34, -0.99) -0.91 (-1.09, -0.73)	<.0001 <.0001
DIA3005 (26) High Glycemic	Cana 300 mg Cana 100 mg	43 46	10.62 ± 0.15 10.59 ± 0.13	-2.56±0.22 -2.13±0.22		
Add-on to AHA Monotherapy						
DIA3006 (26) Add-on to metformin	Cana 300 mg Cana 100 mg Placebo	360 365 181	7.95 ± 0.05 7.94 ± 0.05 7.96 ± 0.07	-0.94 ± 0.04 -0.79 ± 0.04 -0.17 ± 0.06	-0.77(-0.91,-0.64) -0.62 (-0.76,-0.48)	<.0001 <.0001
DIA3009 (52) Add-on to metform	Cana 300 mg Cana 100 mg Glimepiride ↑6/8 mg	474 478 473	7.79 ± 0.04 7.78 ± 0.04 7.83 ± 0.04	-0.93 ± 0.04 -0.82 ± 0.04 -0.82 ± 0.04	-0.12 (-0.22, -0.02) -0.01 (-0.11, 0.09)	0.0158 0.8074
Add-on to Dual Combination AHA Therapy						
DIA3002 (26) + metformin + sulfonylurea	Cana 300 mg Cana 100 mg Placebo	152 155 150	8.13 ± 0.08 8.13 ± 0.07 8.12 ± 0.07	-1.06 ± 0.08 -0.85 ± 0.08 -0.13 ± 0.08	-0.92 (-1.11, -0.73) -0.71 (-0.90, -0.52)	<.0001 <.0001
DIA3012 (26) + metformin + pioglitazone	Cana 300 mg Cana 100 mg Placebo	112 113 114	7.84 ± 0.09 7.99 ± 0.09 8.00 ± 0.09	-1.03 ± 0.07 -0.89 ± 0.07 -0.26 ± 0.07	-0.76 (-0.95, -0.57) -0.62 (-0.81, -0.44)	<.0001 <.0001
DIA3015 (52) + metformin + sulfonylurea	Cana 300 mg Sitagliptin 100mg	365 374	8.13 ± 0.05 8.12 ± 0.05	-0.66 ± 0.05 -1.03 ± 0.05	-0.37 (-0.50, -0.25)	<.0001
Special Population						
DIA3010 (26)[1] older adults	Cana 300 mg Cana 100 mg Placebo	229 239 232	7.69 ± 0.05 7.77 ± 0.05 7.76 ± 0.05	-0.73 ± 0.06 -0.60 ± 0.06 -0.03 ± 0.06	-0.70 (-0.84, -0.57) -0.57 (-0.71, -0.44)	<.0001 <.0001

DIA3004 (26)[2] Moderate renal impairment	Cana 300 mg Cana 100 mg Placebo	89 88 87	7.97 ± 0.09 7.89 ± 0.10 8.02 ± 0.10	-0.44 ± 0.09 -0.32 ± 0.09 -0.03 ± 0.09	-0.42 (-0.65, -0.19) -0.29 (-0.53, -0.06)	0.0004 0.0131
DIA3008 (18) Sulphonylurea substudy[3]	Cana 300 mg Cana 100 mg Placebo	39 40 40	8.28 ± 0.16 8.29 ± 0.13 8.49 ± 0.18	-0.79 ± 0.15 -0.70 ± 0.15 0.04 ± 0.15	-0.83 (-1.24, -0.42) -0.74 (-1.14, -0.33)	0.0001 0.0005
DIA3008 (18) Insulin substudy[2]	Cana 300 mg Cana 100 mg Placebo	572 551 545	8.27 ± 0.04 8.34 ± 0.04 8.24 ± 0.04	-0.72 ± 0.03 -0.63 ± 0.03 0.02 ± 0.03	-0.74 (-0.82, -0.65) -0.65 (-0.74, -0.56)	<.0001 <.0001

[1] ≥55 to ≤80 years of age [2] eGFR ≥ 30 to <50 mL/min/1.73 m^2
[3] population 1 [4] population 2

Canagliflozin (both doses) was shown to be non-inferior to glimepiride in Study DIA3009 and to sitagliptin in Study DIA3015. Both studies used pre-specified non-inferiority margins of 0.3%. This margin is used routinely in sitagliptin-controlled studies, and is no larger than margins routinely used in glimepiride-controlled studies. In Study DIA3009, Canagliflozin 300 mg was also shown to be superior to glimepiride (p=0.016) although the mean treatment difference was small (-0.12%).

In Study DIA3004 in patients with moderate renal impairment, canagliflozin 100mg and 300mg were both statistically superior to placebo. Mean effect sizes vs placebo were modest in this population, -0.42% for 300mg and -0.29% for 100 mg. Effect sizes for subgroups defined by baseline eGFR (< 45 vs > 45 mL/min/1.73 m^2) were not statistically different (interaction p > 0.10).

Canagliflozin exhibited a modest dose response. Depending on the particular population, canagliflozin 300 mg showed additional 0.1% to 0.25% mean reductions in HbA1c over canagliflozin 100 mg.

Analyses of HbA1c by subgroups defined by eGFR at baseline based on integrated datasets were consistent with the results in Study DIA3004 alone. In the integrated analyses, subjects with lower eGFR values at baseline (< 45 mL/min/1.73 m^2) had smaller treatment differences than subjects with higher eGFR values at baseline (≥ 45 mL/min/1.73 m^2). The difference in effects between the subgroups was not statistically significant (interaction p > 0.10).

Subgroup analyses were conducted based on two different age cutoffs, 65 and 75 years of age. Analyses of HbA1c by age subgroups based on integrated datasets showed that older subjects (≥65 or ≥75 years of age) had smaller mean treatment differences than younger subjects (<65 or <75 years of age). The statistical evaluation of observed subgroup differences produced results that were not consistent across the two datasets of interest. Age-by-treatment interaction p-values were statistically significant for dataset PC-2 (both interaction p-values < 0.10) but not for dataset PC-1 (both interaction p-values > 0.10).

Considerations regarding efficacy:

The sponsor computed the percent of patients achieving HbA1c <7% at the end of study using all mITT patients, including those who had baseline HbA1c < 7%. The number of patients achieving HbA1c <7% should be calculated based on patients with HbA1c>7% at baseline, which was conducted by this reviewer. A HbA1c <7% responder is the patient who completed

the final study visit with HbA1c <7%. That is, dropouts were counted as non responders even if HbA1c was <7%.

Recommendations:
Recommendations for the proposed label are included in part 5.4.

2. INTRODUCTION

2.1 Overview

Canagliflozin is an orally-active inhibitor of sodium-glucose co-transporter 2 (SGLT2). The expression of SGLT2 is limited to the kidney. The low-affinity/high-capacity SGLT2 transporter in the proximal renal tubule reabsorbs the majority of glucose filtered by the renal glomerulus. Pharmacological inhibition of SGLT2 is expected to decrease renal glucose reabsorption, and thereby increase urinary glucose excretion and lower plasma glucose in patients with type 2 diabetes mellitus (T2DM). Therefore, canagliflozin provides an insulin-independent approach for control of hyperglycemia, with a low risk for inducing hypoglycemia, weight loss, and blood pressure.

The sponsor, Janssen Research & Development, LLC (hereafter referred to as the sponsor) on behalf of Janssen Pharmaceuticals, Inc, submitted NDA 204042 on May 31, 2012 for the use of canagliflozin (proposed tradename INVOKANA) 100 mg and 300 mg once-daily (qd) as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM).

The sponsor submitted data of 9 phase 3 studies for supporting the efficacy of canagliflozin as monotherapy, in combination with metformin, sulfonylurea, metformin and sulfonylurea, metformin and a thiazolidinedione (pioglitazone), and in combination with insulin (with or without other antihyperglycemic agents) as shown in Table 2.1. The efficacy of canagliflozin was compared to a DPP-4 inhibitor (sitagliptin) and a sulfonylurea (glimepiride). Data of studies in special populations of patients with T2DM are also included for efficacy analysis: subjects with renal impairment (eGFR =30 to <50 mL/min/1.73 m2); older subjects (age ≥ 55 years); and subjects with or at high risk for cardiovascular (CV) complications (add-on to sulphonyurea and insulin, respectively).

Table 2.1. Phase 3 Trials Overview

Study	Design	Main Treatment Period	Extension	# of Subjects per Arm	Study Population
Monotherapy		26 weeks	26 weeks		HbA1c (%)
DIA3005 Main study	R,DB,PC, PG			Placebo 192 CANA 100 mg 195 CANA 300 mg 197	≥7 to ≤10
High Glycemic substudy	R,DB,PC	26 weeks	NA	CANA 100 mg 47 CANA 300 mg 44	>10 to ≤12
Add-on to AHA Monotherapy					
DIA3006 Add-on to metformin	R,DB,PC, AC,PG	26 weeks	26 weeks	Placebo 183 CANA 100 mg 368 CANA 300 mg 367 Sitaglipin 100mg 366	≥7 to ≤10.5
DIA3009 Add-on to metform	R,DB,AC, PG	52 weeks	52 weeks	CANA 100 mg 483 CANA 300 mg 485 Glimepiride ↑6/8 mg 482	≥7 to ≤9.5
Add-on to Dual Combination AHA Therapy					
DIA3002 Add-on to metformin + sulfonylurea	R,DB,PC, PG	26 weeks	26 weeks	Placebo 156 CANA 100 mg 157 CANA 300 mg 156	≥7 to ≤10.5
DIA3012 Add-on to metformin + pioglitazone	R,DB,PC, PG	26 weeks	26 weeks	Placebo 115 CANA 100 mg 113 CANA 300 mg 114	≥7 to ≤10.5
DIA3015 Add-on to metformin + sulfonylurea	R,DB,AC, PG	52 weeks	NA	CANA 300 mg 377 Sitagliptin 100 mg 378	
Special Population					
DIA3010 older adults (≥55 to ≤80 years of age)	R,DB,PC, PG	26 weeks	78 weeks	Placebo 237 CANA 100 mg 241 CANA 300 mg 236	≥7 to ≤10.5
DIA3004 Moderate renal impairment (eGFR ≥ 30 to <50 mL/min)	R,DB,PC, PG	26 weeks	26 weeks	Placebo 190 CANA 100 mg 90 CANA 300 mg 89	≥7 to ≤10
DIA3008					≥7 to ≤10.5
Sulphonylurea substudy[1]	R,DB,PC, PG	18 weeks	NA	Placebo 45 CANA 100 mg 42 CANA 300 mg 40	
Insulin substudy[2]	R,DB,PC, PG	18 weeks	NA	Placebo 565 CANA 100 mg 566 CANA 300 mg 587	≥7 to ≤10.5
					≥7 to ≤10.5

Note: AC = active-controlled, AHA = anti-hyperglycemic agent, CANA = canagliflozin, DB = double-blind, eGFR = estimated glomerular filtration rate, PC = placebo-controlled, PG = parallel group, R = randomized.
[1] Reviewed population 1 which served as the primary population
[2] Reviewed population 2 which served as the primary population

2.2 Data Sources

The sponsor submitted this NDA including the study data to the FDA CDER Electronic Document Room (EDR). The submission is recorded in the EDR with the link shown below. The data were submitted in SAS Xport transport format.

Application:	NDA 204042/0000
Company	Janssen
Drug	Canagliflozin
CDER EDR link	\\CDSESUB1\EVSPROD\NDA204042\0000
Letter date	5/31/2012

All graphs and tables in the review were created by this reviewer unless otherwise noted.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Review the quality and integrity of the submitted data. Relevant issues include:

- Whether it is possible to reproduce the primary analysis dataset from tabulation or "raw" datasets : yes
- Whether it is possible to trace how the primary endpoint was derived from the original data source (e.g., case report form): yes.
- Whether it is possible to verify the randomized treatment assignments: yes
- Findings from the Division of Scientific Investigation or other source(s) that question the usability of the data: NA

There was a dataset of study DIA3009 not submitted originally in NDA204042/0000. We sent an information request to the sponsor and received the dataset afterward in NDA204042/0013.

3.2 Evaluation of Efficacy

This section provides efficacy evaluations of the 9 phase 3 studies designed to establish the efficacy and safety of canagliflozin in the trials of monotherapy, add-on to other anti-hyperglycemic agent (s), and special populations.

The primary endpoint for all Phase 3 studies was the change in HbA1c from baseline to the end of the study.

Major secondary endpoints included

- changes from baseline to the end of the study in FPG
- changes from baseline to the end of the study in 2-hour post-meal glucose
- proportion of subjects achieving an HbA1c target (<7.0%) at the end of the study
- percent change from baseline to the end of the study in body weight,
- percent change from baseline to the end of the study in HDL-C
- percent change from baseline to the end of the study in fasting triglycerides (TG)
- percent change from baseline to the end of the study in systolic blood pressure (SBP)

Endpoints selected to further elucidate the effect of canagliflozin on body composition included BMI, waist circumference, and lean and fat mass assessed by DXA and regional fat distribution (visceral and subcutaneous fast stores) using an abdominal CT scan (in selected studies). Additional effects of canagliflozin on other comorbidities were explored by examining the change from baseline in DBP and percent changes from baseline in other fasting serum lipid parameters (including serum cholesterol, low density lipoprotein-cholesterol [LDL-C] and ratio of LDL-C to HDL-C) and in free fatty acid (FFA).

The key efficacy endpoint related to body weight in the Phase 3 studies was the percent change in body weight at the primary assessment timepoint. Additional endpoints of interest compared across studies included the proportion of subjects reaching a 0.5% reduction in body weight, the absolute change from baseline in body weight, and the absolute and percent changes from baseline in BMI and in waist circumference (data on BMI and waist circumference endpoints are presented in the individual CSRs).

The sponsor defined the following analysis sets for the evaluation of efficacy:

- Modified intent-to-treat (mITT): All randomized subjects who took at least 1 dose of double-blind study drug (primary analysis set)
- Per protocol: All mITT subjects who completed the required period of treatment for the primary endpoint, were not initiated on rescue therapy (i.e., documented in the eCRF by the investigator) prior to the visit for the primary endpoint, and had no major protocol deviations within this treatment period.
- Completers: All mITT subjects who completed the required period of double-blind treatment for the primary endpoint, and were not initiated on rescue medication (documented in the eCRF by the investigator) prior to the visit for the primary endpoint.

All efficacy analyses were based on mITT analysis set.

The sponsor's pre-specified primary analysis of HbA1c used an analysis of covariance (ANCOVA) model using the last observation carried forward method (LOCF) for missing observations. In general, the ANCOVA model included terms for treatment and randomization stratification factor(s) (if applicable) as fixed effects and the corresponding baseline HbA1c value as a covariate. In Study DIA3004, an additional covariate of baseline eGFR was included in the model. Least-squares (LS) mean treatment differences between each canagliflozin group and the comparator (either placebo or active comparator) and their two-sided 95% confidence intervals (CI) were estimated from the model for each individual study.

I performed supportive analysis using the Per Protocol analysis set. As an additional supportive analysis, change from baseline in HbA1c was analyzed using mixed model repeated measures (MMRM). The MMRM analysis was based on observed data and included the fixed, categorical effects of treatment, stratification factors, visit, and treatment-by-visit interaction as fixed effects and the corresponding baseline HbA1c value as a covariate. An unstructured covariance was used to model the within-patient errors.

In the two non-inferiority studies (DIA3009 and DIA3015), a non-inferiority margin of 0.3% was used for comparisons of canagliflozin with sitagliptin after 52 weeks of treatment (DIA3015) and canagliflozin vs. glimepiride after 52 weeks of treatment (DIA3009).

For each Phase 3 study, a pre-specified sequential testing procedure by the sponsor was applied to testing the treatment differences of the primary and major secondary efficacy endpoints, to control the family-wise error rate at 5%. Each study followed a pre-specified testing hierarchy, and in some studies, the testing proceeded to testing 2 families of tests using the Hochberg procedure for endpoints of SBP, HDL-C, TG, and HOMA2-%B (DIA3012 only), conditional upon the statistical significance of the prior test(s). The sequences varied with each study, depending on whether the study was placebo-controlled, active-controlled, or a study in a special population.

In addition to the sponsor's method for the primary analysis, this reviewer used the completers' data for longitudinal graphs.

Sponsor's analysis of major secondary efficacy endpoints was performed using the mITT analysis set; analyses based on the PP analysis set were performed as supportive analyses. The continuous secondary endpoints (change from baseline in FPG, 2-hour PPG, and SBP, and percent change from baseline in fasting HDL-C, fasting triglycerides, and body weight at Week 26) were analyzed with an ANCOVA model similar to that described for the primary analysis (i.e., treatment and stratification factor(s) as fixed effects, and the corresponding baseline value as a covariate [with baseline eGFR as an additional covariate for analyses of FPG, body weight, and BMI in DIA3004]). Categorical variables (e.g., proportion of subjects with HbA1c <7.0%) were analyzed using a logistic regression model with treatment and stratification factor(s) (if applicable) as fixed factors and baseline HbA1c as covariate (with baseline eGFR as additional covariate in DIA3004). Treatment differences in terms of each canagliflozin group minus the comparator (either placebo or active comparator) and 95% CIs for each variable were estimated from the respective model for each individual study. The proportion of subjects receiving rescue therapy or withdrawn from the study due to the need for rescue medication between each of the canagliflozin groups and placebo, with 95% CI, was provided. (Note: DIA3015 did not include glycemic rescue criteria.).

3.2.1 Monotherapy Trial

3.2.1.1 Study DIA3005

The study DIA3005 was entitled: "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin as Monotherapy in the Treatment of Subjects With Type 2 Diabetes Mellitus Inadequately Controlled With Diet and Exercise" This study included a 52-week Main study (comprised of a 26-week placebo-controlled core study followed by a 26-week active-controlled extension that enrolled subjects with a baseline HbA1c ≥7 to ≤10) and a 26-week High Glycemic Substudy (that enrolled subjects with a HbA1c value >10% and ≤12%).

A total of 587 subjects were randomized to placebo, canagliflozin 100 mg and canagliflozin 300 mg in a 1:1:1 manner in the Main Study, and 91 subjects were randomized to canagliflozin 100 mg and canagliflozin 300 mg in a 1:1 manner in the High Glycemic Substudy. Randomization of the Main study was stratified according to: (1) whether or not a subject was taking AHA(s) at screening, and (2) whether or not a subject participated in the FS-MMTT. Subjects in the High Glycemic Substudy were randomly assigned to 1 of 2 canagliflozin treatment groups (100 mg and 300 mg), stratified according to whether or not a subject was taking AHA(s) at screening.

For more information about the study design see Appendix 1.1.

3.2.1.1.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.1.1.1.

Table 3.2.1.1.1. Patient disposition and demographic information in Study DIA3005

A: Main Study

	Cana 100 mg	Cana 300 mg	Placebo
Randomized	196 (100%)	197 (100%)	194 (100%)
mITT*	195 (99%)	197 (100%)	192 (99%)
Per Protocol	166 (85%)	171 (87%)	121 (62%)
Completers	168 (86%)	171 (87%)	121 (62%)
Rescued	5 (3%)	4 (2%)	44 (23%)
Age (years) Mean(SE) Range ≥ 65	 54.9 (0.8) 25 - 78 38 (19%)	 55.1 (0.7) 25 - 78 35 (18%)	 55.6 (0.8) 24 - 78 41 (21%)
Gender: % males	81 (41%)	89 (45%)	88 (45%)
Race: % White	124 (63%)	137 (70%)	134 (69%)
Country: % U.S.	62 (32%)	52 (26%)	56 (29%)
Baseline HbA1c: <8.5%	95 (48%)	101 (51%)	114 (59%)

Baseline BMI: <30 kg/m^2	92 (47%)	87 (44%)	87 (45%)
AHA at screening: % yes	96 (49%)	95 (48%)	92 (47%)
Baseline eGFR(mL/min/1.73m^2)			
<60	10 (5%)	12 (6%)	10 (5%)
60 to <90	107 (55%)	105 (53%)	112 (58%)
≥90	78 (40%)	80 (41%)	70 (36%)

B: High Glycemic Substudy

	Cana 100 mg	**Cana 300 mg**
Randomized	47 (100%)	44 (100%)
mITT*	47 (100%)	44 (100%)
Per Protocol	38 (81%)	38 (86%)
Completers	38 (81%)	38 (86%)
Rescued	3 (6%)	2 (5%)
Age (years)		
Mean(SE)	49.6 (1.6)	48.6 (1.6)
Range	27 - 77	27 - 67
≥ 65	5 (11%)	2 (5%)
Gender: % males	23 (49%)	29 (66%)
Race: % White	25 (53%)	30 (68%)
Country: % U.S.	15 (32%)	15 (34%)
Baseline HbA1c: <8.5%	25 (53%)	22 (50%)
Baseline BMI: <30 kg/m^2	11 (23%)	10 (23%)
Baseline eGFR(mL/min/1.73m^2)		
<60	2 (4%)	1 (2%)
60 to <90	20 (43%)	21 (48%)
≥90	25 (53%)	22 (50%)

* The primary efficacy analysis population

Baseline HbA1c comparison between arms is in Appendix Figure 1.1. The Kaplan-Meier Plot of Time to dropout is in Appendix Figure 1.2.

3.2.1.1.2 Results and Conclusions

The sponsor's results of primary and secondary analyses were verified by this reviewer as shown in Table 3.2.1.1.2 for the main study and Table 3.2.1.1.3 for the high glycemic substudy, respectively. These results are supportive to canagliflozin (300 mg, and then 100 mg) over placebo.

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Table 3.2.1.1.2. Glycemic Parameters at Week 26 for Canagliflozin (300 mg and 100 mg) and Placebo in Patients with Type 2 Diabetes (Study DIA3005 Main Study)

A: Primary Endpoint

Endpoint	**Placebo**		**Canagliflozin** 100 mg		**Canagliflozin** 300 mg	
HbA1c (%)	n		n		n	
Baseline mean ± SE	189	7.97 ± 0.07	191	8.06 ± 0.07	193	8.01 ± 0.07
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	189	0.14 ± 0.06	191	-0.77 ± 0.06	194	-1.03 ± 0.06
MMRM	182	0.05 ± 0.05	183	-0.78 ± 0.05	191	-1.03 ± 0.05
PP* (by sponsor)	121	-0.18 ± 0.07	165	-0.79 ± 0.06	171	-1.06 ± 0.06
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.91 (-1.09, -0.73)		-1.16 (-1.34, -0.98)
MMRM				-0.83 (-0.97, -0.68)		-1.08 (-1.23, -0.94)
PP* (by sponsor)				-0.61 (-0.78, -0.44)		-0.88 (-1.05, -0.71)
Patients (%) achieving HbA1c <7[1,2]		28 (16%)		64 (38%)		91(55%)
LOCF[2]		32 (19%)		67 (39%)		95(57%)
sponsor's results (LOCF) [3]		39(21%)		85(45%)		121(62%)

* This reviewer obtained the same results as the sponsor

[1] Based on patients at baseline with HbA1c>7%, placebo n=172, cana 100 mcg n=170, and cana 300 mg n=166

[2] completers

[3] Sponsor used all mITT patients, including those who had baseline HbA1c < 7%.

B: Secondary Endpoints

Endpoint	**Placebo**		**Canagliflozin** 100 mg		**Canagliflozin** 300 mg	
FPG (mmol/L)	n		n		n	
Baseline mean ± SE	185	9.23 ± 0.16	188	9.57 ± 0.17	192	9.57 ± 0.17
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	184	0.46 ± 0.14	188	-1.51 ± 0.13	192	-1.94 ± 0.13
MMRM	183	0.004± 0.11	187	-1.53 ± 0.11	189	-1.94 ± 0.11
PP	113	-0.24± 0.15	157	-1.52 ± 0.12	154	-2.00 ± 0.12
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-1.97 (-2.34, -1.60)		-2.41 (-2.78, -2.03)
MMRM				-1.53 (-1.83, -1.23)		-1.94 (-2.24, -1.64)
PP				-1.28 (-1.65, -0.91)		-1.76 (-2.13, -1.39)
2-hour PPG (mmol/L)						
Baseline mean ± SE	126	12.74± 0.31	154	13.87 ± 0.33	157	14.10 ± 0.32
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	126	0.29 ± 0.23	154	-2.38 ± 0.21	157	-3.27 ± 0.21
PP	111	-0.18 ± 0.24	152	-2.35 ± 0.20	155	-3.20 ± 0.20
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-2.67 (-3.28, -2.05)		-3.55 (-4.17, -2.94)
PP				-2.18 (-2.79, -1.56)		-3.02 (-3.64, -2.41)

Body Weight (kg)						
Baseline mean ± SE	190	87.48 ±1.41	192	85.89 ± 1.55	194	86.92 ± 1.48
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	190	-0.6 ± 0.2	192	-2.8 ± 0.2	194	-3.9 ± 0.2
PP	121	-0.60 ± 0.28	166	-2.52 ± 0.23	171	-3.67 ± 0.23
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-2.2 (-2.9, -1.6)		-3.3 (-4.0, -2.6)
PP				-1.92 (-2.63, -1.21)		-3.07 (-3.78. -2.37)
Systolic BP (mmHg)						
Baseline mean ± SE	190	127.7 ± 1.0		126.7 ± 0.9		128.5 ± 0.9
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	190	0.38 ± 0.78	192	-3.34 ± 0.77	195	-5.04 ± 0.77
PP	121	0.20 ± 0.98	166	-2.57 ± 0.83	171	-5.44 ± 0.82
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-3.71 (-5.86, -1.57)		-5.42 (-7.56, -3.28)
PP				-2.77 (-5.28, -0.26)		-5.64 (-8.14, -3.15)

Table 3.2.1.1.3. Glycemic Parameters in High Glycemic Substudy after 26 Weeks Treatment with Canagliflozin (300 mg and 100 mg) and Placebo in Patients with Type 2 Diabetes (mITT, Study DIA3005)

	Canagliflozin 100 mg		**Canagliflozin** 300 mg	
HbA1c (%)	n		n	
Baseline mean ± SE	46	10.59 ± 0.13	43	10.62 ± 0.15
Adj. Mean Change from baseline±SE (95% CI)				
LOCF* (by sponsor)	46	-2.13±0.22 (-2.57, -1.69)	43	-2.56±0.23 (-3.02, -2.11)
MMRM	43	-2.27±0.18 (-2.63, -1.91)	39	-2.56±0.19 (-2.92, -2.19)
PP	37	-2.63±0.19 (-3.01, -2.24)	38	-2.61±0.19 (-2.98, -2.23)
Patients (%) achieving HbA1c <7[1,2]		8 (17%)		5 (12%)
LOCF[1]		8 (17%)		5 (12%)
sponsor's results (LOCF) [3]	47	8 (17%)	44	5 (12%)
FPG (mmol/L)	n		n	
Baseline mean ± SE	45	13.19 ± 0.46	43	13.50 ± 0.49
Adj. Mean Change from baseline±SE (95% CI)				
LOCF (by sponsor)	45	-4.54±0.36 (-5.25, -3.82)	43	-4.78±0.36 (-5.52, -4.07)
MMRM	45	-4.46±0.29 (-5.04, -3.89)	41	-4.68±0.29 (-5.25, -4.12)
PP	34	-4.59±0.32 (-5.22,-3.96)	34	-4.58±0.31 (-5.19, -3.97)
2-hour PPG (mmol/L)				
Baseline mean ± SE	30	18.34 ± 0.68	34	19.68 ± 0.86
Adj. Mean Change from baseline±SE (95% CI)				
LOCF* (by sponsor)	30	-6.58±0.56 (-7.71, -5.45)	34	-6.98±0.52 (-8.02, -5.93)
PP	30	-6.57±0.55 (-7.67, -5.47)	33	-7.18±0.51 (-8.21, -6.15)
Body Weight (kg)				
Baseline mean ± SE	46	83.22 ± 3.38	43	81.63 ± 2.88
Adj. Mean Change from baseline±SE (95% CI)				
LOCF* (by sponsor)	46	-3.0±0.6 (-4.2, -1.8)	43	-3.8±0.6 (-5.0, -2.6)

PP	38	-2.51±0.58 (-3.67, -1.34)	38	-3.58 ±0.58 (-4.73, -2.44)
Systolic BP (mmHg)				
Baseline mean ± SE Adj. Mean Change from baseline±SE (95% CI) LOCF* (by sponsor) PP	 46 38	 -4.47±1.75 (-7.95, -0.98) -4.72±1.89 (-8.49,-0.94)	 43 38	 -4.97±1.80 (-8.55,-1.39) -5.48±1.87 (-9.20,-1.75)

* This reviewer obtained the same results as the sponsor
[1] Based on patients at baseline with HbA1c>7%, cana 100 mcg n=46, and cana 300 mg n=43
[2] completers
[3] Sponsor used all mITT patients, including those who had baseline HbA1c ≤ 7%.

The time course of the completer's HbA1c difference from baseline over time is shown in Appendix Figures 1.3.
This reviewer looked at the relationship between patients' baseline levels and their corresponding changes in HbA1c reduction from baseline to Week 26 (LOCF) as shown in Appendix Figure 1.4. The treatment-baseline interaction is significant at alpha=0.10 level for either dose (cacn 100 mg, p=0.0020; cana 300 mg, p=0.0006) for the main study.

3.2.2 Add-on to AHA Monotherapy Trials

3.2.2.1 DIA3006 Add-on to metformin

Study DIA3006 was "A randomized, double-blind, placebo and active-controlled, 4-arm, parallel-group, multicenter study to evaluate the efficacy, safety, and tolerability of canagliflozin) compared with sitagliptin and placebo in the treatment of subjects with Type 2 diabetes mellitus with inadequate glycemic control on metformin monotherapy". The duration of this study is 52 weeks (comprised of a 26-week placebo-controlled core study followed by a 26-week active-controlled extension).

A total of 1284 adult subjects were randomly in a 2:2:2:1 ratio to once daily administration of canagliflozin 100 mg, canagliflozin 300 mg, sitagliptin 100 mg, or matching placebo added to stable doses of metformin IR in monotherapy and entered into the 26-week placebo- and active-controlled double-blind treatment period (Period I). Randomization was stratified according to whether the subject was on metformin monotherapy or metformin and an SU agent at screening.

For more information about the study design see Appendix 2.1.

3.2.2.1.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.2.1.1.

Table 3.2.2.1.1. Patient disposition and demographic information in Study DIA3006

Study population	Canagliflozin		Placebo	Sitagliptin
	100 mg	300 mg		100 mg
Randomized	368 (100%)	367 (100%)	183 (100%)	366 (100%)
mITT*	368 (100%)	367 (100%)	183 (100%)	366 (100%)

Per Protocol	313 (85%)	320 (87%)	130 (71%)	297 (81%)
Completers	317 (86%)	322 (88%)	130 (71%)	299 (82%)
Rescued	6 (2%)	1 (0.2%)	27 (15%)	23 (6%)
Age (years)				
Mean(SE)	55.4 (0.5)	55.2 (0.5)	55.2 (0.7)	55.4 (0.5)
Range	27 - 78	21 – 78	26 – 72	33 – 78
≥ 65	53 (14%)	56 (15%)	37 (20%)	57 (16%)
Gender: % males	174 (100%)	165 (100%)	94 (100%)	172 (100%)
Race: % White	252 (47%)	256 (45%)	129 (51%)	264 (47%)
Country: % U.S.			(100%)	
Baseline HbA1c: <8.5%	271 (74%)	260 (71%)	132 (72%)	269 (73%)
Baseline BMI: <30 kg/m^2	145 (39%)	173 (48%)	89 (49%)	159 (43%)
AHA at screening: % yes	105 (29%)	104 (28%)	54 (300%)	100 (27%)
Baseline eGFR (mL/min/1.73m^2)				
<60	12 (3%)	5 (1%)	9 (5%)	14 (4%)
60 to <90	179 (49%)	193 (53%)	101 (55%)	192 (52%)
≥90	177 (48%)	169 (46%)	73 (40%)	160 (44%)

Baseline HbA1c comparison between arms is in Appendix Figure 2.1. The Kaplan-Meier Plot of Time to dropout is in Appendix Figure 2.2.

3.2.2.1.2 Results and Conclusions

The sponsor's results of primary and secondary analyses were verified by this reviewer as shown in Table 3.2.2.1.2. These results are supportive to canagliflozin (300 mg, and then 100 mg) over placebo.

Table 3.2.2.1.2. Glycemic Parameters at Week 26 for Canagliflozin (300 mg and 100 mg) and Placebo in Patients with Type 2 Diabetes (Study DIA3006)

A: Primary Endpoint

Endpoint	**Placebo**		**Canagliflozin** 100 mg		**Canagliflozin** 300 mg		**Sitagliptin** 100 mg	
HbA1c (%)	n		n		n		n	
Baseline mean ± SE	181	7.96 ± 0.07	365	7.94 ± 0.05	360	7.95 ± 0.05	354	7.92 ± 0.05
Adj. Mean Change from baseline±SE								
LOCF* (by sponsor)	181	-0.17±0.06	365	-0.79 ± 0.04	360	-0.94 ± 0.04	354	-0.82 ± 0.04
MMRM	172	-0.25 ±0.05	355	-0.77 ± 0.04	361	-0.93 ± 0.04	355	-0.82 ± 0.04
PP* (by sponsor)	129	-0.45 ±0.06	312	-0.83 ± 0.04	318	-0.99 ± 0.04	296	-0.91 ± 0.04
Cana−P, adjusted LS Mean (95% CI)								
LOCF* (by sponsor)				-0.62(-0.76,-0.48)		-0.77(-0.91,-0.64)		-0.66(-0.79,-0.52)

MMRM PP* (by sponsor)				-0.52 (-0.64,-0.41) -0.38 (-0.53,-0.24)		-0.68(-0.80,-0.57) -0.54(-0.68,-0.39)		-0.57(-0.69,-0.45) -0.46(-0.60,-0.31)
achieving HbA1c <7[1,2] LOCF[1] sponsor's (LOCF) [3]		35 (22%) 38 (24%) 54 (30%)		120 (37%) 131 (40%) 166 (45%)		152 (49%) 165 (53%) 208 (58%)		136 (45% 147 (48%) 193 (54%)

* This reviewer obtained the same results as the sponsor

[1] Based on patients at baseline with HbA1c>7%, placebo n=158, cana 100 mcg n=327, and cana 300 mg n=312, Sita 100 mg n=305

[2] completers

[3] Sponsor used all mITT patients, including those who had baseline HbA1c < 7%.

B: Secondary Endpoints

Endpoint	**Placebo**		**Canagliflozin** 100 mg		**Canagliflozin** 300 mg		**Sitagliptin** 100 mg	
FPG (mmol/L)	n		n		n		n	
Baseline mean ± SE	181	9.12± 0.16	365	9.36 ± 0.12	360	9.59 ± 0.13	355	9.38 ± 0.12
Adj. Mean Change from baseline±SE								
LOCF* (by sponsor)	181	0.14± 0.14	365	-1.52 ± 0.10	360	-2.10 ± 0.11	354	-1.12 ± 0.11
PP	127	-0.63±0.14	307	-1.54 ± 0.09	315	-2.10 ± 0.09	294	-1.30 ± 0.09
T−P, adj. LS Mean (95% CI)								
LOCF* (by sponsor)				-1.65(-1.99,-1.32)		-2.23(-2.57,-1.90)		-1.26(-1.59,-0.93)
PP				-0.91 (-1.22, -0.60)		-1.47(-1.78,-1.16)		-0.67(-0.98,-0.35)
2-hour PPG (mmol/L)								
Baseline mean ± SE	129	13.81±0.32	298	14.30±0.22	288	14.54±0.24	295	14.23±0.21
Adj. Mean Change from baseline±SE								
LOCF* (by sponsor)	129	-0.55±0.27	298	-2.66±0.18	288	-3.17±0.19	295	-2.74±0.19
PP	109	-1.34±0.28	285	-2.67±0.18	281	-3.15 ± 0.18	269	-2.81 ±0.18
T−P, adj. LS Mean (95% CI)								
LOCF* (by sponsor)				-2.12(-2.73,-1.51)		-2.62(-3.24,-2.01)		-2.19(-2.80,-1.58)
PP				-1.33 (-1.94,-0.72)		-1.81(-2.43,-1.20)		-1.48(-2.09,-0.86)
Body Weight (kg)								
Baseline mean ± SE	181	86.69 ±1.67	365	88.73 ± 1.17	360	85.44 ± 1.09	355	87.59 ± 1.11
Adj. Mean Change from baseline±SE								
LOCF* (by sponsor)	181	-1.2±0.3	365	-3.7±0.2	360	-4.2±0.2	355	-1.2±0.2
PP	129	-1.31±0.29	313	-3.36±0.19	318	-3.68±0.19	297	-1.20±0.19
T−P, adj. LS Mean (95% CI)								
LOCF* (by sponsor)				-2.5(-3.1, -1.9)		-2.9(-3.5,-2.3)		-0.0 (-0.6,0.6)
PP				-2.06 (-2.70, -1.42)		-2.37(-3.01,-1.73)		0.11 (-0.54, 0.76)
Systolic BP (mmHg)								
Baseline mean ± SE	181	128.05±0.947	365	128.04±0.67	360	128.69±0.69	355	127.96±0.72
Adj. Mean Change from baseline±SE								
LOCF* (by sponsor)	181	1.52±0.83	365	-3.84±0.60	360	-5.06±0.61	355	-1.83±0.61
PP	130	1.64±0.97	313	-3.88±0.65	319	-5.53±0.64	297	-1.95±0.66
T−P, adj. LS Mean (95% CI)								
LOCF* (by sponsor)				-5.36(-7.28, -3.44)		-6.58(-8.50,-4.65)		-3.34(-5.27,-1.41)
PP				-5.51(-7.75, -3.28)		-7.16(-9.38,-4.93)		-3.59(-5.79,-1.38)

The time course of the completer's HbA1c difference from baseline over time is shown in Appendix Figures 2.3.

This reviewer looked at the relationship between patients' baseline levels and their corresponding changes in HbA1c reduction from baseline to Week 26 (LOCF) as shown in Appendix Figure 2.4. The treatment-baseline interaction is significant at alpha=0.10 level between canagliflozin at either dose and placebo (both p<0.0001), but not significant between sitagliptin and placebo.

3.2.2.2 DIA3009 Active-Controlled Study Versus Glimepiride in Combination with Metformin

The study DIA3009 was a randomized, double-blind, active comparator-controlled, 3-arm, parallel-group, 2-year (104 weeks), multicenter study to evaluate the efficacy, safety, and tolerability of CANAGLIFLOZIN (100 mg and 300 mg) compared with glimepiride in the treatment of subjects with T2DM, 18 to 80 years of age, inclusive, who are not optimally controlled on metformin monotherapy (recommended at ≥2,000 mg/d or if unable to tolerate, ≥1,500 mg/d is acceptable).

The primary endpoint is the change from baseline to Week-52 of the HbA1c-lowering efficacy of CANAGLIFLOZIN after 52 weeks of treatment. A noninferiority margin of 0.3% was selected to compare canagliflozin 100 mg and canagliflozin 300 mg with glimepiride after 52 weeks of treatment.

A total of 1452 subjects were randomly assigned in a 1:1:1 ratio to 1 of 3 treatments groups, to receive either 100 or 300 mg of canagliflozin, or glimepiride. The randomization was stratified based on whether the subject was taking a stable dosage of metformin before screening versus whether the subject was required to increase the dosage of metformin therapy, and/or discontinue the use of a second antihyperglycemic agent at the time of study entry, and by country. Subjects randomly assigned to glimepiride received a starting dosage of 1 mg once daily followed by titrating up to the maximum dose of 6 or 8 mg once daily.

For more information about the study design and the sponsor's hierarchical testing procedure in testing the treatment differences (CANAGLIFLOZIN two dose groups versus glimepiride respectively) for the primary and secondary endpoints to preserve the overall Type I error rate of 5% see Appendix 3.1.

3.2.2.2.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.2.2.1.

Table 3.2.2.2.1. Patient disposition and demographic information in Study DIA3009

	Canagliflozin		Glimepiride
	100 mg	300 mg	
Randomized	483 (100%)	485 (100%)	484 (100%)
mITT*	483 (100%)	485 (100%)	482 (99.6%)
Per Protocol	361 (75%)	357 (74%)	336 (69%)

Completers	365 (76%)	357 (74%)	337 (70%)
Rescued	32 (7%)	24 (5%)	51 (11%)
Age (years) Mean(SE) Range ≥ 65	 56.2 (0.4) 22 - 79 84 (17%)	 55.6 (0.4) 26 - 79 74 (15%)	 56.2 (0.4) 28 - 79 81 (17%)
Gender: % males	252 (52%)	241 (50%)	263 (54%)
Race: % White	324 (67%)	334 (69%)	322 (67%)
Country: % U.S.			
Baseline HbA1c: <8.5%	383 (79%)	377 (78%)	372 (77%)
Baseline BMI: <30 kg/m^2	215 (45%)	224 (46%)	234 (48%)
AHA at screening: % yes	173 (36%)	178 (37%)	171 (35%)
Baseline eGFR (mL/min/1.73m^2) <60 60 to <90 ≥90	 15 (3%) 232 (48%) 236 (49%)	 13 (3%) 232 (48%) 240 (49%)	 10 (2%) 251 (52%) 220 (45%)

The baseline levels of HbA1c in the two arms are compared in a box plot as shown in Appendix Figure 3.1. The Kaplan-Meier Plot of Time to dropout is in Appendix Figure 3.2.

3.2.2.2.2 Results and Conclusions

The noninferiority of canagliflozin (300 mg, and then 100 mg) with respect to glimepiride using mITT with LOCF on the primary endpoint, HbA1c change from baseline to week 52, was demonstrated. Superiority of canagliflozin 300 mg to glimepiride was also demonstrated. These results were shown in Table 3.2.2.2.2.

Table 3.2.2.2.2 Glycemic Parameters at Week 52 for Canagliflozin (100 mg and 300 mg) and Glimepiride in Patients with Type 2 Diabetes (Study DIA3009)

A: Primary Endpoint

Endpoint	**Glimepiride**		**Canagliflozin** 100 mg		**Canagliflozin** 300 mg	
HbA1c (%)	n		n		n	
Baseline mean ± SE	473	7.83 ± 0.04	478	7.78 ± 0.04	474	7.79 ± 0.04
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	473	-0.81 ± 0.04	478	-0.82 ± 0.04	474	-0.93 ± 0.04
MMRM ok	448	-0.82 ± 0.03	456	-0.86 ± 0.03	446	-0.98 ± 0.03
PP* (by sponsor)	334	-0.97 ± 0.04	360	-0.92 ± 0.04	354	-1.02 ± 0.04

Cana−glim, adj. LS Mean(95% CI)						
LOCF* (by sponsor)				-0.01 (-0.11, 0.08)		-0.12 (-0.22, -0.02)
MMRM ok				-0.04 (-0.13, 0.04)		-0.16 (-0.25, -0.08)
PP* (by sponsor)				0.05 (-0.05, 0.14)		-0.06 (-0.15, 0.03)
Patients (%) achieving HbA1c <7[1,2]		181 (44%)		184 (44%)		196 (48%)
LOCF[1]		215 (52%)		205 (49%)		226 (56%)
sponsor's results (LOCF) [3]		264 (56%)		256 (54%)		285 (60%)

* This reviewer obtained the same results as the sponsor

[1] Based on patients at baseline with HbA1c>7%, Glimepiride n=411, cana 100 mcg n=419, and cana 300 mg n=405

[2] completers

[3] Sponsor used all mITT patients, including those who had baseline HbA1c < 7%.

B: Secondary Endpoints

Endpoint	**Glimepiride**		**Canagliflozin** 100 mg		**Canagliflozin** 300 mg	
FPG (mmol/L)	n		n		n	
Baseline mean ± SE	477	9.20 ± 0.10	477	9.18 ± 0.09	476	9.09 ± 0.09
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	477	-1.02 ± 0.09	477	-1.35 ± 0.09	476	-1.52 ± 0.09
PP	335	-1.29± 0.09	356	-1.47 ± 0.09	352	-1.71 ± 0.09
Cana−glim, adj. LS Mean (95% CI)						
LOCF* (by sponsor)				-0.33 (-0.56, -0.11)		-0.51 (-0.73, -0.28)
PP				-0.18 (-0.40, 0.03)		-0.42 (-0.63, -0.20)
Body Weight (kg)						
Baseline mean ± SE	478	85.58± 0.91	479	86.81± 0.92	480	86.56 ± 0.88
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	478	1.0 ± 0.2	479	-4.2 ± 0.2	480	-4.7 ± 0.2
PP *	336	1.14 ± 0.23	360	-3.92 ± 0.22	355	-4.51 ± 0.22
Cana−glim, adj. LS Mean (95% CI)						
LOCF* (by sponsor)				-5.2 (-5.7, -4.7)		-5.7 (-6.2, -5.1)
PP*				-5.06 (-5.61,-4.51)		-5.65 (-6.20, -5.10)
Systolic BP (mmHg)						
Baseline mean ± SE	480	129.53±0.62	479	129.97 ± 0.57	480	130.00 ± 0.63
Adj. Mean Change from baseline±SE						
LOCF *(by sponsor)	480	0.2 ± 0.57	479	-3.27 ± 0.57	480	-4.56 ± 0.57
PP	336	-0.39 ± 0.68	360	-3.56 ± 0.67	357	-5.44 ± 0.66
Cana−glim, adj. LS Mean (95% CI)						
LOCF* (by sponsor)				-3.48 (-4.88, -2.07)		-4.76 (-6.17, -3.36)
PP				-3.17 (-4.82, -1.53)		-5.05 (-6.70, -3.41)

* This reviewer obtained the same results as the sponsor

The time course plot is in Appendix Figure 3.3. This reviewer looked at the relationship between patients' baseline levels and their corresponding changes in HbA1c reduction from baseline to Week 52 (LOCF) as shown in Appendix Figure 3.4. The treatment-baseline interaction is not significant at alpha=0.10 level.

3.2.3 Add-on to Dual Combination AHA Therapy

3.2.3.1 DIA3002 Add-on to metformin + sulfonylurea

Study DIA3002 was "A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicenter Study, to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Sulphonylurea Therapy." The duration of the study included a 52-weeks double-blind treatment phase (26-week core double-blind treatment period and a 26-week double-blind extension treatment period).

A total of 469 subjects were randomized to placebo, canagliflozin 100 mg, and canagliflozin 300 mg in a 1:1:1 manner stratified according to (1) entering or not entering the AHA adjustment period (i.e., on or not on protocol-specified doses of metformin and an SU at screening); and (2) whether or not a subject participated in the FS-MMTT.

For more information about the study design see Appendix 4.1.

3.2.3.1.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.3.1.1.

Table 3.2.3.1.1. Patient disposition and demographic information in Study DIA3002

	Canagliflozin 100 mg	**Canagliflozin** 300 mg	**Placebo**
Randomized	157 (100%)	156 (100%)	156 (100%)
mITT*	157 (100%)	156 (100%)	156 (100%)
Per Protocol	126 (80%)	120 (77%)	102 (65%)
Completers	127 (81%)	126 (81%)	107 (69%)
Rescued	2 (1%)	3 (2%)	20 (13%)
Age (years) Mean(SE) Range ≥ 65	 57.3 (0.8) 27 - 79 36 (23%)	 56.0 (0.7) 34 - 78 22 (14%)	 56.7 (0.7) 31 - 79 26 (17%)
Gender: % males	76 (48%)	87 (56%)	76 (49%)
Race: % White	132 (84%)	129 (83%)	129 (83%)
Country: % U.S.	62 (39%)	52 (33%)	56 (36%)
Baseline HbA1c: <8.5%	108 (69%)	103 (66%)	106 (68%)
Baseline BMI: <30 kg/m^2	54 (34%)	48 (31%)	57 (37%)
AHA at screening: % yes	32 (20%)	31 (20%)	32 (21%)
Baseline eGFR (mL/min/1.73m^2)	5 (3%)	2 (1%)	8 (5%)

<60 60 to <90 ≥90	80 (51%) 72 (46%)	80 (51%) 74 (47%)	75 (48%) 73 (47%)

Baseline HbA1c comparison between arms is in Appendix Figure 4.1. The Kaplan-Meier Plot of Time to dropout is in Appendix Figure 4.2.

3.2.3.1.2 Results and Conclusions

The sponsor's results of primary and secondary analyses were verified by this reviewer as shown in Table 3.2.3.2 (for the main study and Table 3.2.3.2 for the high glycemic substudy, respectively). These results are supportive to canagliflozin (300 mg, and then 100 mg) over placebo.

Table 3.2.3.1.2. Glycemic Parameters at Week 26 for Canagliflozin (300 mg and 100 mg) and Placebo in Patients with Type 2 Diabetes (Study DIA3002)

A: Primary Endpoint

Endpoint	**Placebo**		**Canagliflozin 100 mg**		**Canagliflozin 300 mg**	
HbA1c (%)	n		n		n	
Baseline mean ± SE	150	8.12 ± 0.07	155	8.13 ± 0.07	152	8.13 ± 0.08
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	150	-0.13 ± 0.08	155	-0.85 ± 0.07	152	-1.06 ± 0.08
MMRM	146	-0.22 ± 0.06	154	-0.88 ± 0.06	152	-1.09 ± 0.06
PP* (by sponsor)	102	-0.33 ± 0.09	125	-0.87 ± 0.08	118	-1.06 ± 0.08
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.71 (-0.90, -0.52)		-0.92 (-1.11, -0.73)
MMRM				-0.66 (-0.82, -0.51)		-0.87 (-1.03, -0.72)
PP* (by sponsor)				-0.54 (-0.76, -0.32)		-0.73 (-0.96, -0.51)
Patients (%) achieving HbA1c <7[1,2]		23 (16%)		51 (36%)		67 (47%)
LOCF[1]		26 (18%)		58 (41%)		78 (55%)
sponsor's results (LOCF)[3]		27 (18%)		67 (43%)		86 (57%)

* This reviewer obtained the same results as the sponsor
[1] Based on patients at baseline with HbA1c≥7%, placebo n=142, cana 100 mcg n=141, and cana 300 mg n=142
[2] Completers
[3] Sponsor used all mITT patients, including those who had baseline HbA1c < 7%.

B: Secondary Endpoints

Endpoint	**Placebo**		**Canagliflozin** 100 mg		**Canagliflozin** 300 mg	
FPG (mmol/L)	n		n		n	
Baseline mean ± SE	150	9.42 ± 0.18	155	9.60 ± 0.18	152	9.34 ± 0.17
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	150	0.23 ± 0.20	155	-1.01 ± 0.20	152	-1.69 ± 0.20
PP	102	-0.38 ± 0.21	122	-1.09 ± 0.20	118	-1.75 ± 0.20
Cana−P, adjusted LS Mean (95% CI)						

LOCF* (by sponsor) PP				-1.24 (-1.75, -0.73) -0.71 (-1.24, -0.17)		-1.92 (-2.43, -1.41) -1.37 (-1.91, -0.84)
Body Weight (kg)						
Baseline mean ± SE Percent Change from baseline±SE LOCF* (by sponsor) PP Cana−P, adjusted LS Mean (95% CI) LOCF* (by sponsor) PP	150 150 102	90.82 ±1.84 -0.67 ± 0.28 -0.64 ± 0.31	156 156 126	93.49 ± 1.79 -2.06 ± 0.28 -2.00 ± 0.29 -1.4 (-2.1, -0.7) -1.37 (-2.13, -0.60)	154 154 120	93.46 ± 1.78 -2.64 ± 0.28 -2.60 ± 0.29 -2.0 (-2.7, -1.3) -1.97 (-2.74, -1.20)
Systolic BP (mmHg)						
Baseline mean ± SE Adj. Mean Change from baseline±SE LOCF* (by sponsor) PP Cana−P, adjusted LS Mean (95% CI) LOCF* (by sponsor) PP	 150 102 *	 -2.65 ± 0.98 -2.68 ± 1.16	 156 126 *	 -4.89 ± 0.98 -4.86 ± 1.09 -2.24 (-4.71, 0.24) -2.18 (-5.06, 0.70)	 154 120 *	 -4.27 ± 0.98 -4.80 ± 1.11 -1.62 (-4.11, 0.87) -2.13 (-5.04, 0.79)

* This reviewer obtained the same results as the sponsor

The time course of the completer's HbA1c difference from baseline over time is shown in Appendix Figures 4.3.

This reviewer looked at the relationship between patients' baseline levels and their corresponding changes in HbA1c reduction from baseline to Week 26 (LOCF) as shown in Appendix Figure 4.4. The treatment-by-baseline interactions between each dose of canagliflozin and placebo is significant at alpha=0.10 level (CANA 100 mg p-value=0.0088, and CANA 300 mg p-value=0.0124).

3.2.3.2 DIA3012 Add-on to metformin + pioglitazone

Title of Study DIA3012: "A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, 26-Week Multicenter Study with a 26-Week Extension to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 (Canagliflozin) Compared with Placebo in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Pioglitazone Therapy" The duration of the study included the 52-week double-blind treatment phase (26-week core double-blind treatment period and a 26-week double-blind extension treatment period).

A total of 344 subjects were randomized to placebo, canagliflozin 100 mg, and canagliflozin 300 mg in a 1:1:1 manner. The randomization was stratified by 1) entering or not entering the AHA adjustment period (i.e., on or not on protocol-specified doses of metformin and pioglitazone at screening); 2) dose of pioglitazone at randomization (30 or 45 mg).

For more information about the study design see Appendix 5.1.

3.2.3.2.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.3.2.1.

Table 3.2.3.2.1. Patient disposition and demographic information in Study DIA3012

	Canagliflozin		Placebo
	100 mg	300 mg	
Randomized	115 (100%)	114 (100%)	115 (100%)
mITT*	113 (98%)	114 (100%)	115 (100%)
Per Protocol	103 (90%)	101 (89%)	78 (68%)
Completers	103 (90%)	101 (89%)	79 (69%)
Rescued	1 (1%)	0 (0%)	14 (12%)
Age (years)			
Mean(SE)	56.6 (1.0)	56.8 (1.0)	58.1 (0.9)
Range	27 - 76	31 - 76	38 - 78
≥ 65	30 (26%)	30 (26%)	30 (26%)
Gender: % males	77 (67%)	63 (55%)	76 (66%)
Race: % White	83 (72%)	90 (79%)	79 (69%)
Country: % U.S.	55 (48%)	56 (49%)	43 (37%)
Baseline HbA1c: <8.5%	79 (69%)	84 (74%)	84 (73%)
Baseline BMI: <30 kg/m^2	45 (39%)	46 (40%)	42 (37%)
AHA at screening: % yes	60 (52%)	59 (52%)	62 (54%)
Baseline eGFR(mL/min/1.73m^2)			
<60	8 (7%)	10 (9%)	7 (6%)
60 to <90	69 (60%)	54 (47%)	61 (53%)
≥90	36 (31%)	50 (44%)	47 (41%)

Baseline HbA1c comparison between arms is in Appendix Figure 5.1 The Kaplan-Meier Plot of Time to dropout is in Appendix Figure 5.2.

3.2.3.2.2 Results and Conclusions

The sponsor's results of primary and secondary analyses were verified by this reviewer as shown in Table 3.2.3.2.2. These results are supportive to canagliflozin (300 mg, and then 100 mg) over placebo.

Table 3.2.3.2.2. Glycemic Parameters at Week 26 for Canagliflozin (300 mg and 100 mg) and Placebo in Patients with Type 2 Diabetes (Study DIA3012)

A: Primary Endpoint

Endpoint	**Placebo**		**Canagliflozin** 100 mg		**Canagliflozin** 300 mg	
HbA1c (%)	n		n		n	
Baseline mean ± SE	114	8.00 ± 0.09	113	7.99 ± 0.09	112	7.84 ± 0.09
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	114	-0.26 ± 0.07	113	-0.89 ± 0.07	112	-1.03 ± 0.07
MMRM	110	-0.30 ± 0.06	110	-0.90 ± 0.06	110	-1.03 ± 0.06
PP* (by sponsor)	78	-0.48 ± 0.08	101	-0.93 ± 0.07	101	-1.03 ± 0.07
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.62 (-0.81, -0.44)		-0.76 (-0.95, -0.58)
MMRM				-0.60 (-0.76, -0.44)		-0.73 (-0.89, -0.57)
PP* (by sponsor)				-0.45 (-0.65, -0.26)		-0.55 (-0.75, -0.35)
Patients (%) achieving HbA1c <7[1,2]		20 (20%)		38 (38%)		51 (53%)
LOCF[1]		25 (26%)		41 (41%)		58 (60%)
sponsor's results (LOCF) [3]		37 (32%)		53 (47%)		72 (64%)

* This reviewer obtained the same results as the sponsor

[1] Based on patients at baseline with HbA1c>7%, placebo n=98, cana 100 mcg n=101, and cana 300 mg n=97

[2] Completers

[3] Sponsor used all mITT patients, including those who had baseline HbA1c < 7%.

B: Secondary Endpoints

	Placebo		**Canagliflozin 100 mg**		**Canagliflozin 300 mg**	
FPG (mmol/L)	n		n		n	
Baseline mean ± SE	114	9.13 ± 0.21	113	9.38 ± 0.20	112	9.11 ± 0.22
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	114	0.14± 0.15	113	-1.49 ± 0.16	112	-1.84 ± 0.16
PP	77	-0.42± 0.16	101	-1.63 ± 0.14	100	-1.87 ± 0.14
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-1.63 (-2.05, -1.21)		-1.98 (-2.40, -1.56)
PP				-1.22 (-1.63, -0.81)		-1.45 (-1.86, -1.04)
Body Weight (kg)						
Baseline mean ± SE	114	93.98± 2.10	113	94.17 ± 2.09	112	94.38 ± 2.46
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	114	-0.13 ± 0.32	113	-2.84 ± 0.33	112	-3.81 ± 0.33
PP	78	-0.15 ± 0.38	103	-2.82 ± 0.33	101	-3.81 ± 0.34
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-2.7 (-3.6, -1.8)		-3.7 (-4.6, -2.8)
PP				-2.66 (-3.63, -1.70)		-3.65 (-4.63, -2.68)
Systolic BP (mmHg)						
Baseline mean ± SE						
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	114	-1.24 ± 1.03	113	-5.30 ± 1.04	112	-4.70 ± 1.04
PP	78*	-0.43 ± 1.23	103	-5.12 ± 1.07	101	-4.61 ± 1.08
Cana−P, adjusted LS Mean (95% CI)			*		*	
LOCF* (by sponsor)				-4.1 (-6.9, -1.3)		-3.5 (-6.3, -0.6)
PP				-4.69 (-7.80, -1.58)		-4.19 (-7.31, -1.06)

* This reviewer obtained the same results as the sponsor

The time course of the completer's HbA1c difference from baseline over time is shown in Appendix Figures 5.3.

This reviewer looked at the relationship between patients' baseline levels and their corresponding changes in HbA1c reduction from baseline to Week 26 (LOCF) as shown in Appendix Figure 5.4. The treatment-baseline interaction is significant at alpha=0.10 level between each dose of canagliflozin and placebo (both p<=0.01).

3.2.3.3 DIA3015 Add-on to metformin + sulfonylurea

Study DIA3015: "A Randomized, Double-Blind, Active-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Versus Sitagliptin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Sulphonylurea Therapy." The duration of the study included a 52-week double-blind treatment phase.

A total of 756 subjects were randomized to treatment arms (canagliflozin 300 mg or sitagliptin 100 mg) in a 1:1 ratio, stratified according to (1) whether or not the Week -2 HbA1c value for the subject is ≥9.0%, and (2) whether or not a subject would participate in the FS-MMTT procedure.

The primary efficacy endpoint was the change in HbA1c from baseline through Week 52.

For more information about the study design see Appendix 6.1.

3.2.3.3.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.1.

Table 3.2.3.3.1. Patient disposition and demographic information in Study DIA3015

	Canagliflozin 300 mg	Sitagliptin 100 mg
Randomized	378 (100%)	378 (100%)
mITT*	377 (99.7%)	378 (100%)
Per Protocol	247 (65%)	207 (55%)
Completers	254 (67%)	210 (56%)
Age (years) Mean(SE) Range ≥ 65	 56.5 (0.5) 30 - 91 71 (19%)	 56.6 (0.5) 20 - 85 71 (19%)
Gender: % males	207 (55%)	215 (57%)
Race: % White	255 (67%)	257 (68%)
Country: % U.S.	122 (32%)	100 (26%)

Baseline HbA1c: <8.5%	251 (66%)	239 (63%)
Baseline BMI: <30 kg/m^2	182 (48%)	173 (46%)
AHA at screening: HbA1c <9 % yes	248 (66%)	248 (66%)
Baseline eGFR (mL/min/1.73m^2)		
<60	19 (5%)	22 (6%)
60 to <90	188 (50%)	194 (51%)
≥90	170 (45%)	162 (43%)

Baseline HbA1c comparison between arms is in Appendix Figure 6.1 The Kaplan-Meier Plot of Time to dropout is in Appendix Figure 6.2.

3.2.3.3.2 Results and Conclusions

Canagliflozin 300 mg was shown to be both non-inferior with respect to sitagliptin 100 mg, and statistical superior to sitagliptin 100 mg (at alpha=0.05 level, two-sided, non-inferiority margin 0.3%) after 52 weeks of treatment. These results were shown in Table 3.2.3.3.2.

Table 3.2.3.3.2. Glycemic Parameters at Week 52 for Canagliflozin (300 mg and 100 mg) and Sitagliptin in Patients with Type 2 Diabetes (Study DIA3015)

A: Primary Endpoint

Endpoint	**Canagliflozin 300 mg**		**Sitagliptin 100 mg**	
HbA1c (%)	n		n	
Baseline mean ± SE	374	8.12 ± 0.05	365	8.13 ± 0.05
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	374	-1.03 ± 0.05	365	-0.66 ± 0.05
MMRM	363	-1.03 ± 0.04	358	-0.65 ± 0.04
PP* (by sponsor)	245	-1.15 ± 0.05	206	-0.94 ± 0.05
Cana−sita, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)		-0.37 (-0.50, -0.25)		
MMRM		-0.39 (-0.49, -0.29)		
PP* (by sponsor)		-0.21 (-0.34, -0.08)		
Patients (%) achieving HbA1c <7[1,2]		130 (38%)		78 (24%)
LOCF[1]		158 (46%)		101 (31%)
sponsor's results (LOCF) [3]		178 (48%)		129 (35%)

* This reviewer obtained the same results as the sponsor
[1] Based on patients at baseline with HbA1c>7%, cana 300 mcg n=346, and sita 100 mg n=329
[2] Completers
[3] Sponsor used all mITT patients, including those who had baseline HbA1c < 7%.

B: Secondary Endpoints

Endpoint	**Canagliflozin** 300 mg		**Sitagliptin 100 mg**	
FPG (mmol/L)	n		n	
Baseline mean ± SE	373	9.42 ± 0.17	365	9.09 ± 0.17
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	373	-1.66 ± 0.12	365	-0.32 ± 0.12
PP	245	-1.78 ± 0.13	203	-0.86 ± 0.15
Cana−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)		-1.34 (-1.66, -1.01)		
PP		-0.92 (-1.28, -0.56)		
Body Weight (kg)				
Baseline mean ± SE	375	87.58 ± 1.20	367	89.61 ± 1.21
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	375	-2.5 ± 0.2	367	0.3 ± 0.2
PP	247	-2.58 ± 0.23	207	0.33 ± 0.26
Cana−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)		-2.8 (-3.3, -2.2)		
PP		-2.91 (-3.55,-2.27)		
Systolic BP (mmHg)				
Baseline mean ± SE	375	-131.23 ± 0.68	367	130.07 ± 0.73
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	375	-5.06 ± 0.66	367	0.85 ± 0.67
PP	247	-5.22 ± 0.80	207	1.38 ± 0.90
Cana−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)		-5.91 (-7.64, -4.17)		
PP		-6.60 (-8.82, -4.38)		

* This reviewer obtained the same results as the sponsor

The time course of the completer's HbA1c difference from baseline over time is shown in Appendix Figures 6.3.

This reviewer looked at the relationship between patients' baseline levels and their corresponding changes in HbA1c reduction from baseline to Week 52 (LOCF) as shown in Appendix Figure 6.4. The treatment-baseline interaction is significant at alpha=0.10 level (p-value=0.0302).

3.2.4 Special Population

3.2.4.1 DIA3010 older adults (≥55 to ≤80 years of age)

Study DIA3010: "A Randomized, Double-Blind, Placebo-controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Compared With Placebo in the Treatment of Older Subjects With Type 2 Diabetes Mellitus Inadequately Controlled on Glucose Lowering Therapy." The duration of the study included the 26-week core placebo-controlled and the double-blind treatment period followed by a 78-week extension.

A total of 716 subjects were randomized to placebo, canagliflozin 100 mg, and canagliflozin 300 mg in a 1:1:1 manner, stratified based on (1) T-score of lumbar spine (< -1.5 or = -1.5) (2) on or not on a PPARγ Agent (pioglitazone).

Primary endpoint was HbA1c from baseline to Week 26 visit.

For more information about the study design see Appendix 7.1.

3.2.4.1.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.4.1.1.

Table 3.2.4.1.1. Patient disposition and demographic information in Study DIA3010

	Canagliflozin		
	Canagliflozin 100 mg	**Canagliflozin** 300 mg	**Placebo**
Randomized	241 (100%)	236 (100%)	239 (100%)
mITT*	241 (100%)	236 (100%)	237 (99%)
Per Protocol	219 (91%)	206 (87%)	171 (72%)
Completers	221 (92%)	208 (88%)	172 (72%)
Rescued	5 (2%)	1 (0.4%)	26 (11%)
Age (years) Mean(SE) Range ≥ 65	 64.2 (0.4) 55 - 80 98 (41%)	 63.4 (0.4) 55 - 79 87 (37%)	 63.1 (0.4) 55 - 80 85 (36%)
Gender: % males	124 (51%)	129 (55%)	143 (60%)
Race: % White	194 (80%)	175 (74%)	185 (77%)
Country: % U.S.	98 (41%)	97 (41%)	103 (43%)
Baseline HbA1c: <8.5%	196 (81%)	197 (83%)	186 (78%)
Baseline BMI: <30 kg/m^2	90 (37%)	93 (39%)	87 (36%)
AHA at screening: % yes	27 (11%)	24 (10%)	27 (11%)
Baseline eGFR(mL/min/1.73m^2) <60 60 to <90 ≥90	 33 (14%) 153 (64%) 55 (23%)	 26 (11%) 149 (63%) 61 (26%)	 35 (15%) 154 (64%) 48 (20%)

Baseline HbA1c comparison between arms is in Appendix Figure 7.1 The Kaplan-Meier Plot of Time to dropout is in Appendix Figure 7.2.

3.2.4.1.2 Results and Conclusions

The sponsor's results of primary and secondary analyses were verified by this reviewer as shown in Table 3.2.4.1.2. These results are supportive to canagliflozin (300 mg, and then 100 mg) over placebo.

Table 3.2.4.1.2. Glycemic Parameters at Week 26 for Canagliflozin (300 mg and 100 mg) and Placebo in Patients with Type 2 Diabetes (Study DIA3010)

A: Primary Endpoint

Endpoint	Placebo		Canagliflozin 100 mg		Canagliflozin 300 mg	
HbA1c (%)	n		n		n	
Baseline mean ± SE	232	7.76 ± 0.05	239	7.77 ± 0.05	229	7.69 ± 0.05
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	232	-0.03 ± 0.06	239	-0.60 ± 0.06	229	-0.73 ± 0.06
MMRM	233	-0.09 ± 0.05	235	-0.65 ± 0.05	227	-0.78 ± 0.05
PP* (by sponsor)	169	-0.21 ± 0.07	215	-0.68 ± 0.06	205	-0.80 ± 0.06
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.57 (-0.71, -0.44)		-0.70 (-0.84, -0.57)
MMRM				-0.56 (-0.67, -0.45)		-0.69 (-0.80, -0.58)
PP* (by sponsor)				-0.47 (-0.61, -0.34)		-0.60 (-0.73, -0.46)
Patients (%) achieving HbA1c <7[1,2]		35 (18%)		84 (42%)		96 (49%)
LOCF[1]		42 (21%)		88 (44%)		102 (53%)
sponsor's results (LOCF)[3]		65 (28%)		114 (48%)		134 (59%)

* This reviewer obtained the same results as the sponsor
[1] Based on patients at baseline with HbA1c>7%, placebo n=199, cana 100 mcg n=202, and cana 300 mg n=194
[2] Completers
[3] Sponsor used all mITT patients, including those who had baseline HbA1c < 7%.

B: Secondary Endpoints

	Placebo		Canagliflozin 100 mg		Canagliflozin 300 mg	
FPG (mmol/L)	n		n		n	
Baseline mean ± SE	231	8.68 ± 0.14	239	8.93 ± 0.14	229	8.49 ± 0.14
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	231	0.41 ± 0.16	239	-1.00 ± 0.16	229	-1.13 ± 0.16
PP	165	-0.28± 0.15	211	-1.15 ± 0.15	203	-1.25 ± 0.15
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-1.41 (-1.76, -1.07)		-1.54 (-1.88, -1.19)
PP				-0.86 (-1.18, -0.54)		-0.97 (-1.29, -0.64)
Body Weight (kg)						
Baseline mean ± SE	234	91.31 ± 1.15	240	88.43 ± 1.01	229	88.76 ± 1.13
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	234	-0.15 ± 0.26	240	-2.43 ± 0.26	229	-3.11 ± 0.26
PP	171	-0.23 ± 0.26	218	-2.44 ± 0.25	206	-3.09 ± 0.25

Cana−P, adjusted LS Mean (95% CI) LOCF* (by sponsor) PP				 -2.3 (-2.8, -1.7) -2.21 (-2.75, -1.66)		 -3.0 (-3.5, -2.4) -2.86 (-3.41, -2.30)
Systolic BP (mmHg)						
Baseline mean ± SE Adj. Mean Change from baseline±SE LOCF* (by sponsor) PP Cana−P, adjusted LS Mean (95% CI) LOCF* (by sponsor) PP	234 234 171	131.42± 0.80 1.10 ± 1.04 0.78 ± 1.18	240 240 218	130.58 ± 0.85 -3.52 ± 1.04 -3.74 ± 1.12 -4.63 (-6.85, -2.40) -4.52 (-6.98, -2.05)	229 229 206	131.11± 0.96 -6.79 ± 1.06 -7.46 ± 1.14 -7.89 (-10.14, -5.64) -8.24 (-10.73, -7.74)

* This reviewer obtained the same results as the sponsor

The time course of the completer's HbA1c difference from baseline over time is shown in Appendix Figures 7.3.

This reviewer looked at the relationship between patients' baseline levels and their corresponding changes in HbA1c reduction from baseline to Week 26 (LOCF) as shown in Appendix Figure 7.4. The treatment-baseline interaction is not significant at alpha=0.10 level.

3.2.4.2 DIA3004 Moderate renal impairment (eGFR ≥ 30 to <50 mL/min)

Title of Study DIA3004: "A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, 26-Week, Multicenter Study With a 26-Week Extension, to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Compared in the Treatment of Subjects With Type 2 Diabetes Mellitus Who Have Moderate Renal Impairment. "The duration of treatment included a 26-week double-blind placebo-controlled core period and a 26-week double-blind, placebo-controlled extension phase.

A total of 272 adult subjects (≥25 years of age) with T2DM who were inadequately controlled on their current diabetes treatment regimen (i.e., HbA1c of ≥7.0% and ≤10.5%) and had moderate renal impairment (eGFR ≥30 and <50 mL/min/1.73m2) were randomized in a 1:1:1 ratio to addition of once-daily administration of canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo added to their ongoing stable diabetes treatment regimen (e.g., diet, exercise, and antihyperglycemic agent [AHA] therapy) at entry into the 26-week, core placebo-controlled, double-blind period (26-week core period).

The primary efficacy endpoint was the change in HbA1c from baseline to Week 26.

For more information about the study design see Appendix 8.1.

3.2.4.2.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.4.2.1.

Table 3.2.4.2.1. Patient disposition and demographic information in Study DIA3004

	Canagliflozin 100 mg	**Canagliflozin** 300 mg	**Placebo**
Randomized	90 (100%)	91 (100%)	91 (100%)
mITT*	90 (100%)	89 (98%)	90 (99%)
Per Protocol	68 (76%)	78 (86%)	65 (71%)
Completers	72 (80%)	79 (87%)	65 (71%)
Rescued	4 (4%)	3 (3%)	13 (14%)
Age (years)			
Mean(SE)	69.3 (0.9)	67.8 (0.9)	68.0 (0.9)
Range	39 - 85	46 - 90	45 - 96
≥ 65	63 (70%)	56 (62%)	63 (69%)
Gender: % males	58 (64%)	48 (53%)	57 (63%)
Race: % White	71 (79%)	66 (73%)	78 (86%)
Country: % U.S.	14 (16%)	17 (19%)	16 (18%)
Baseline HbA1c: <8.5%	68 (76%)	66 (73%)	64 (70%)
Baseline BMI: <30 kg/m^2	26 (29%)	32 (35%)	29 (32%)
AHA at screening: % yes	19 (21%)	22 (24%)	18 (20%)
Baseline eGFR (mL/min/1.73m^2)			
<45	73 (81%)	69 (78%)	68 (76%)
≥45	17 (18%)	20 (22%)	22 (24%)

Baseline HbA1c comparison between arms is in Appendix Figure 8.1. The Kaplan-Meier Plot of Time to dropout is in Appendix Figure 8.2.

3.2.4.2.2 Results and Conclusions

The sponsor's results of primary and secondary analyses were verified by this reviewer as shown in Table 3.2.4.2.2. These results are supportive to canagliflozin (300 mg, and then 100 mg) over placebo.

Table 3.2.4.2.2. Glycemic Parameters at Week 26 for Canagliflozin (300 mg and 100 mg) and Placebo in Patients with Type 2 Diabetes (Study DIA3004)

A: Primary Endpoint

Endpoint	**Placebo**		**Canagliflozin** 100 mg		**Canagliflozin** 300 mg	
HbA1c (%)	n		n		n	
Baseline mean ± SE	87	8.02 ± 0.10	88	7.89 ± 0.10	89	7.97 ± 0.09
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	87	-0.03 ± 0.09	88	-0.33 ± 0.09	89	-0.44 ± 0.09

MMRM	85	-0.10 ± 0.08	84	-0.33 ± 0.08	85	-0.48 ± 0.08
PP* (by sponsor)	63	-0.16 ± 0.10	67	-0.32 ± 0.10	77	-0.48 ± 0.09
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.30 (-0.53, -0.07)		-0.40 (-0.63, -0.17)
MMRM				-0.23 (-0.44, -0.02)		-0.38 0.58, -0.17)
PP* (by sponsor)				-0.17 (-0.42, 0.09)		-0.33 (-0.57, -0.08)
Patients (%) achieving HbA1c <7[1,2]		8 (11%)		15 (20%)		21 (25%)
LOCF[1]		10 (13%)		18 (24%)		23 (28%)
sponsor's results (LOCF) [3]		15 (17%)		24 (27%)		29 (33%)

* This reviewer obtained the same results as the sponsor
[1] Based on patients at baseline with HbA1c>7%, placebo n=76, cana 100 mcg n=76, and cana 300 mg n=83
[2] Completers
[3] Sponsor used all mITT patients, including those who had baseline HbA1c < 7%.

B: Secondary Endpoints

Endpoint	**Placebo**		**Canagliflozin** 100 mg		**Canagliflozin** 300 mg	
FPG (mmol/L)	n		n		n	
Baseline mean ± SE	88	8.93 ± 0.26	90	9.41 ± 0.27	88	8.80 ± 0.34
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	88	0.03 ± 0.28	90	-0.83 ± 0.28	88	-0.65 ± 0.28
PP	61	-0.39± 0.30	67	-1.06 ± 0.29	74	-0.87 ± 0.28
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.85 (-1.58, -0.13)		-0.67 (-1.41, -0.06)
PP				-0.67(-1.42, 0.09)		-0.48 (-1.22, 0.26)
Body Weight (kg)						
Baseline mean ± SE	88	92.73 ±1.87	90	90.46 ± 1.94	89	90.23 ± 1.92
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	88	0.32 ± 0.31	90	-1.25 ± 0.30	89	-1.50 ± 0.30
PP	65	0.18 ± 0.34	68	-1.15 ± 0.33	78	-1.38 ± 0.30
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-1.6 (-2.3, -0.8)		-1.8 (-2.6, -1.0)
PP				-1.33 (-2.17, -0.49)		-1.56 (-2.37, -0.75)
Systolic BP (mmHg)						
Baseline mean ± SE	89	132.05± 1.45	90	135.90 ±1.38	89	136.72 ±1.58
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	89	-0.32 ± 1.49	90	-6.05 ± 1.48	89	-6.44 ± 1.48
PP	65	-2.08 ± 1.74	68	-6.28 ± 1.69	78	-6.19 ± 1.56
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-5.73 (-9.54, -1.91)		-6.12 (-9.96, -2.28)
PP				-4.21 (-8.52, 0.10)		-4.11 (-8.32, 0.09)

* This reviewer obtained the same results as the sponsor

The time course of the completer's HbA1c difference from baseline over time is shown in Appendix Figures 8.3.

This reviewer looked at the relationship between patients' baseline levels and their corresponding changes in HbA1c reduction from baseline to Week 26 (LOCF) as shown in Appendix Figure 8.4. The treatment-baseline interaction is not significant at alpha=0.10 level.

3.2.4.3 DIA3008 Combination Therapy with Sulphonylurea Substudy

Title of the Study: "A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of canagliflozin on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus (Sulphonylurea substudy)."

A total of 127 subjects were randomized into Population 1 (see Appendix 9.1) to each of the 3 treatment groups (i.e., canagliflozin 100 mg, canagliflozin 300 mg, or placebo), stratified based on the sponsor's predefined AHA medications(s) strata.

The primary efficacy endpoint was the change in HbA1c from baseline through Week 18 LOCF.

For more information about the study design see Appendix 9.1.

3.2.4.3.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.4.3.1.

Table 3.2.4.3.1. Patient disposition and demographic information in Study DIA3008, Sulphonylurea Substudy (Population 1).

	Canagliflozin 100 mg	**Canagliflozin** 300 mg	**Placebo**
Randomized	42 (100%)	40 (100%)	45 (100%)
mITT*	42 (100%)	40 (100%)	45 (100%)
Per Protocol	37 (88%)	38 (95%)	34 (76%)
Completers	37 (88%)	38 (95%)	34 (76%)
Rescued	2 (5%)	1 (2.5%)	9 (20%)
Age (years)			
Mean(SE)	64.19 (0.8)	65.5 (0.7)	64.8 (0.8)
Range	52 - 81	47 - 82	44 - 78
≥ 65	20 (48%)	23 (57%)	26 (58%)
Gender: % males	24 (57%)	22 (55%)	26 (58%)
Race: % White	30 (71%)	31 (78%)	34 (76%)
Country: % U.S.	3 (7%)	5 (12.5%)	5 (11%)
Baseline HbA1c: <8.5%	24 (57%)	24 (60%)	25 (56%)
Baseline BMI: <30 kg/m^2	23 (55%)	28 (70%)	21 (47%)
AHA at screening: % yes	42 (100%)	40 (100%)	45 (100%)
Baseline eGFR (mL/min/1.73m^2)			
<60	13 (31%)	16 (40%)	15 (33%)
60 to <90	22 (52%)	19 (47%)	24 (53%)
≥90	6 (14%)	5 (13%)	5 (11%)

Baseline HbA1c comparison between arms is in Appendix Figure 9.1. The Kaplan-Meier Plot of Time to dropout is in Appendix Figure 9.2.

3.2.4.3.2 Results and Conclusions

The sponsor's results of primary and secondary analyses were verified by this reviewer as shown in Table 3.2.4.3.2. These results are supportive to canagliflozin (300 mg, and then 100 mg) over placebo.

Table 3.2.3.3.2. Glycemic Parameters at Week 18 for Canagliflozin (300 mg and 100 mg) and Placebo in Patients with Type 2 Diabetes (Study DIA3008, Sulphonylurea Substudy, Population 1)

A: Primary Endpoint

Endpoint	**Placebo**		**Canagliflozin** 100 mg		**Canagliflozin** 300 mg	
HbA1c (%)	n		n		n	
Baseline mean ± SE ok	40	8.49 ± 0.18	40	8.29 ± 0.13	39	8.28 ± 0.16
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	40	0.04 ± 0.15	40	-0.70 ± 0.15	39	-0.79 ± 0.15
MMRM	45	0.04 ± 0.14	39	-0.72 ± 0.14	36	-0.77 ± 0.14
PP* (by sponsor)	34	-0.14 ± 0.15	37	-0.70 ± 0.14	38	-0.74 ± 0.14
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.74 (-1.14, -0.33)		-0.83 (-1.24, -0.41)
MMRM				-0.76 (-1.15, -0.37)		-0.81 (-1.21, -0.42)
PP* (by sponsor)				-0.56 (-0.96, -0.16)		-0.60 (-1.00, -0.20)
Patients (%) achieving HbA1c <[1,2]		2 (5%)		10 (25%)		11 (30%)
LOCF[1]		2 (5%)		10 (25%)		11 (30%)
sponsor's results (LOCF)[3]		2 (5%)		10 (25%)		13 (33%)

* This reviewer obtained the same results as the sponsor
[1] Based on patients at baseline with HbA1c>7%, placebo n=39, cana 100 mcg n=40, and cana 300 mg n=37
[2] Completers
[3] Sponsor used all mITT patients, including those who had baseline HbA1c < 7%.

B: Secondary Endpoints

Endpoint	**Placebo**		**Canagliflozin** 100 mg		**Canagliflozin** 300 mg	
FPG (mmol/L)	n		n		n	
Baseline mean ± SE ok	43	10.27± 0.41	39	10.29 ± 0.40	39	9.84 ± 0.33
Adj. Mean Change from baseline±SE						
LOCF (by sponsor)	43	0.46 ± 0.14	39	-1.51 ± 0.13	39	-1.94 ± 0.13
LOCF	43	0.67 ± 0.32	39	-1.41 ± 0.34	39	-2.00 ± 0.34
PP	34	-0.30 ± 0.33	36	-1.49 ± 0.32	38	-1.95 ± 0.31

Cana−P, adjusted LS Mean (95% CI) LOCF (by sponsor) LOCF PP				 -1.97 (-2.34, -1.60) -2.07 (-2.99, -1.15) -1.79 (-2.70, -0.88)		 -2.41 (-2.78, -2.03) -2.66 (-3.59, -1.74) -2.25 (-3.14, -1.36)
Body Weight (kg)						
Baseline mean ± SE Adj. Mean Change from baseline±SE LOCF* (by sponsor) PP Cana−P, adjusted LS Mean (95% CI) LOCF* (by sponsor) PP	41 44 33	85.29±3.1 -0.21 ± 0.48 -0.39 ± 0.44	39 40 37	84.7±2.7 -0.62 ± 0.51 -0.59 ± 0.42 -0.4 (-1.8, -1.0) -0.20 (-1.40, 1.00)	38 39 38	80.8 ± 3.2 -1.98 ± 0.51 -1.67 ± 0.41 -1.8 (-3.2, -0.4) -1.28 (-2.48, -0.08)
Systolic BP (mmHg)						
Baseline mean ± SE Adj. Mean Change from baseline±SE LOCF* (by sponsor) PP Cana−P, adjusted LS Mean (95% CI) LOCF* (by sponsor) PP	44 44 34	137.3±2.0 -3.38 ± 2.21 -5.32 ± 2.55	40 40 37	138.0 ±1.6 -3.49 ± 2.33 -3.04 ± 2.46 -0.10 (-6.45, 6.25) 2.27 (-4.75, 9.29)	39 39 38	133.5 ±2.2 -5.15 ± 2.37 -4.98 ± 2.43 -1.77 (-8.21, 4.67) 0.34 (-6.65, 7.33)

* This reviewer obtained the same results as the sponsor

The time course of the completer's HbA1c difference from baseline over time is shown in Appendix Figures 9.3.

This reviewer looked at the relationship between patients' baseline levels and their corresponding changes in HbA1c reduction from baseline to Week 18 (LOCF) as shown in Appendix Figure 9.4. The treatment-by-baseline interaction is not significant at alpha=0.10 level.

3.2.4.4 DIA3008 Combination Therapy with Insulin

Title of this Study: "A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of canagliflozin on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus (Insulin substudy)." The duration of this substudy was 18 weeks.

A total of 2,074 randomized subjects comprised Population 1 (=20 IU, see Appendix 10.1) of the insulin substudy, with 691, 692, and 691 subjects randomized to placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively.

The primary efficacy endpoint was the change in HbA1c from baseline through Week 18 LOCF.

For more information about the study design see Appendix 10.1.

3.2.4.4.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.4.4.1.

Table 3.2.4.4.1. Patient disposition and demographic information in Study DIA3008 Insulin Substudy (Population 2)

	Canagliflozin 100 mg	**Canagliflozin** 300 mg	**Placebo**
Randomized	566 (100%)	587 (100%)	565 (100%)
mITT*	566 (100%)	587 (100%)	565 (100%)
Per Protocol	500 (88%)	515 (88%)	465 (82%)
Completers	506 (89%)	520 (89%)	465 (82%)
Rescued	24 (4%)	24 (4%)	57 (10%)
Age (years)			
Mean(SE)	62.4 (0.3)	63.3(0.3)	62.3(0.3)
Range	32 - 82	37 - 85	38 - 82
≥ 65	227 (40%)	255 (43%)	212 (38%)
Gender: % males	379 (67%)	384 (65%)	380 (67%)
Race: % White	448 (79%)	462 (79%)	440 (78%)
Country: % U.S.	106 (19%)	118 (20%)	98 (17%)
Baseline HbA1c: <8.5%	322 (57%)	359 (61%)	356 (63%)
Baseline BMI: <30 kg/m^2	169 (30%)	170 (29%)	155 (27%)
AHA at screening: %			
Insulin alone	183 (32%)	184 (31%)	187 (33%)
Insulin+ metformin	241 (43%)	246 (42%)	244 (43%)
Insulin+ other AHA(s)	142 (25%)	157 (27%)	134 (24%)
Baseline eGFR (mL/min/1.73m^2)			
<60	103 (18%)	127 (22%)	118 (21%)
60 to <90	327 (58%)	352 (60%)	335 (59%)
≥90	135 (24%)	107 (18%)	112 (20%)

Baseline HbA1c comparison between arms is in Appendix Figure 10.1. The Kaplan-Meier Plot of Time to dropout is in Appendix Figure 10.2.

3.2.4.4.2 Results and Conclusions

The sponsor's results of primary and secondary analyses were verified by this reviewer as shown in Table 3.2.4.4.2. These results are supportive to canagliflozin (300 mg, and then 100 mg) over placebo.

Table 3.2.4.4.2. Glycemic Parameters at Week 18 for Canagliflozin (300 mg and 100 mg) and Placebo in Patients with Type 2 Diabetes (Study DIA3008 Insulin Substudy, Population 2)

A: Primary Endpoint

Endpoint	**Placebo**		**Canagliflozin** 100 mg		**Canagliflozin** 300 mg	
HbA1c (%)	n		n		n	
Baseline mean ± SE	545	8.24 ± 0.04	551	8.34 ± 0.04	572	8.27 ± 0.04
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	517	0.01 ± 0.03	540	-0.63 ± 0.03	562	-0.72 ± 0.03
MMRM	514	0.00 ± 0.03	533	-0.64 ± 0.03	539	-0.74 ± 0.03
PP* (by sponsor)	454	-0.01 ± 0.03	494	-0.65 ± 0.03	510	-0.74 ± 0.03
Cana−P, adjusted LS Mean (95% CI)						
LOCF *(by sponsor)				-0.65 (-0.73, -0.56)		-0.73 (-0.82, -0.64)
MMRM				-0.64 (-0.73, -0.56)		-0.74 (-0.83, -0.66)
PP* (by sponsor)				-0.63 (-0.72, -0.54)		-0.72 (-0.81, -0.63)
Patients (%) achieving HbA1c <7[1,2]		32 (6%)		90 (17%)		120 (22%)
LOCF[1]		34 (7%)		96 (18%)		125 (23%)
sponsor's results (LOCF) [3]		40 (8%)		107 (20%)		139 (25%)

* This reviewer obtained the same results as the sponsor

[1] Based on patients at baseline with HbA1c>7%, placebo n=499, cana 100 mcg n=525, and cana 300 mg n=540

[2] Completers

[3] Sponsor used all mITT patients, including those who had baseline HbA1c < 7%.

B: Secondary Endpoints

Endpoint	**Placebo**		**Canagliflozin 100 mg**		**Canagliflozin 300 mg**	
FPG (mmol/L)	n		n		n	
Baseline mean ± SE ok	547	9.38 ± 0.12	556	9.43 ± 0.11	568	9.33 ± 0.12
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	547	0.22 ± 0.11	556	-1.03 ± 0.11	568	-1.39 ± 0.11
PP	447	0.02 ± 0.11	487	-1.14 ± 0.11	506	-1.47 ± 0.11
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-1.25 (-1.55, -0.96)		-1.61 (-1.90, -1.31)
PP				-1.16 (-1.46, -0.86)		-1.49 (-1.79, -1.19)
Body Weight (kg)						
Baseline mean ± SE	551	97.71 ±0.95	559	96.88 ± 0.89	576	96.72 ± 0.86
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	551	0.06 ± 0.12	559	-1.82 ± 0.12	576	-2.34 ± 0.11
PP	460	0.09 ± 0.13	495	-1.81 ± 0.12	513	-2.34 ± 0.12
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-1.9 (-2.2, -1.6)		-2.4 (-2.7, -2.1)
PP				-1.89 (-2.23, -1.55)		-2.42 (-2.76, -2.09)
Systolic BP (mmHg)						
Baseline mean ± SE	551	138.17± 0.69	559	136.98± 0.71	577	138.19± 0.70
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	551	-2.50 ± 0.54	559	-5.07 ± 0.54	577	-6.87 ± 0.53
PP	460	-2.76 ± 0.59	496	-5.13 ± 0.57	513	-7.41 ± 0.56
Cana−P, adjusted LS Mean (95% CI)						
LOCF *(by sponsor)				-2.58 (-4.06, -1.09)		-4.38 (-5.85, -2.90)
PP				-2.37 (-3.95, -0.78)		-4.65 (-6.22, -3.07)

* This reviewer obtained the same results as the sponsor

The time course of the completer's HbA1c difference from baseline over time is shown in Appendix Figures 10.3.

This reviewer looked at the relationship between patients' baseline levels and their corresponding changes in HbA1c reduction from baseline to Week 18 (LOCF) as shown in Appendix Figure 10.4. The treatment-by-baseline interaction is significant at alpha=0.10 level between each dose of canagliflozin and placebo (p-value<0.001).

3.2.5 Integrated Analyses

3.2.5.1 Integrated Analysis of HbA1c in Patients with Moderate Renal Impairment

To provide information on the efficacy of canagliflozin in a larger group of T2DM subjects with moderate renal impairment, a prespecified objective was to evaluate the changes in the primary endpoint HbA1c in a population of subjects with a baseline eGFR of ≥30 to <60 mL/min/1.73m^2 selected from the placebo-controlled Phase 3 studies that permitted enrollment of subjects with an eGFR in this range, including DIA3004, DIA3005 (excluding High Glycemic substudy), DIA3008 (all subjects including SU and Insulin substudies), and DIA3010. In DIA3008, subjects with eGFR ≥30 mL/min/1.73 m^2 were eligible to participate; subjects with an eGFR of ≥50 mL/min/1.73 m^2 were eligible for participation in DIA3005 and DIA3010. The sponsor's reported findings were verified by this reviewer as shown below in Table 3.2.5.1. Analyses were stratified by study.

Table 3.2.5.1. Results for Canagliflozin (300 mg and 100 mg) in Patients with Type 2 Diabetes with Moderate Renal Impairment (eGFR ≥30 to <60 mL/min) (mITT/LOCF)

HbA1c (%)	**Placebo**		**Canagliflozin** 100 mg		**Canagliflozin** 300 mg	
eGFR ≥30 to 60 mL/min/1.73 m^2	n		n		n	
Baseline mean ± SE	356	7.98 ± 0.05	326	8.09 ± 0.05	354	8.07 ± 0.05
Adj. Mean Change from baseline±SE						
LOCF *(by sponsor)	356	-0.14 ± 0.06	326	-0.52 ± 0.06	354	-0.62 ± 0.06
PP	289	-0.32 ± 0.06	285	-0.63 ± 0.06	309	-0.72 ± 0.06
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.38 (-0.50, -0.26)		-0.47 (-0.60, -0.35)
PP				-0.31 (-0.44, -0.18)		-0.40 (-0.53, -0.28)
eGFR < 45 mL/min/1.73 m^2	n		n		n	
Baseline mean ± SE	108	8.10 ± 0.09	118	8.08 ± 0.09	122	8.10 ± 0.08
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	108	0.05 ± 0.19	118	-0.18 ± 0.19	122	-0.34 ± 0.19
PP	85	-0.48 ± 0.25	92	-0.76 ± 0.26	106	-0.84 ± 0.26
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.23 (-0.45, -0.01)		-0.39 (-0.61, -0.17)
PP				-0.28 (-0.53, -0.03)		-0.36 (-0.61, -0.12)

eGFR ≥ 45 mL/min/1.73 m^2	n		n		n	
Baseline mean ± SE	248	7.98 ± 0.06	208	8.11 ± 0.06	232	8.10 ± 0.06
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	248	-0.10 ± 0.07	208	-0.57 ± 0.07	232	-0.62 ± 0.07
PP ok	204	-0.28 ± 0.07	193	-0.61 ± 0.07	203	-0.72 ± 0.07
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.47 (-0.61, -0.32)		-0.52 (-0.66, -0.38)
PP				-0.34 (-0.49, -0.18)		-0.44 (-0.59, -0.29)
Weight (Kg)						
Baseline mean ± SE	376	92.37 ± 1.04	335	90.28 ± 1.10	360	90.09 ± 1.02
Adj. % Change from baseline±SE						
LOCF* (by sponsor)	376	-0.5 ± 0.2	335	-2.0 ± 0.2	360	-2.4 ± 0.2
PP	290	-0.59 ± 0.22	285	-2.11 ± 0.22	309	-2.41 ± 0.21
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-1.6 (-2.0, -1.1)		-1.9 (-2.3, -1.5)
PP				-1.51 (-2.02, -1.00)		-1.82 (-2.32, -1.32)

* This reviewer obtained the same results as the sponsor

These findings, which include data from Studies DIA3004, DIA3005, DIA3008 and DIA3010, were similar to the findings of DIA3004 alone. Subjects with lower eGFR values at baseline (< 45 mL/min/1.73 m^2) had smaller mean treatment differences than subjects with higher eGFR values at baseline (≥ 45 mL/min/1.73 m^2). The difference in effects sizes between the renal subgroups was not statistically significant (interaction p > 0.10).

3.2.5.2 Integrated Analysis of HbA1c by Age Subgroups in All Patients in Placebo-Controlled Studies

Subgroups analyses (stratified by study) of HbA1c were conducted based on pooled patient populations from placebo-controlled studies. Subgroups were defined by age category (< 65 vs ≥ 65 years of age, and < 75 vs ≥ 75 years of age).

There were two integrated placebo-controlled datasets. The first one (PC-1) submitted by the sponsor consisted of the overall pooled population of placebo-controlled studies and comprised subjects from the mITT analysis sets of DIA3005 Main Study, DIA3006 (excluding sitagliptin), DIA3008 SU sub-study (Population 1), DIA3002, DIA3012, and the DIA3008 Insulin sub-study (Population 2). The sponsor's reported findings were identical to FDA analyses on this pooled dataset and are shown in Table 4. The other dataset (PC-2) consisted of PC-1 and subjects from the mITT analysis sets of DIA3004 (subjects with moderate renal impairment) and DIA3010 (older adults, ≥55 to ≤80 years of age). The efficacy findings from PC-2 are shown in Table 3.2.5.2.

Table 3.2.5.2. HbA1c Results for Canagliflozin (300 mg and 100 mg) in Patients with Type 2 Diabetes (Integrated Placebo-Controlled Studies, PC-1)

	Placebo		Canagliflozin 100 mg		Canagliflozin 300 mg	
A1c (%), All patients	n		n		n	
Baseline mean ± SE	1191	8.11 ± 0.03	1404	8.14 ± 0.02	1419	8.11 ± 0.02
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	1191	-0.15 ± 0.02	1404	-0.84 ± 0.02	1419	-0.98 ± 0.02
PP	928	-0.32 ± 0.06	1244	-0.63 ± 0.06	1263	-0.72 ± 0.06
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.69 (-0.75, -0.63)		-0.83 (-0.89, -0.77)
PP				-0.31 (-0.44, -0.18)		-0.40 (-0.53, -0.28)
A1C (%), < 65 years old	n		n		n	
Baseline mean ± SE	836	8.18 ± 0.03	1004	8.16 ± 0.03	1008	8.11 ± 0.03
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	836	-0.15 ± 0.03	1004	-0.87 ± 0.03	1008	-1.02 ± 0.03
PP	641	-0.36 ± 0.03	895	-0.92 ± 0.03	904	-1.07 ± 0.03
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.72 (-0.79, -0.65)		-0.87 (-0.94, -0.80)
PP				-0.56 (-0.63, -0.48)		-0.71 (-0.79, -0.64)
A1C (%), ≥ 65 years old	n		n		n	
Baseline mean ± SE	355	7.95 ± 0.04	400	8.10 ± 0.04	411	8.09 ± 0.04
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	355	-0.11 ± 0.04	400	-0.72 ± 0.04	411	-0.85 ± 0.04
PP	287	-0.24 ± 0.05	349	-0.78 ± 0.04	359	-0.90 ± 0.04
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.61 (-0.72, -0.50)		-0.74 (-0.84, -0.63)
PP				-0.54 (-0.465, -0.43)		-0.66 (-0.77, -0.55)
A1C (%), < 75 years old						
Baseline mean ± SE	1143	8.12 ± 0.03	1345	8.14 ± 0.03	1351	8.12 ± 0.03
Adj. % Change from baseline±SE						
LOCF* (by sponsor)	1143	-0.15 ± 0.02	1345	-0.84 ± 0.02	1351	-1.00 ± 0.02
PP	890	-0.33 ± 0.03	1195	-0.89 ± 0.02	1199	-1.04 ± 0.02
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.69 (-0.75, -0.63)		-0.85 (-0.91, -0.78)
PP				-0.56 (-0.63, -0.50)		-0.72 (-0.78, -0.65)
A1C (%), ≥ 75 years old						
Baseline mean ± SE	48	7.86 ± 0.12	59	8.13 ± 0.12	68	7.87 ± 0.09
Adj. % Change from baseline±SE						
LOCF* (by sponsor)	48	-0.13 ± 0.14	59	-0.77 ± 0.12	1351	-0.68 ± 0.12
PP	38	-0.41 ± 0.15	49	-0.77 ± 0.12	64	-0.75 ± 0.12
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.65 (-0.96, -0.33)		-0.55 (-0.85, -0.26)
PP				-0.36 (-0.68, -0.03)		-0.34 (-0.63, -0.04)

* This reviewer obtained the same results as the sponsor

Table 3.2.5.3. HbA1c Results for Canagliflozin (300 mg and 100 mg) in Patients with Type 2 Diabetes (Integrated Placebo-Controlled Studies, PC-1 + DIA3004 and DIA3010)

	Placebo		Canagliflozin 100 mg		Canagliflozin 300 mg	
A1C (%), PC	n		n		n	
Baseline mean ± SE	1510	8.05 ± 0.02	1731	8.08 ± 0.02	1737	8.04 ± 0.02
Adj. Mean Change from baseline±SE						
LOCF	1510	-0.11 ± 0.02	1731	-0.76 ± 0.02	1737	-0.90 ± 0.02
PP	1164	-0.28 ± 0.02	1531	-0.80 ± 0.02	1547	-0.94 ± 0.02
Cana−P, adjusted LS Mean (95% CI)						
LOCF				-0.65 (-0.70, -0.59)		-0.79 (-0.84, -0.74)
PP				-0.52 (-0.57, -0.46)		-0.66 (-0.72, -0.60)
A1C (%), < 65 years old	n		n		n	
Baseline mean ± SE	1009	8.13 ± 0.03	1167	8.12 ± 0.03	1184	8.06 ± 0.03
Adj. Mean Change from baseline±SE						
LOCF	1009	0.10 ± 0.03	1167	-0.80 ± 0.03	1184	-0.96 ± 0.03
PP	763	-0.31 ± 0.03	1040	-0.85 ± 0.03	1064	-1.00 ± 0.03
Cana−P, adjusted LS Mean (95% CI)						
LOCF				-0.70 (-0.77, -0.63)		-0.85 (-0.92, -0.79)
PP				-0.54 (-0.61, -0.47)		-0.70 (-0.76, -0.63)
A1C (%), ≥ 65 years old	n		n		n	
Baseline mean ± SE	501	7.89 ± 0.04	564	7.89 ± 0.04	553	8.00 ± 0.04
Adj. Mean Change from baseline±SE						
LOCF	501	-0.12 ± 0.04	564	-0.65 ± 0.03	553	-0.77 ± 0.04
PP	401	-0.22 ± 0.04	491	-0.69 ± 0.03	483	-0.81 ± 0.04
Cana−P, adjusted LS Mean (95% CI)						
LOCF				-0.54 (-0.63, -0.45)		-0.66 (-0.75, -0.57)
PP				-0.47 (-0.56, -0.38)		-0.59 (-0.68, -0.50)
A1C (%), < 75 years old						
Baseline mean ± SE	1429	8.06 ± 0.02	1629	8.09 ± 0.02	1636	8.05 ± 0.02
Adj. % Change from baseline±SE						
LOCF	1429	-0.11 ± 0.02	1629	-0.77 ± 0.02	1636	-0.92 ± 0.02
PP	1102	-0.28 ± 0.02	1446	-0.81 ± 0.02	1453	-0.96 ± 0.02
Cana−P, adjusted LS Mean (95% CI)						
LOCF				-0.66 (-0.71, -0.60)		-0.81 (-0.86, -0.75)
PP				-0.53 (-0.59, -0.48)		-0.68 (-0.74, -0.63)
A1C (%), ≥ 75 years old						
Baseline mean ± SE	81	7.88 ± 0.09	102	7.94 ± 0.09	101	7.89 ± 0.07
Adj. % Change from baseline±SE						
LOCF	81	-0.19 ± 0.10	102	-0.65 ± 0.09	101	-0.67 ± 0.10
PP	62	-0.39 ± 0.11	85	-0.67 ± 0.10	94	-0.69 ± 0.09
Cana−P, adjusted LS Mean (95% CI)						
LOCF				-0.46 (-0.70, -0.23)		-0.48 (-0.71, -0.24)
PP				-0.28 (-0.53, -0.02)		-0.29 (-0.54, -0.05)

For both datasets, older subjects (≥65 or ≥75 years of age) had smaller treatment differences than younger subjects (<65 or <75 years of age). The differences between subgroups were statistically significant for dataset PC-2 (interaction p-values < 0.10) but not for dataset PC-1 (interaction p-values > 0.10).

3.3 Evaluation of Safety

An evaluation of the safety of canagliflozin presented in this submission is included in the clinical review by Dr. Hyon Kwon.

3.4 Benefit:Risk Assessment (Optional)

I did not conduct a benefit:risk analysis.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Efficacy analyses of the primary endpoint were performed across subgroups defined by sex, age (<65 years, ≥65 years), race (white, others), country (USA, non-USA), use of anti-hyperglycemic agent (Yes, No), baseline HbA1c level (<8.5%, ≥8.5%), baseline BMI (<30 Kg/m^2, ≥30 Kg/m^2), and baseline eGFR levels. The results were taken from ANCOVA analyses using LOCF method for dealing with missing values.

The results are shown in the forest plots between treatments (see Appendix Figures 11.1 -11.9).

There are some trends commonly seen in subgroup analyses, such as numerically smaller efficacy in subjects with lower baseline HbA1c level (<8.5%), lower baseline eGFR levels, elder (≥65 years), and white.

Some significant treatment-subgroup interactions were observed at alpha=0.10 level, for example,

- significant treatment-by-baseline HbA1c level (<8.5%, ≥8.5%) interaction was observed in studies DIA3005 (p<0.0001), DIA3006 (p<0.01), DIA2012 (p<0.01), and DIA3008 insulin substudy population 2 (p<0.001)
- a significant treatment-by-age (<65 years, ≥65 years) interactions are observed in studies DIA3006 (p<0.01),
- a significant treatment-by-baseline eGFR level interaction was observed in DIA3008 insulin substudy population 2 (p<0.01)

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The sponsor did not submit dataset advs.xpt data (body weight data) for DIA3009. FDA sent an information request to the sponsor on 11/28/2012 and the data were submitted to FDA on 11/29/2012, \\CDSESUB1\EVSPROD\NDA204042\0013.

The sponsor computed the percentage of patients achieving HbA1c <7% at the end of study using all mITT patients, including those who had baseline HbA1c < 7%. The number of patients achieving HbA1c <7% should be calculated based on patients with HbA1c>7% at baseline. A HbA1c <7% responder is the patient who completed the final study visit with HbA1c <7%. That is, dropouts were counted as non responders even if HbA1c was <7%.

5.2 Collective Evidence

All superiority comparisons of canagliflozin 300 mg and 100 mg doses vs placebo in HbA1c change from baseline, the primary efficacy endpoint, were significant in all studies. The results were based on LOCF as the primary method for accounting for missing data. Analyses using MMRM were consistent with the primary results with LOCF.

In Study DIA3009, canagliflozin 100mg and 300mg were shown to be non-inferior to Glimepiride 6 to 8 mg at 52 weeks using a non-inferiority margin of 0.3% for HbA1c. Canagliflozin 300 mg was also shown to be statistically superior to glimepiride (p=0.016) although the treatment difference was relatively small (-0.12%).

In Study DIA3015, canagliflozin 300 mg was shown to be non-inferior to sitagliptin 100 mg at 52 weeks using a non-inferiority margin of 0.3%. Canagliflozin 300 mg was also shown to be superior to sitagliptin ($p < 0.001$) based on an observed treatment difference of -0.37%.

In Study DIA3004 in patients with moderate renal impairment, canagliflozin 100 mg and 300 mg were both statistically superior to placebo. The HbA1c effect sizes vs placebo were modest in this population, -0.42% for 300 mg and -0.29% for 100 mg. The superiority of canagliflozin 100 mg over placebo was not supported by the analysis based on per protocol population (p=0.19). The secondary endpoint, the change of fasting plasma glucose from placebo was not significant on the per protocol population at alpha=0.05 level for both canagliflozin doses (p=0.20 for canagliflozin 300 mg and p=0.0827 for canagliflozin 100 mg). Effect sizes for subgroups based on baseline eGFR (< 45 vs > 45 mL/min/1.73 m^2) were found to be not statistically different (interaction $p > 0.10$).

There was a modest dose response for canagliflozin. Depending on the particular population, canagliflozin 300 mg showed additional 0.1% to 0.25% reductions in HbA1c over canagliflozin 100 mg.

Analyses of HbA1c by subgroups defined by eGFR at baseline based on integrated datasets were consistent with the results in Study DIA3004 alone. In the integrated analyses, subjects with lower eGFR values at baseline (< 45 mL/min/1.73 m^2) had smaller treatment differences than subjects with higher eGFR values at baseline (≥ 45 mL/min/1.73 m^2). The difference in effects between the subgroups was not statistically significant (interaction $p > 0.10$).

Subgroup analyses were conducted based on two different age cutoffs, 65 and 75 years of age. Analyses of HbA1c by age subgroups based on integrated datasets showed that older subjects (≥65 or ≥75 years of age) had smaller mean treatment differences than younger subjects (<65 or <75 years of age). The statistical evaluation of observed subgroup differences produced results

that were not consistent across the two datasets of interest. Age-by-treatment interaction p-values were statistically significant for dataset PC-2 (both interaction p-values < 0.10) but not for dataset PC-1 (both interaction p-values > 0.10).

5.3 Conclusions and Recommendations

All superiority comparisons of canagliflozin 300 mg and 100 mg doses vs placebo in HbA1c change from baseline, the primary efficacy endpoint, were significant in all studies. The results were based on LOCF as the primary method for accounting for missing data. Analyses using MMRM were consistent with the primary results with LOCF.

Canagliflozin (both doses) was shown to be non-inferior to glimepiride in Study DIA3009 and to sitagliptin in Study DIA3015. Both studies used pre-specified non-inferiority margins of 0.3%. In Study DIA3009, Canagliflozin 300 mg was also shown to be superior to glimepiride (p=0.016) although the mean treatment difference was small (-0.12%).

In Study DIA3004 in patients with moderate renal impairment, canagliflozin 100mg and 300mg were both statistically superior to placebo. Mean effect sizes vs placebo were modest in this population, -0.42% for 300mg and -0.29% for 100 mg. Effect sizes for subgroups defined by baseline eGFR (< 45 vs > 45 mL/min/1.73 m^2) were not statistically different (interaction p > 0.10).

Canagliflozin exhibited a modest dose response. Depending on the particular population, canagliflozin 300 mg showed additional 0.1% to 0.25% mean reductions in HbA1c over canagliflozin 100 mg.

Analyses of HbA1c by subgroups defined by eGFR at baseline based on integrated datasets were consistent with the results in Study DIA3004 alone. In the integrated analyses, subjects with lower eGFR values at baseline (< 45 mL/min/1.73 m^2) had smaller treatment differences than subjects with higher eGFR values at baseline (≥ 45 mL/min/1.73 m^2). The difference in effects between the subgroups was not statistically significant (interaction p > 0.10).

Subgroup analyses were conducted based on two different age cutoffs, 65 and 75 years of age. Analyses of HbA1c by age subgroups based on integrated datasets showed that older subjects (≥65 or ≥75 years of age) had smaller mean treatment differences than younger subjects (<65 or <75 years of age). The statistical evaluation of observed subgroup differences produced results that were not consistent across the two datasets of interest. Age-by-treatment interaction p-values were statistically significant for dataset PC-2 (both interaction p-values < 0.10) but not for dataset PC-1 (both interaction p-values > 0.10).

5.4 Labeling Recommendations (as applicable)

The statistical review addresses statements in the label (section 14) concerning:

1. The number of patients achieving HbA1c <7% should be calculated based on patients with HbA1c>7% at baseline. A HbA1c <7% responder is the patient who completed the final study visit with HbA1c <7%. That is, dropouts were counted as non responders even if HbA1c was <7%.
2. Figures 2 and 3 should be based on completers.

3. In "Combination Therapy With Sulfonylurea" (data from DIA3008 Sulfonylurea substudy),
   - in the 2nd paragraph, change [redacted] to "Week 18"
   - [redacted]
   - [redacted]
4. In "Active-Controlled Study Versus Sitagliptin in Combination with Metformin and Sulfonylurea" [redacted] The result should not be listed in Table 10.
5. In "Combination Therapy with Insulin (with or Without Other Anti-Hyperglycemic Agents)" (DIA3008 insulin substudy), Table 12 [redacted]
6. In "Patients with Renal Impairment" (data from DIA3004),
   - [redacted] therefore the result should not be listed in Table 14.
   - [redacted] should be removed from Table 14.

APPENDICES
Appendix 1. Study DIA3005

Appendix 1.1. Additional study design information

At entry into the extension period, subjects in the canagliflozin treatment group (100 mg or 300 mg) of the Main study continued treatment, while subjects on placebo were switched to active therapy in a blinded fashion (treatment with sitagliptin 100 mg over encapsulated to match double-blind canagliflozin and placebo capsules). No hypothesis testing was specified for the High Glycemic Substudy. Upon completion of the 26-week High Glycemic Substudy, subjects did not enter the 26-week extension period.

The primary efficacy endpoint was the change in HbA1c from baseline through Week 26. The LOCF method was applied when the Week 26 values were missing. In subjects receiving rescue medication, measurements made before rescue were used as the last observations.

The secondary efficacy endpoints at Week 26 were;

- Proportion of subjects achieving HbA1c <7 %
- Change from baseline in FPG (mmol/L)
- Change from baseline in 2-hour PPG (mmol/L)
- change from baseline in body weight
- Change from baseline in SBP (mmHg)
- change from baseline in HDL-C

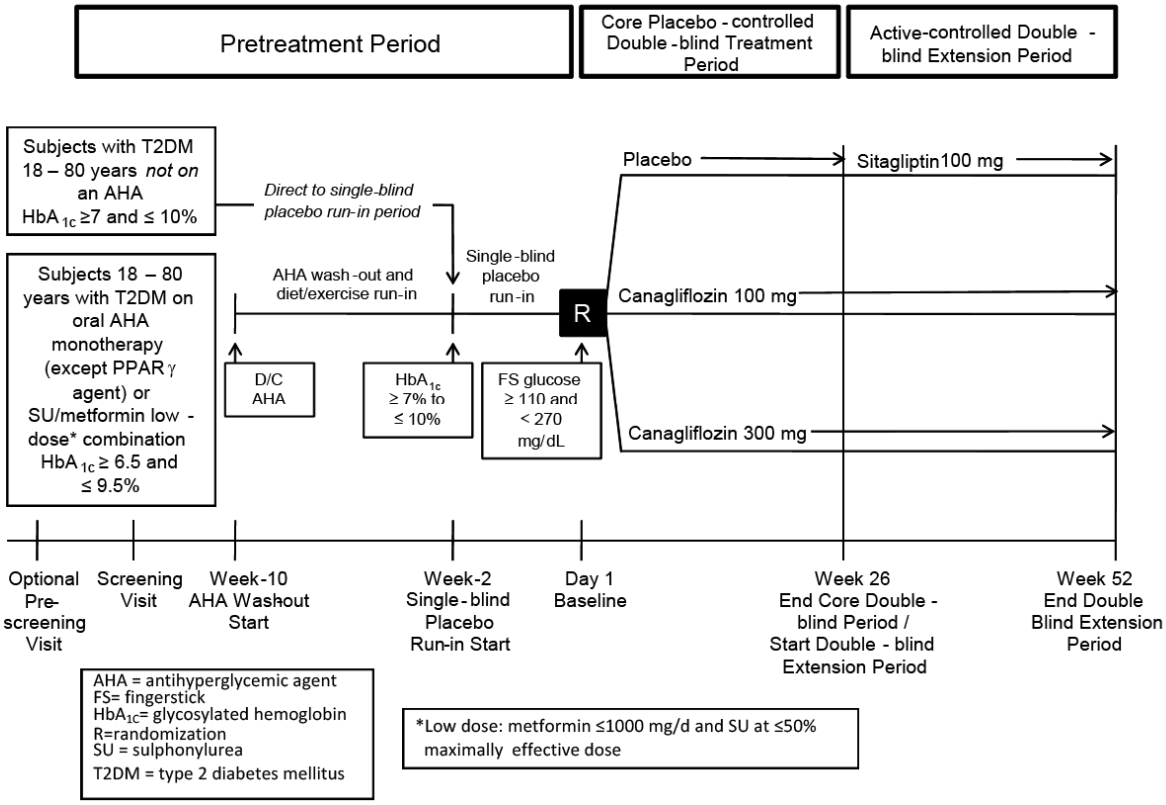
Sample size determination

- Main Study: The primary objective was to demonstrate the superiority of canagliflozin to placebo, as measured by the change in HbA1c from baseline to Week 26. Assuming a group difference of 0.5% and a common standard deviation of 1.0% with respect to change in HbA1c, and using a 2-sample, 2-sided t-test with type I error rate of 0.05, it was estimated that 85 randomized subjects per group would be required to achieve at least 90% power. To enhance the safety database of canagliflozin, approximately 150 subjects per treatment group (a total of 450 subjects) were to be randomly assigned.
- High Glycemic Substudy: As no hypothesis testing was specified and analysis was to be descriptive only, no sample size determination was required for the High Glycemic Substudy.

This study was a multi-national, multi-centre trial with a total of 90 centers participated in 17 countries (33 in North America, 29 in Europe, 10 in Central/South America and 18 in the rest of world).

The sponsor's design diagram of the study NN304-1689 is shown in Figure 1.

Figure 1. Overview of the study design, DIA3005.



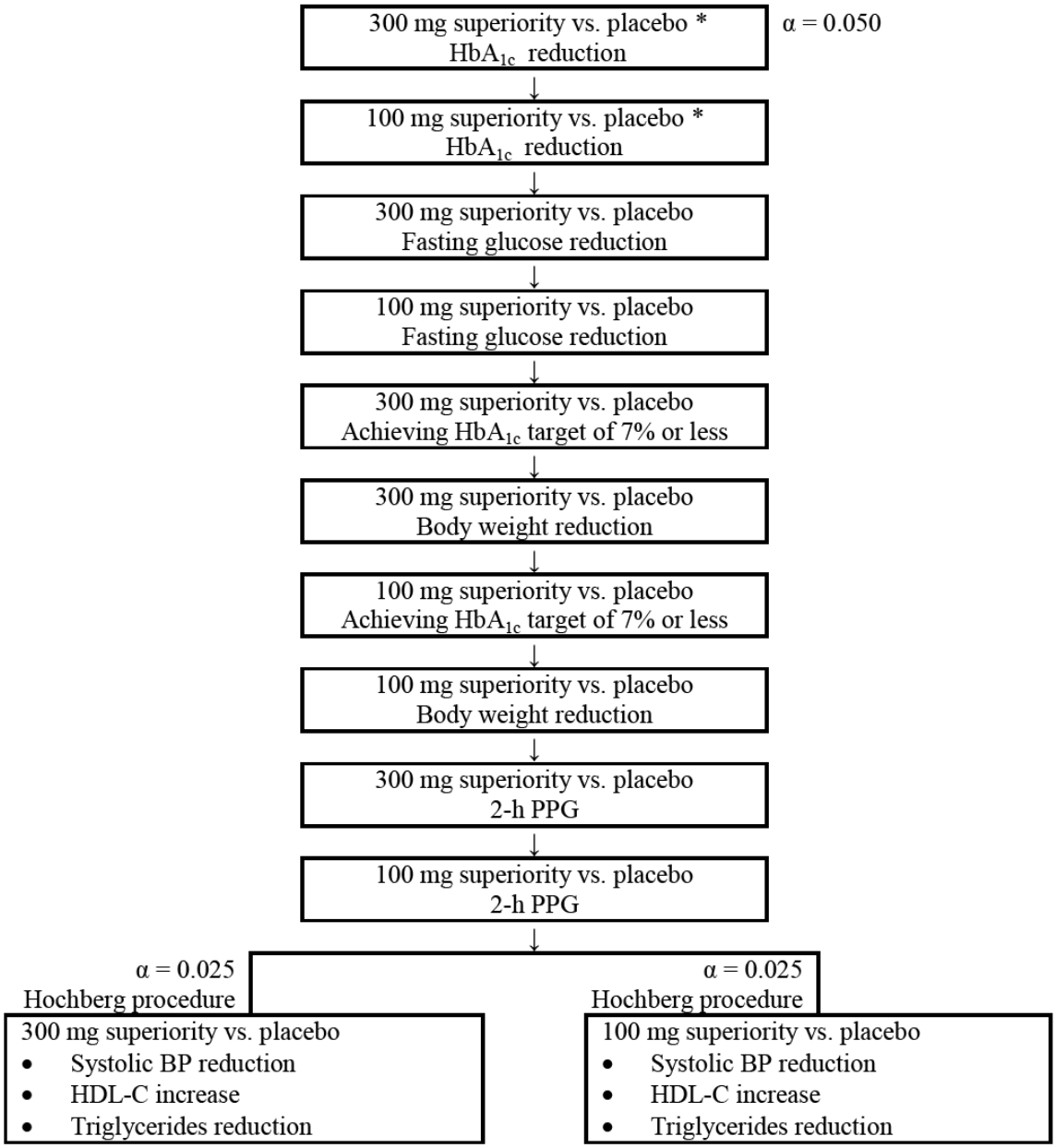
Statistical Methodologies

The efficacy objective was to test superiority of canagliflozin (300 mg, and then 100 mg) to placebo (Week 26).

The sponsor's primary analysis was based on the mITT analysis set and used an analysis of covariance (ANCOVA) model with treatment and stratification factors (whether or not a subject was taking AHA(s) at screening and whether or not a subject would participate in the FS-MMTT) as fixed effects, and the corresponding baseline HbA1c value as a covariate. The primary efficacy endpoint analysis comparing canagliflozin versus placebo was also conducted based on the PP analysis set and 26-week completers' analysis set as supporting analyses.

According to the sponsor's plan for multiplicity adjustment, the hypotheses of primary efficacy endpoint and major secondary efficacy endpoints would be tested sequentially as illustrated in Figure 3.2.2. The type I error would be controlled at 0.05.

Figure 3.2.2. Multiplicity Adjustment

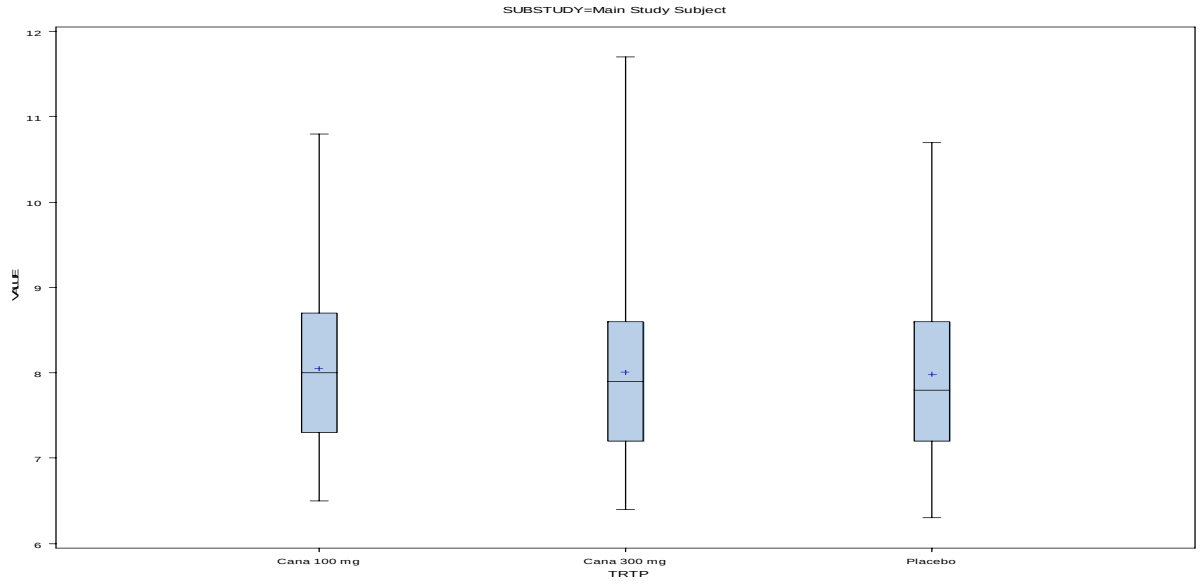


HDL-C=high-density lipoprotein cholesterol; HbA_{1c}= hemoglobin A_{1c}; PPG=postprandial plasma glucose

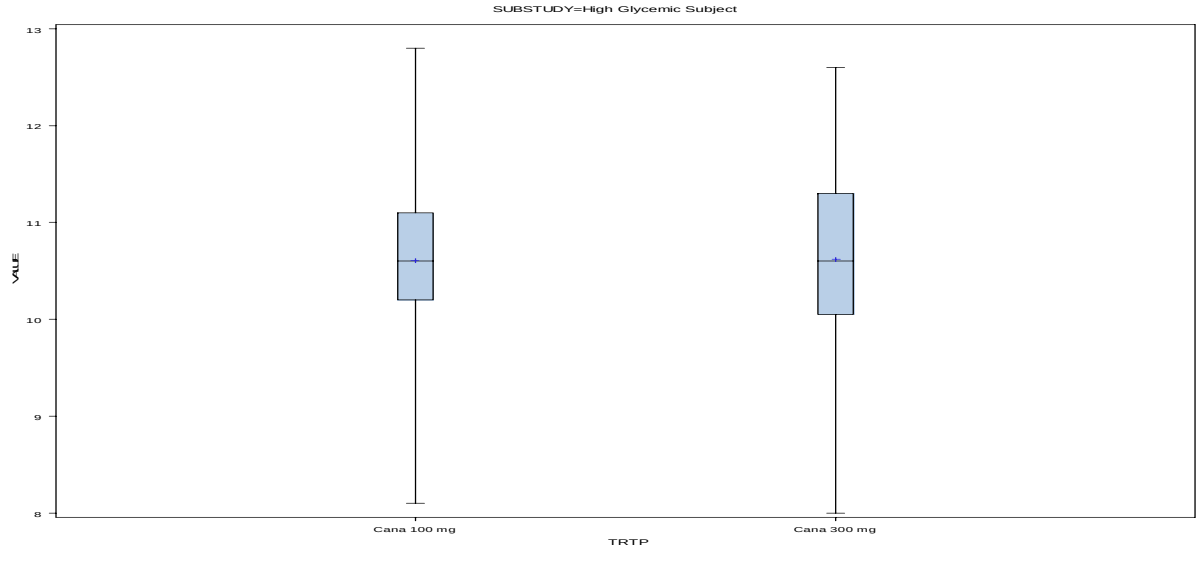
Appendix Figure 1.1. Baseline Levels of HbA1c in Different Treatment Groups in Study DIA3005.

In each boxplot the bottom and top of the box are the 25th and 75th percentiles, respectively; the "+" and the line near the middle of the box are the mean and median (50th percentile), respectively; the top line above the box is the maximum observation; and the bottom line below the box is the minimum observation. Across the different treatment groups, the baseline levels of HbA1c appear to have similar means and comparable variations.

A: Main Study

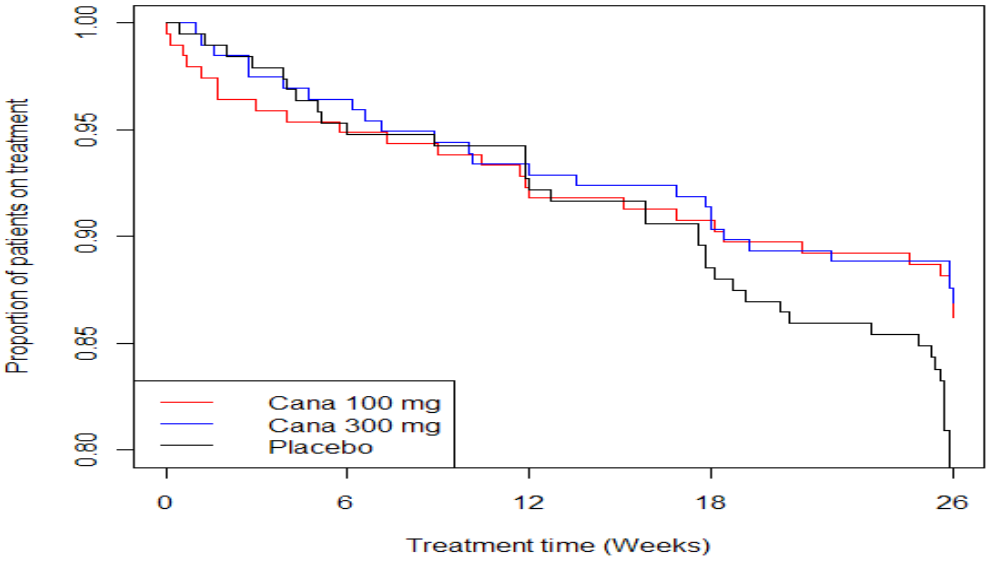


B: High Glycemic Substudy

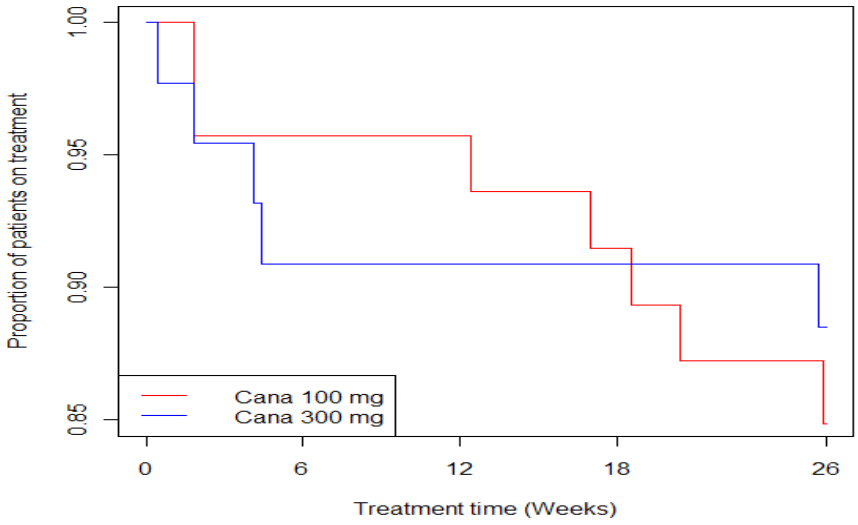


Appendix Figure 1.2. Comparing Time to Dropout during the Treatment Period between Treatment Groups (mITT population, Study DIA3005).

A: Main Study

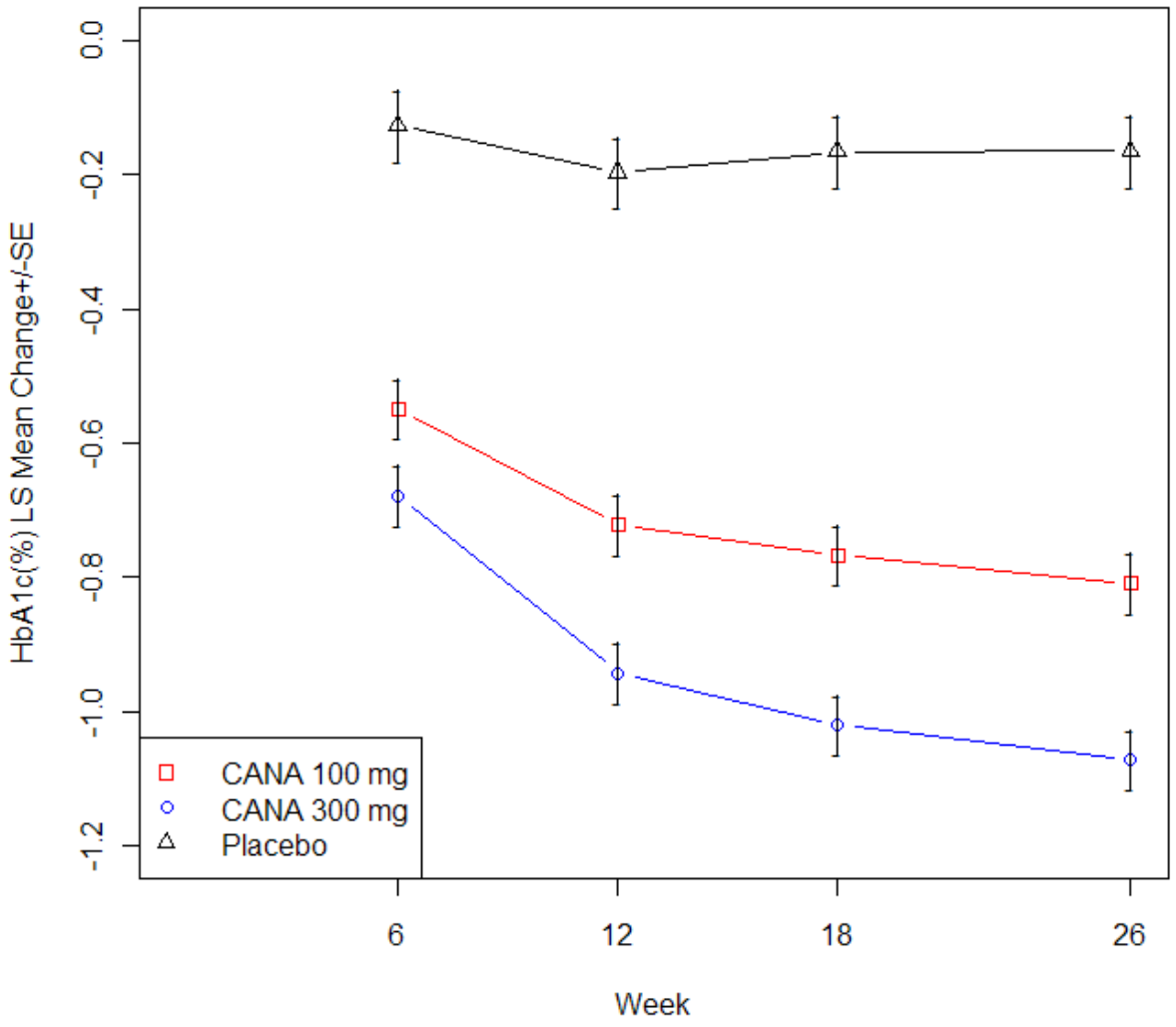


B: High Glycemic Substudy

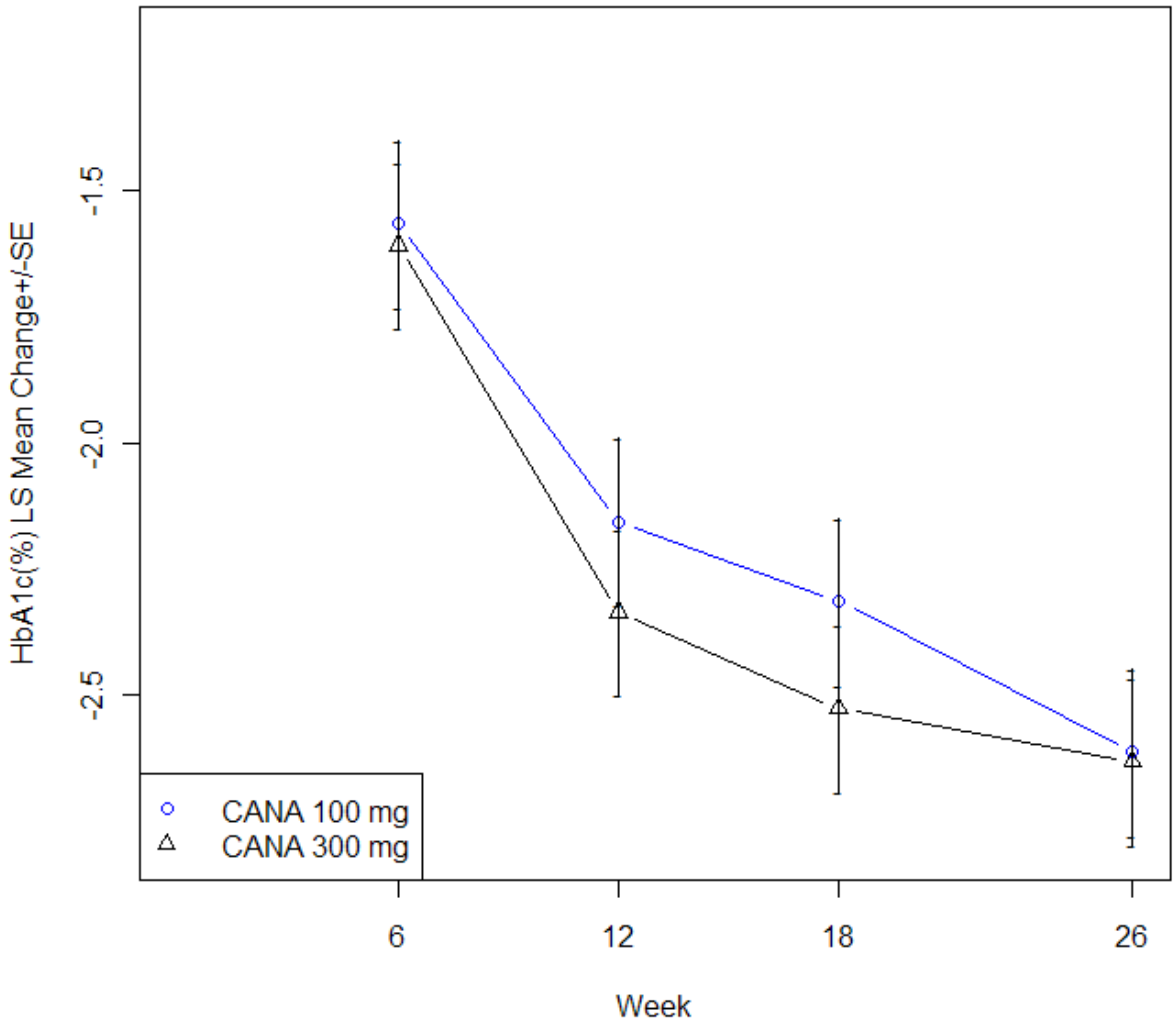


Appendix Figure 1.3. The Time Course of HbA1c Changes from Baseline for Treatment Groups (mITT population) in Study DIA3005 to Week 52.

A: Main Study

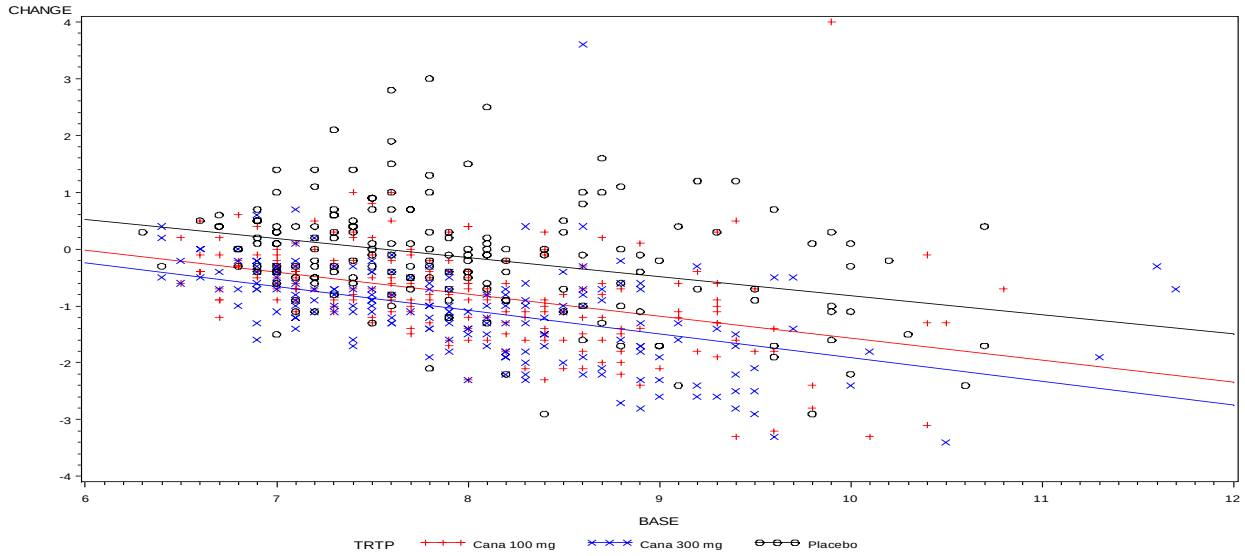


B: High Glycemic Substudy



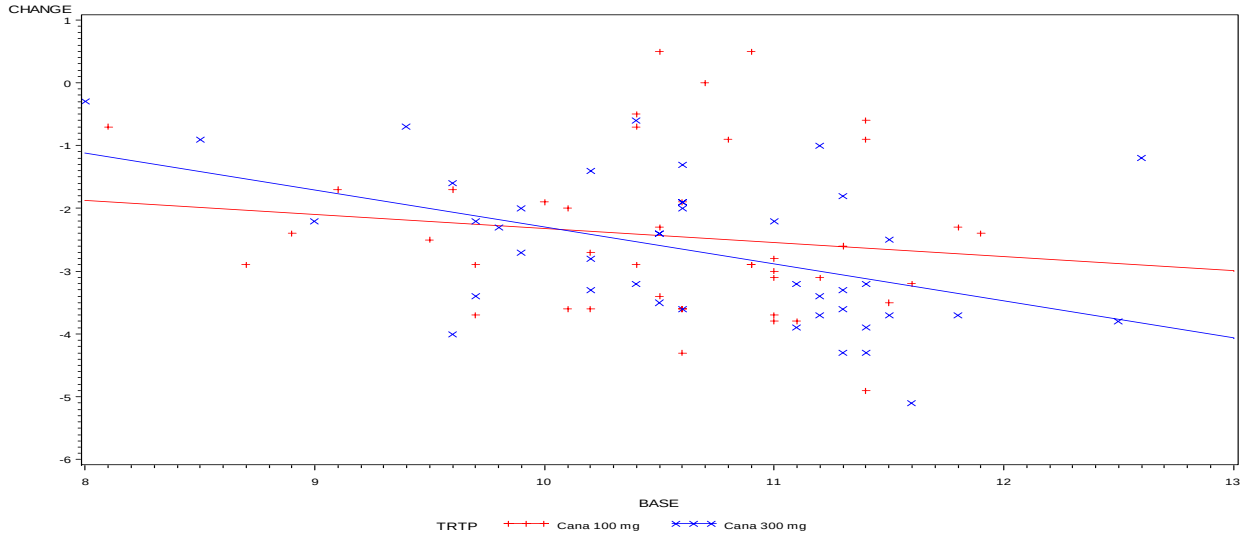
Appendix Figure 1.4. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study DIA3005 at Week 26.

A: Main Study




```
NOTE: Regression equation :  CHANGE(TRTP:Cana 100 mg) =  2.312444 - 0.387864*BASE.
NOTE: Regression equation :  CHANGE(TRTP:Cana 300 mg) =  2.254142 - 0.415981*BASE.
NOTE: Regression equation :  CHANGE(TRTP:Placebo) =  2.537651 - 0.336174*BASE.
```

B: High Glycemic Substudy




```
NOTE: Regression equation :  CHANGE(TRTP:Cana 100 mg) = -0.082312 - 0.223853*BASE.
NOTE: Regression equation :  CHANGE(TRTP:Cana 300 mg) =  3.574134 - 0.587011*BASE.
```

Appendix 2. Study DIA3006

Appendix 2.1. Additional study design information

The total duration of the study, which included the optional prescreening visit, the 2-week run-in period, the 52-week double-blind treatment phase, and the 4-week follow-up was approximately 59 (for subjects on a protocol-specified dose of metformin at study entry) to 71 weeks (for subjects not on a protocol-specified dose of metformin IR at study entry).

The primary endpoint was the change in HbA1c from baseline after 26 Weeks of treatment.

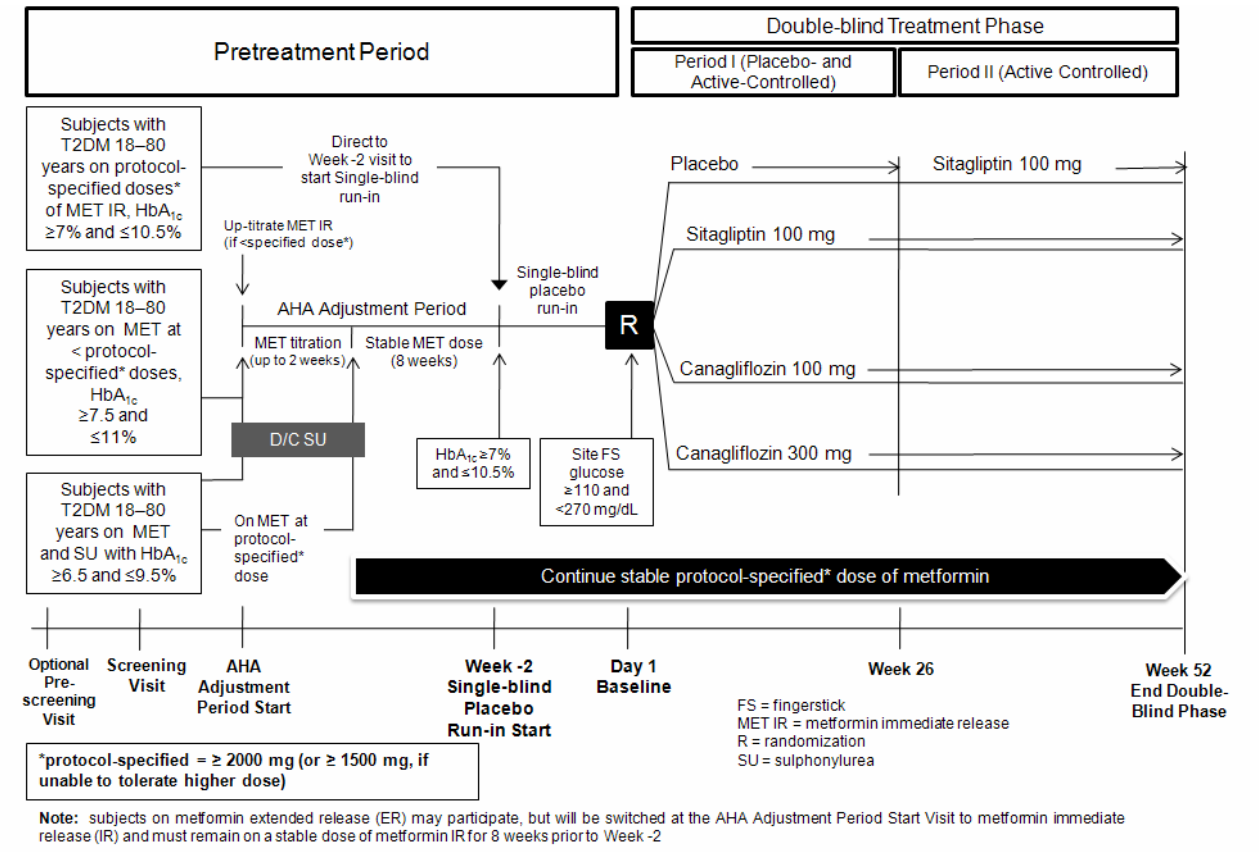
Secondary end points were fasting plasma glucose (FPG), body weight, proportion of subjects with HbA1c .7.0%, 2-hour postprandial plasma glucose (2-h PPG) after a standard meal, HDL-C, systolic blood pressure (SBP) and diastolic blood pressure (DBP), time to rescue therapy and proportion of subjects receiving rescue therapy, and fasting measure of beta-cell function (ie, homeostasis model assessment [HOMA-B]) after 26 weeks and/or 52 weeks of treatment.

Sample size calculations of this trial were based on the primary endpoint HbA1c at end of trial. Assuming a group difference of 0.5% between canagliflozin and placebo group, and a common standard deviation of 1.0% with respect to the change in HbA1c, and using a 2-sample, 2-sided t-test with type I error rate of 0.05, it was estimated that 86 subjects per treatment group would achieve 90% power to demonstrate the superiority of canagliflozin over placebo. A noninferiority margin of 0.3% was used for comparisons of canagliflozin with sitagliptin after 52 weeks of treatment. To support both the superiority and noninferiority objectives for the primary endpoint and per protocol analysis, assuming a discontinuation rate of 35% at Week 52, with a 2:2:2:1 treatment assignment ratio for canagliflozin 100 mg, canagliflozin 300 mg, sitagliptin 100 mg, or placebo, it was estimated that 360 subjects would need to be randomly assigned to each of the 3 active treatment groups and approximately 180 subjects to the placebo group. A total of approximately 1,260 subjects would be randomly assigned to treatment in this study.

This study was a multi-national, multi-centre trial with 169 study centers in 22 countries, including 55 centers in North America (50 in the United States [US], 5 in Mexico), 51 centers in Europea (3 in Bulgaria, 5 in Czech Republic, 4 in Estonia, 3 in Greece, 3 in Italy, 5 in Latvia, 5 in Poland, 2 in Portugal, 11 in Russia, 8 in Slovakia, and 2 in Sweden), 23 centers in Central/South America (7 in Argentina, 8 in Colombia and 8 in Peru), and 40 centers in the rest of world (10 in India, 5 in Malaysia, 2 in Singapore, 6 in Thailand, 5 in Turkey and 12 in Ukraine).

The sponsor's design diagram of the study NN304-1689 is shown in Figure 1.

Figure 1: Study Design



Statistical Methodologies

The efficacy objective was to assess the effect of canagliflozin relative to placebo on HbA1c after 26 weeks of treatment. determine whether the effect (change in HbA1c) of insulin detemir was at least as good of that achieved with NPH insulin at end of treatment period (non-inferiority).

The sponsor planned to test the following hypotheses:

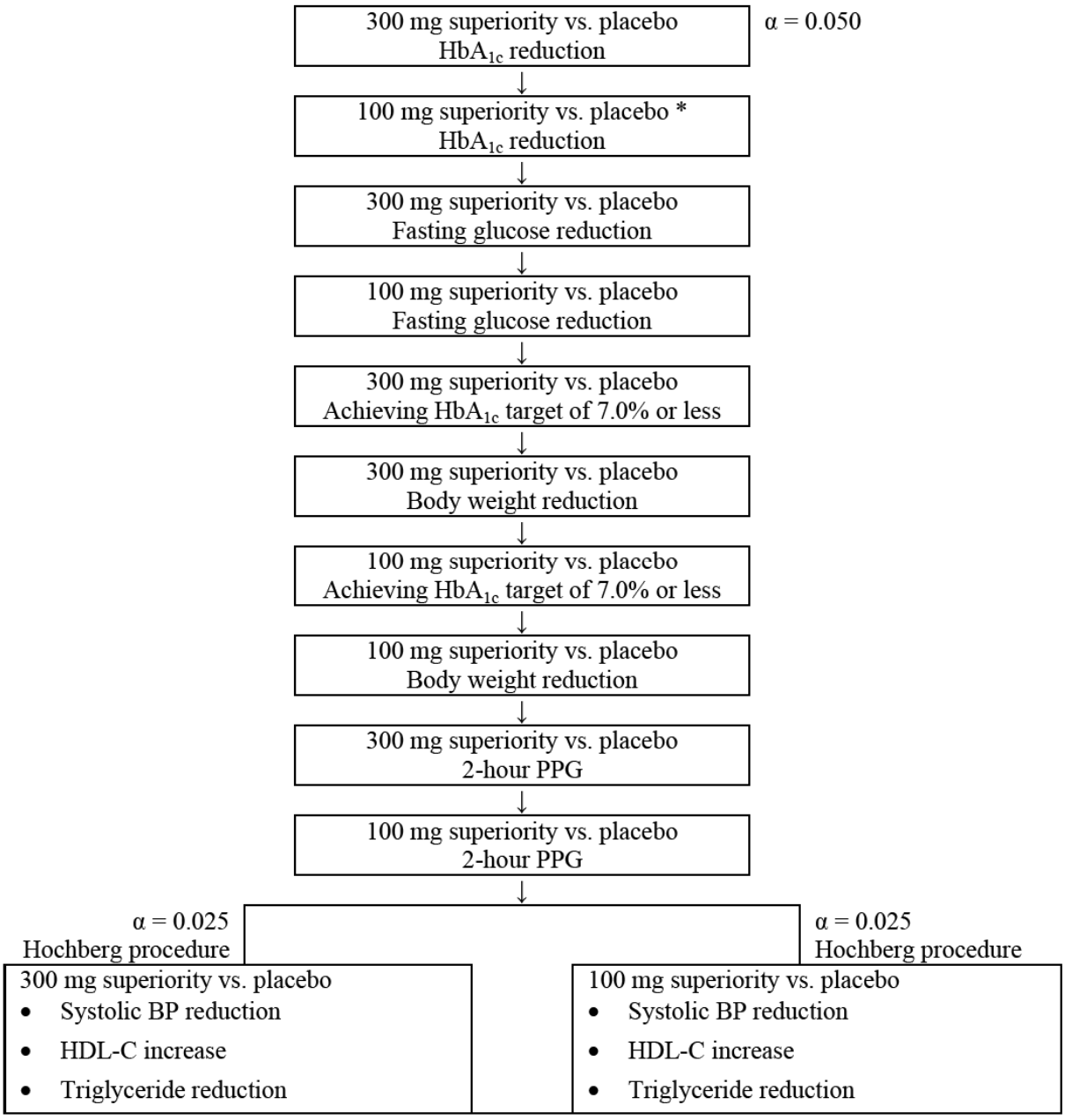
Superiority of canagliflozin (300 mg, and then 100 mg) to placebo (Week 26)

Non-inferiority of canagliflozin (300 mg, and then 100 mg) to sitagliptin (100 mg) (Week 52)

The sponsor's primary analysis used an analysis of covariance (ANCOVA) model with treatment and stratification factors as fixed effects and its corresponding baseline value as covariate to be performed on the mITT population using the LOCF approach for missing data. In subjects receiving rescue therapy, their measurements made prior to rescue would be used as the last observation.

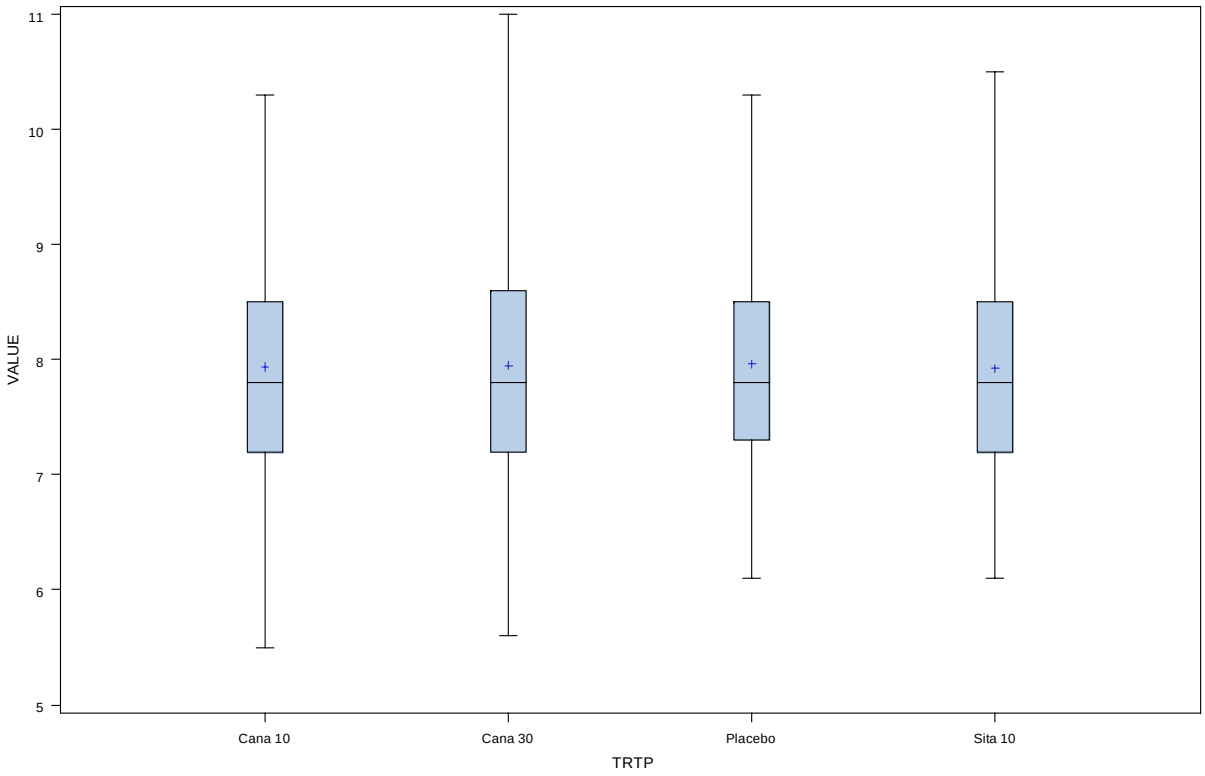
The sponsor proposed the following approach for multiplicity adjustment (Figure 2):

Figure 2. Multiplicity Adjustment

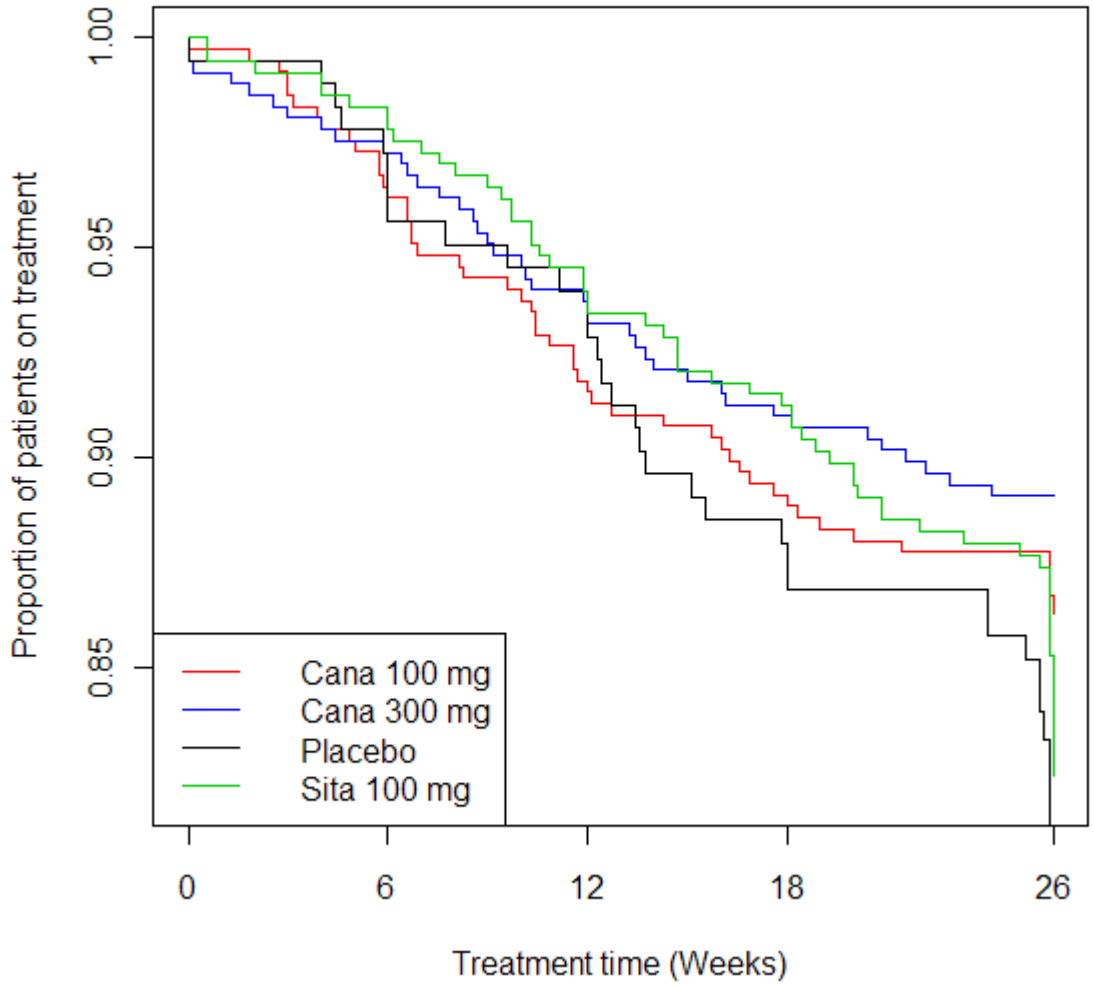


Appendix Figure 2.1. Baseline Levels of HbA1c in Different Treatment Groups (DIA3006).

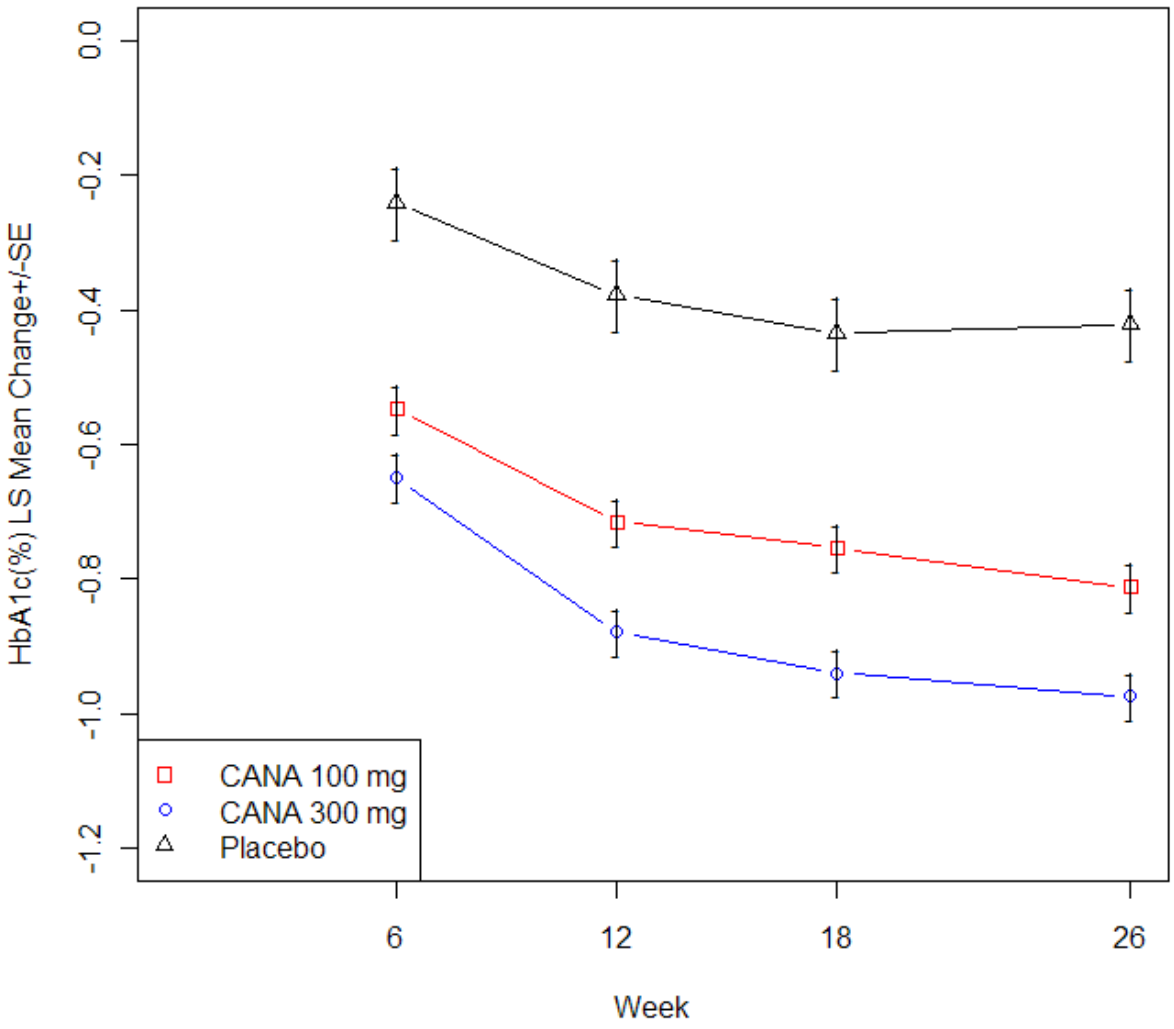
In each boxplot the bottom and top of the box are the 25th and 75th percentiles, respectively; the "x" and the line near the middle of the box are the mean and median (50th percentile), respectively; the top line above the box is the maximum observation; and the bottom line below the box is the minimum observation. Across the different treatment groups, the baseline levels of HbA1c appear to have similar means and comparable variations.



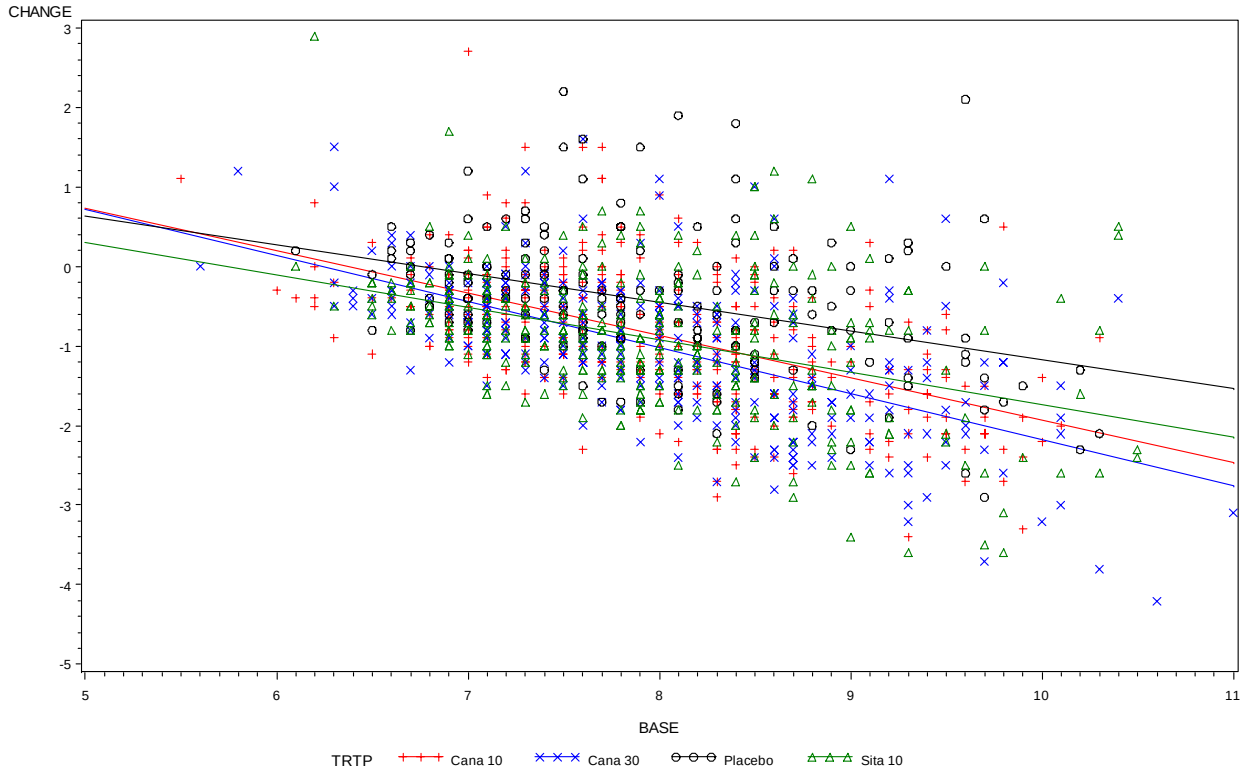
Appendix Figure 2.2. Comparing Time to Dropout during the Treatment Period between Treatment Groups (FAS population, DIA3006).



Appendix Figure 2.3. The The Time Course of HbA1c Changes from Baseline for Treatment Groups (mITT population) in Study DIA3006 to Week 26.



Appendix Figure 2.4. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study DIA3006 at Week 26.



Appendix 3. Study DIA3009

Appendix 3.1. Additional study design information

The primary objective was to compare the glycosylated hemoglobin (HbA1c)-lowering efficacy of canagliflozin 100 mg and canagliflozin 300 mg with glimepiride after 52 weeks of treatment.
Eligible subjects were men and women (427 subjects per treatment group), 18 to 80 years of age, inclusive, with a diagnosis of T2DM who are not optimally controlled on metformin monotherapy with screening HbA1c ≥7% and ≤9.5 %.

Primary hypothesis: After 52 weeks of treatment, at least one of the CANAGLIFLOZIN dosages (100 or 300 mg daily) would be noninferior to glimepiride as assessed by the change in HbA1c from baseline.

The study consists of 3 phases: (1) a pretreatment phase (consisting of an optional prescreening visit, a 1-week screening period, and either a 2-week run-in period or a 12 week metformin dose titration and dose stabilization period immediately followed by the 2-week run in period), (2) a 104-week double-blind treatment phase (including a baseline visit on Day 1), and (3) a posttreatment phase (consisting of a telephone follow-up contact [or optional study visit, at the discretion of the investigator] for all subjects approximately 28 days after the last dose of study drug). The total duration of the study, including the optional prescreening visit, is approximately 109 to 122 weeks for each subject, depending on the length of the pretreatment phase.
It is estimated that 1,281 patients would be enrolled and randomly assigned to treatment in this study. Subjects would be randomly assigned in a 1:1:1 ratio to 1 of 3 treatments groups, to receive either 100 or 300 mg of canaflozin, or glimepiride, and would take their first dose of study drug on Day 1. Up-and down-titration may occur at any time during the duration of the study.

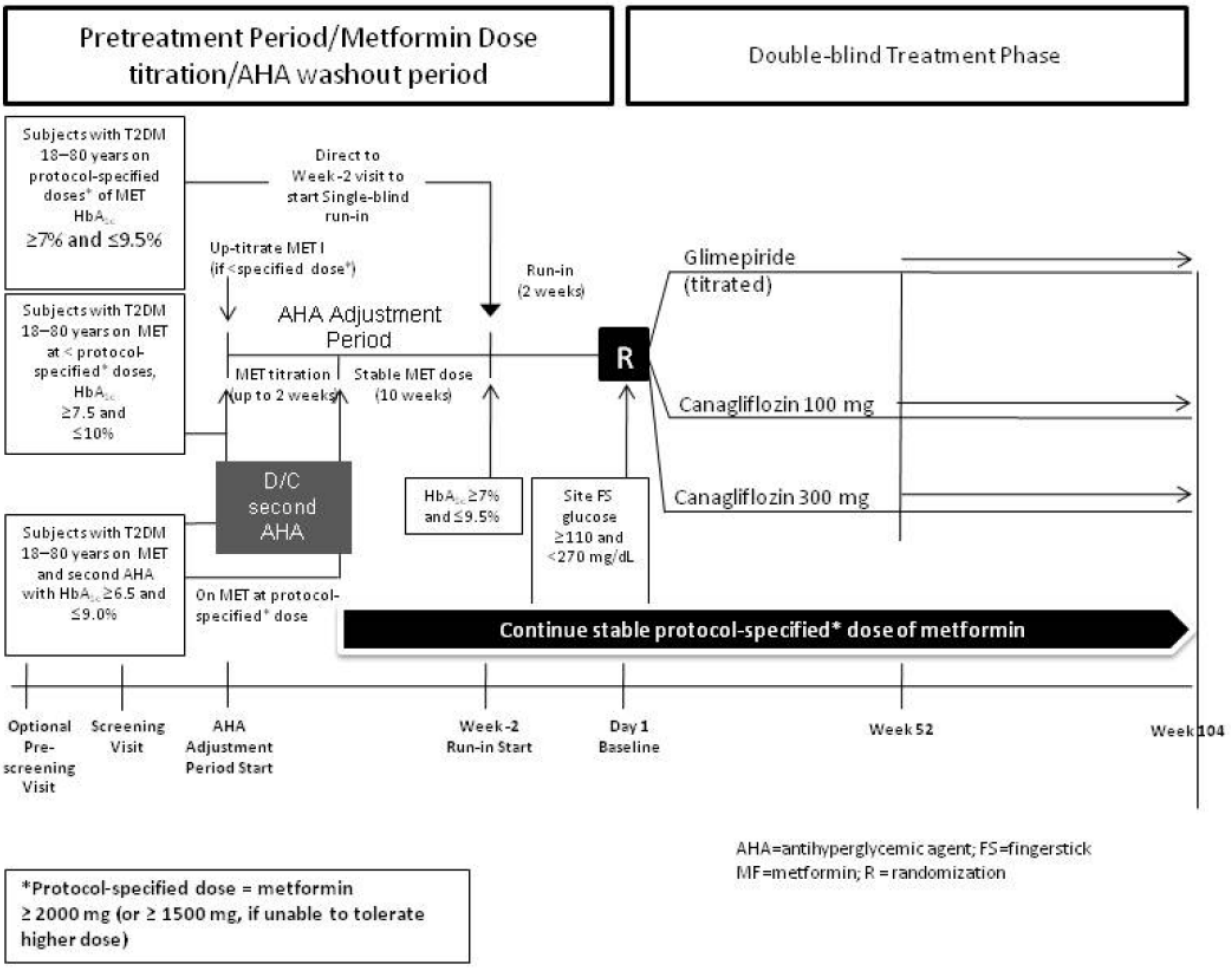
Secondary end points included the change from baseline to Week-52 in body weight, FPG, BMI, the change and percent change from baseline in fasting serum lipid profiles, and the change from baseline in the ratio of fasting LDL-cholesterol to HDL-cholesterol.

Sample size calculations of this trial were based on the primary endpoint HbA1c at end of trial by assuming a group difference of 0.0% and a common standard deviation of 1.0% with respect to change in HbA1c, and using a 2-sample, 1-sided t-test with Type I error rate of 0.0125 for the comparison of each CANAGLIFLOZIN dose with glimepiride. A noninferiority margin of 0.3% was selected. It was estimated that 277 subjects per group completing the Week 52 evaluations would be required to achieve 90% power in the PP analysis. Assuming a discontinuation rate of 35% in 52 weeks, approximately 1,281 subjects (or 427 subjects per arm) would be randomly assigned to treatment in order to meet the sample size required for the per protocol analysis.

This study was a multi-national, multi-centre trial with a total of 157 study centers in 19 countries, including 54 centers in North America, 39 centers in Europea, 9 centers in Central/South America, and 55 centers in the rest of world.

The sponsor's design diagram of the study DIA3009 is shown in Figure 1.

Figure 1. Overview of the study design, DIA3009.



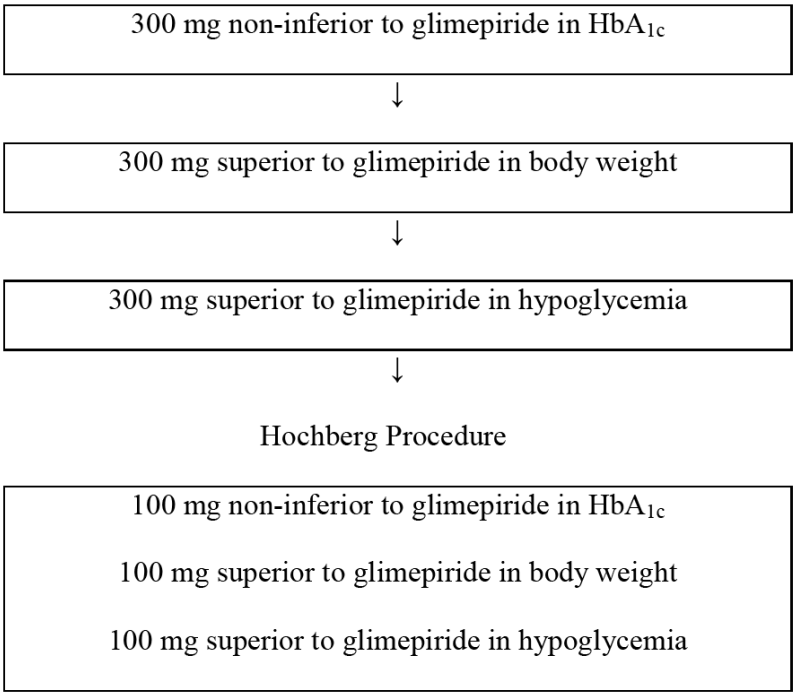
Statistical Methodologies

The primary objective of this study is to demonstrate the noninferiority of at least one of the two CANAGLIFLOZIN doses to glimepiride in glycemic efficacy as measured by the change in HbA1c from baseline to Week 52. A non-inferiority margin of 0.3% had been selected.

The primary hypothesis was tested: After 52 weeks of treatment, at least one of the canagliflozin dosages (100 mg or 300 mg daily) would be noninferior to glimepiride as assessed by the change in HbA1c from baseline.

The sponsor's primary efficacy analysis would be based on the mITT analysis set. An analysis of covariance (ANCOVA) model with treatment and stratification factors (whether or not a subject underwent the metformin dose stabilization/AHA washout period prior to run-in, and country) as fixed effects, and the baseline HbA1c value as a covariate would be used for the primary efficacy analysis. The LOCF method would be applied when the Week 52 values are missing. The treatment differences (each canagliflozin group minus glimepiride) in the Least-Squares means (LS means) their 2-sided 95% CIs, and the associated p-values would be estimated based on this model. The upper bound of the 95% CI of the treatment difference in LS means would be compared with the non-inferiority margin 0.3%. Analysis based on the PP set would also be conducted for the confirmatory purpose.
To assess the durability of glycemic control, a longitudinal profile of HbA1c would be presented by treatment group. The rates of HbA1c change from Week 26 to Week 104 would be estimated and the comparisons between each dose group of CANAGLIFLOZIN and glimepiride would be made. For supportive analysis, the estimates of treatment from mixed effect modeling for the change of HbA1c from Week 26 would be derived. A longitudinal plot of the estimates would be presented. The analysis of durability which involves comparing groups on changes of HbA1c after randomization from Week 26 to Week 104 would be considered as descriptive analyses only.
For multiplicity issues, the sponsor used a hierarchical testing procedure in testing the treatment differences (CANAGLIFLOZIN two dose groups versus glimepiride respectively) for the primary and secondary endpoints to preserve the overall Type I error rate of 5% as shown in Figure 2.

Figure 2. Multiplicity Adjustment, DIA3009

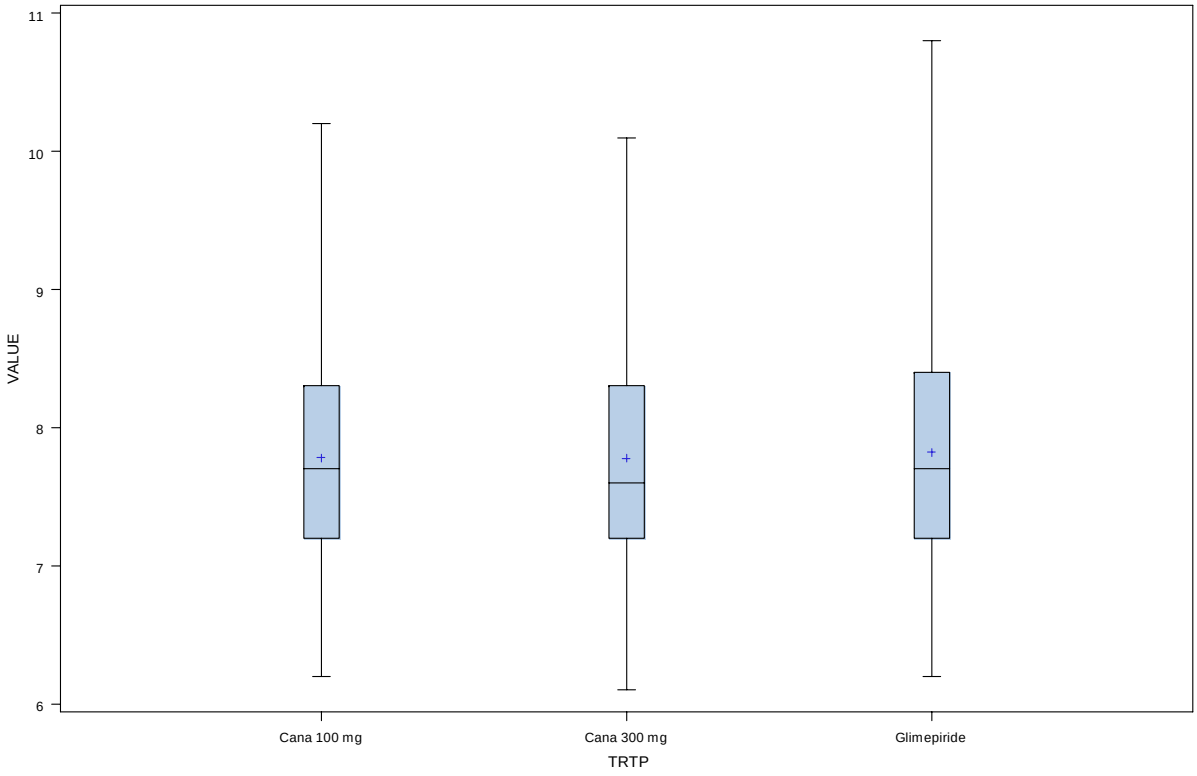


For the comparison of each CANAGLIFLOZIN dose group versus glimepiride, when the non-inferiority for the primary efficacy endpoint is claimed by demonstrating the upper bound of the 2-sided 95% CI of the treatment difference is less than the 0.3% margin, and if the upper bound is less than 0.0%, the superiority for the primary endpoint would be further claimed.

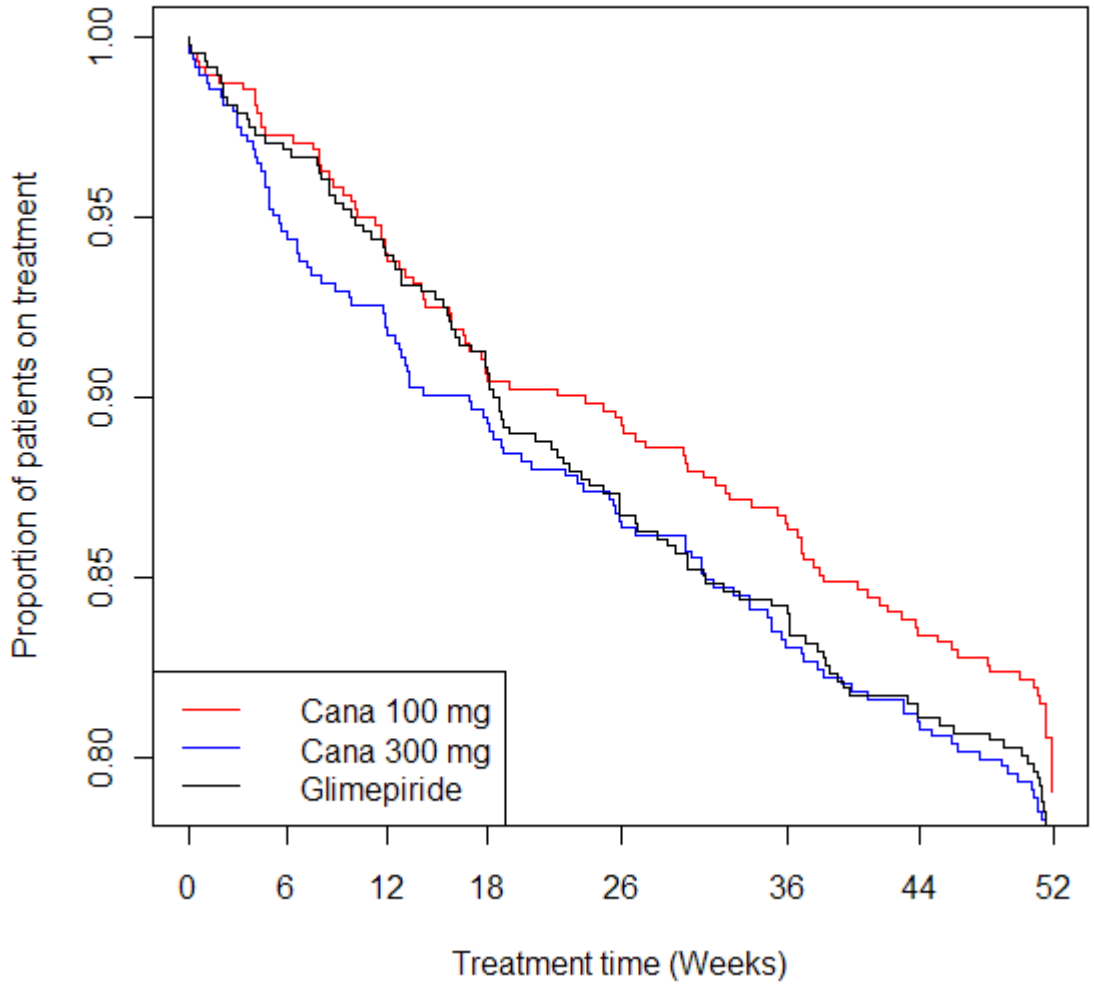
In each boxplot the bottom and top of the box are the 25th and 75th percentiles, respectively; the "x" and the line near the middle of the box are the mean and median (50th percentile), respectively; the top line above the box is the

maximum observation; and the bottom line below the box is the minimum observation. Across the different treatment groups, the baseline levels of HbA1c appear to have similar means and comparable variations.

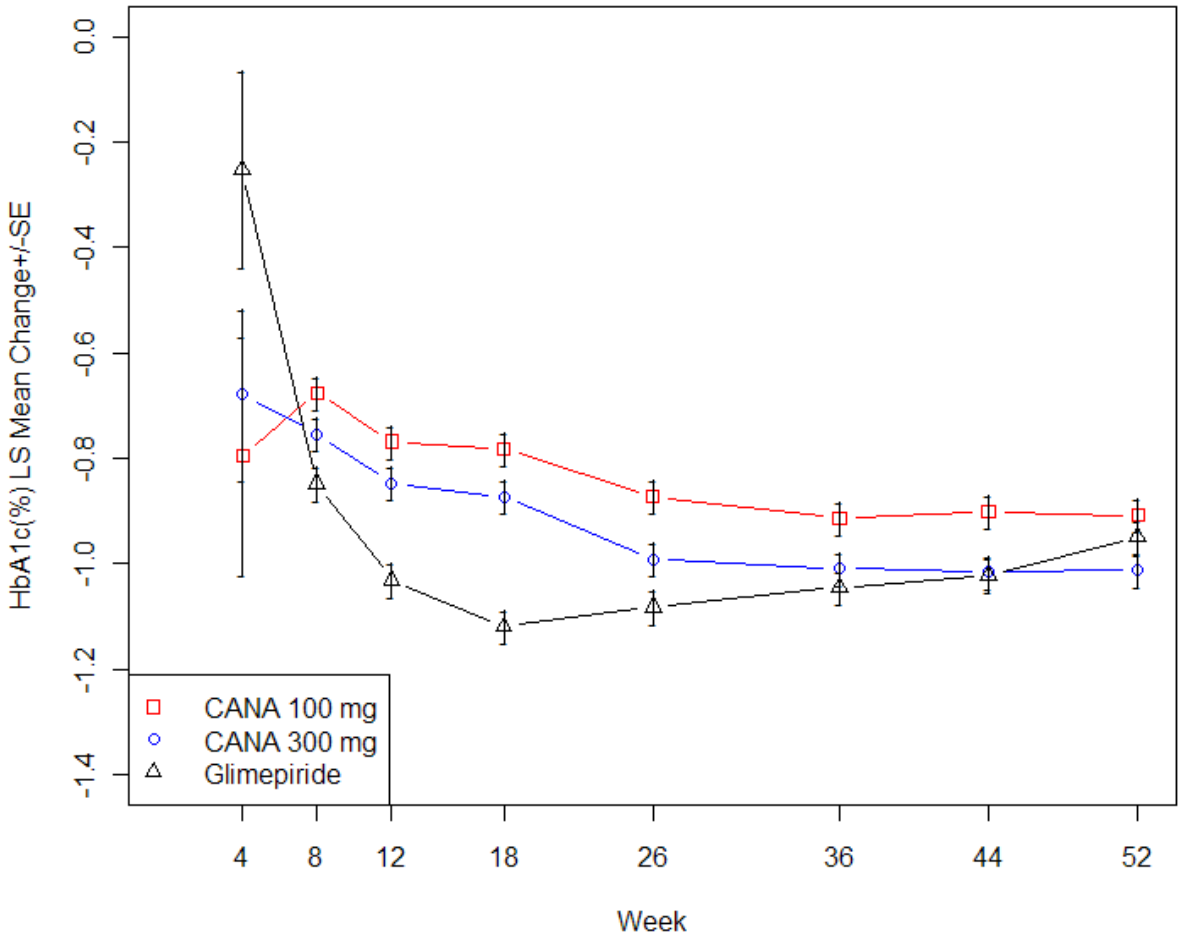
Appendix Figure 3.1. Baseline Levels of HbA1c in Different Treatment Groups (DIA3009).



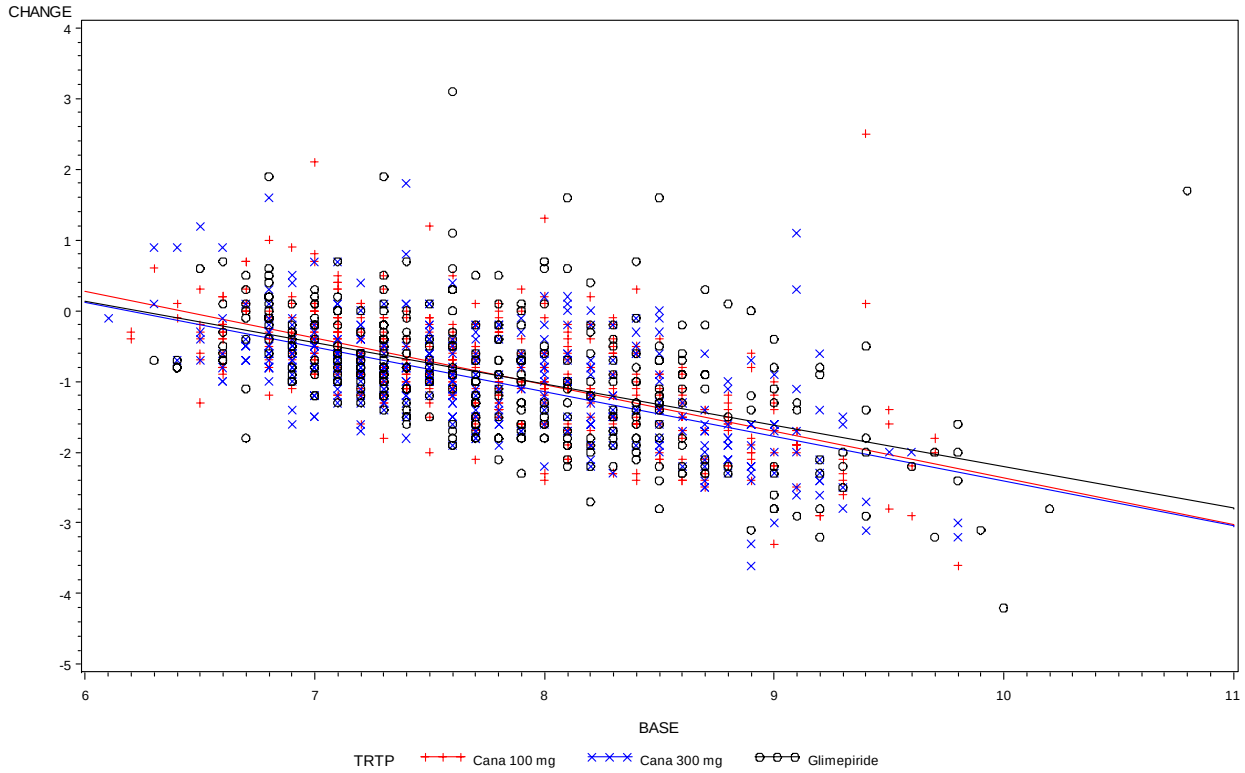
Appendix Figure 3.2. Comparing Time to Dropout during the Treatment Period between Treatment Groups (FAS population, DIA3009).



Appendix Figure 3.3. The Time Course of HbA1c Changes from Baseline in Study DIA3009 to Week 52.



Appendix Figure 3.4. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study DIA3009 at Week 52.




```
NOTE: Regression equation :  CHANGE(TRTP:Cana 100 mg) =  4.243547 - 0.660935*BASE.
NOTE: Regression equation :  CHANGE(TRTP:Cana 300 mg) =  3.898997 - 0.63051*BASE.
NOTE: Regression equation :  CHANGE(TRTP:Glimepiride) =  3.655564 - 0.586448*BASE.
```

Appendix 4 DIA3002

Appendix 4.1

The primary efficacy endpoint was the change in HbA1c from baseline through Week 26.

The primary objectives were to assess the effect of canagliflozin relative to placebo on glycosylated hemoglobin (HbA1c) after 26 weeks of treatment and to assess the safety and tolerability of canagliflozin.
Eligible subjects were insulin detemir naïve, diagnosed with type 1 diabetes, 2-16 years of age and have been diagnosed with type 1 diabetes for a minimum of 12 months prior to inclusion in this trial. Furthermore the subjects must have a total daily insulin dose ≤ 2.00 U/kg and the screening HbA1c should be ≤ 11%.

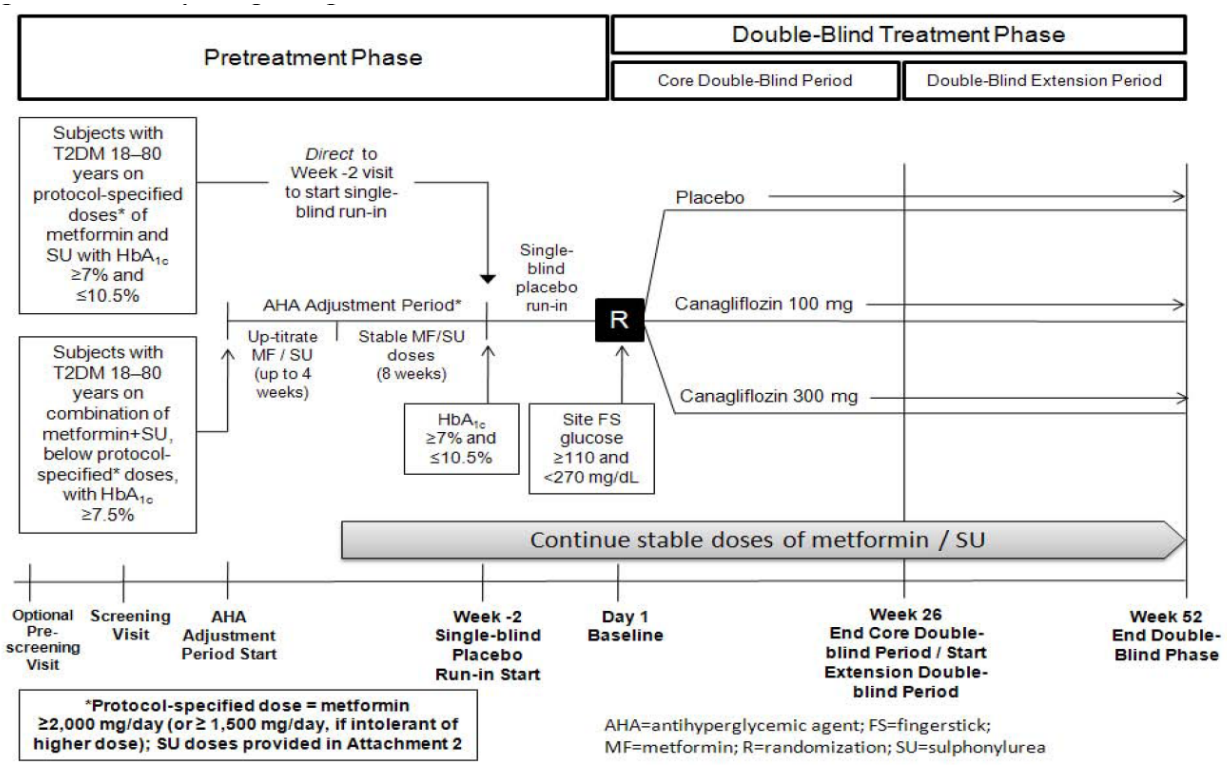
Secondary end points included fasting plasma glucose (FPG), the proportion of subjects with HbA1c <7.0% or <6.5%, body weight, fasting plasma lipids (ie, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], total cholesterol, LDL-C to HDL-C ratio, and triglycerides), systolic blood pressure (SBP) and diastolic blood pressure (DBP), time to rescue medication and proportion of subjects receiving
Sample size calculations of this trial were based on the primary endpoint HbA1c at end of trial with rescue medication, and fasting measure of beta-cell function (ie, homeostasis model assessment [HOMA]- B) after 26 weeks of treatment of canagliflozin relative to placebo.

Sample Size Determination: The primary hypothesis for this study was canagliflozin 300 mg was superior to placebo in reducing HbA1c from baseline at Week 26. Assuming a group difference for HbA1c of 0.5% between canagliflozin and placebo, and a common standard deviation of 1.0% with respect to change in HbA1c, and using a 2-sample, 2-sided t-test with a type I error rate of 0.05, the sponsor estimated that 85 randomized subjects per treatment group were required to achieve at least 90% power. To enhance the safety and tolerability experience with canagliflozin, the sample size was moderately expanded and approximately 150 subjects per treatment group (a total of 450 subjects) were randomly assigned.

This study was a multi-national, multi-centre trial with a total of 85 study centers in 11 countries, including 42 centers in North America (38 in the United States, 4 in Mexico), 24 centers in Europea (6 in France, 6 in the United Kingdom, 4 in Belgium, 4 in Hungary, 4 in Spain), 5 centers in Central America (5 in Guatemala), and 14 centers in the rest of world (5 in Australia, 5 in Russia, 4 in Israel)

The sponsor's design diagram of the study DIA3002 is shown in Figure 1.

Figure 1. Overview of the study design.



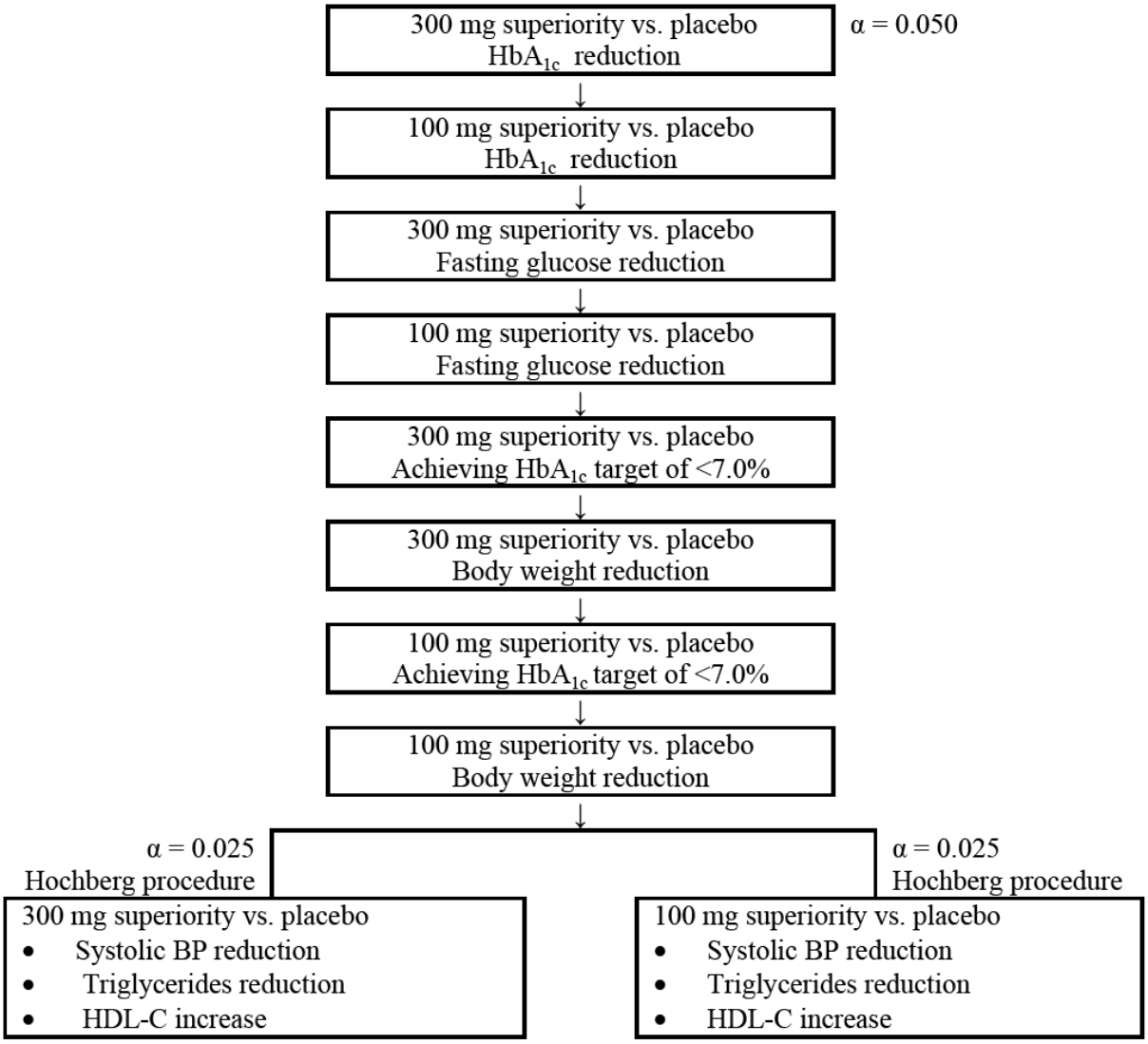
Statistical Methodologies
The primary hypothesis for this study was canagliflozin 300 mg is superior to placebo in reducing HbA1c from baseline at Week 26.

The sponsor's primary analysis was based on the mITT analysis set, an analysis of covariance (ANCOVA) model with treatment and stratification factors (whether or not a subject entered the AHA adjustment period and participation in the FS-MMTT) as fixed effects, and the baseline HbA1c value as a covariate would be used for the primary efficacy analysis. The LOCF method was applied when the Week 26 values are missing.

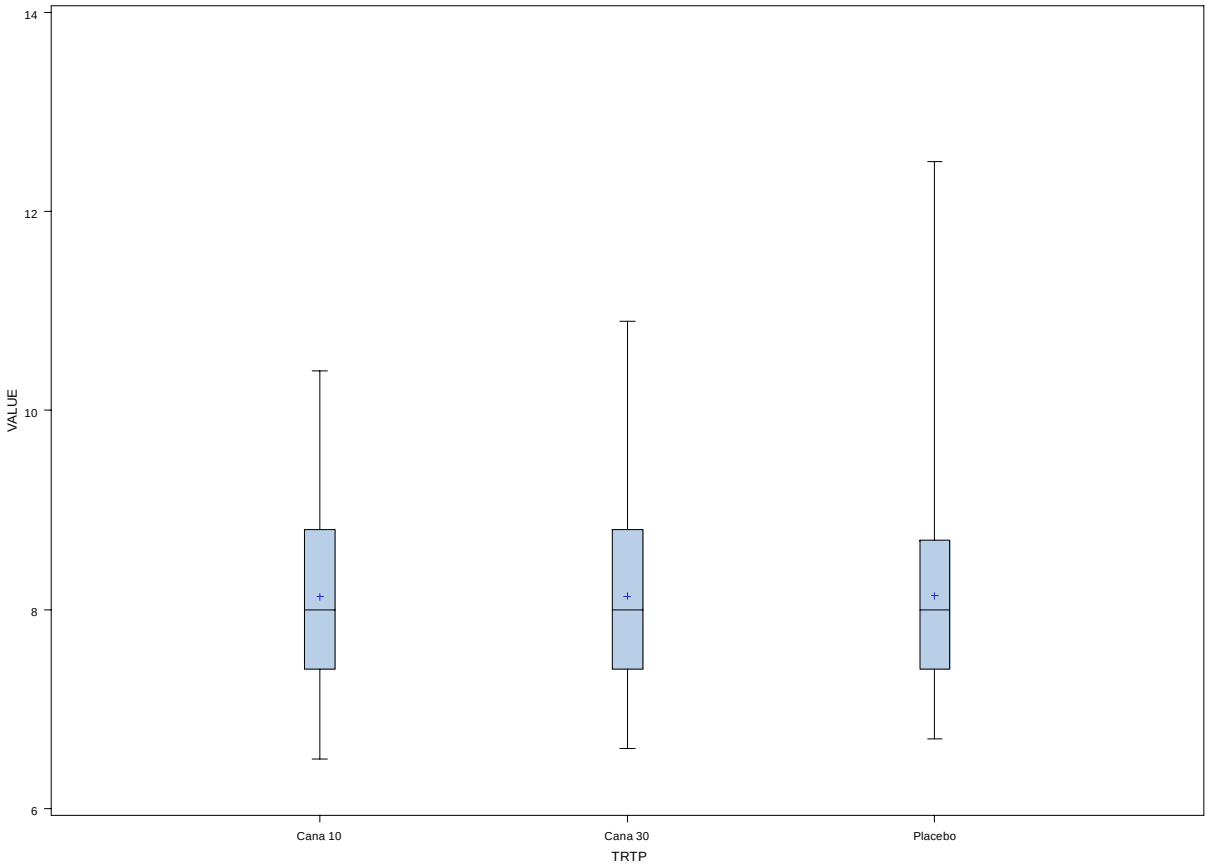
For multiplicity issues, the sponsor used a hierarchical testing procedure for testing the treatment differences (CANAGLIFLOZIN two dose groups versus placebo, respectively) for the

primary and secondary endpoints to preserve the overall Type I error rate of 5% as shown in Figure 2.

Figure 2. Multiplicity Adjustment, DIA3002

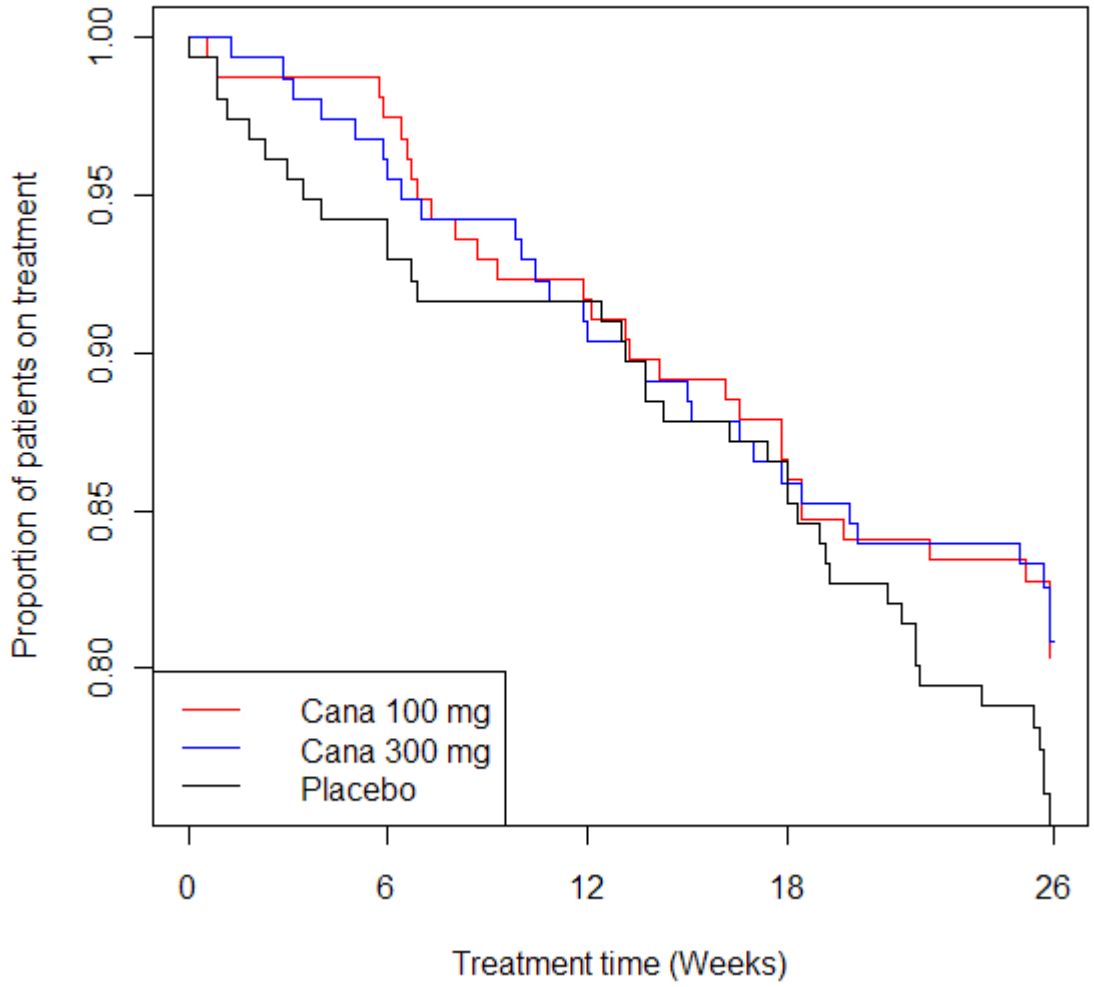


Appendix Figure 4.1. Baseline Levels of HbA1c in Different Treatment Groups (DIA3002).

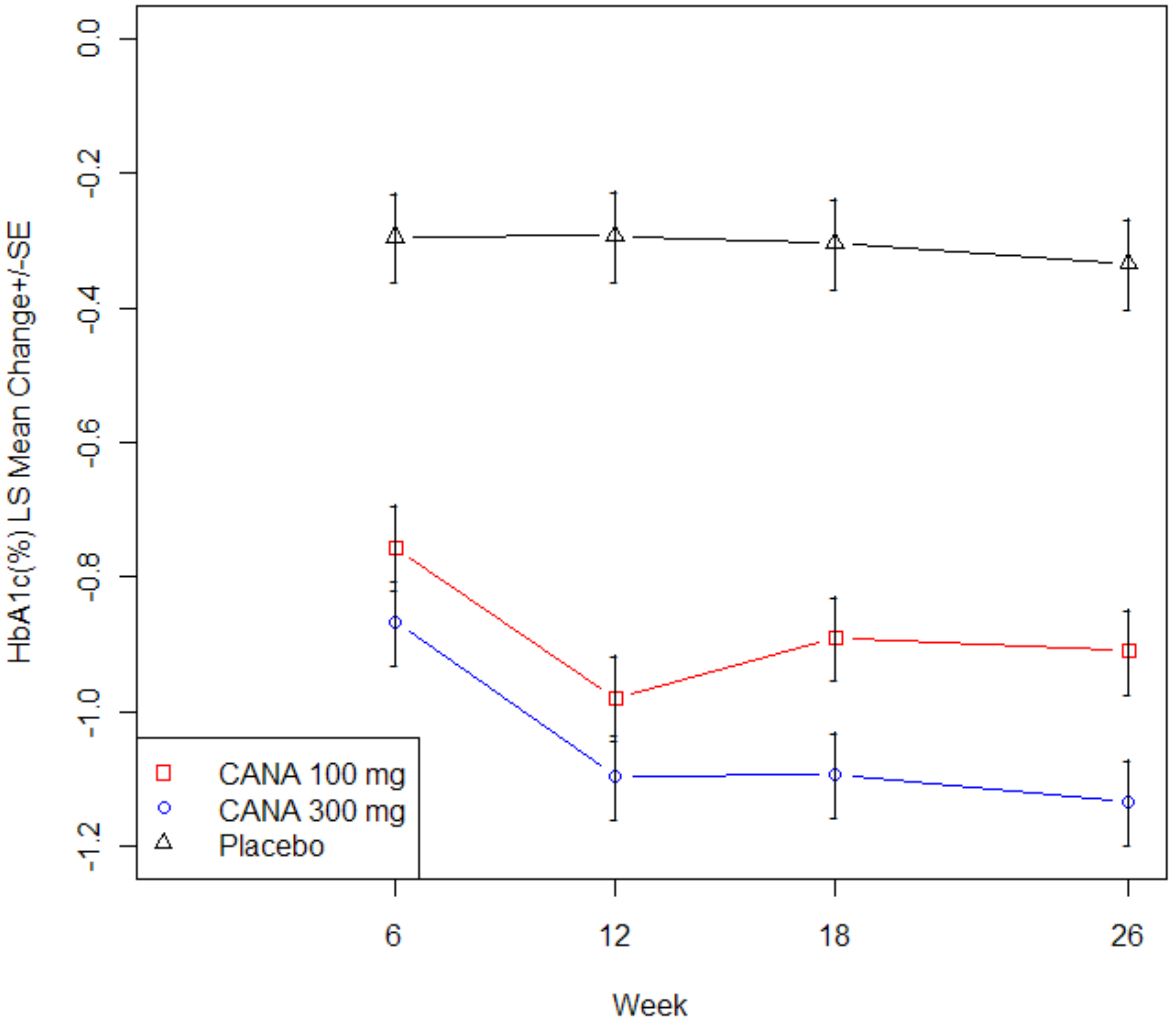


.

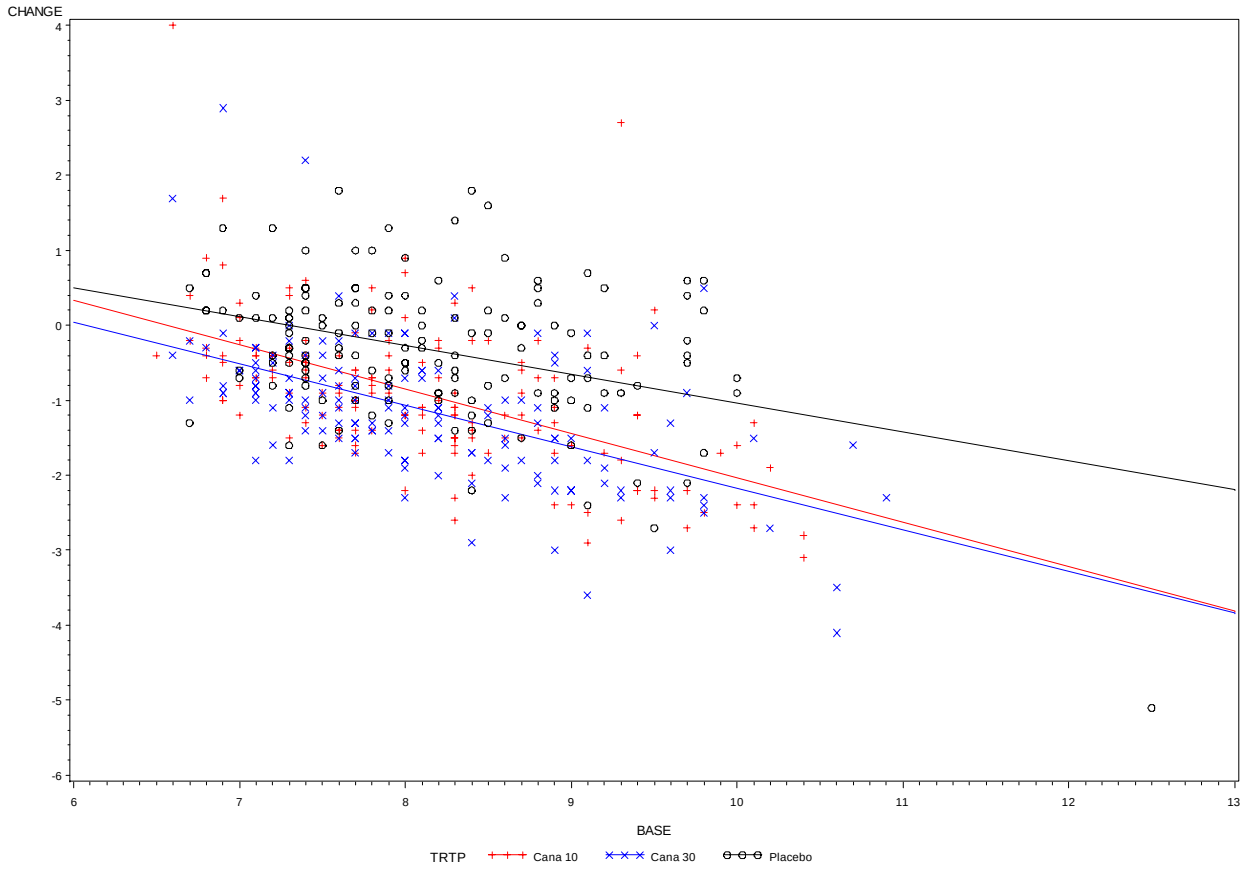
Appendix Figure 4.2. Comparing Time to Dropout during the Treatment Period between Treatment Groups (FAS population, DIA3002).



Appendix Figure 4.3. The Time Course of HbA1c Changes from Baseline in Study DIA3002 to Week 26.



Appendix Figure 4.4. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study DIA3002 at Week 26.




```
Regression equation :  CHANGE(TRTP:Cana 10) =  3.885764 - 0.592015*BASE.
Regression equation :  CHANGE(TRTP:Cana 30) =  3.355441 - 0.552998*BASE.
Regression equation :  CHANGE(TRTP:Placebo) =  2.79951 - 0.384198*BASE.
```

Appendix 5 DIA3012

Appendix 5.1

The primary objectives were to assess the effect of canagliflozin relative to placebo on HbA1c after 26 weeks of treatment and to assess the safety and tolerability of canagliflozin.
Eligible subjects were insulin detemir naïve, diagnosed with type 1 diabetes, 2-16 years of age and have been diagnosed with type 1 diabetes for a minimum of 12 months prior to inclusion in this trial. Furthermore the subjects must have a total daily insulin dose ≤ 2.00 U/kg and the screening HbA1c should be ≤ 11%.

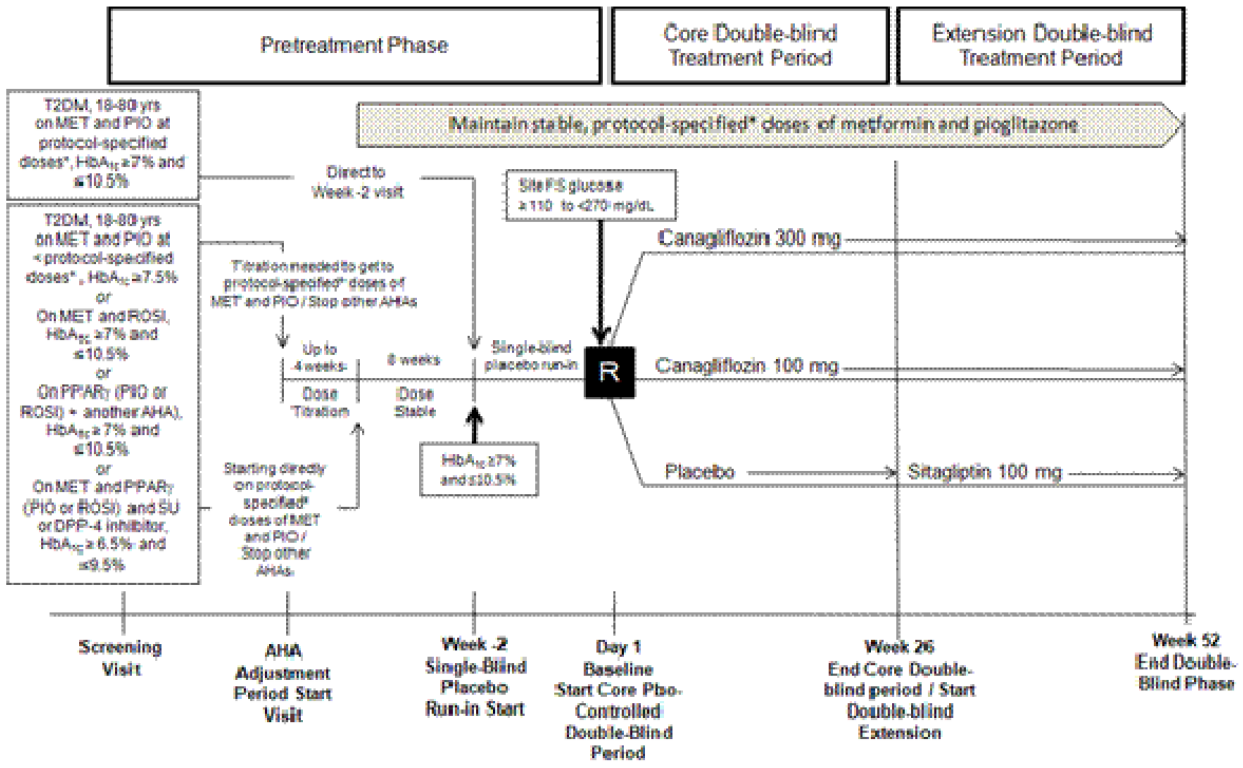
The primary efficacy endpoint was the change in HbA1c from baseline through Week 26.
Secondary end points to assess the effect of canagliflozin relative to placebo were fasting plasma glucose (FPG), body weight, proportion of subjects with HbA1c .7.0% and .6.5%, fasting plasma lipids (ie, low-density lipoprotein-cholesterol [LDL-C], high-density lipoprotein-cholesterol [HDL-C], total cholesterol, LDL-C to HDL-C ratio, and triglycerides), fasting measure of beta cell function (ie, HOMA-B), systolic and diastolic blood pressure, and time to rescue therapy and proportion of subjects receiving rescue therapy.

Sample Size Determination: The primary objective was to demonstrate the superiority of canagliflozin to placebo as measured by the change in HbA1c from baseline at Week 26. Assuming a group difference of 0.5% and a common standard deviation of 1.0% with respect to the change in HbA1c, and using a 2-sample, 2-sided t-test with type I error rate of 0.05, the sponsor estimated that 86 randomized subjects per group were required to achieve at least 90% power. To enhance the safety database of canagliflozin, approximately 120 subjects per treatment group (at total of 360 subjects) were to be randomly assigned.

This study was a multi-national, multi-centre trial with a total of 74 centers in 11 countries including 48 centers in North America (34 in the United States, 12 in Canada, 2 in Mexico), 17 centers in Europea (3 in Finland, 2 in France, 4 in Germany, 1 in Greece, 3 in Spain, 4 in the United Kingdom), and 9 centers in the rest of the world (5 in India, 4 in Thailand).

The sponsor's design diagram of the study NN304-1689 is shown in Figure 1.

Figure 1. Overview of the study design.



FS=fingerstick; R=randomization; creat = serum creatinine; pio = pioglitazone; rosi = rosiglitazone; met = metformin

*protocol-specified doses = metformin ≥ 2000 mg per day (or ≥1500 mg if unable to tolerate higher doses); pioglitazone 30 or 45 mg per day

Statistical Methodologies

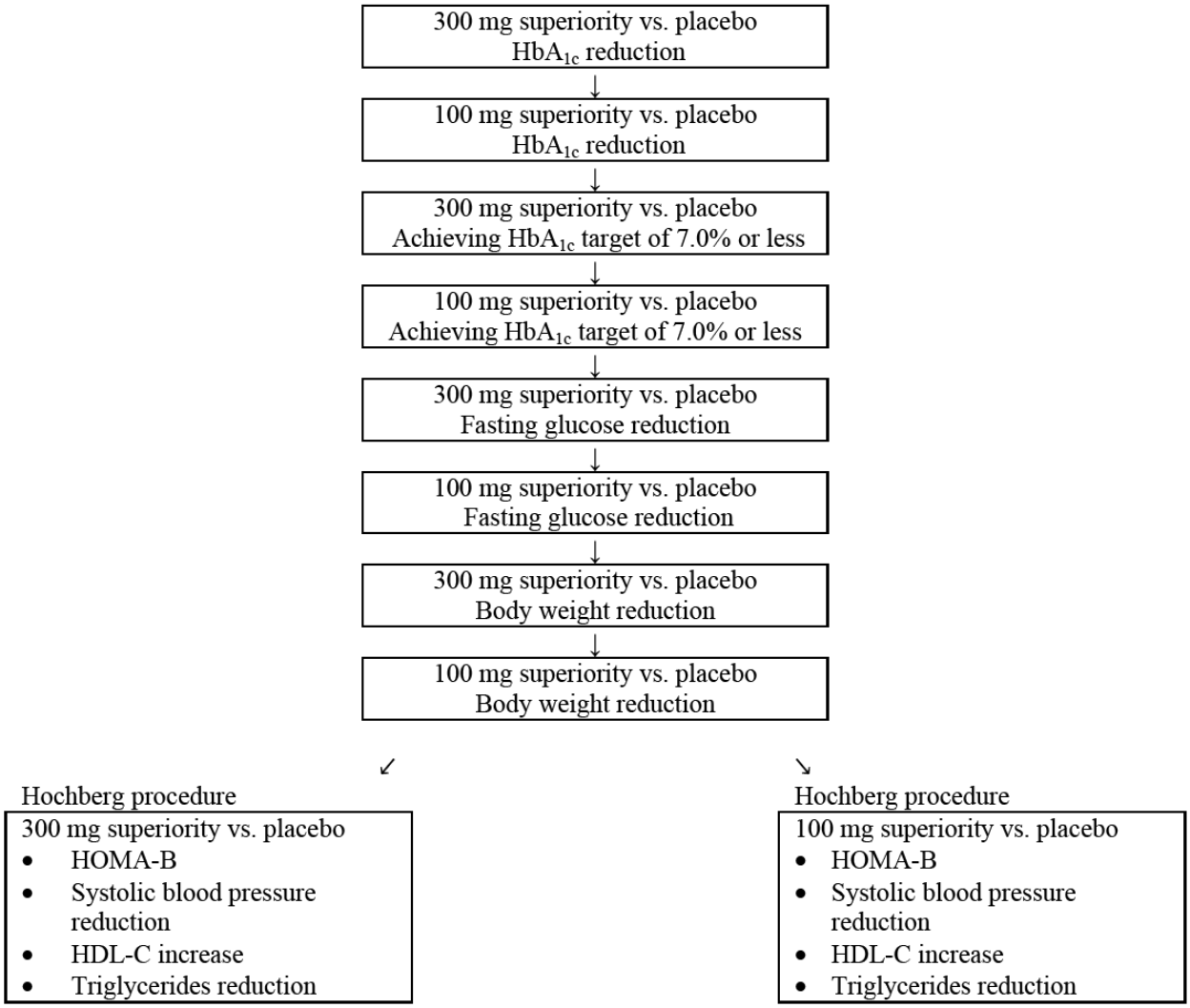
The efficacy objective was to demonstrate the superiority of canagliflozin to placebo as measured by the change in HbA1c from baseline at Week 26.

The primary hypotheses was: After 26 weeks of treatment, canagliflozin 300 mg reduces HbA1c relative to placebo.

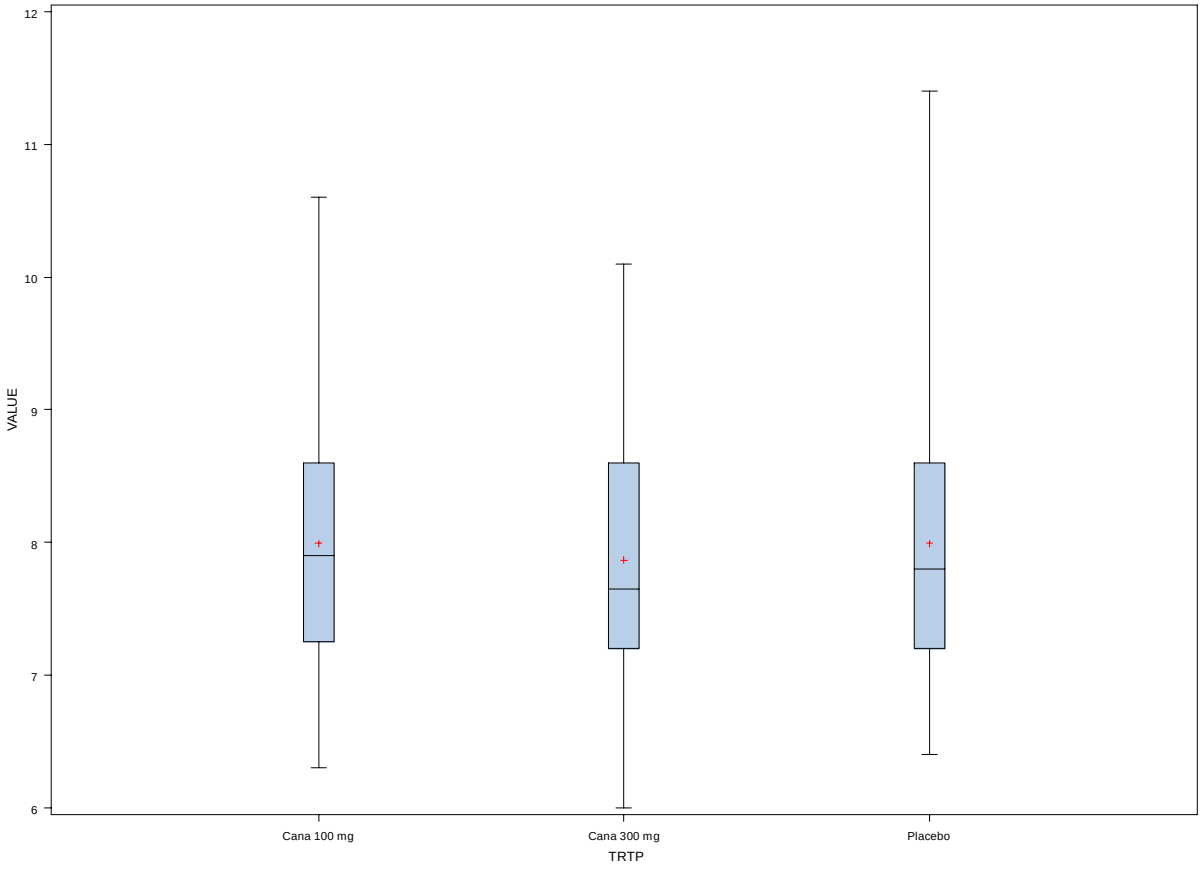
The sponsor's primary analysis was based on the mITT analysis set, an analysis of covariance (ANCOVA) model with treatment and stratification factors (whether or not a subject entered the AHA adjustment period and dose of pioglitazone at randomization [30 or 45 mg]) as fixed effects, and the corresponding baseline HbA1c value as a covariate would be used for the primary efficacy analysis.

According to the sponsor's plan for multiplicity adjustment, the hypotheses of primary efficacy endpoint and major secondary efficacy endpoints would be tested sequentially as illustrated in Figure 2. The type I error would be controlled at 0.05.

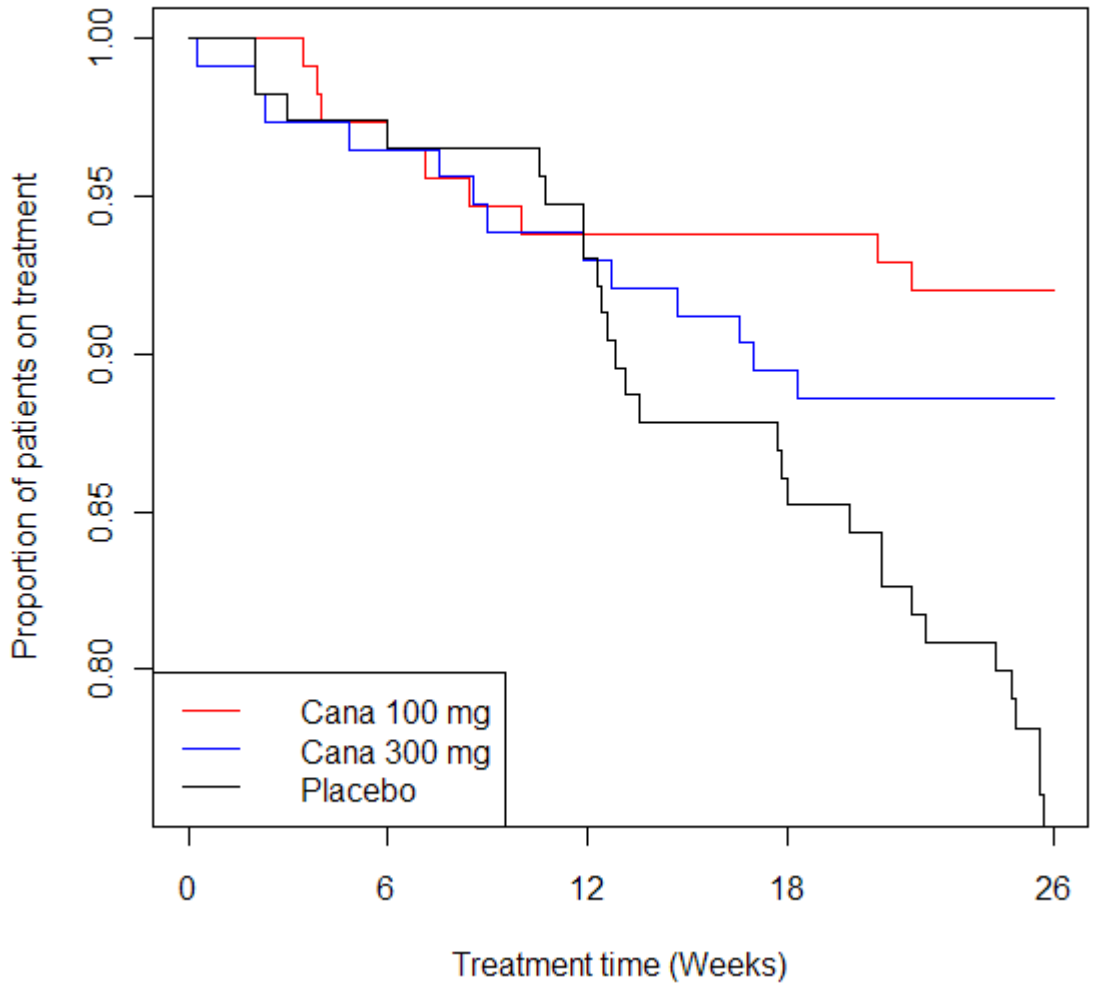
Figure 2. Multiplicity Adjustment


300 mg superiority vs. placebo
HbA1c reduction
100 mg superiority vs. placebo
HbA1c reduction
300 mg superiority vs. placebo
Achieving HbA1c target of 7.0% or less
100 mg superiority vs. placebo
Achieving HbA1c target of 7.0% or less
300 mg superiority vs. placebo
Fasting glucose reduction
100 mg superiority vs. placebo
Fasting glucose reduction
300 mg superiority vs. placebo
Body weight reduction
100 mg superiority vs. placebo
Body weight reduction
Hochberg procedure
300 mg superiority vs. placebo
HOMA-B
Systolic blood pressure reduction
HDL-C increase
Triglycerides reduction
Hochberg procedure
100 mg superiority vs. placebo
HOMA-B
Systolic blood pressure reduction
HDL-C increase
Triglycerides reduction

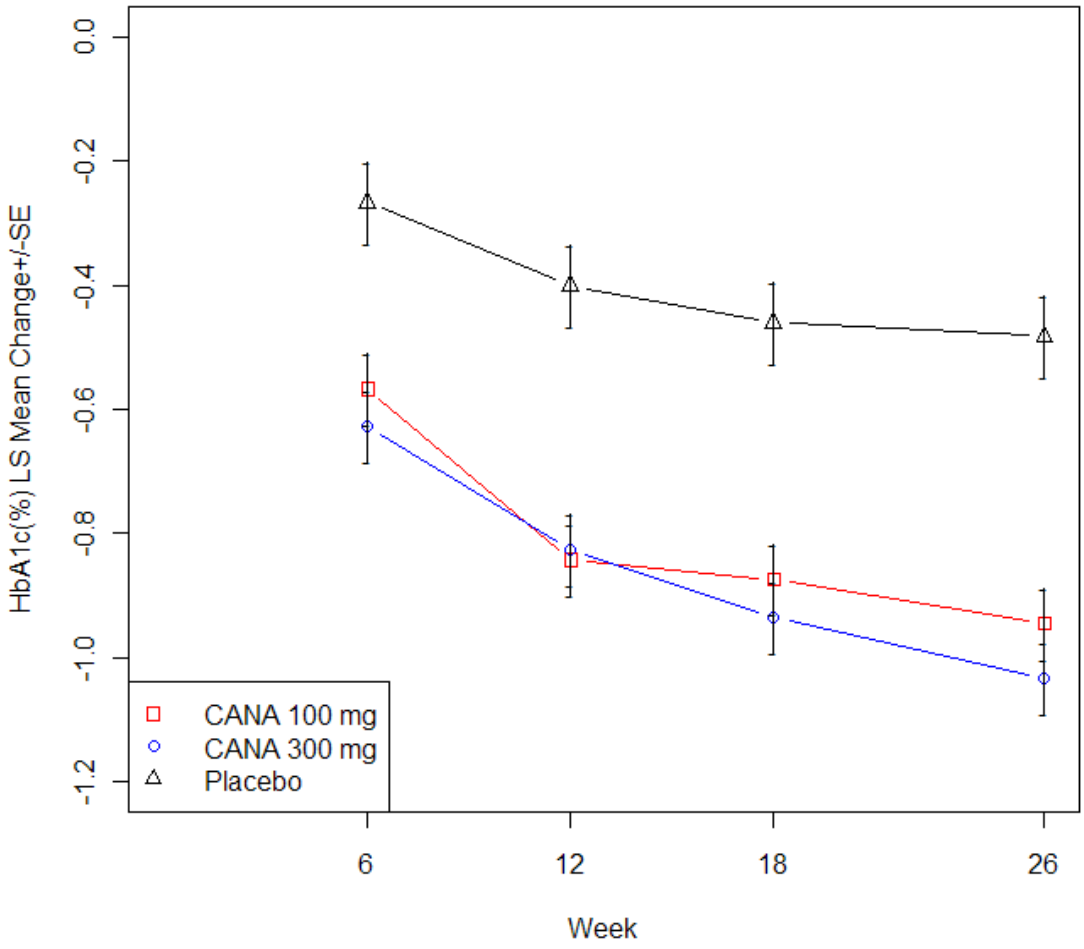
Appendix Figure 5.1. Baseline Levels of HbA1c in Different Treatment Groups.



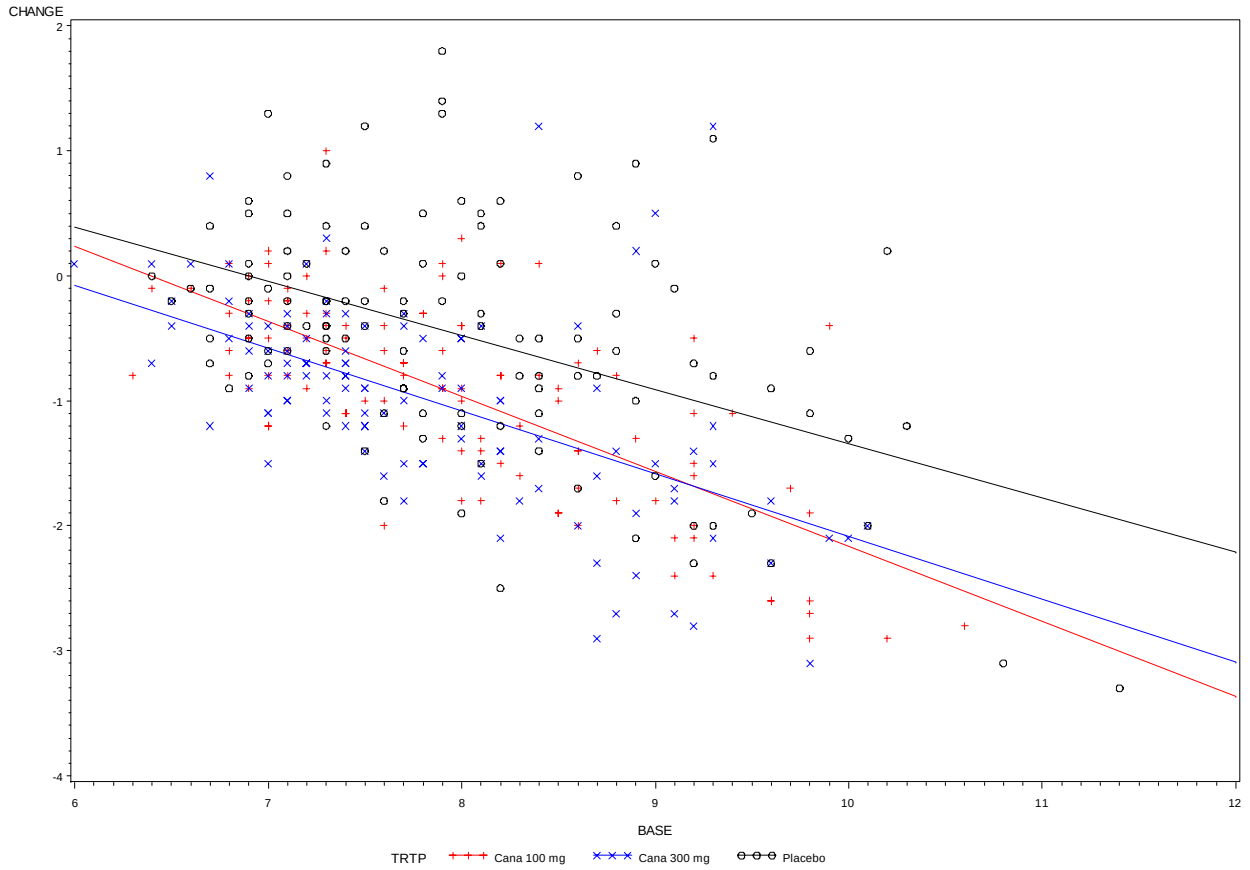
Appendix Figure 5.2. Comparing Time to Dropout during the Treatment Period between Treatment Groups (FAS population, DIA3012).



Appendix Figure 5.3. The Time Course of HbA1c Changes from Baseline in Study DIA3012 to Week 26.



Appendix Figure 5.4. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study DIA3012 at Week 26.




```
Regression equation :  CHANGE(TRTP:Cana 100 mg) =  3.847528 - 0.601253*BASE.
Regression equation :  CHANGE(TRTP:Cana 300 mg) =  2.94609 - 0.503316*BASE.
Regression equation :  CHANGE(TRTP:Placebo) =  2.985363 - 0.432962*BASE.
```

Appendix 6 DIA3015

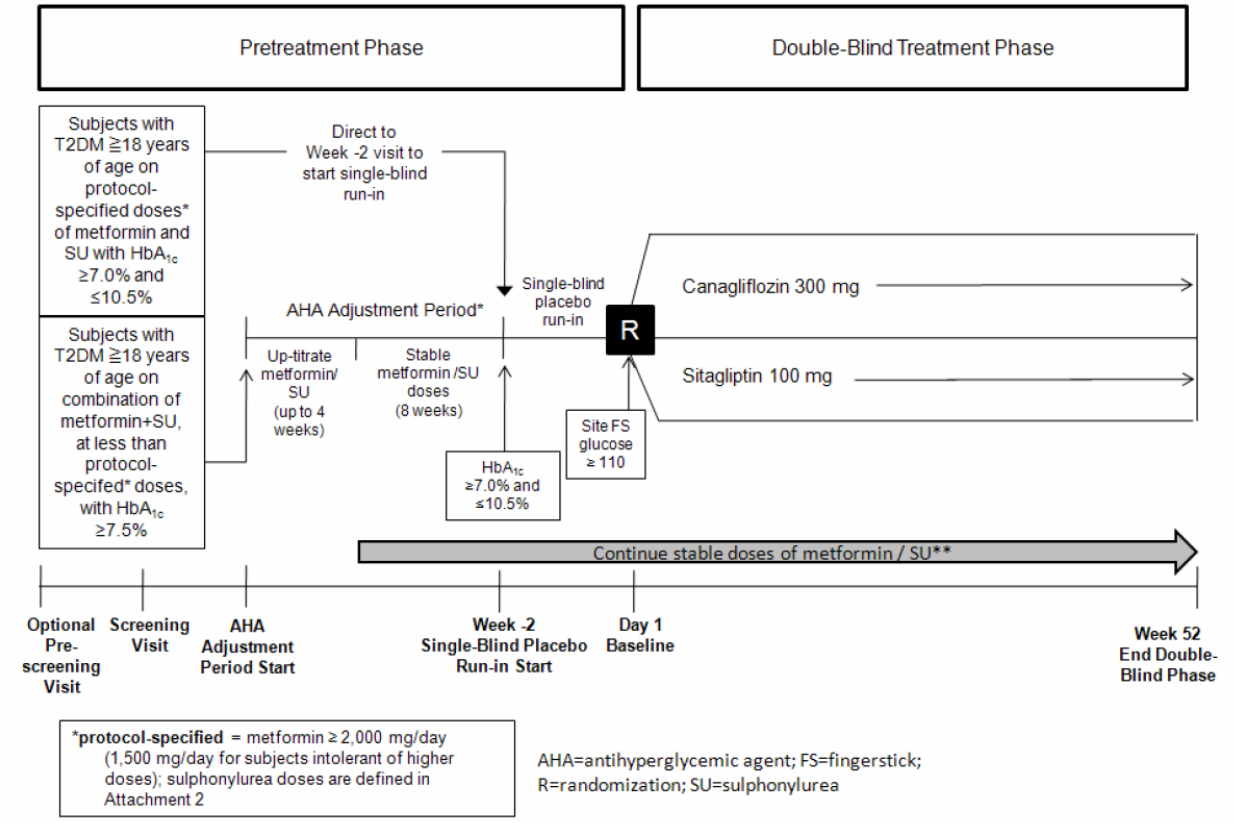
Appendix 6.1

The primary objectives included, in subjects with type 2 diabetes mellitus (T2DM) with inadequate glycemic control on combination therapy with metformin and a sulphonylurea (SU): (1) to assess the addition of treatment with canagliflozin 300 mg compared with sitagliptin 100 mg on glycosylated hemoglobin (HbA1c)-lowering efficacy after 52 weeks; and (2) to assess the safety and tolerability of canagliflozin.

The secondary efficacy endpoints involved in the hypothesis testing of canagliflozin group versus sitagliptin at Week 52 included percent change from baseline in body weight; change from baseline in FPG and SBP; percent change from baseline in fasting triglycerides, and in fasting HDL-C.

Sample Size Determination: The primary hypothesis for this study was to demonstrate that canagliflozin 300 mg was non inferior to sitagliptin in reducing HbA1c from baseline at Week 52. A non-inferiority margin of 0.3% has been selected for non-inferiority testing purposes. Assuming a difference between canagliflozin and sitagliptin of 0.0% and a common standard deviation (SD) of 1.0% with respect to change in HbA1c, and using a 2-sample, 1-sided t-test with a Type I error rate of 0.025, the sponsor estimated that 234 subjects per group would provide approximately 90% power to demonstrate the noninferiority of canagliflozin compared with sitagliptin. Assuming a discontinuation rate of 35% in 52 weeks, based on information from the development of a similar compound,

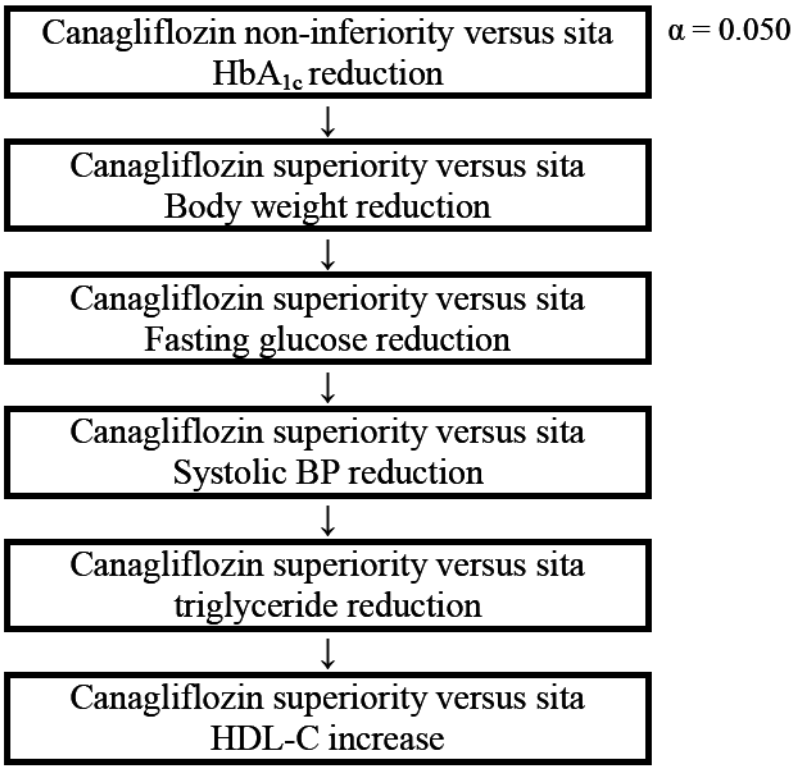
approximately 360 subjects per treatment group (a total of 720 subjects) would be randomly assigned in order to meet the sample size required for the per protocol analysis.
This study was a multi-national, multi-centre trial with a total of 140 study centers in 17 countries participated, 70 of which were in North America (57 in the United States [US], 13 in Canada); 21 of which were in Europea (8 in Poland, 3 in France, 3 in Germany, 2 in Netherlands, 2 in Denmark, 2 in Austria, 1 in Belgium)); 10 of which were in Central/South America (10 in Brazil), and 39 of which were in the rest of world (10 in Ukraine, 8 in South Korea, 6 in India, 5 in New Zealand, 4 in Israel, 4 in Malaysia, 2 in Singapore).
The sponsor's design diagram of the study NN304-1689 is shown in Figure 1.
Figure 1. Overview of the study design.



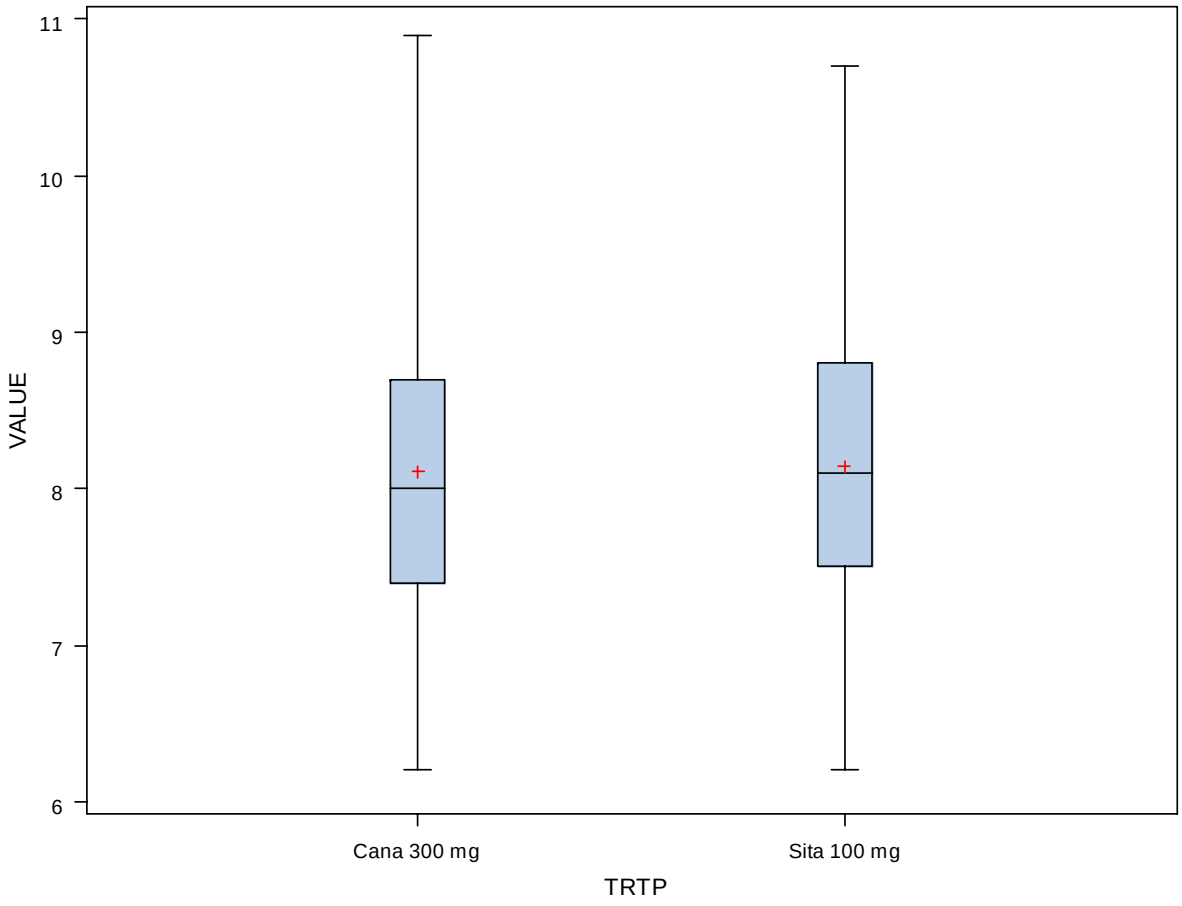
Statistical Methodologies
The efficacy objective was to determine whether the effect (change in HbA1c) of insulin detemir was at least as good of that achieved with NPH insulin at end of treatment period (non-inferiority).
The primary hypothesis was that canagliflozin 300 mg is non-inferior to sitagliptin 100 mg in reducing HbA1c from baseline to Week 52.
The sponsor's primary analysis was based on the mITT analysis set, an analysis of covariance (ANCOVA) model with treatment and stratification factors (whether or not HbA1c value at Week -2 or at the screening visit for subjects directly entering the AHA adjustment period . 9.0%; and whether or not a subject would participate in the FS-MMTT procedure) as fixed effects, and the baseline HbA1c value as covariate would be used for the primary efficacy analysis with LOCF approach for dealing missingness. The upper bound of the 95% CI of the treatment difference in LS means was used in the non-inferiority testing of the comparison with the non-inferiority margin of 0.3%.

According to the sponsor's plan for multiplicity adjustment, the hypotheses of primary efficacy endpoint and major secondary efficacy endpoints would be tested sequentially as illustrated in Figure 2. The type I error would be controlled at 0.05.

Figure 2. Multiplicity Adjustment

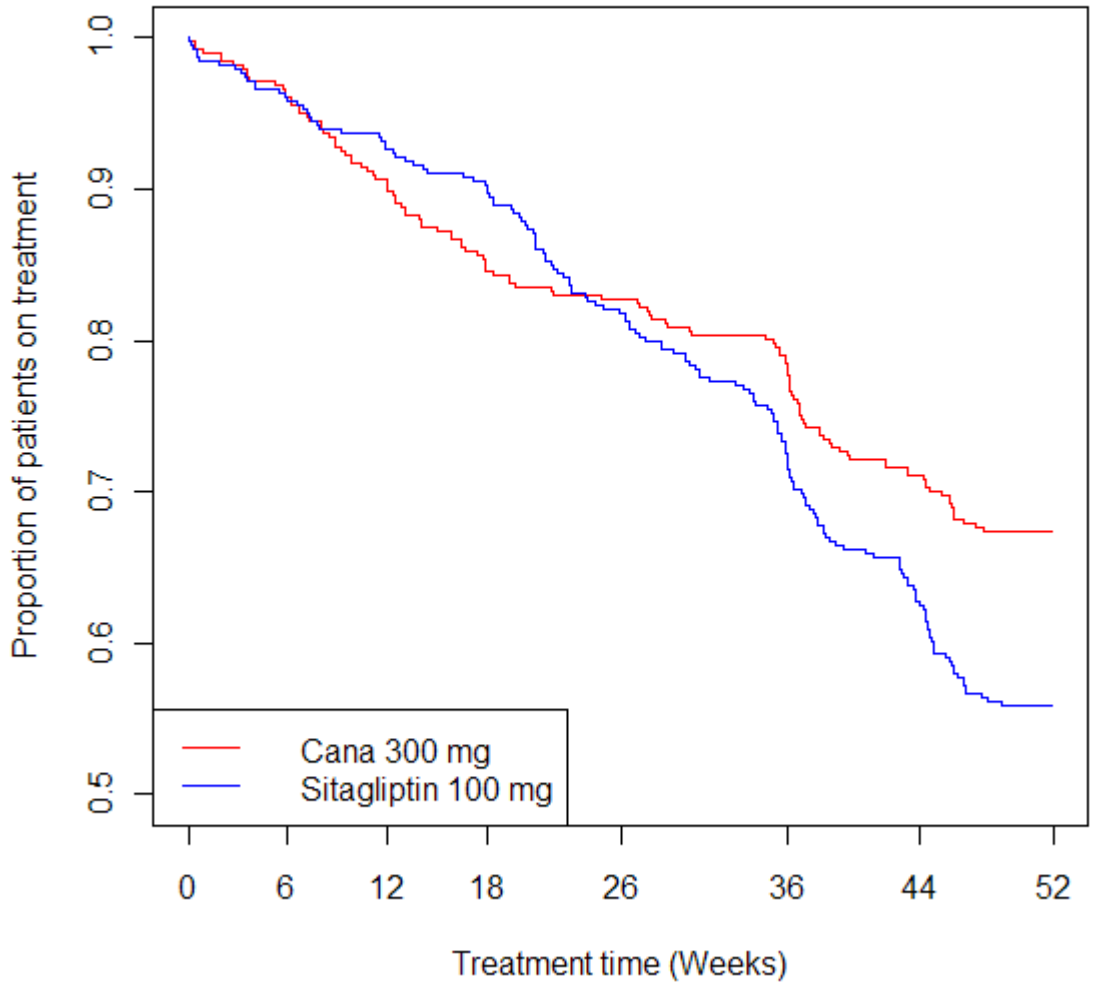


Appendix Figure 6.1. Baseline Levels of HbA1c in Different Treatment Groups (DIA3015).

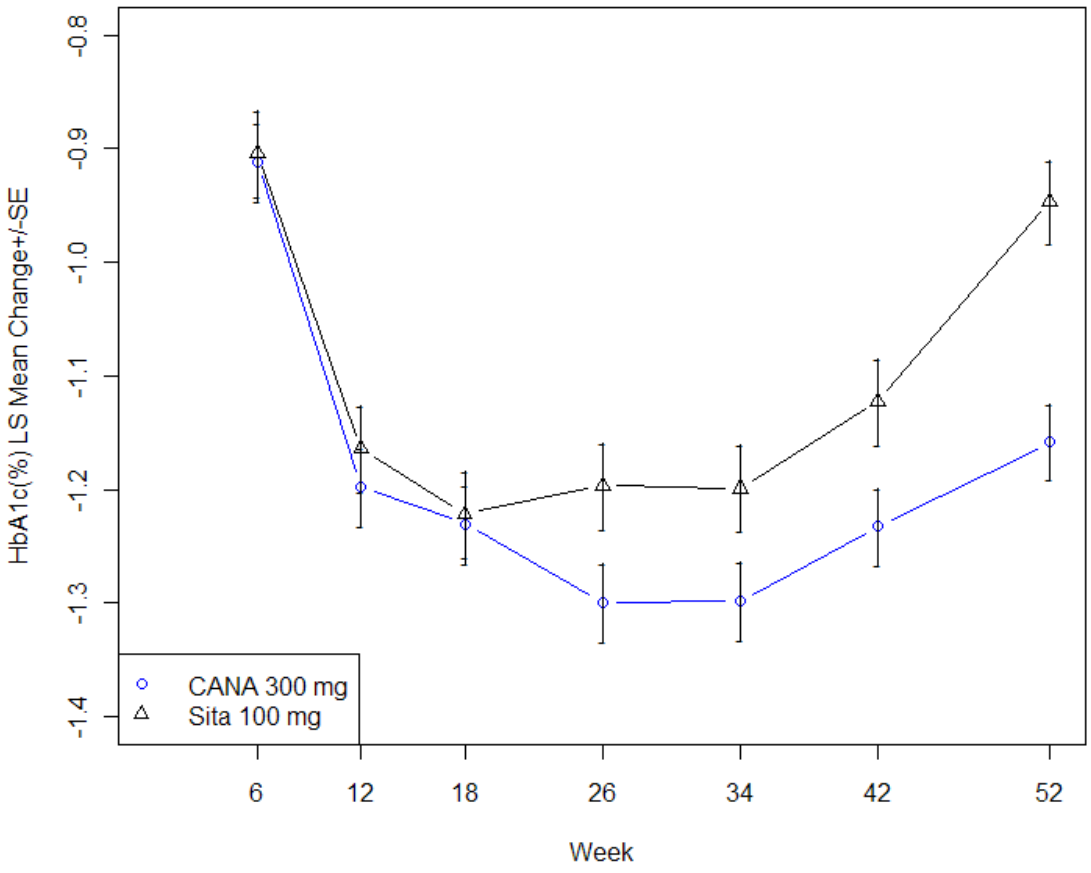


The time to dropout is plotted using Kaplan-Meier curves (Figure 3.2). The dropout rates were comparable across treatment groups in study 20, slightly higher in the glimepiride arm compared to the linagliptin arm.

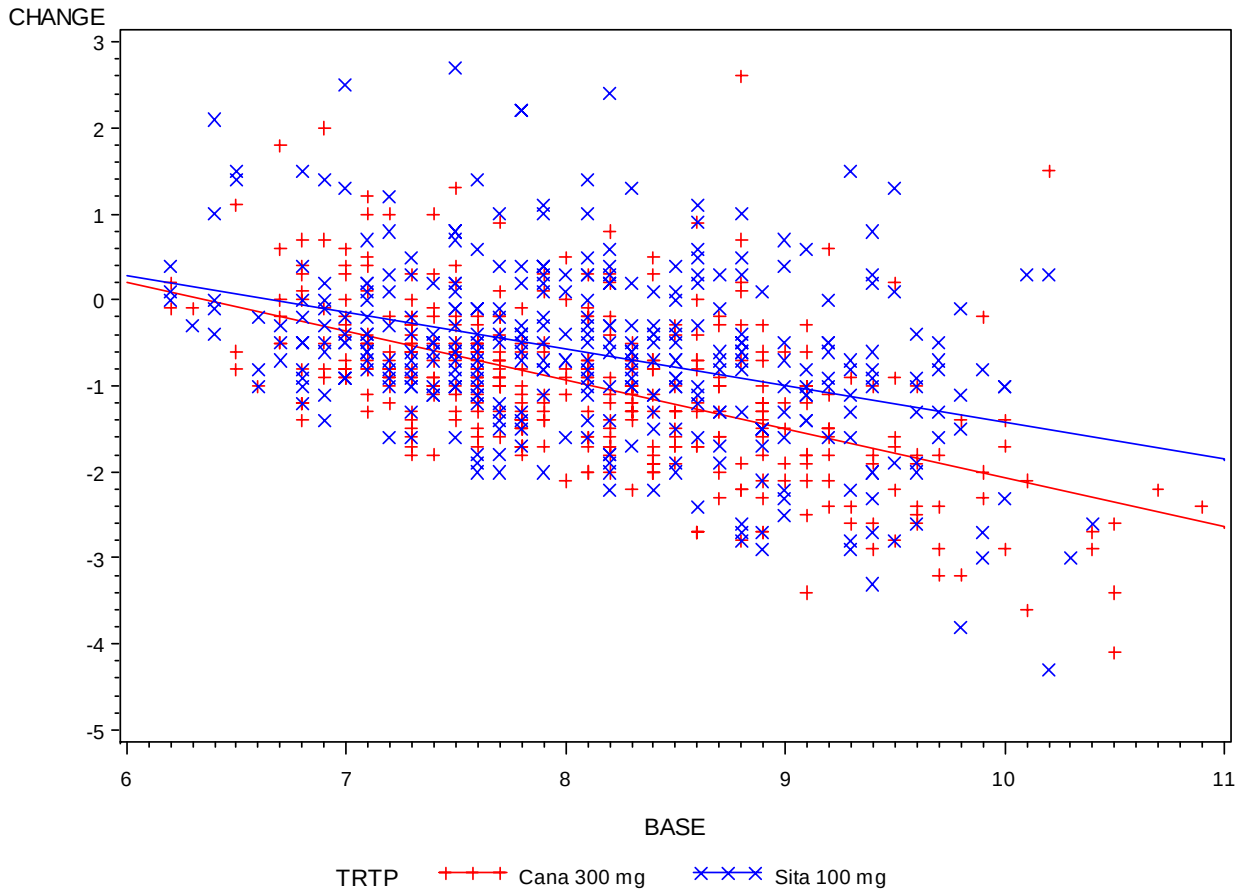
Appendix Figure 6.2. Comparing Time to Dropout during the Treatment Period between Treatment Groups (FAS population, DIA3015).



Appendix Figure 6.3. The Time Course of HbA1c Changes from Baseline in Study DIA3015 to Week 52.



Appendix Figure 6.4. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study DIA3015 at Week 52.




```
Regression equation :  CHANGE(TRTP:Cana 300 mg) =  3.635984 - 0.570972*BASE.
Regression equation :  CHANGE(TRTP:Sita 100 mg) =  2.818627 - 0.424044*BASE.
```

Appendix 7 DIA3010

Appendix 7.1

The primary objectives were to assess the effect of canagliflozin relative to placebo on glycosylated hemoglobin (HbA1c) after 26 weeks of treatment and to assess the safety and tolerability of canagliflozin.

Eligible subjects were required to meet all of the following key acceptance criteria at screening or at the indicated visit: (1) man or woman ≥55 and ≤ 80 years of age with T2DM (women must be at least 3 years postmenopausal), (2) have a HbA1c ≥7.0% to ≤ 10.0% at (pre)screening (3) have a body mass index (BMI) of 20 to 40 kg/m^2, inclusive, at screening.

The total duration of the full study was to be approximately 110 weeks for each subject, depending on the length of the pretreatment phase (including the optional prescreening visit 1 week prior to the screening visit), the 2-week

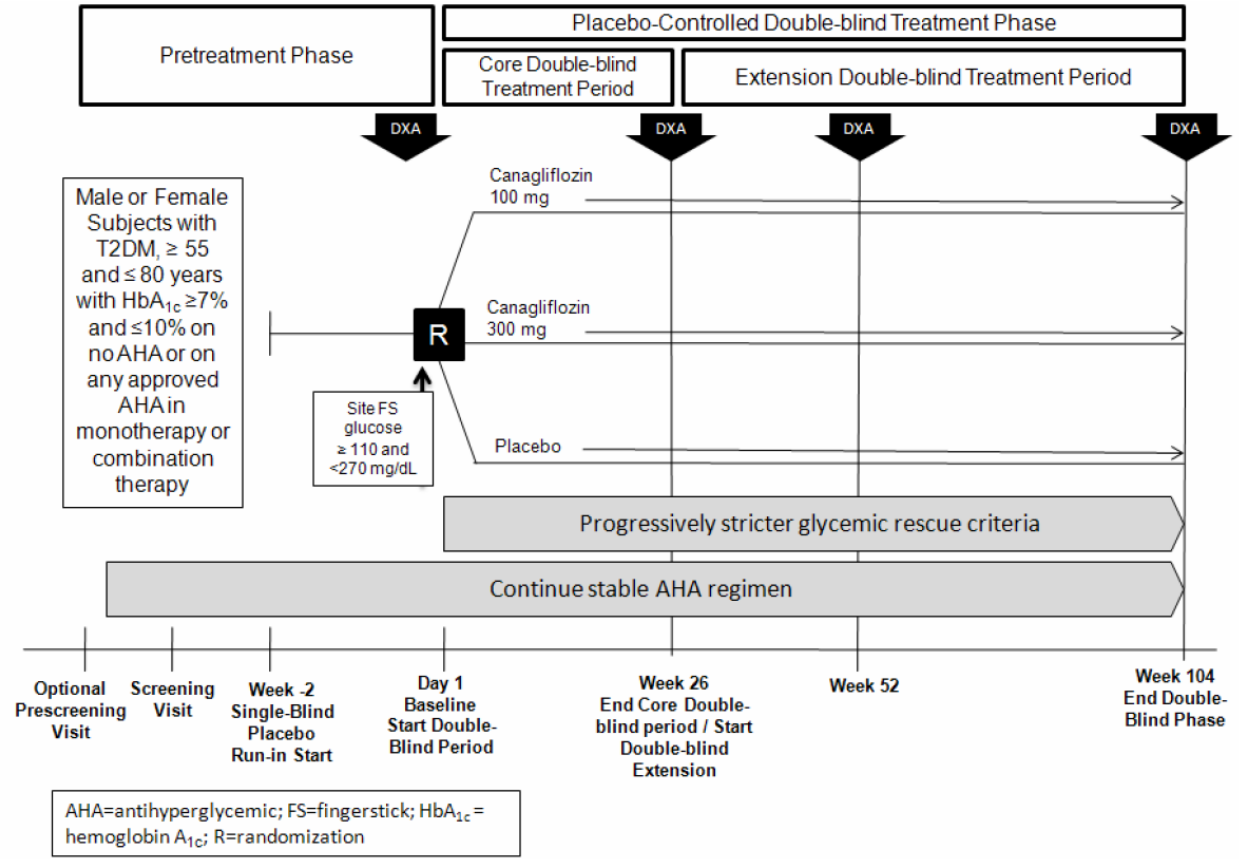
single-blind placebo run-in period (Week -2 visit to the baseline visit on Day 1), the 26-week double-blind placebo-controlled core period, the 78-week double-blind, placebo-controlled extension phase, and a 30-day post-treatment phase for follow-up contact (ie, after the last dose of study drug).

Secondary endpoints included the change from baseline to Week 26 in FPG, SBP, percent change from baseline in body weight, fat mass (FM) (by DXA), fasting triglycerides, and fasting HDL-C, and proportion of subjects with HbA1c <7.0%.

Sample size calculations of this trial were based on the primary hypothesis that addition of canagliflozin 300 mg was superior to addition of placebo in reducing HbA1c from baseline at Week 26. Assuming a group difference of 0.5% between the canagliflozin and placebo group, and a common standard deviation of 1.0% with respect to the change in HbA1c and using a 2-sample, 2-sided t-test with type I error rate of 0.05, the sponsor estimated that 86 subjects per treatment group were required to achieve 90% power to demonstrate the superiority of canagliflozin over placebo. To provide a larger clinical experience, with more detailed safety and tolerability information in older subjects (including a more precise assessment of bone density), 240 subjects were randomized per treatment group. Assuming a drop-out rate of 35%, it was anticipated that at least 156 subjects per treatment group would complete 26 weeks of treatment.

This study was a multi-national, multi-centre trial with a total of 90 study centers in 17 countries participated, including 46 centers in North America (38 in the United States, 8 in Canada), 23 centers in Europea (2 in France, 6 in the United Kingdom, 6 in Poland, 2 in Romania, 4 in Spain, 1 in Switzerland, 1 in Greece, 1 in Sweden), 5 centers in Central/South America (5 in Colombia), and 16 centers in the rest of the world (3 in Australia, 4 in New Zealand, 3 in India, 1 in South Africa, 1 in Hong Kong, 4 in Ukraine). Body composition substudy: 38 study centers in 10 countries.

Figure 1. Overview of the study design.



Statistical Methodologies

The efficacy objective was to assess the effect of the addition of treatment with canagliflozin relative to placebo on HbA1c after 26 weeks of treatment.

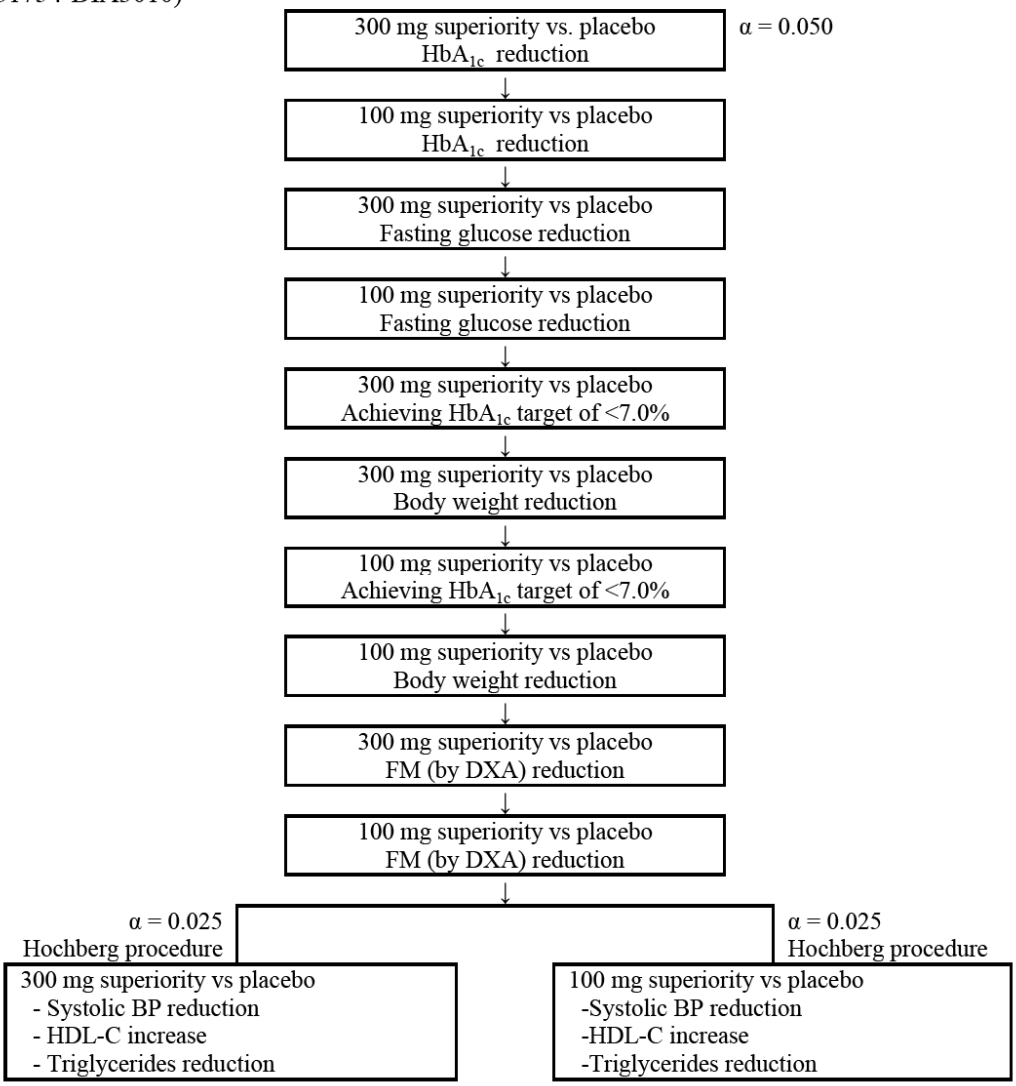
The hypotheses of superiority of canagliflozin (300 mg, and then 100 mg) to placebo were tested on the reduction of HbA1c from baseline relative to placebo.

The sponsor's primary analysis was based on the mITT analysis set, an analysis of covariance (ANCOVA) model with treatment and stratification factors (T-score of lumbar spine <-1.5 or =-1.5, and on or not on PPARγ) as fixed effects, and the corresponding baseline HbA1c value as a covariate would be used for the primary efficacy analysis.

According to the sponsor's plan for multiplicity adjustment, the hypotheses of primary efficacy endpoint and major secondary efficacy endpoints would be tested sequentially as illustrated in Figure 3.2.2. The type I error would be controlled at 0.05.

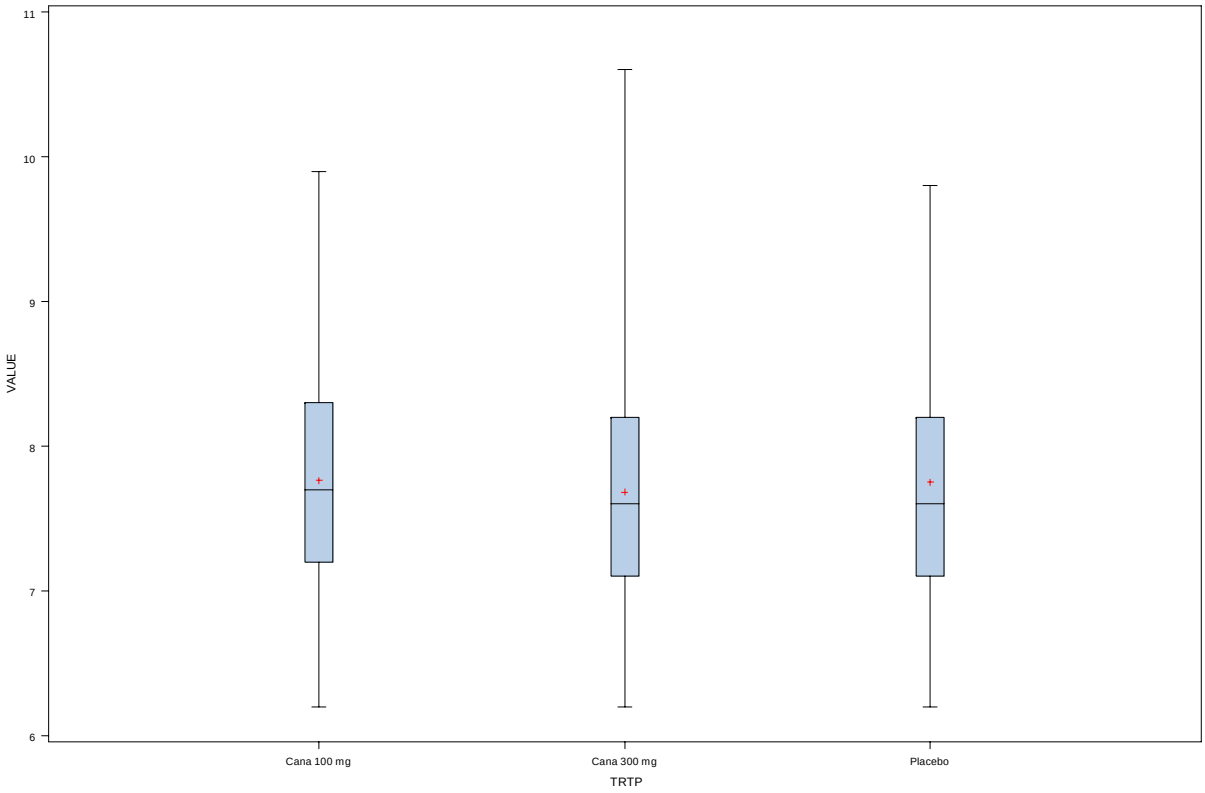
Figure 2. Multiplicity Adjustment

(Study 28431754-DIA3010)

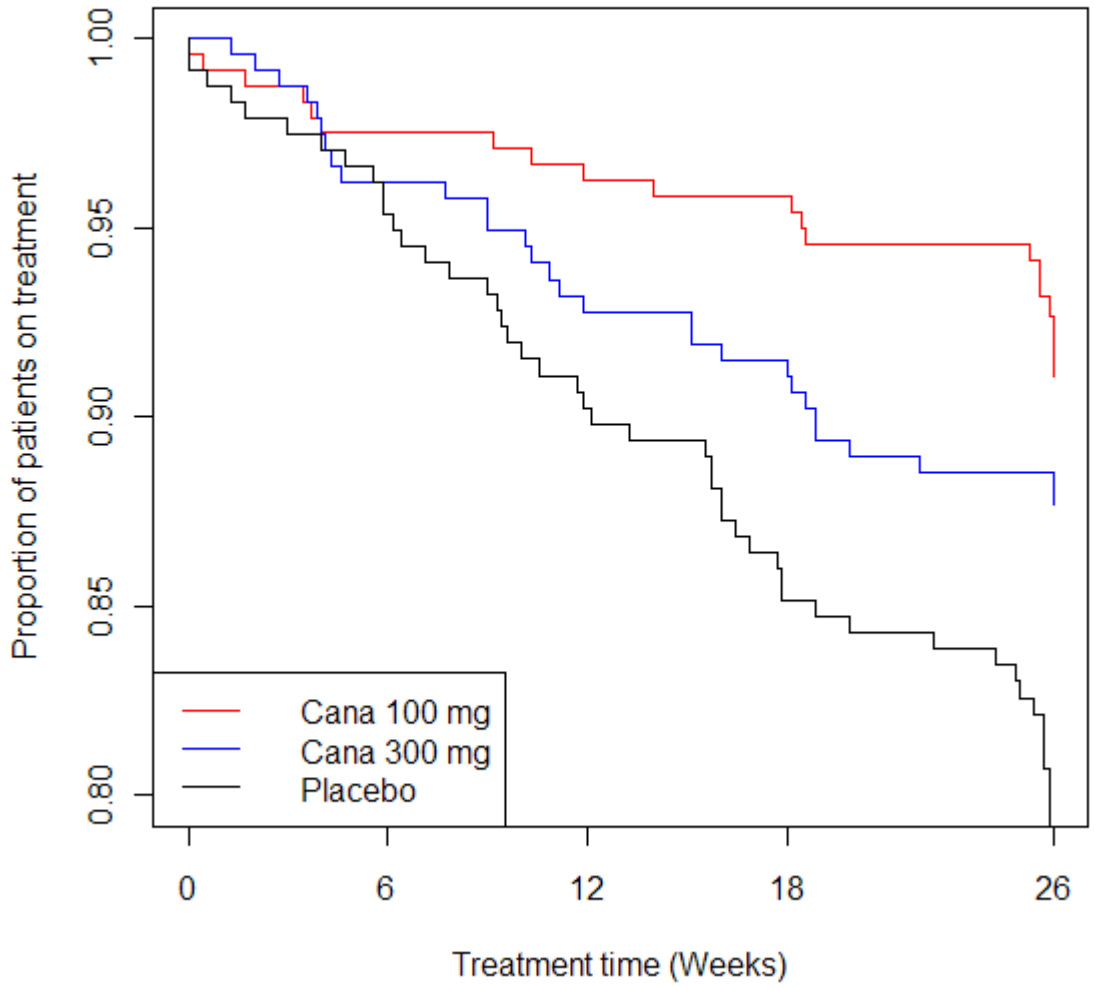


Key: FM=fat mass; DXA= dual-energy X-ray absorptiometry; HbA_{1c}=glycosylated hemoglobin; HDL-C=high-density lipoprotein cholesterol

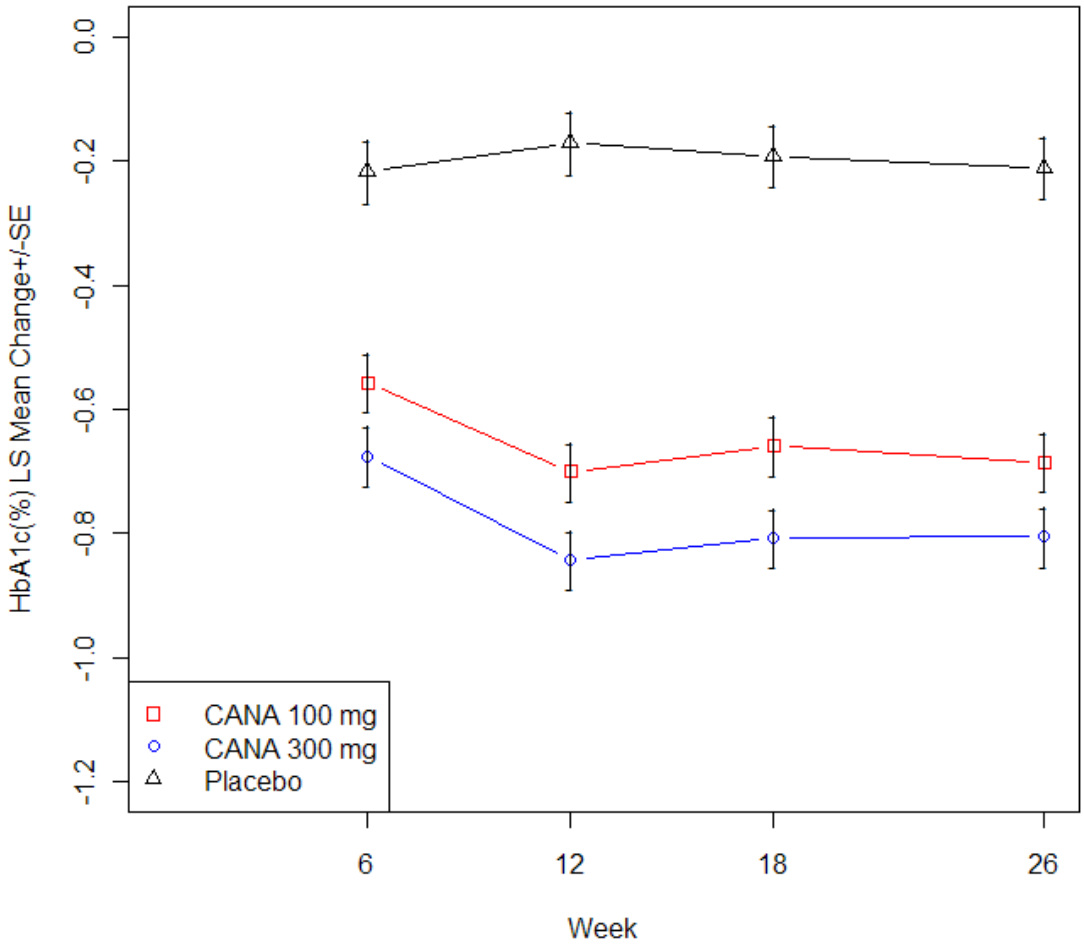
Appendix Figure 7.1. Baseline Levels of HbA1c in Different Treatment Groups in Study DIA3010.



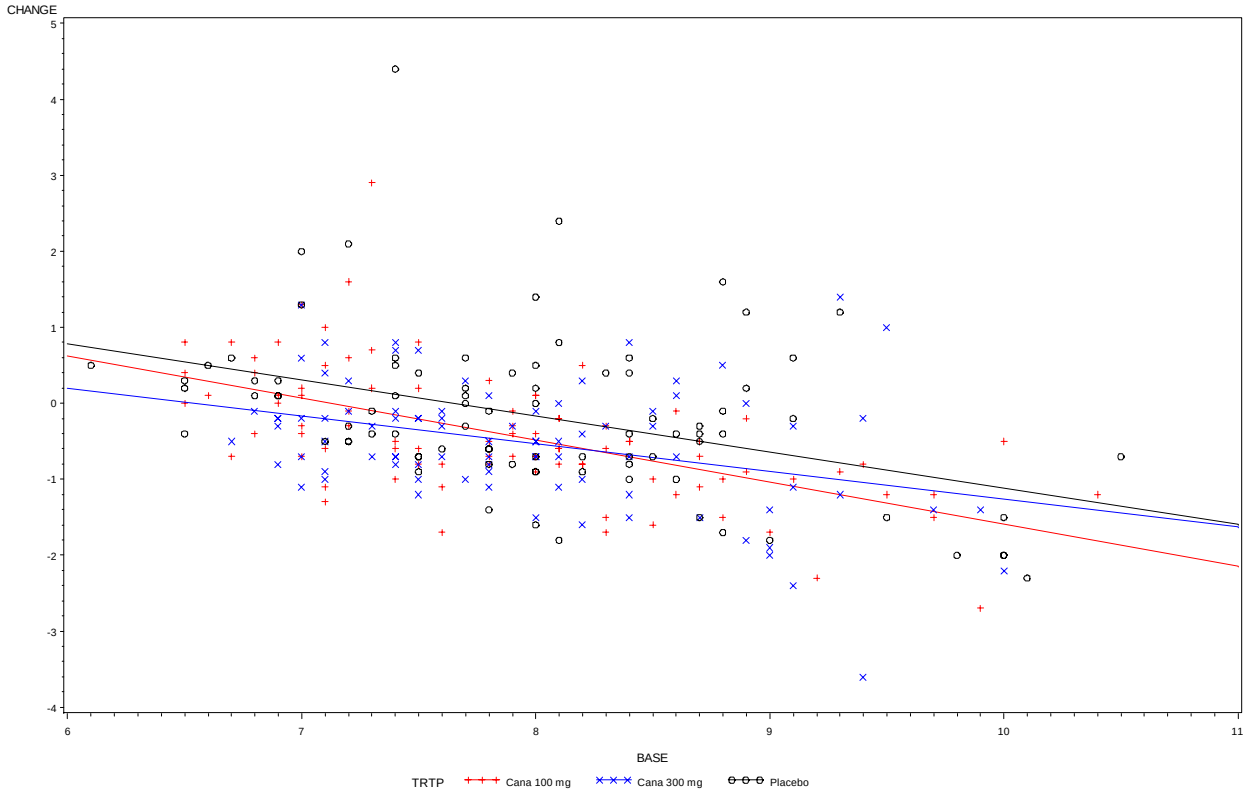
Appendix Figure 7.2. Comparing Time to Dropout during the Treatment Period between Treatment Groups (FAS population, DIA3010).



Appendix Figure 7.3. The Time course of HbA1c Changes from Baseline in Study DIA3010 to Week 26.



Appendix Figure 7.4. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study DIA3010 at Week 26.




```
Regression equation :  CHANGE(TRTP:Cana 100 mg) =  3.212026 - 0.49767*BASE.
Regression equation :  CHANGE(TRTP:Cana 300 mg) =  2.545638 - 0.428446*BASE.
Regression equation :  CHANGE(TRTP:Placebo) =  2.950119 - 0.398359*BASE.
```

Appendix 8 DIA3004

Appendix 8.1

The primary efficacy objective was to assess the effect of the addition of canagliflozin relative to the addition of placebo on glycosylated hemoglobin (HbA1c) after 26 weeks of treatment in adult subjects (.25 years of age) with type 2 diabetes mellitus (T2DM) with inadequate glycemic control on their current diabetes treatment regimen and with moderate renal insufficiency.

Eligible subjects were required to meet all of the following key acceptance criteria at screening or at the indicated visit: (1) adult man or woman ≥25 years of age with T2DM; (2) have a HbA1c ≥7.0% to ≤10.5% at (pre)screening and Week -2 visits; (3) have moderate renal impairment defined as eGFR values≥30 and <50 mL/min/1.73m^2 at the Week -2 visit, together with generally stable renal function; (4) either not on AHA therapy at screening or on a stable regimen of AHA in monotherapy or combination therapy being used in accordance with local prescribing information for patients with T2DM and moderate renal impairment; and (5) have a FPG ≤270 mg/dL (15 mmol/L) at Week -2 visit.

Key secondary end points included changes from baseline to Week 26 in FPG, systolic and diastolic blood pressure, and the proportion of subjects achieving HbA1c <7.0% at Week 26. Additional efficacy endpoints included the percent change from baseline to Week 26 in body weight and in fasting plasma lipids (LDL-C, HDL-C, total

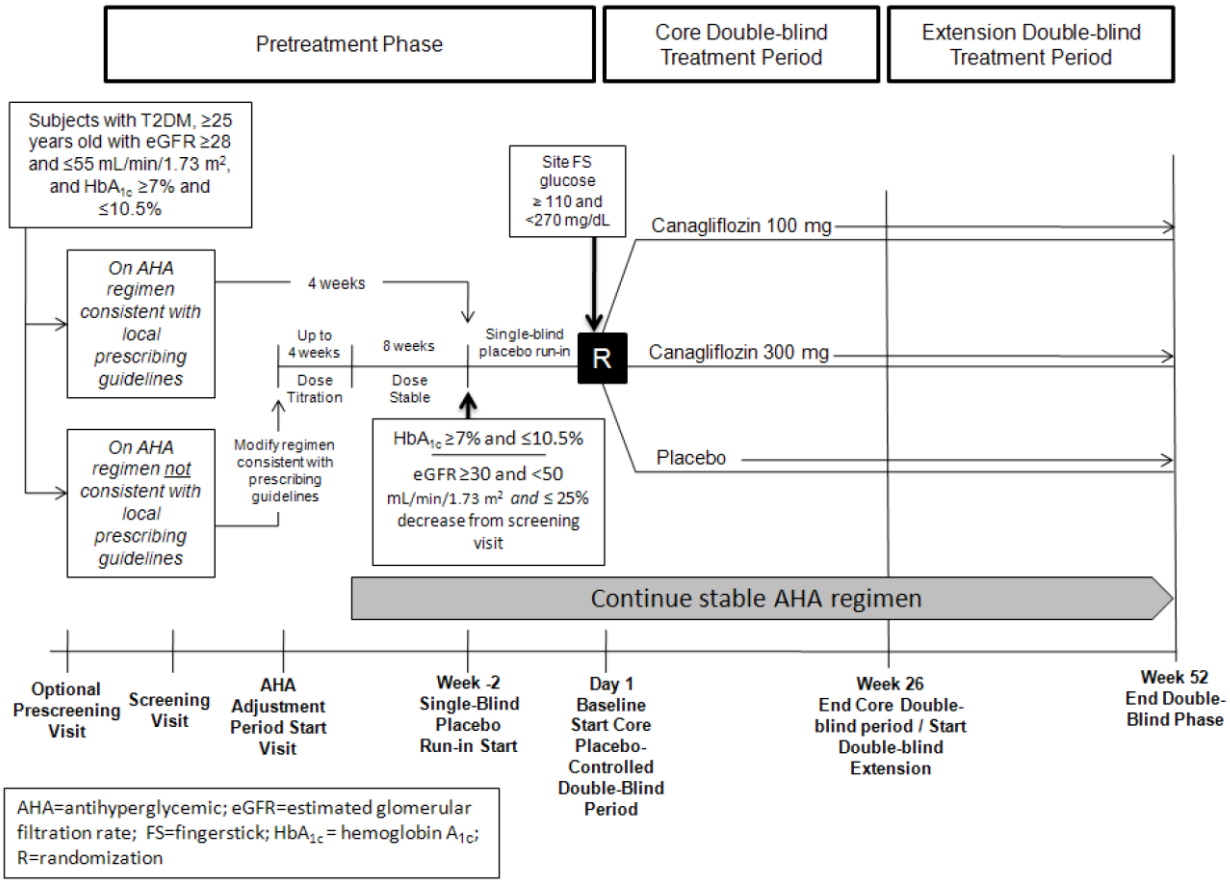
cholesterol, and triglycerides). Time to initiation and proportion of subjects requiring glycemic rescue therapy at Week 26 were secondary efficacy endpoints, as was the proportion of subjects achieving HbA1c <6.5% at Week 26.

Sample Size Determination: The primary hypothesis tested was that addition of canagliflozin was superior to addition of placebo as measured by the change in HbA1c from baseline at Week 26. Assuming a group difference of 0.5% between the canagliflozin and placebo group, and a common standard deviation of 0.85% with respect to the change in HbA1c, and using a 2-sample, 2-sided t-test with type I error rate of 0.05, the sponsor estimated that 61 randomized subjects per treatment group were required to achieve at least 90% power to demonstrate the superiority of canagliflozin over placebo. To provide additional safety information, the study included a modestly greater study sample size of 80 subjects randomized per treatment group (total randomized population of 240 subjects).

This study was a multi-national, multi-centre trial with a total of 89 study centers in 19 countries, including 28 centers in North America (19 in the United States, 8 in Canada, 1 in Mexico), 30 centers in Europea (6 in Belgium, 6 in France, 5 in Germany, 1 in Italy, 3 in Latvia, 3 in Poland, 3 in Romania, 3 in Spain), 3 centers in Central/South America (3 in Brazil), and 28 centers in the rest of world (3 in Australia, 3 in India, 5 in Malaysia, 8 in Russia, 4 in New Zealand, 3 in South Africa, 2 in South Korea)

The sponsor's design diagram of the study NN304-1689 is shown in Figure 1.

Figure 1. Overview of the study design.



Statistical Methodologies
The efficacy objective was to assess the effect of canagliflozin relative to placebo on HbA1c after 26 weeks of treatment.

The primary hypothesis was: After 26 weeks of treatment, canagliflozin 300 mg reduces relative to placebo.

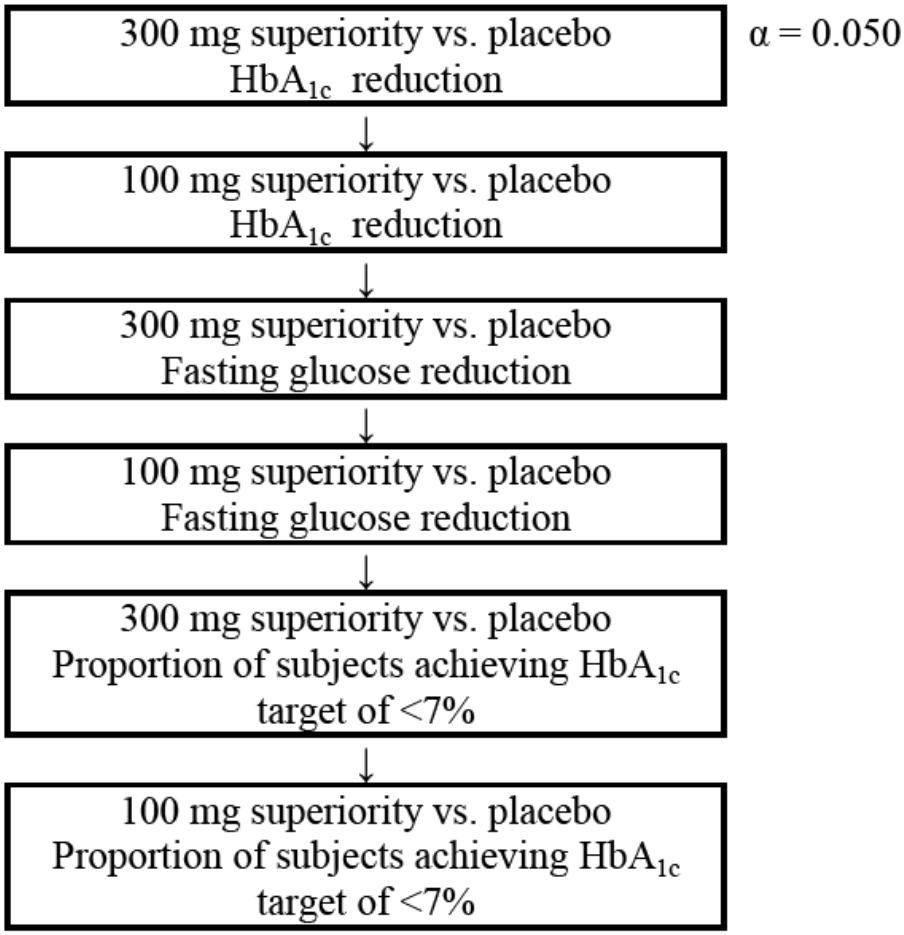
The secondary hypotheses were: After 26 weeks of treatment, canagliflozin 100 mg reduces HbA1c relative to placebo.
After 26 weeks, canagliflozin 300 mg or both doses, relative to placebo:

- Reduce FPG .
- Provide a greater proportion of subjects with target glycemic control (HbA1c <7%)

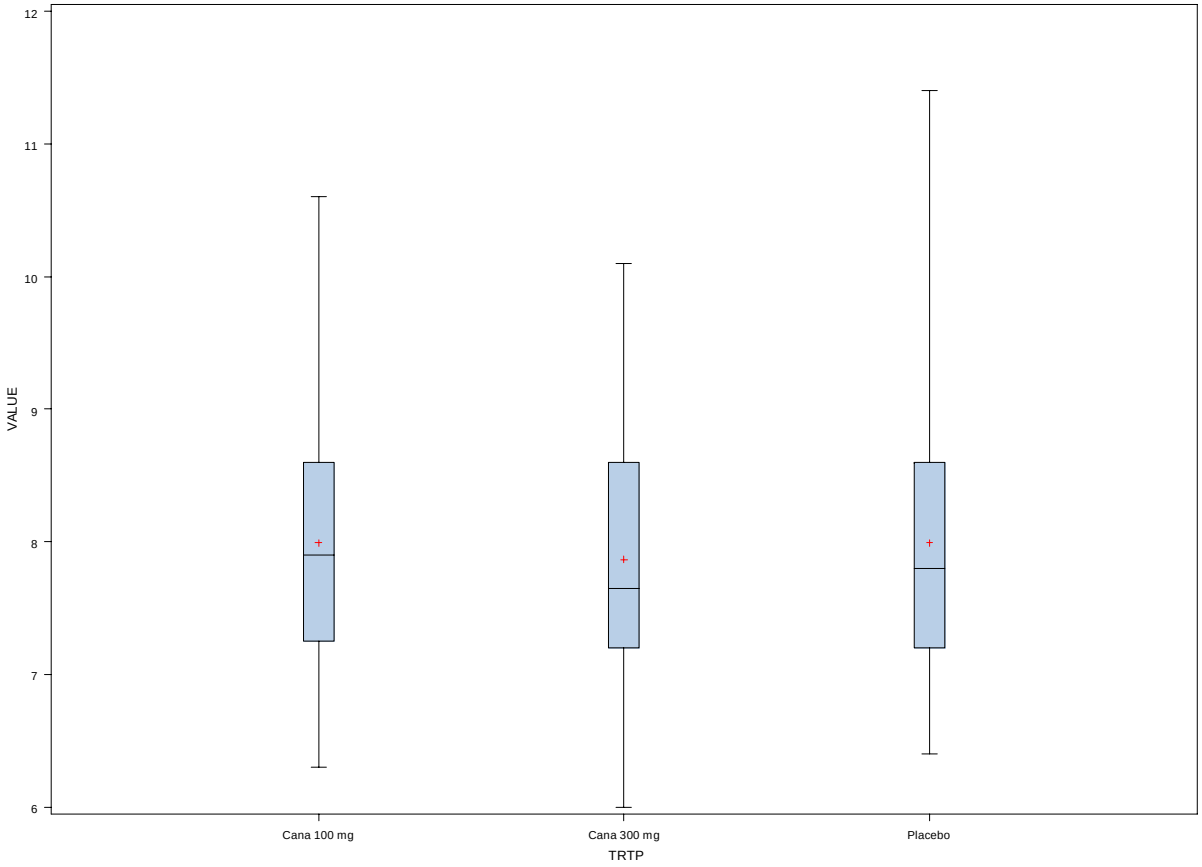
The sponsor's primary analysis was based on the mITT analysis set, an analysis of covariance (ANCOVA) model would be used with treatment and stratification factors (presence or absence of ASCVD, and whether or not the subject was having AHA adjustment period) as fixed effects, and the corresponding baseline HbA1c and baseline eGFR values as covariates would be used for the primary efficacy analysis.

According to the sponsor's plan for multiplicity adjustment, the hypotheses of primary efficacy endpoint and major secondary efficacy endpoints would be tested sequentially as illustrated in Figure 3.2.2. The type I error would be controlled at 0.05.

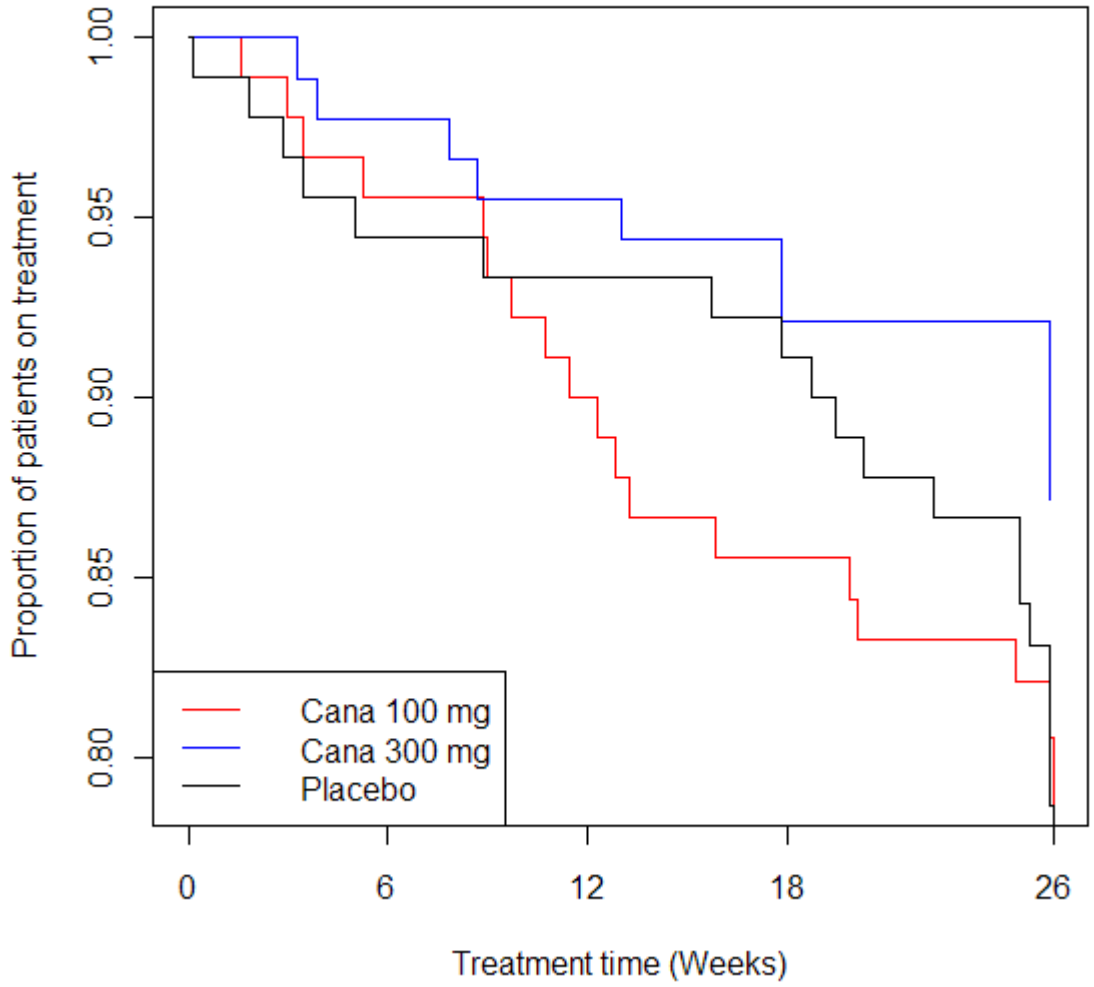
Figure 2. Multiplicity Adjustment



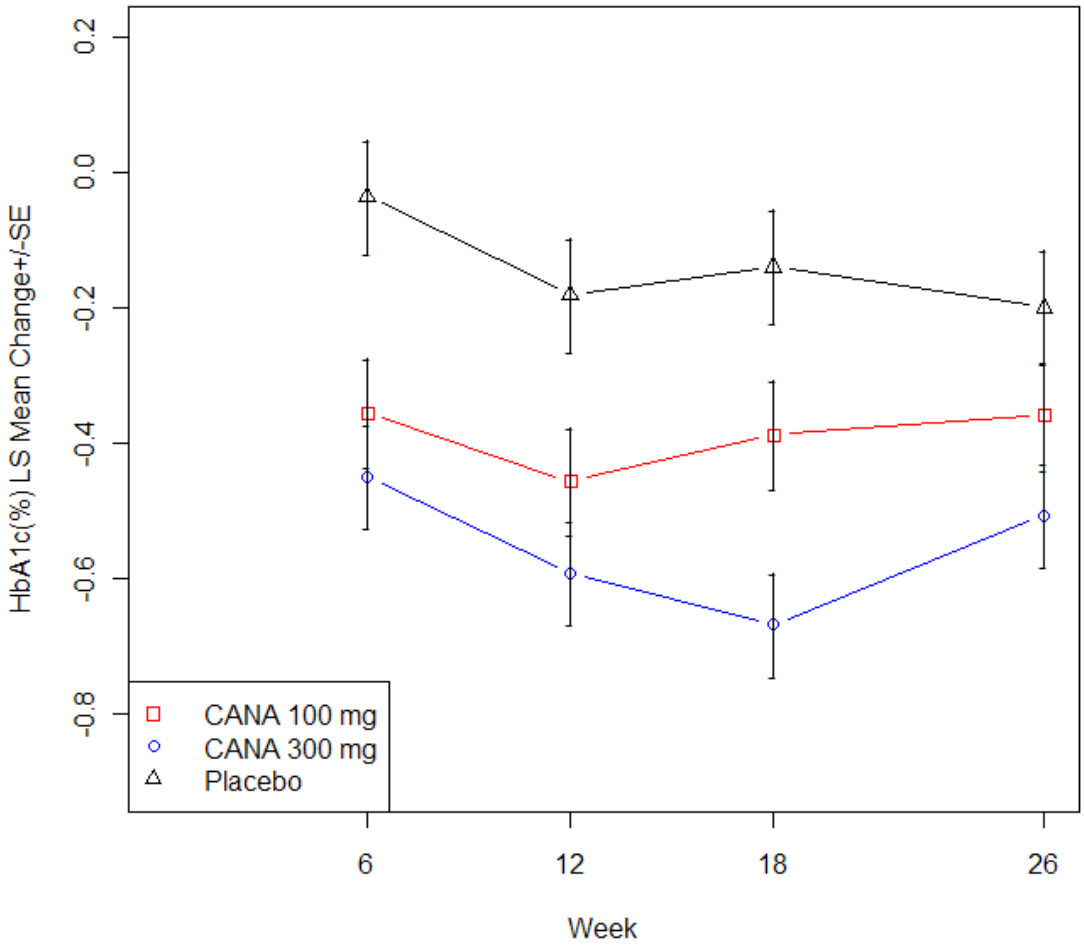
Appendix Figure 8.1. Baseline Levels of HbA1c in Different Treatment Groups (DIA3004).



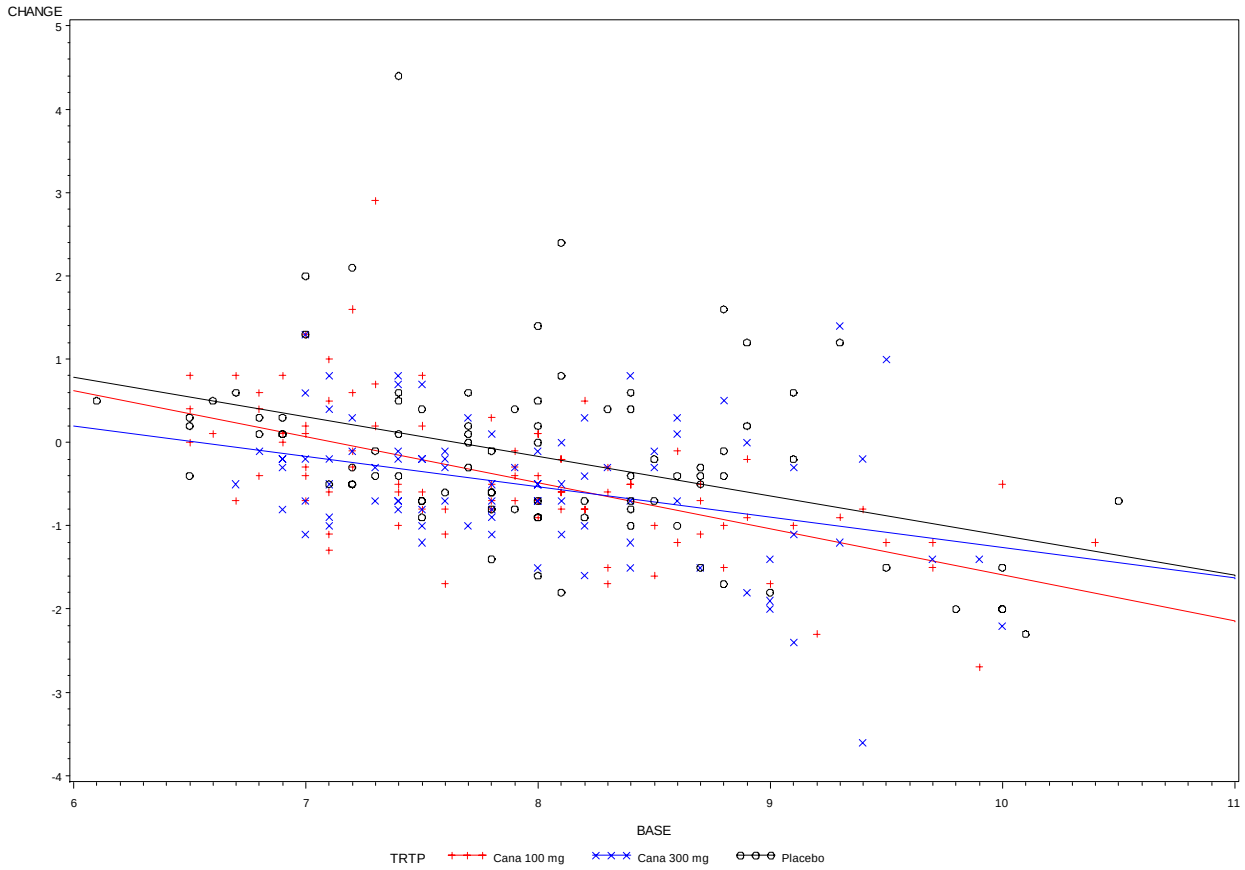
Appendix Figure 8.2. Comparing Time to Dropout during the Treatment Period between Treatment Groups (FAS population) in Study 3004.



Appendix Figure 8.3. The Time Course Plot of HbA1c Changes from Baseline in Study DIA3004 to Week 26.



Appendix Figure 8.4. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study DIA3004 at Week 26.




```
Regression equation :  CHANGE(TRTP:Cana 100 mg) =  3.948994 - 0.55363*BASE.
Regression equation :  CHANGE(TRTP:Cana 300 mg) =  2.382458 - 0.364512*BASE.
Regression equation :  CHANGE(TRTP:Placebo) =  3.635931 - 0.475087*BASE.
```

Appendix 9 DIA3008 Sulphonylurea Substudy

Appendix 9.1

The primary efficacy objective of the SU substudy was to assess the glycosylated hemoglobin (HbA1c)-lowering efficacy (change from baseline in HbA1c) of canagliflozin relative to placebo after 18 weeks of treatment.

Eligible subjects were man or woman ≥30 years of age with a diagnosis of T2DM with HbA1c level ≥7.0% to ≤10.5% and history or high risk of CV disease (as defined in sponsor's protocol) at screening and be either (1) not currently on AHA therapy or (2) on AHA monotherapy or combination therapy with any approved agent: eg, SU, metformin, pioglitazone, alpha-glucosidase inhibitor, GLP-1 analogue, DPP-4 inhibitor, or insulin.

Subjects who participated in CANVAS had balanced (1:1:1) randomization to each of the 3 treatment groups (ie, canagliflozin 100 mg, canagliflozin 300 mg, or placebo) within the following predefined strata based upon AHA medications(s) that the subject was receiving at the run-in visit and continued into the double-blind treatment phase. The subjects who participated in the SU substudy were randomized into Stratum 4 (except as noted below).

- Stratum 1: insulin monotherapy =20 units per day, on stable doses at least 10 weeks before the run-in visit
- Stratum 2: insulin =20 units per day plus metformin, on stable doses at least 10 weeks before the run-in visit, and no other background AHA therapy
- Stratum 3: insulin =20 units per day plus any other AHA(s) on stable dose(s) for at least 10 weeks before the run-in visit
- Stratum 4: SU monotherapy (at doses specified in Attachment 1 of the protocol), on stable doses at least 10 weeks before the run-in visit
- Stratum 5: pioglitazone =30 mg/day plus metformin =2,000 mg/day (or at least 1,500 mg/day for subjects who have a history of not being able to tolerate higher metformin doses) and no other background AHA therapy, on stable doses at least 10 weeks before the run-in visit
- Stratum 6: subjects not in one of the above AHA subgroups

In order to provide the most robust and comprehensive assessment of the effect of canagliflozin added to background SU monotherapy, the the sponsor defined the following 3 populations for the purpose of analysis:

- Population 1: Subjects on protocol-specified doses of SU monotherapy regardless of the stratification used for randomization.
- Population 2: All subjects on SU monotherapy regardless of SU monotherapy dose and of the stratification used for randomization.
- Population 3: All subjects randomized to Stratum 4, regardless of whether the subject was taking SU monotherapy.

With respect to the primary efficacy endpoint and major secondary endpoint analyses, Population 1 serves as the primary population, and Population 2 and 3 are to support the assessment of efficacy in Population 1.

Major secondary end points (at Week 18 LOCF comparing to placeb0) included body weight, FPG, systolic blood pressure, proportion of subjects with HbA1c <7%, fasting HDL-C and triglycerides after 18 weeks of treatment.

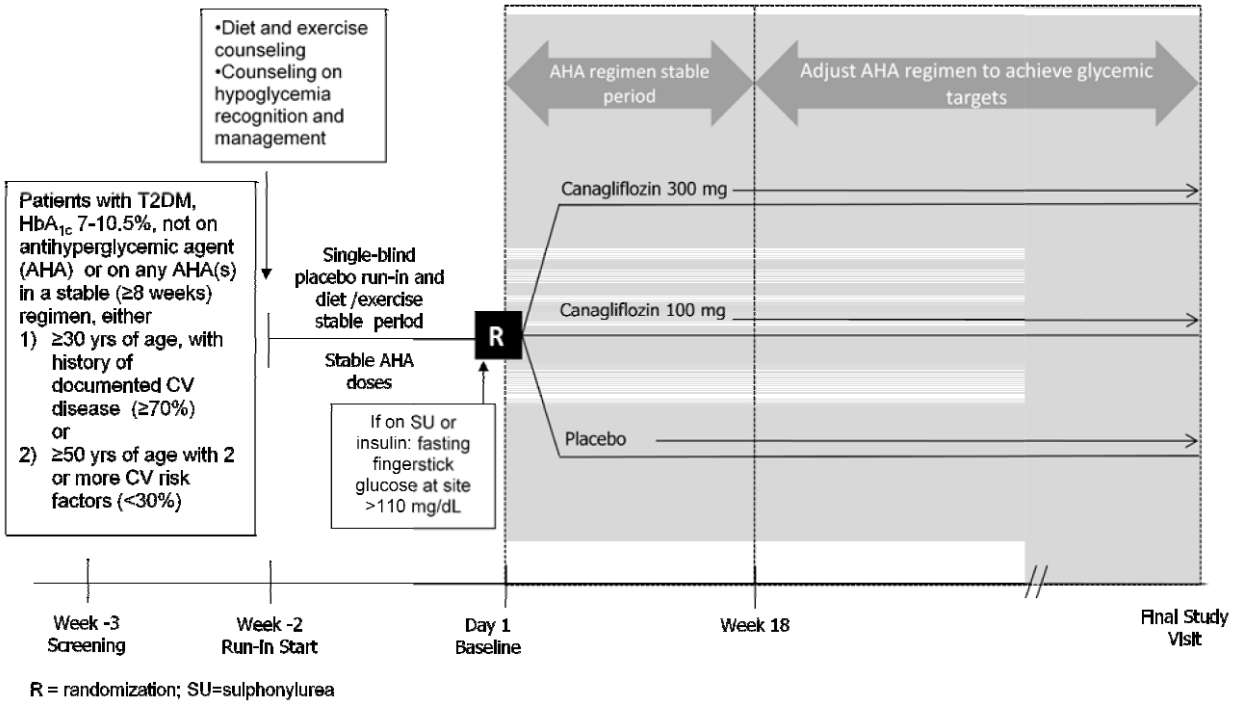
Sample size calculations of this trial were based on the primary endpoint HbA1c at end of trial. Assuming a group difference of 0.50% and a common SD of 0.75% with respect to change in HbA1c, and using a 2-sample, 2-sided t-test with Type I error rate of 0.05, it was estimated that 150 randomized subjects (50 subjects in each of the 3 treatment groups) would provide 90% power.

This study was a multi-national, multi-centre trial with (for the subjects in Population 1) a total of 80 centers in 18 countries (16 in North America [4 in Canada, 1 in Mexico, and 11 in the United States], 17 in Europea [1 in Belgium, 1 in Czech Republic, 1 in Germany, 3 in Hungary, 3 in Netherlands, 3 in Norway, 3 in Poland, and 2 in Spain], 3 in Central/South America [3 in Argentina] and 44 in the rest of world (ROW) [2 in Australia, 15 in India, 1 in Malaysia, 2 in New Zealand, 16 in Russian Federation, and 8 in Ukraine]). Overall the distribution of subjects enrolled across geographic regions was 17% (n=22) to centers in North America, 14% (n=18) to centers in Europe, 2% (n=3) to centers in Central/South America, and 66% (n=84) to centers in ROW.

This reviewer reviewed the data of Population 1, the primary population for analysis.

The sponsor's design diagram of the study NN304-1689 is shown in Figure 1.

Figure 1. Overview of the study design.



R = randomization; SU=sulphonylurea

Statistical Methodologies

The efficacy objective was to determine whether the effect (change in HbA1c) of insulin detemir was at least as good of that achieved with NPH insulin at end of treatment period (non-inferiority).

The primary hypothesis was "In subjects with T2DM, with inadequate glycemic control, who have a history of or a high risk of CV disease, after 18 weeks of treatment, canagliflozin provides a greater improvement in HbA1c relative to placebo (change from baseline in HbA1c)."

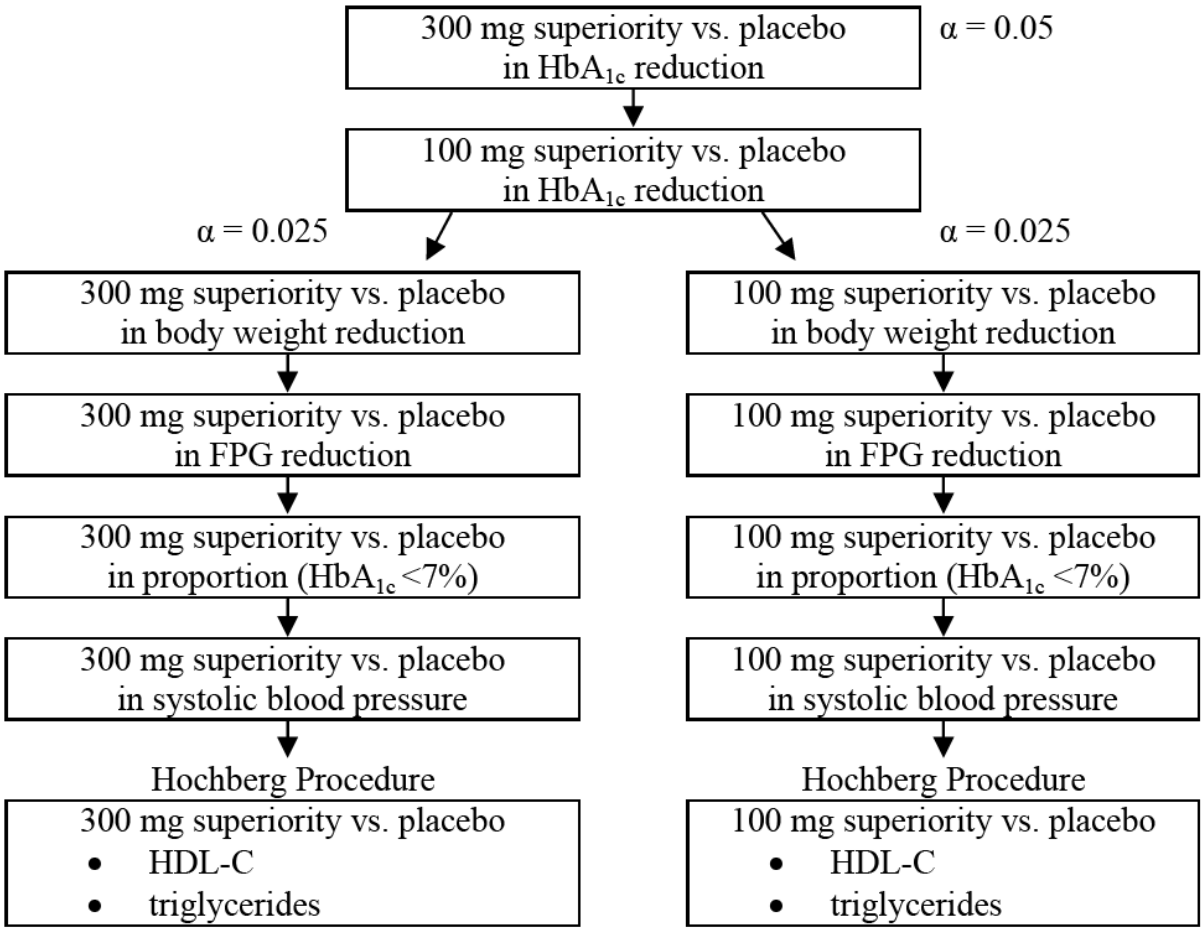
The secondary substudy hypotheses were after 18 weeks, in subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, relative to placebo, canagliflozin:

- reduces body weight
- reduces FPG
- leads to a greater proportion of subjects achieving HbA1c <7.0%
- reduces systolic blood pressure (SBP)
- increases HDL-C concentrations
- lowers triglyceride concentrations

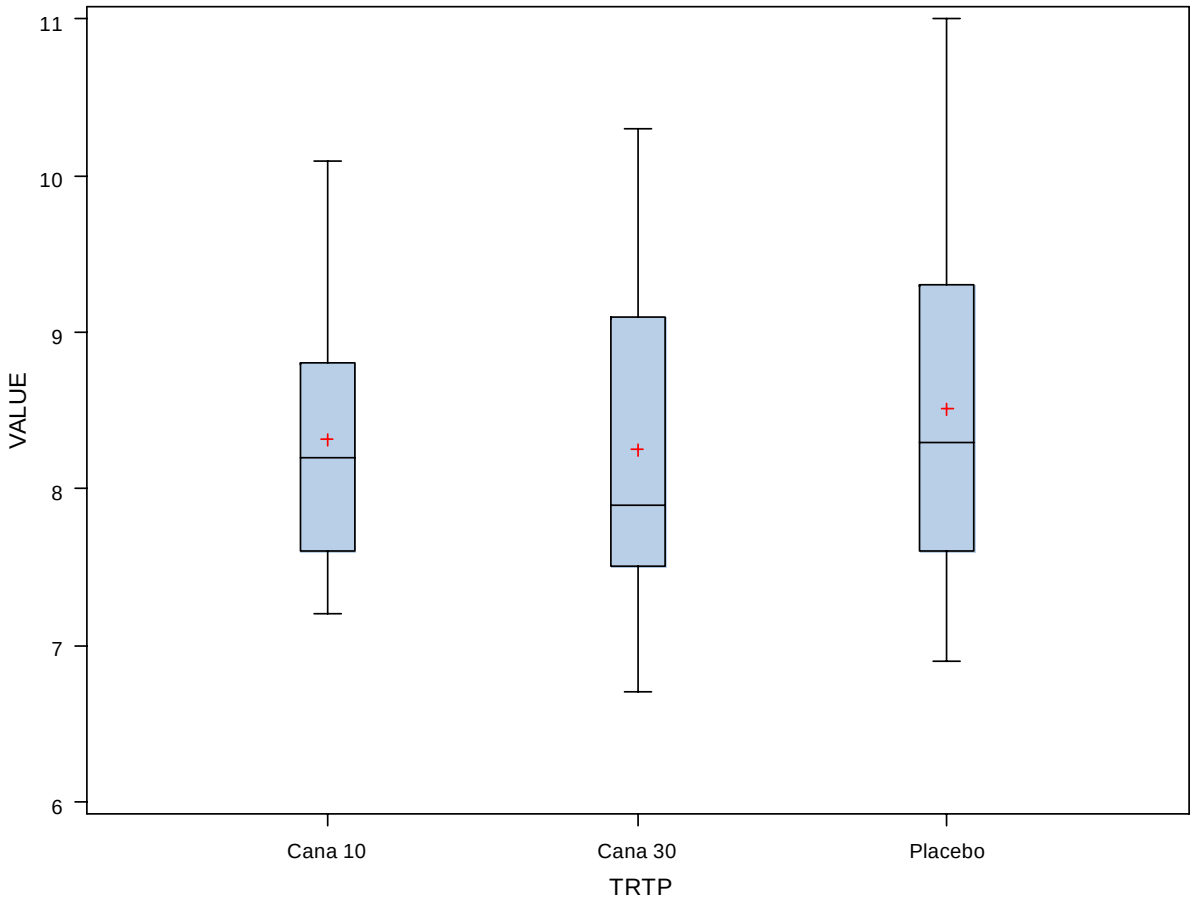
The sponsor's primary analysis was based on the mITT analysis set, an analysis of covariance (ANCOVA) model including treatment as a fixed effect and the corresponding baseline HbA1c value as a covariate would be used for the primary efficacy analysis.

According to the sponsor's plan for multiplicity adjustment, the hypotheses of primary efficacy endpoint and major secondary efficacy endpoints would be tested sequentially as illustrated in Figure 3.2.2 (for Population 1). The type I error would be controlled at 0.05.

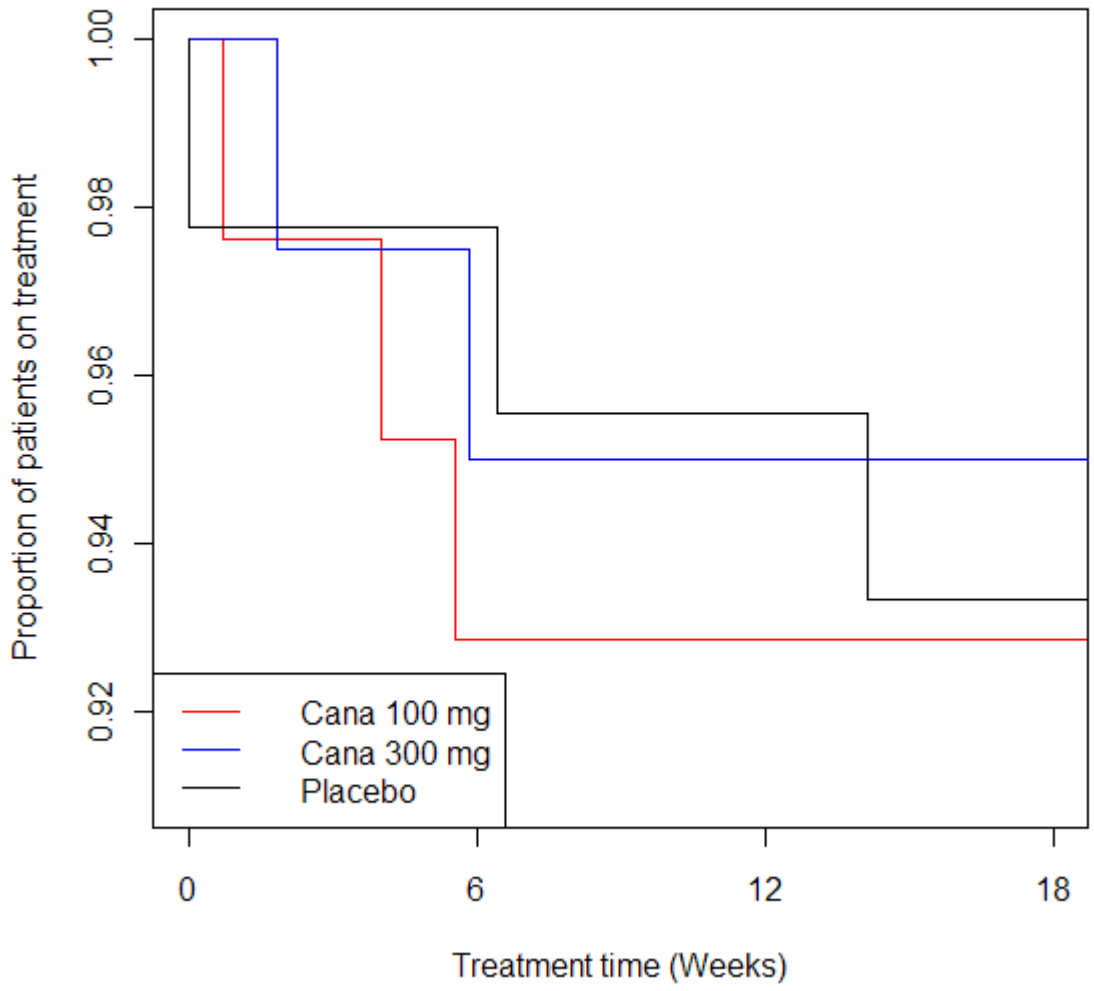
Figure 2. Multiplicity Adjustment, DIA3008 SU Substudy Population 1



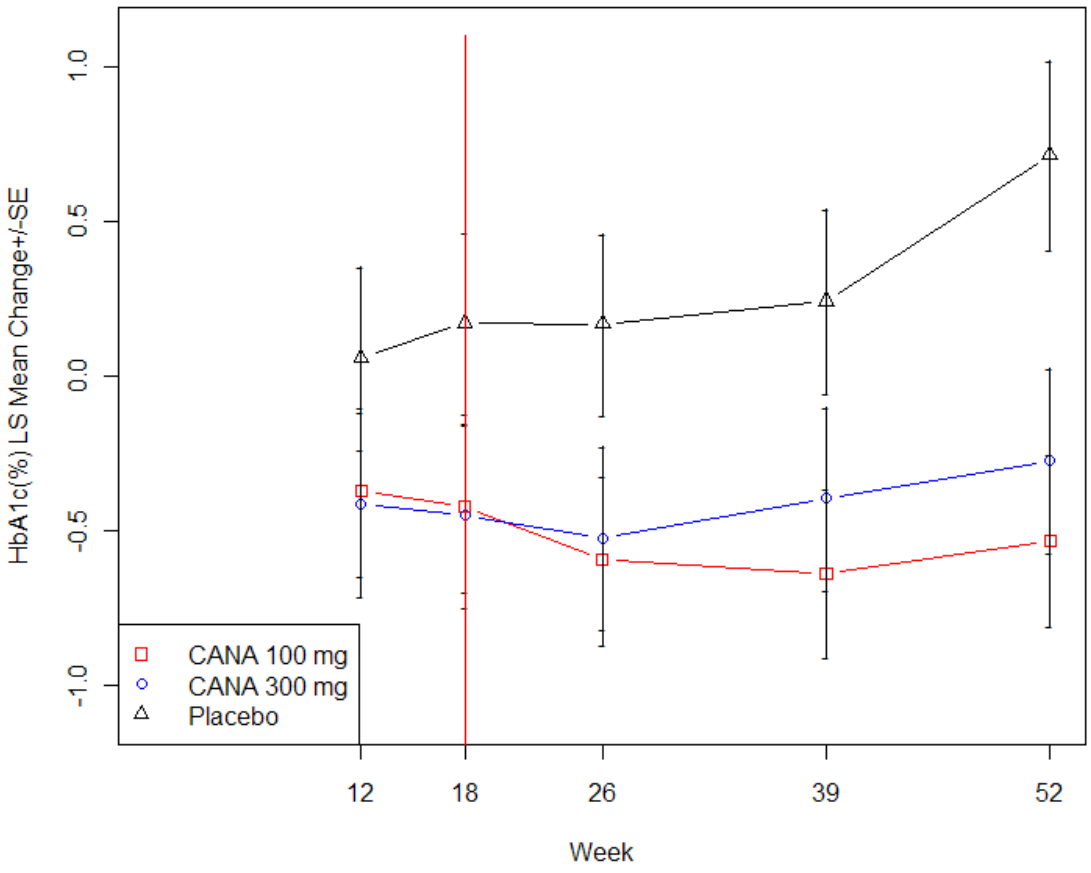
Appendix Figure 9.1. Baseline Levels of HbA1c in Different Treatment Groups in Study DIA3008 (SU, pop1).



Appendix Figure 9.2. Comparing Time to Dropout during the Treatment Period between Treatment Groups (FAS population) in Study DIA3008 (SU, pop1).

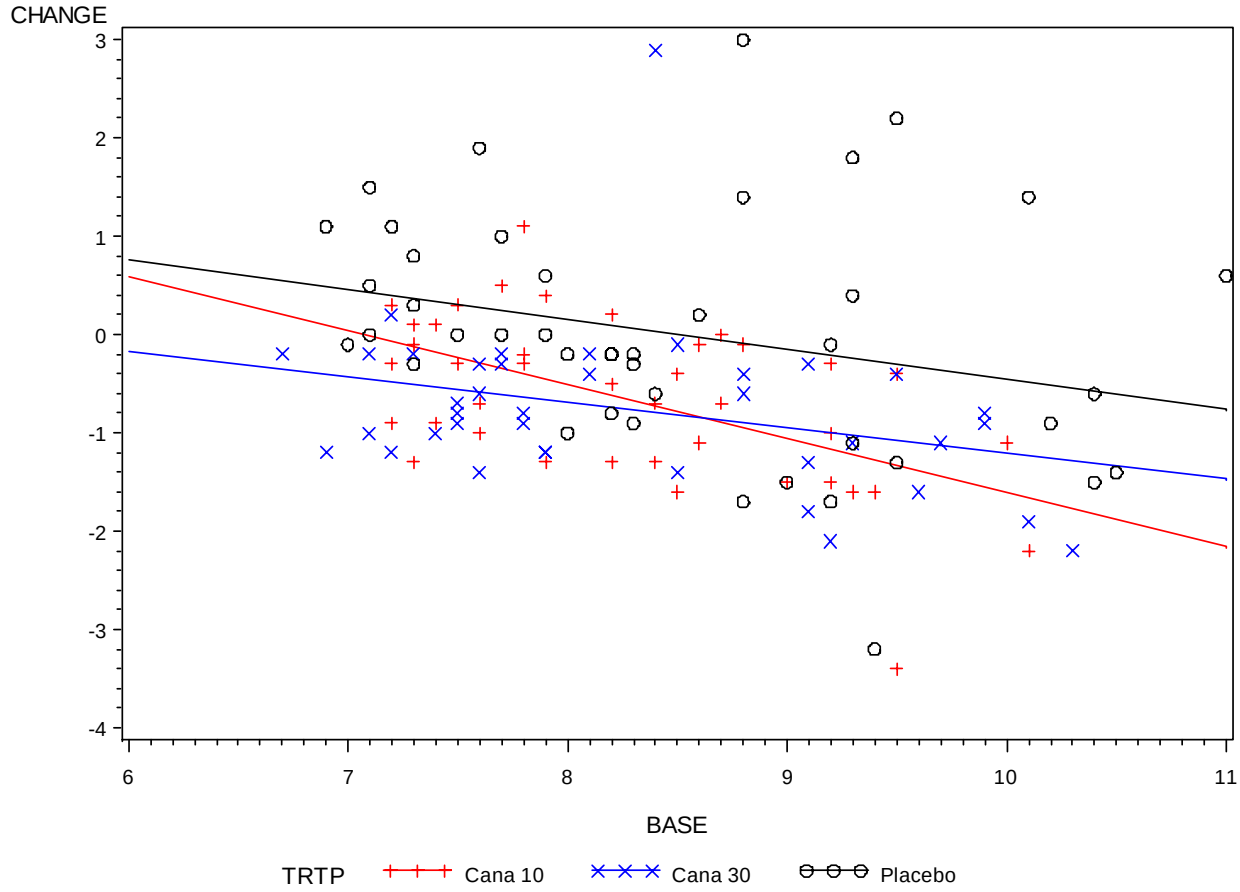


Appendix Figure 9.3. The Time Course Plot of HbA1c Changes from Baseline in Study DIA3008 (SU, pop1) to Week 52.



Note: Week 18 is the primary endpoint time.

Appendix Figure 9.4. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study DIA3008 (SU, pop1) at Week 18.




```
Regression equation :  CHANGE(TRTP:Cana 10) =  3.870841 - 0.547448*BASE.
Regression equation :  CHANGE(TRTP:Cana 30) =  1.39172 - 0.260301*BASE.
Regression equation :  CHANGE(TRTP:Placebo) =  2.562124 - 0.301179*BASE.
```

Appendix 10 DIA3008 Insulin Substudy

Appendix 10.1

The primary efficacy objective of the insulin substudy was to assess the glycosylated hemoglobin (HbA1c)-lowering efficacy (change from baseline in HbA1c) of canagliflozin relative to placebo after 18 weeks of treatment.

Eligible subjects were man or woman ≥30 years of age with a diagnosis of T2DM with HbA1c level ≥7.0% to ≤10.5% and history or high risk of CV disease (as defined in sponsor's protocol) at screening and be either (1) not currently on AHA therapy or (2) on AHA monotherapy or combination therapy with any approved agent: eg, SU, metformin, pioglitazone, alpha-glucosidase inhibitor, GLP-1 analogue, DPP-4 inhibitor, or insulin.

Subjects who participated in the CANVAS had balanced (1:1:1) randomization to each of the 3 treatment groups (ie, canagliflozin 100 mg, canagliflozin 300 mg, or placebo) within the following predefined strata by the sponsor based upon AHA(s) that the subject was receiving at the run-in visit and continued into the double-blind treatment phase.

- Stratum 1: insulin monotherapy =20 units per day, on stable doses at least 10 weeks before the run-in visit
- Stratum 2: insulin =20 units per day plus metformin, on stable doses at least 10 weeks before the run-in visit, and no other background AHA therapy
- Stratum 3: insulin =20 units per day plus any other AHA(s) on stable dose(s) for at least 10 weeks before the run-in visit

Three populations for analysis were defined in conjunction with the strata listed above:

- Population 1 (Insulin =20 IU/day Group; =20 IU), comprised of all subjects randomized to Strata 1, 2, and 3 (considered the secondary population for analysis),
- Population 2 (Insulin =30 IU/day Group; =30 IU), comprised of all subjects randomized to Strata 1, 2, and 3 who were taking insulin =30 units per day at study entry (considered the primary population for analysis),
- Population 3 (Insulin / Metformin Population: Insulin =30 IU/day + Metformin Group; =30 IU + Met), comprised of subjects randomized to the Population 2 who were taking insulin =30 units per day and metformin >2000 mg at study entry.

A total of 1,718 randomized subjects comprised Population 2 (=30 IU; includes 83% of the subjects in Population 1) of the insulin substudy with 565, 566, and 587 subjects randomized to placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. A total of 432 randomized subjects were taking insulin =30 units/day and metformin =2000 mg/day at study entry (Population 3 [=30 IU + Met]) of the insulin substudy, with 145, 139, and 148 subjects randomized to placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively.

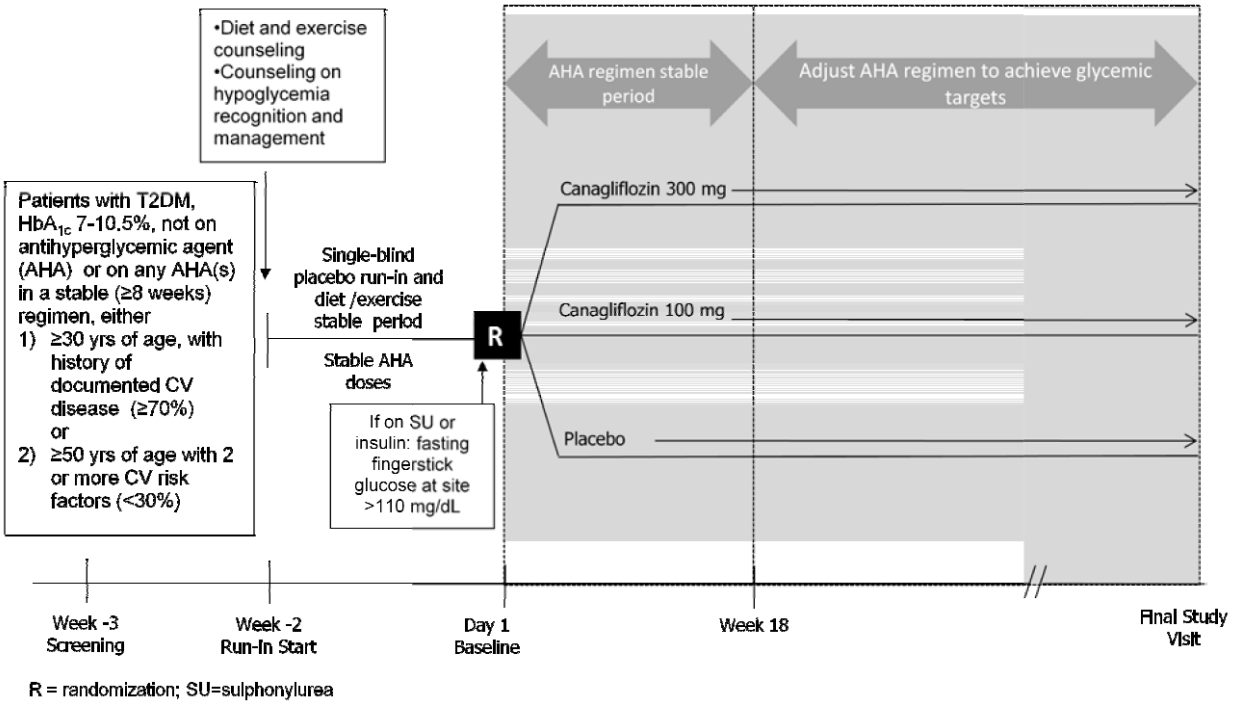
Major secondary end points (at Week 18 LOCF comparing to placebo) included body weight, FPG, systolic blood pressure, proportion of subjects with HbA1c <7%, fasting HDL-C and triglycerides after 18 weeks of treatment.

Sample size calculations of this trial were based on the primary endpoint HbA1c at end of trial. Assuming a group difference of 0.50% and a common SD of 1.0% with respect to change in HbA1c, and using a 2-sample, 2-sided t-test with Type I error rate of 0.05, it was estimated that 258 randomized subjects (86 subjects in each of the 3 treatment groups) would provide 90% power.

This study was a multi-national, multi-centre trial with a total of 330 centers in 23 countries (81 centers in North America [15 in Canada, 7 in Mexico, and 59 in the US], 16 centers in Central/South America [14 in Argentina and 2 in Colombia], 112 centers in Europea [5 in Belgium, 7 in Czech Republic, 6 in Estonia, 10 in Germany, 7 in Hungary, 21 in Netherlands, 8 in Norway, 14 in Poland, 15 in Spain, 9 in Sweden, and 10 in United Kingdom], and 121 centers in the rest of the world [16 in Australia, 39 in India, 4 in Israel, 7 in Malaysia, 5 in New Zealand, 40 in Russia, and 10 in Ukraine])

The sponsor's design diagram of DIA3008 insulin substudy is shown in Figure 1. (the same as SU substudy)

Figure 1. Overview of the study design.



R = randomization; SU=sulphonylurea

Statistical Methodologies

The efficacy objective was to determine whether the effect (change in HbA1c) of insulin detemir was at least as good of that achieved with NPH insulin at end of treatment period (non-inferiority).

The primary hypothesis was "In subjects with T2DM, with inadequate glycemic control, who have a history of or a high risk of CV disease, after 18 weeks of treatment, canagliflozin provides a greater improvement in HbA1c relative to placebo (change from baseline in HbA1c)."

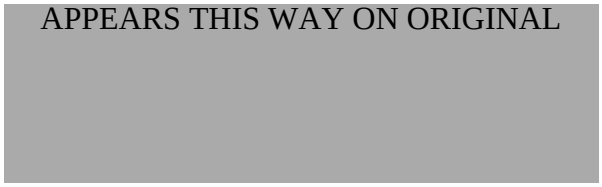
The secondary substudy hypotheses were after 18 weeks, in subjects with T2DM, with inadequate glycemic control, who have a history or high risk of CV disease, relative to placebo, canagliflozin:

- reduces body weight
- reduces FPG
- leads to a greater proportion of subjects achieving HbA1c <7.0%
- reduces systolic blood pressure (SBP)
- increases HDL-C concentrations
- lowers triglyceride concentrations

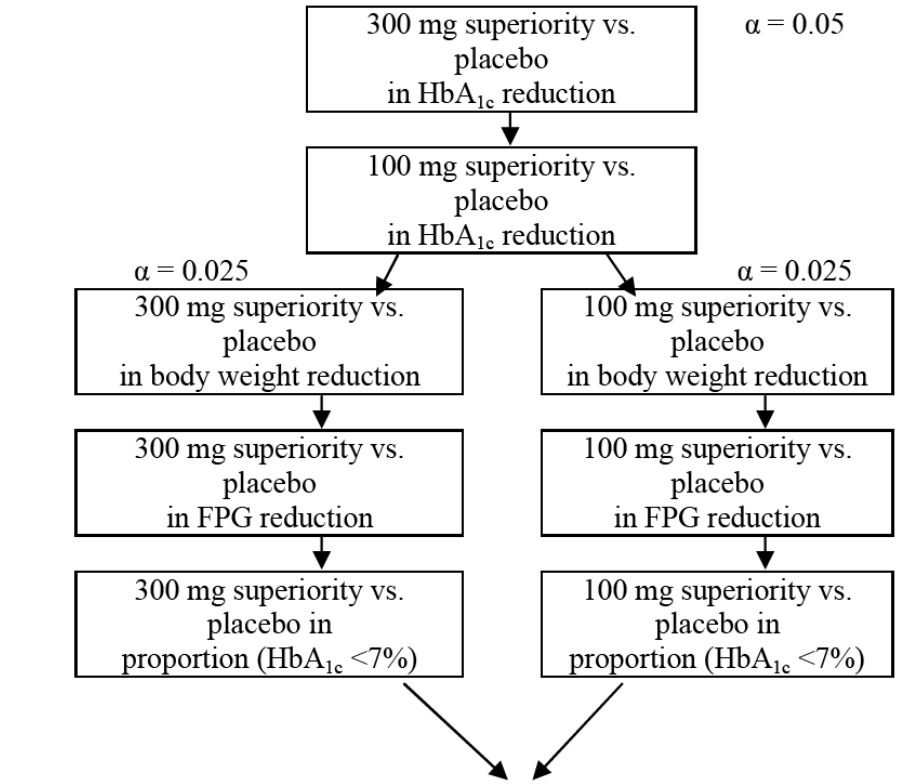
The sponsor's primary analysis was based on the mITT analysis set, an analysis of covariance (ANCOVA) model including treatment as a fixed effect An analysis of covariance (ANCOVA) model with treatment and stratification factors (whether or not a subject was taking AHA(s) at screening and whether or not a subject participated in the FS-MMTT) as fixed effects and HbA1c baseline value as covariate, based on the mITT analysis set, was used for the primary efficacy analysis. The treatment difference (canagliflozin minus and the corresponding baseline HbA1c value as a covariate would be used for the primary efficacy analysis.

According to the sponsor's plan for multiplicity adjustment, the hypotheses of primary efficacy endpoint and major secondary efficacy endpoints would be tested sequentially as illustrated in Figure 3.2.2. (the same as SU substudy?) The type I error would be controlled at 0.05.

Figure 2. Multiplicity Adjustment

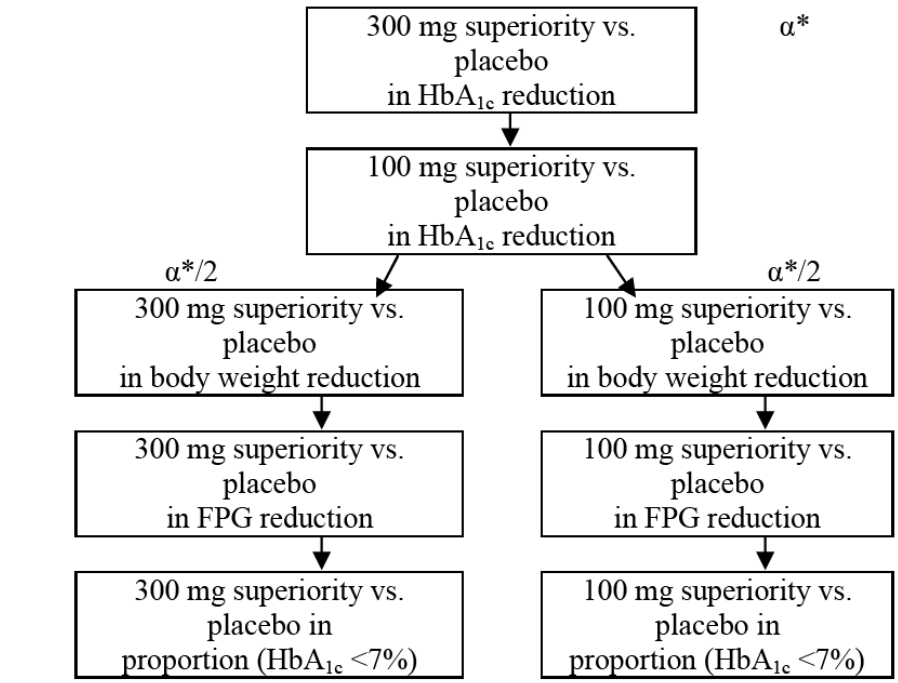


Population 1

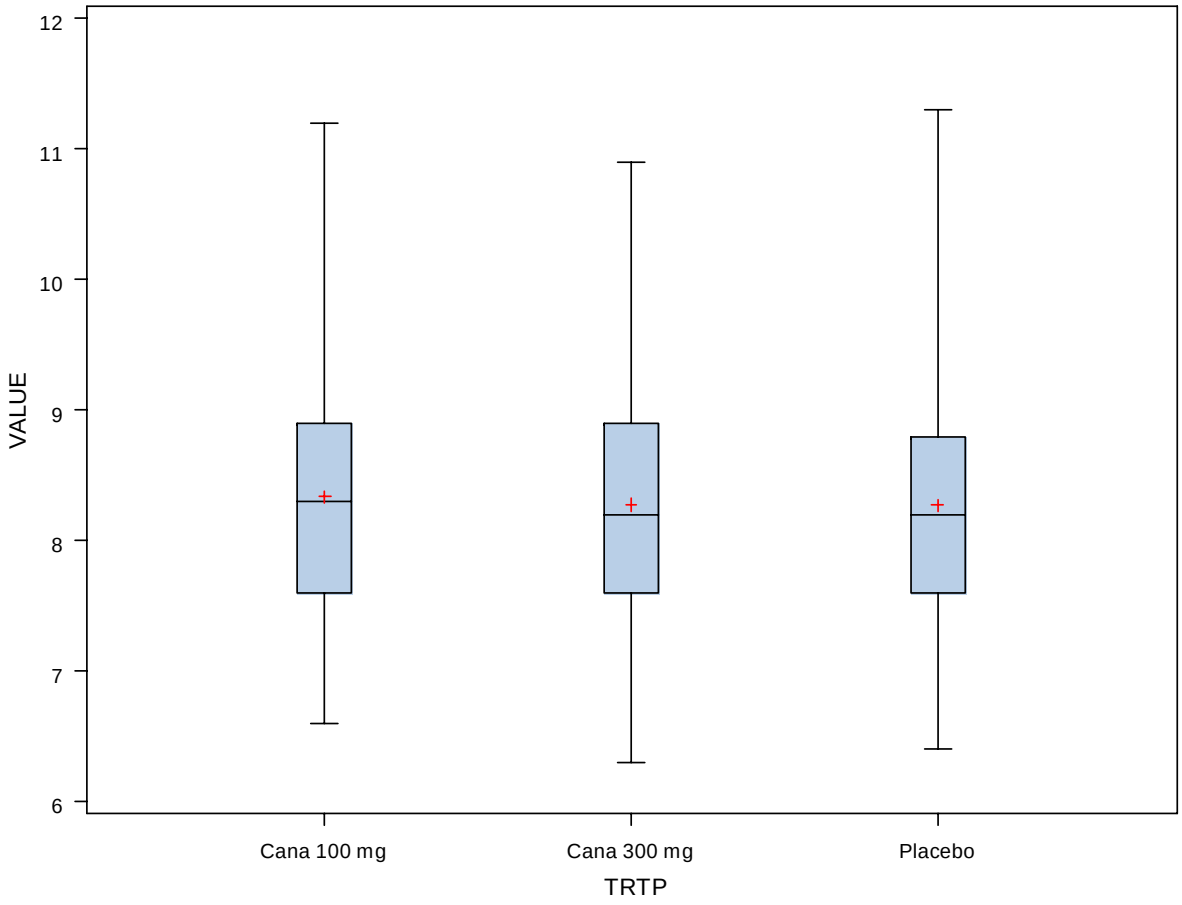


Testing proceeds conditionally based on the previous testing sequence. The alpha level to be used (denoted by α* below) was 0.05 if both testing sequences were successful or 0.025 if only 1 testing sequence is successful.

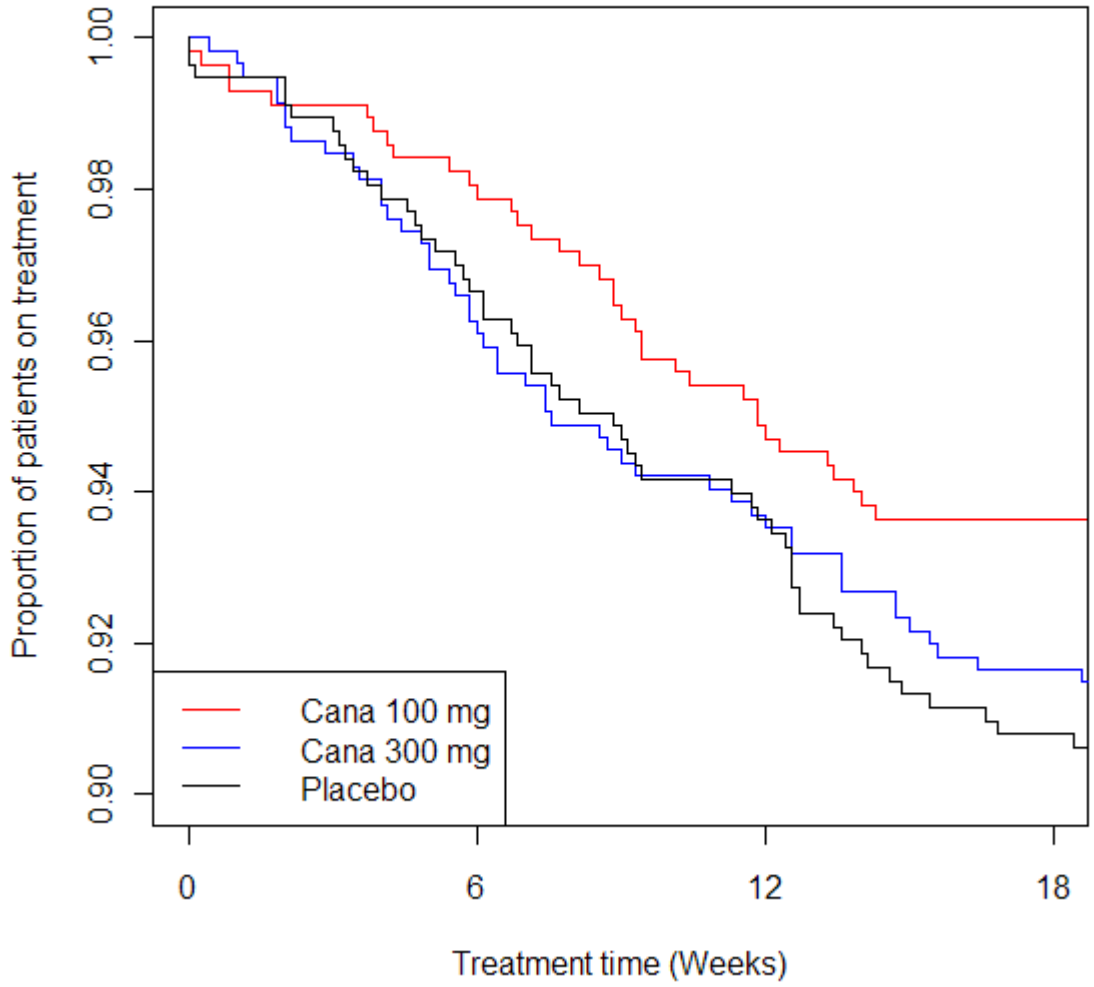
Population 2



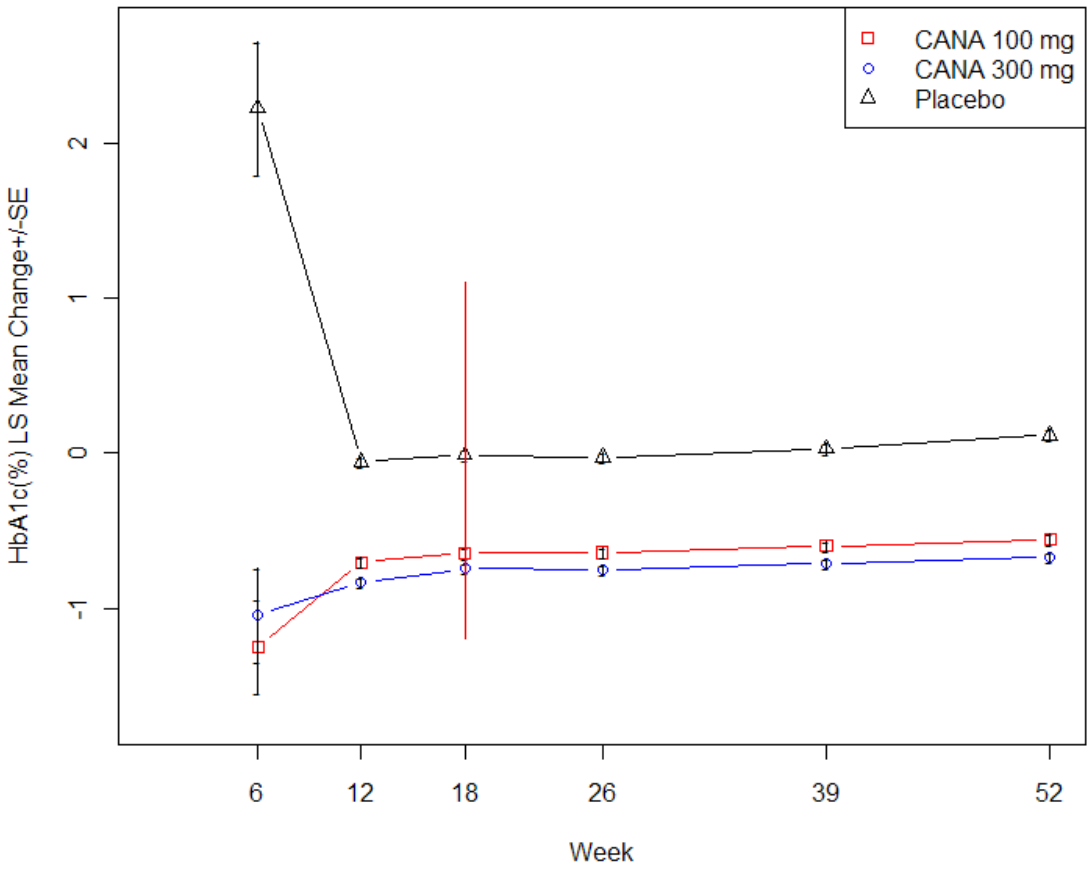
Appendix Figure 10.1. Baseline Levels of HbA1c in Different Treatment Groups (DIA3008 INS POP2).



Appendix Figure 10.2. Comparing Time to Dropout during the Treatment Period between Treatment Groups (FAS population, DIA3008 INS POP2).

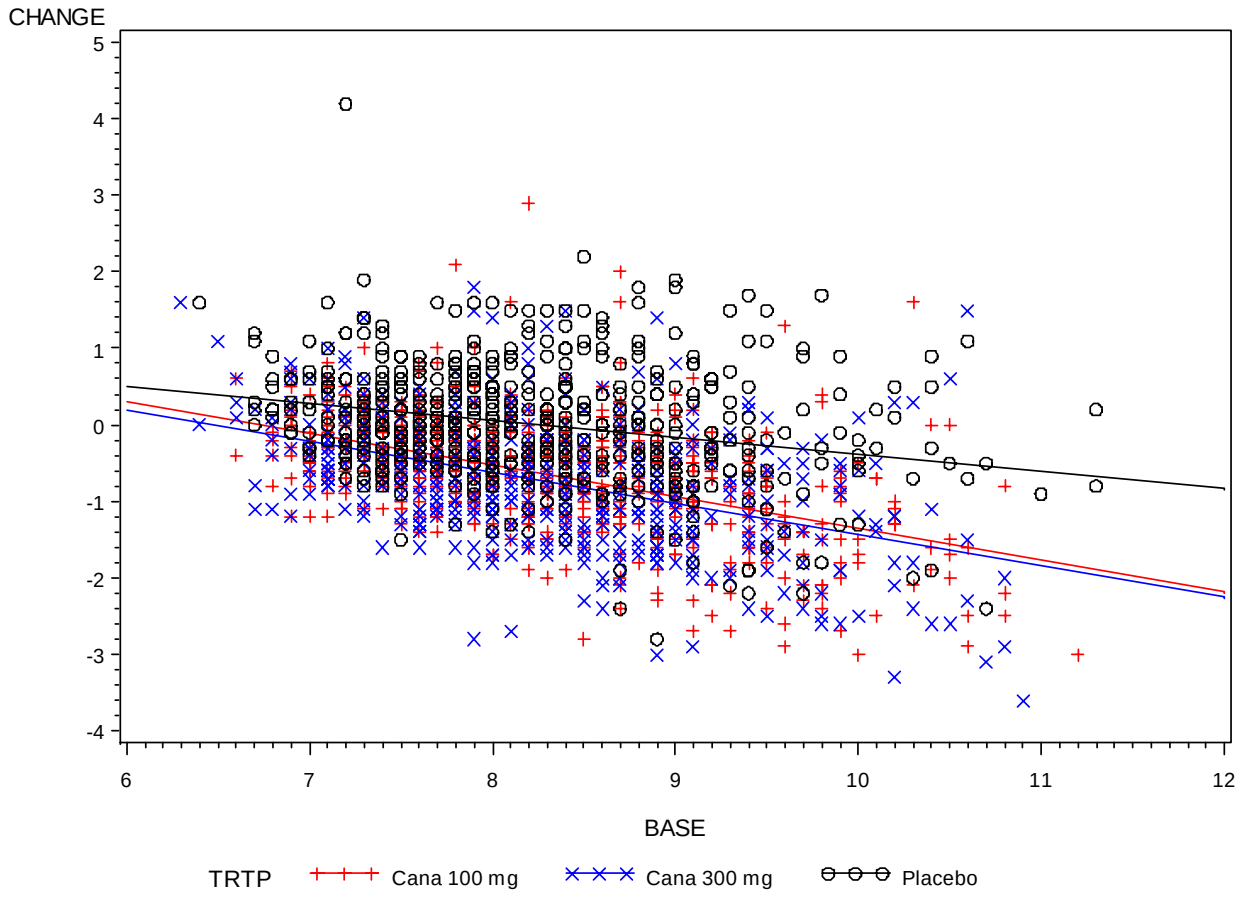


Appendix Figure 10.3. The Time Course Plot of HbA1c Changes from Baseline in Treatments in Study DIA3008 (INS, pop2) to Week 18.



Note: Week 18 is the primary endpoint time.

Appendix Figure 10.4. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study DIA3008 (INS POP2) at Week 18.

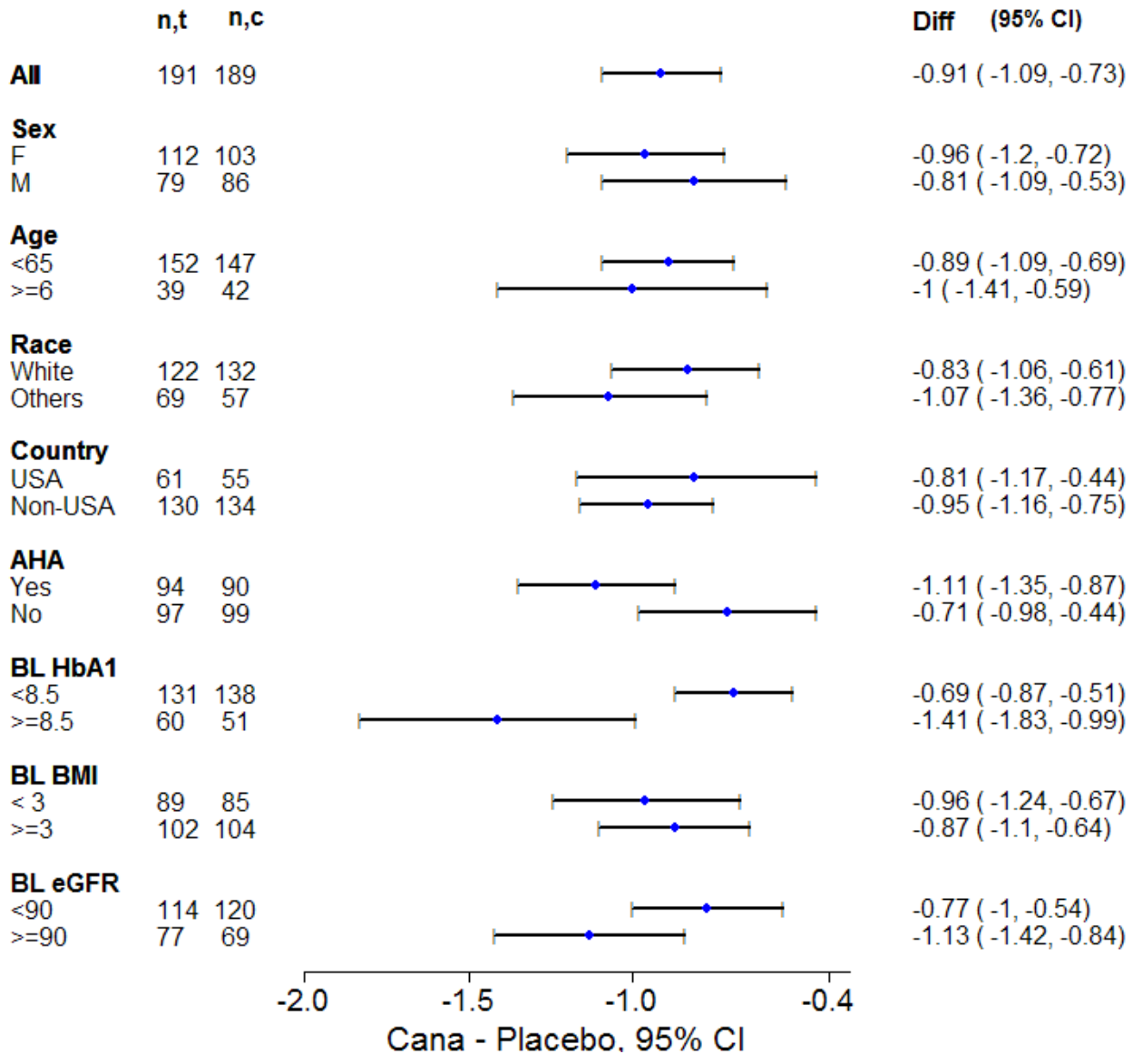



```
Regression equation :  CHANGE(TRTP:Cana 100 mg) =  2.814984 - 0.417236*BASE.
Regression equation :  CHANGE(TRTP:Cana 300 mg) =  2.638966 - 0.406925*BASE.
Regression equation :  CHANGE(TRTP:Placebo) =  1.861885 - 0.225122*BASE.
```

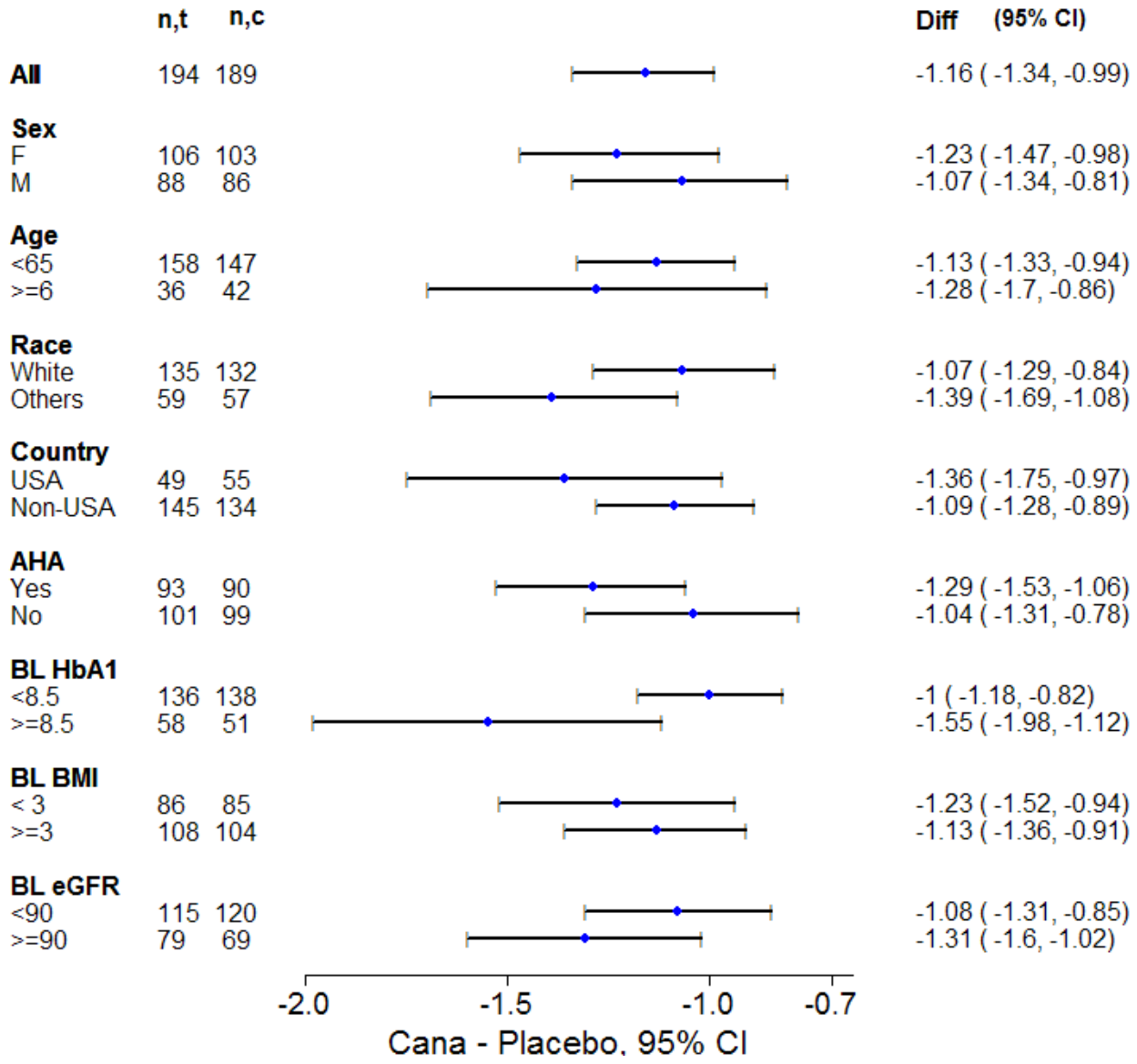
Appendix 11 Forest Plots of Subgroup Analysis

Appendix Figure 11.1. The Forest Plot of HbA1c Changes from Baseline to Week 26 between Canagliflozin and placebo Treatments in Study DIA3005 (LOCF).

Canagliflozin 100 mg vs. Placebo

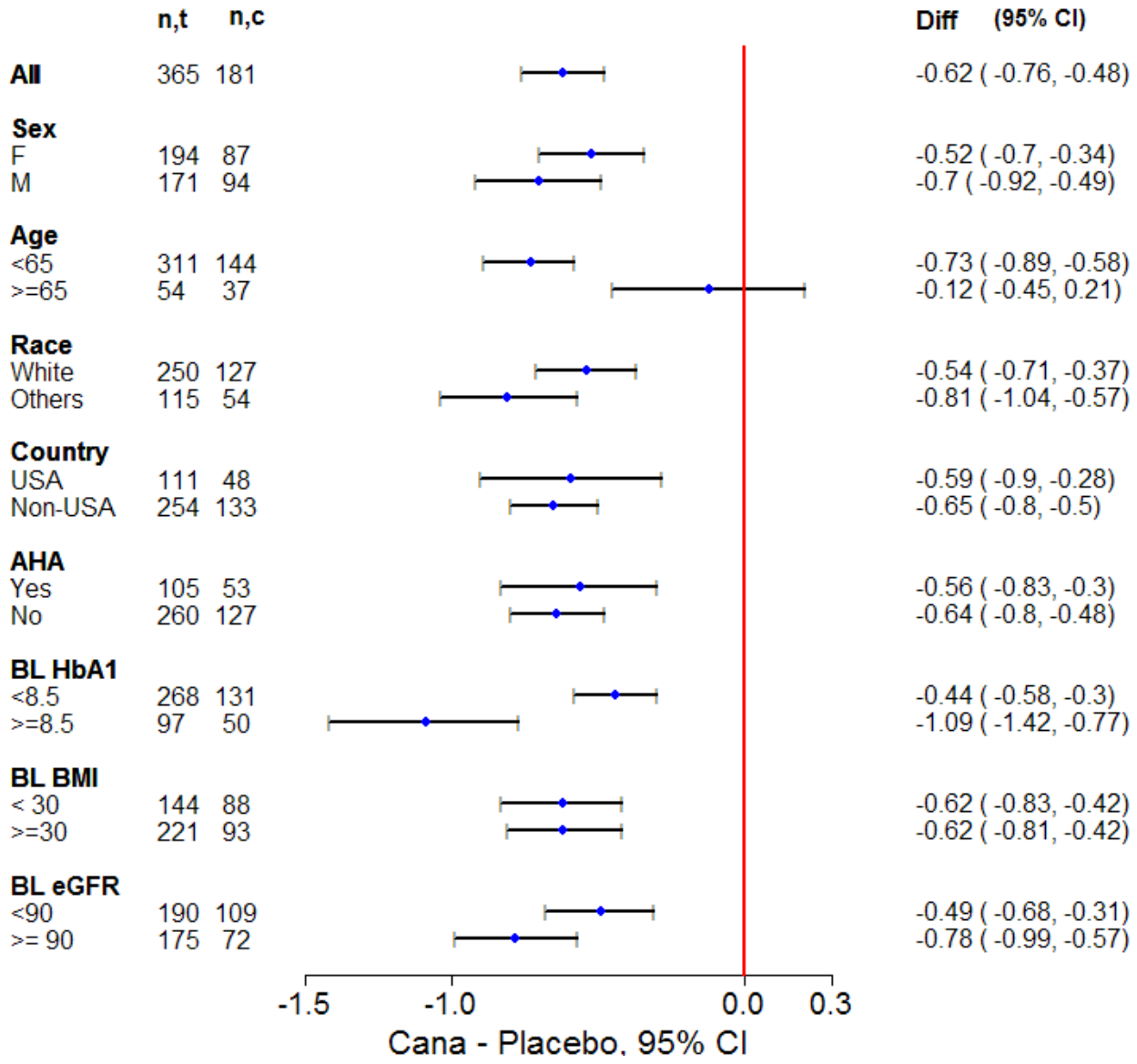


Canagliflozin 300 mg vs. Placebo



Appendix Figure 11.2. The Forest Plot of HbA1c Changes from Baseline to Week 26 between Canagliflozin and placebo Treatments in Study DIA3006 (LOCF).

CANA 100 mg vs. Placebo



CANA 300 mg vs. Placebo

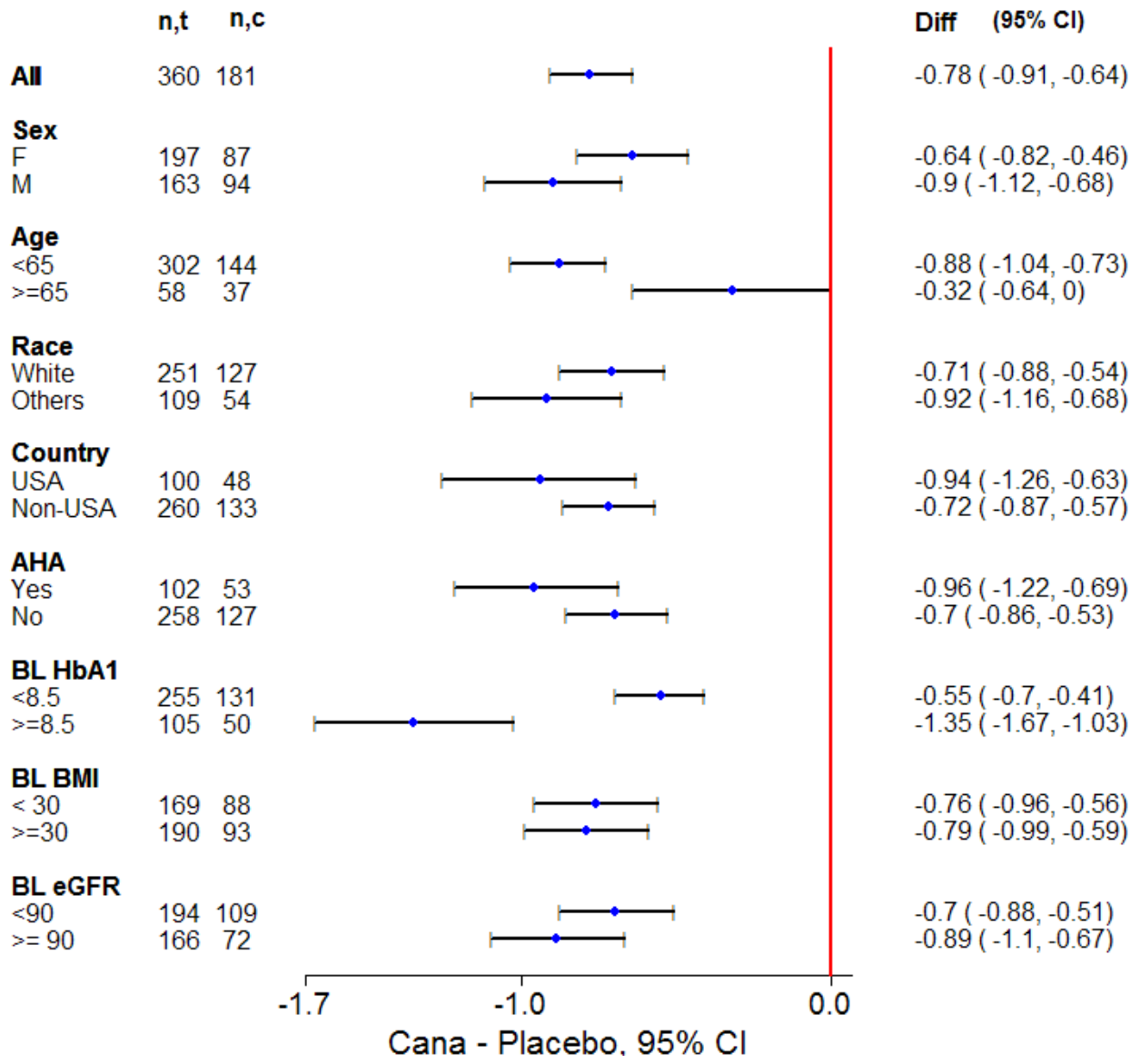
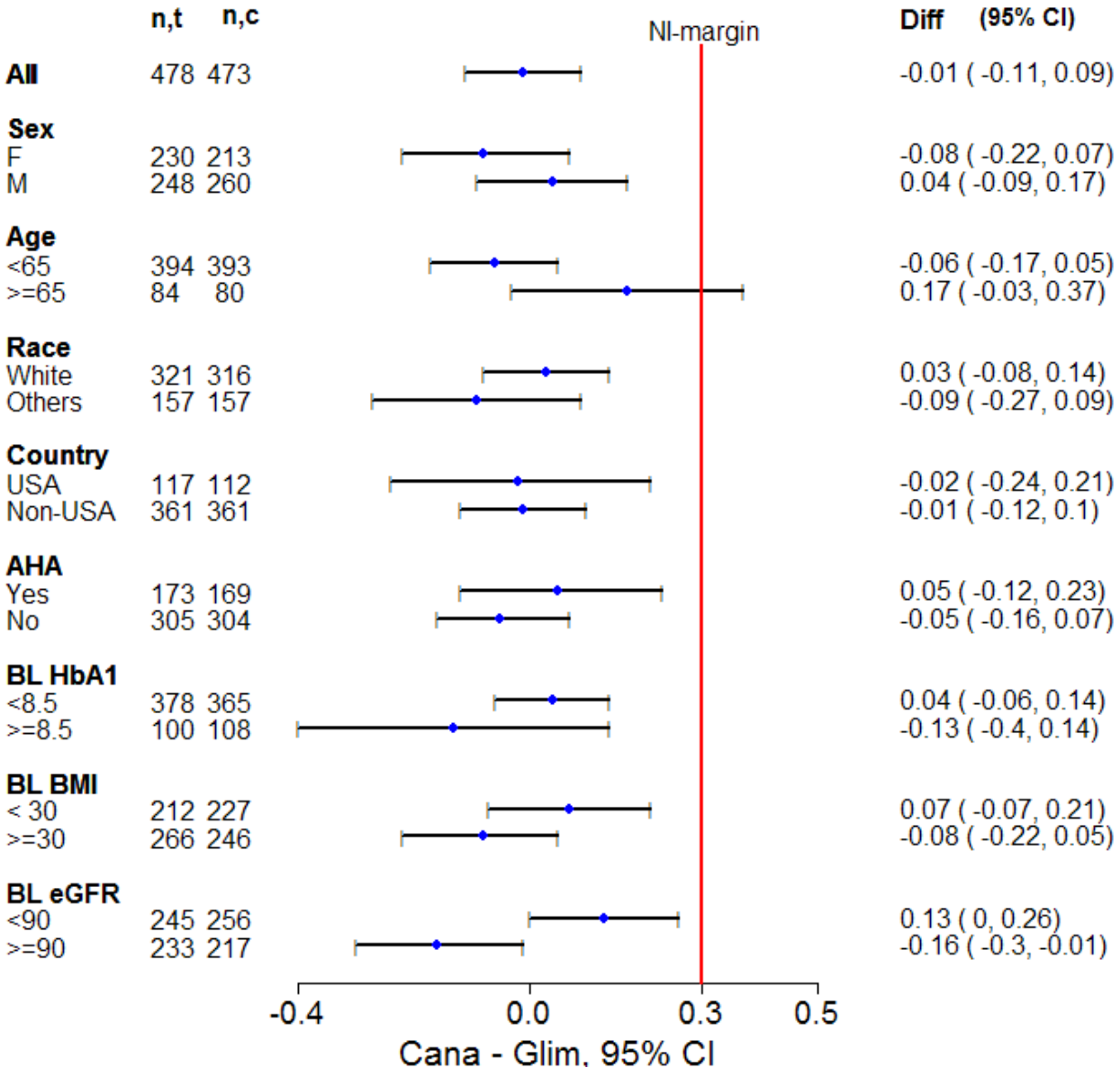
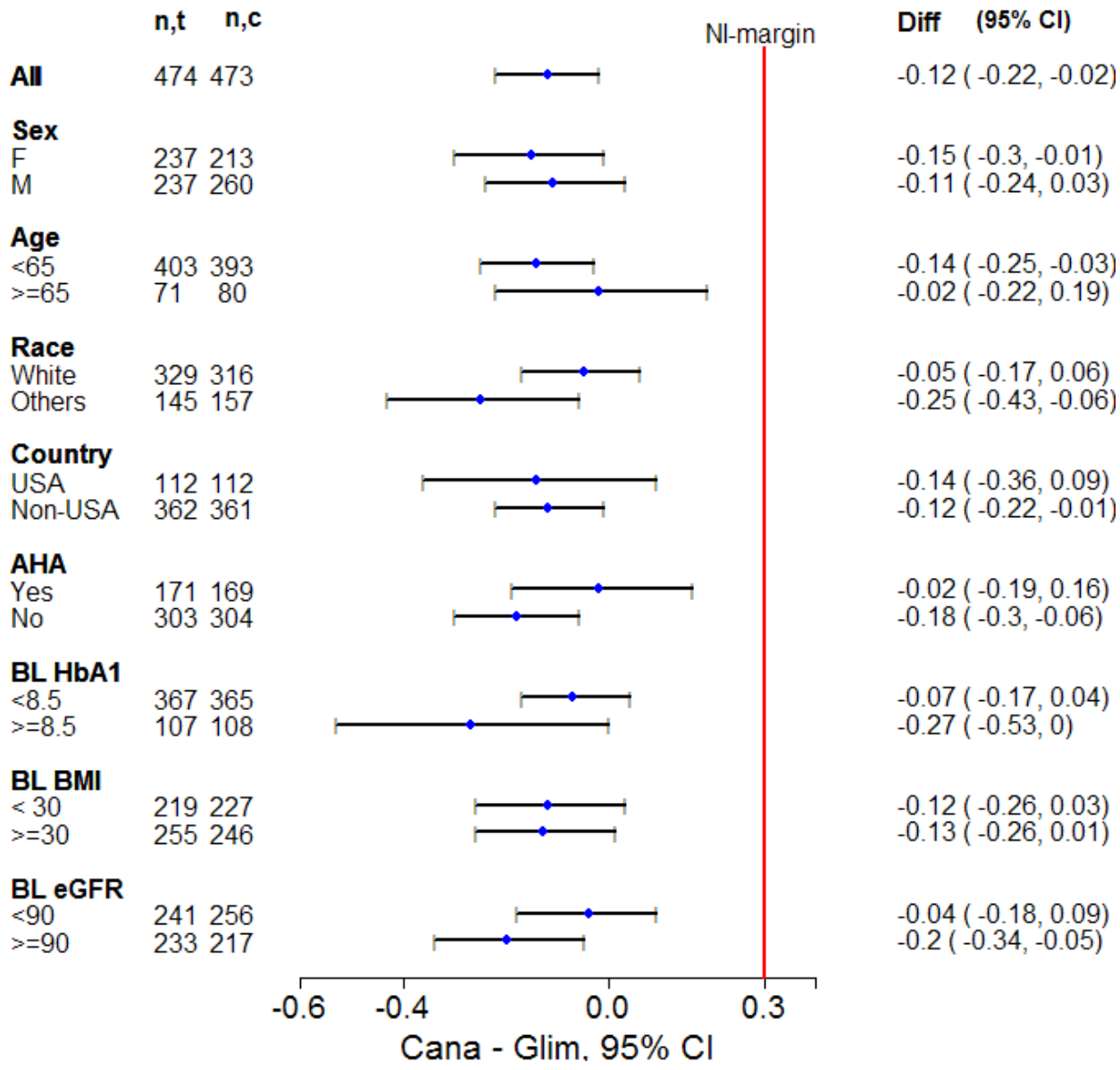


Figure 11.3. The Forest Plot of HbA1c Changes from Baseline between Canagliflozin and Glimrpiride Treatments to Week 52 in Study DIA3009 (LOCF).

CANA 100 mg vs. Glimepiride

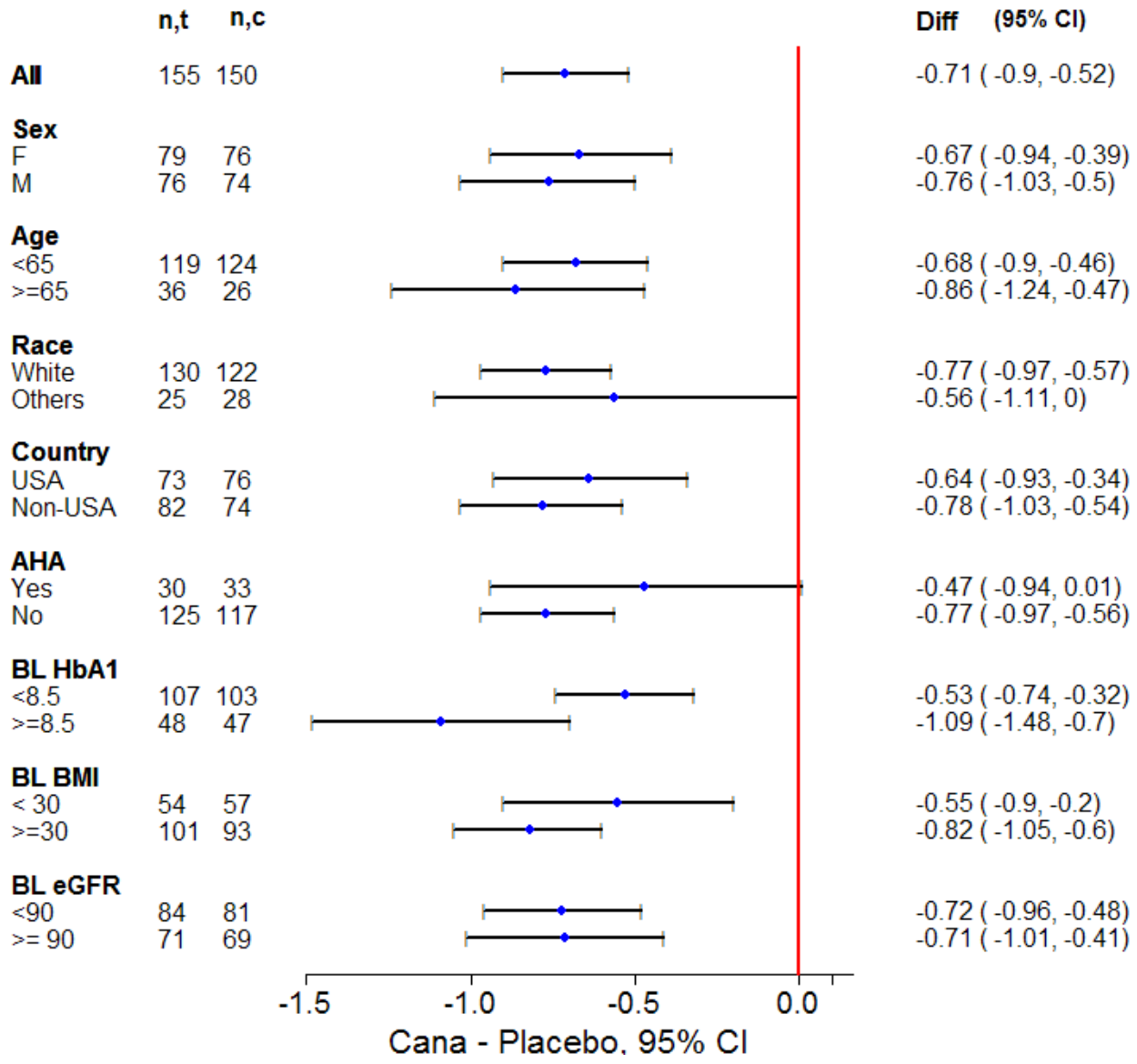


CANA 300 mg vs. Glimepiride

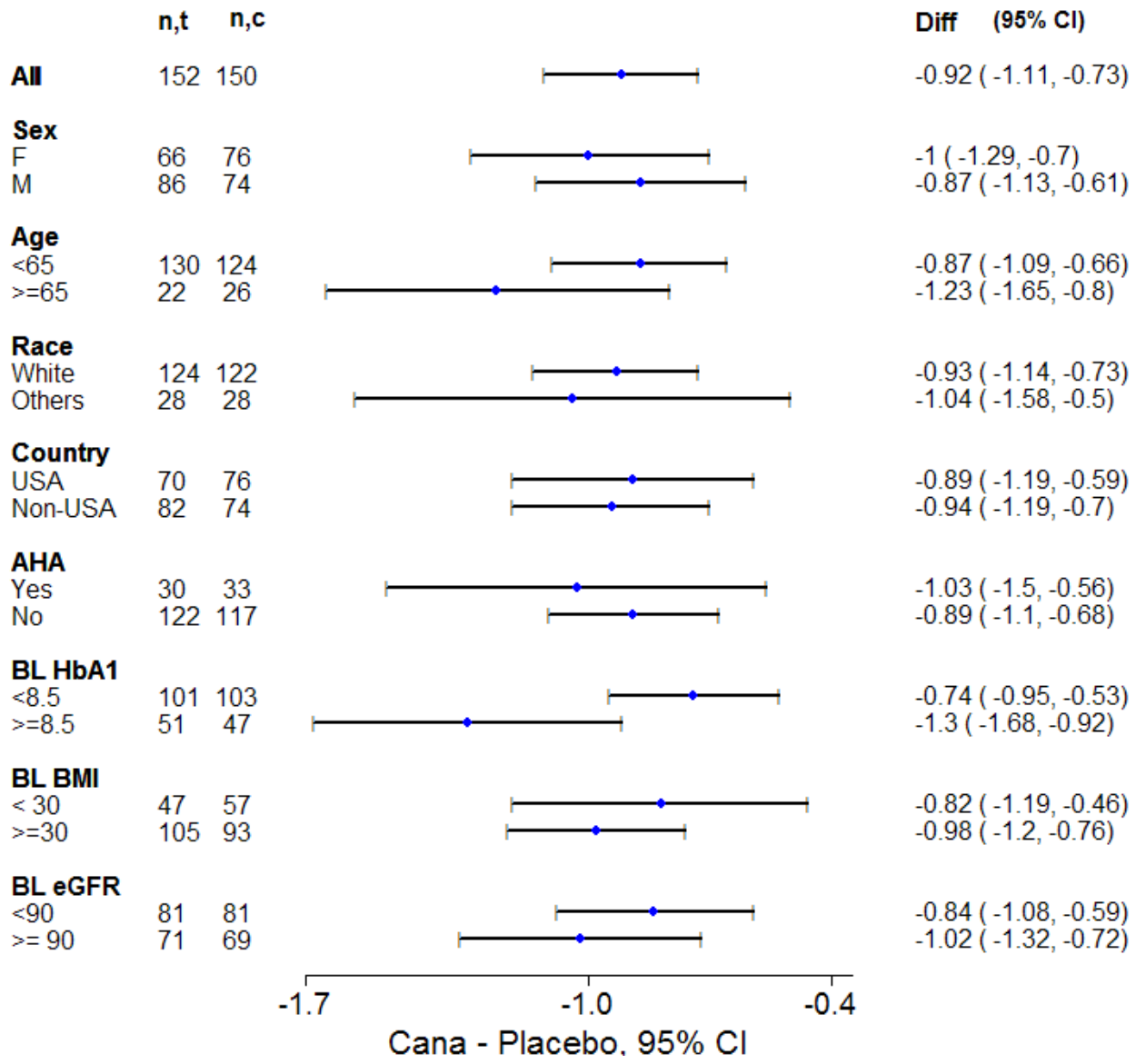


Appendix Figure 11.4. The Forest Plot of HbA1c Changes from Baseline to Week 26 between Canagliflozin and placebo Treatments in Study DIA3002 (LOCF).

CANA 100 mg vs. Placebo

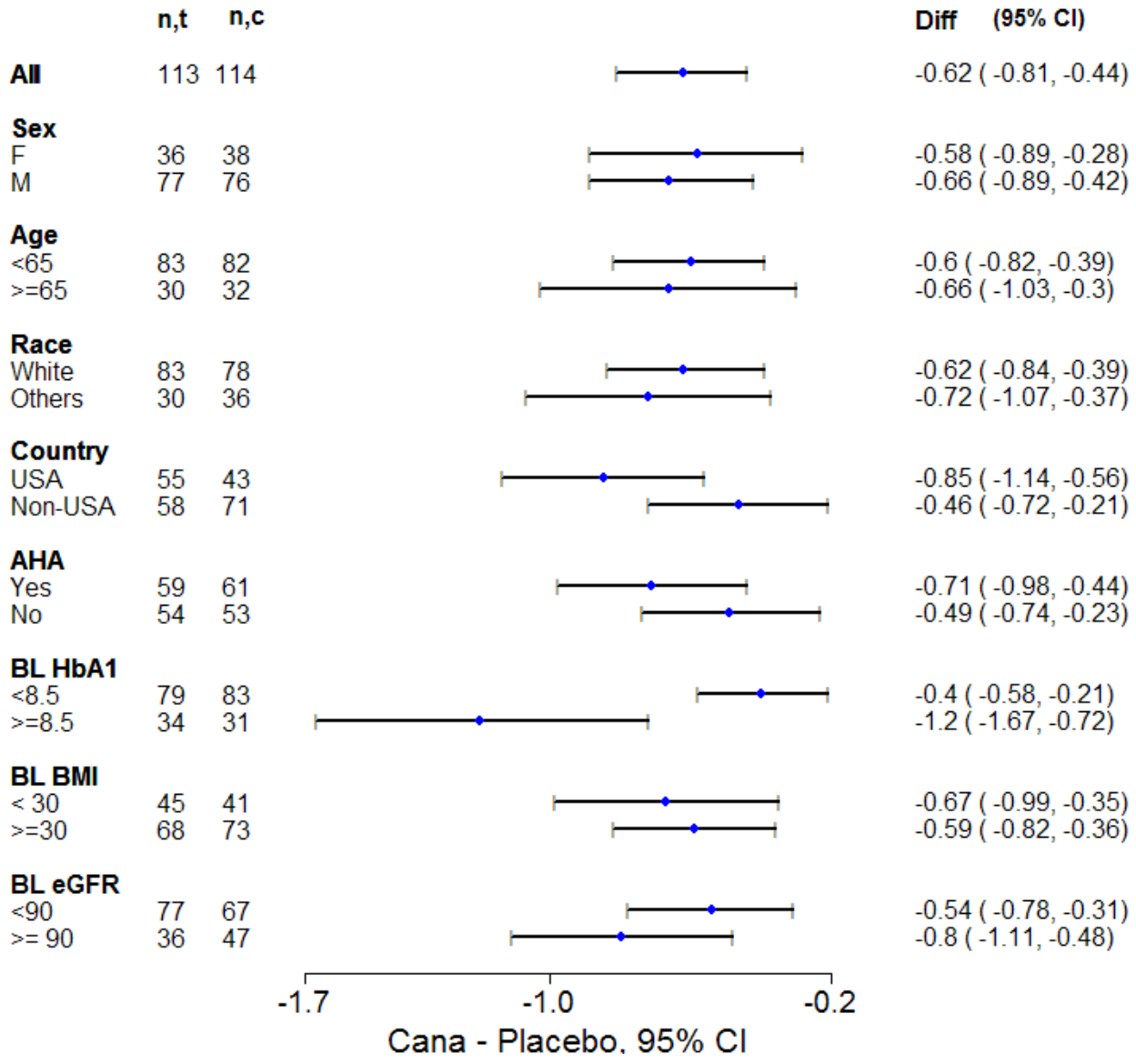


CANA 300 mg vs. Placebo

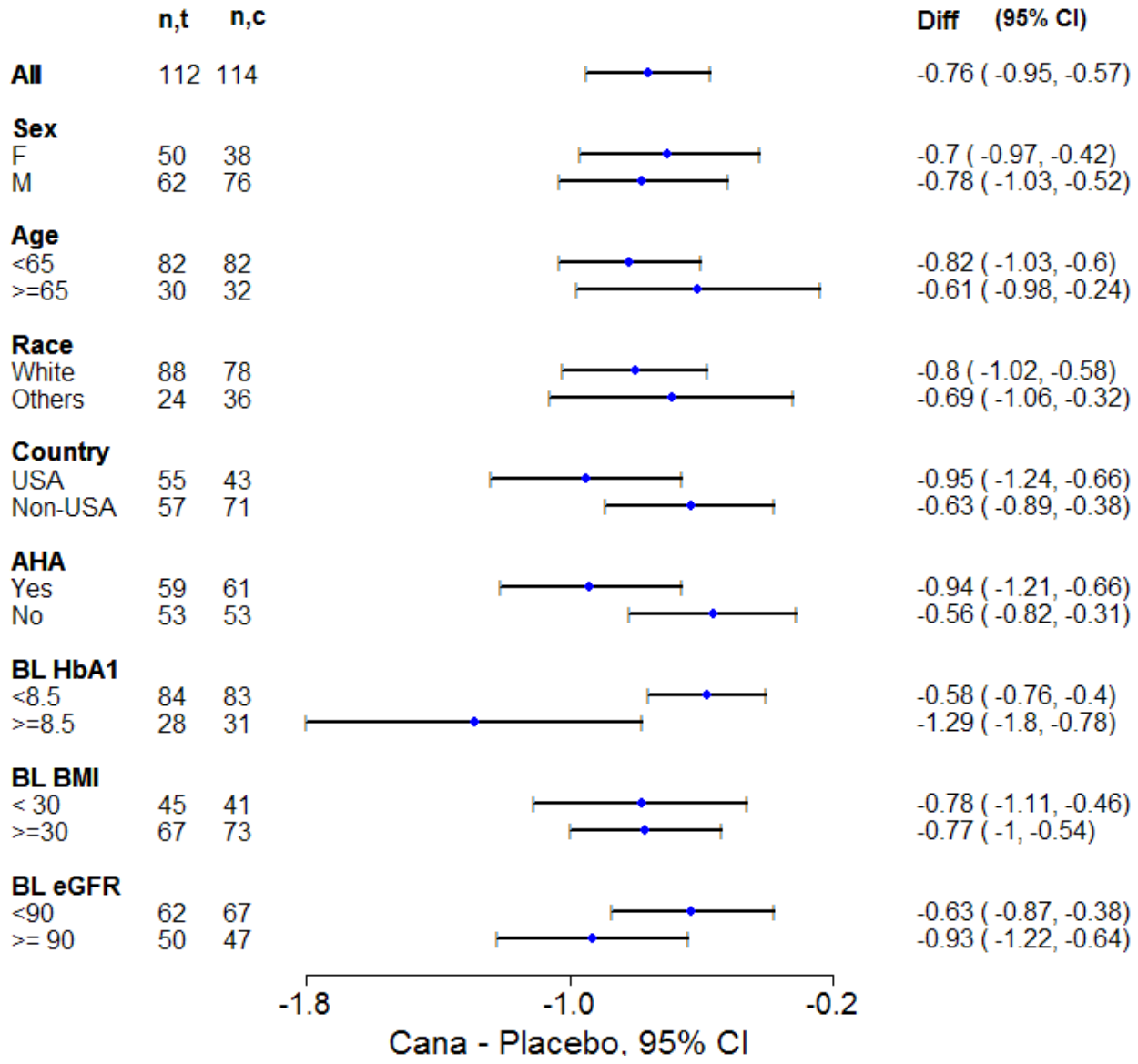


Appendix Figure 11.5. The Forest Plot of HbA1c Changes from Baseline between Canagliflozin and Placebo to Week 26 in Study DIA3012 (LOCF).

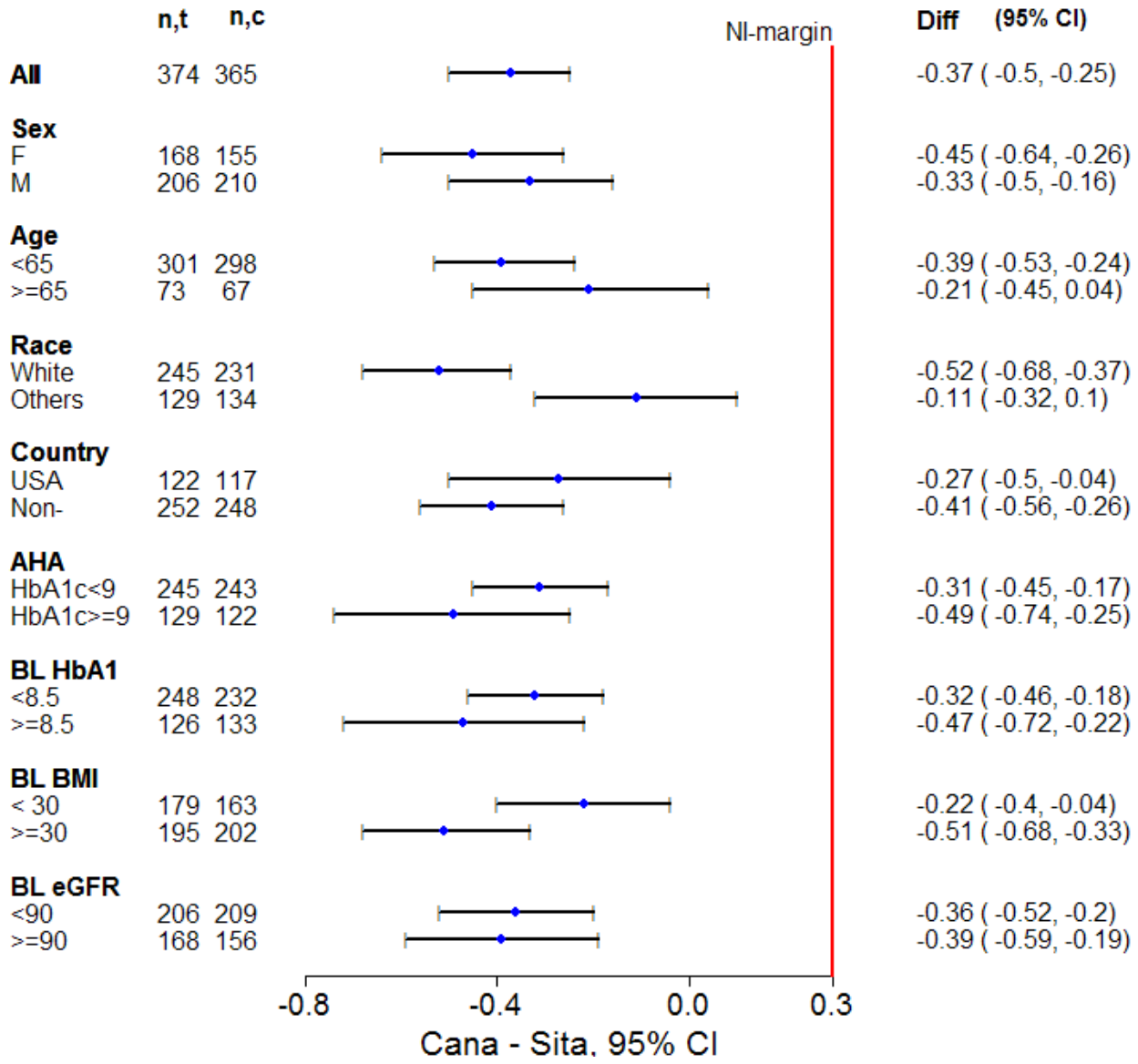
CANA 100 mg vs. Placebo



CANA 300 mg vs. Placebo

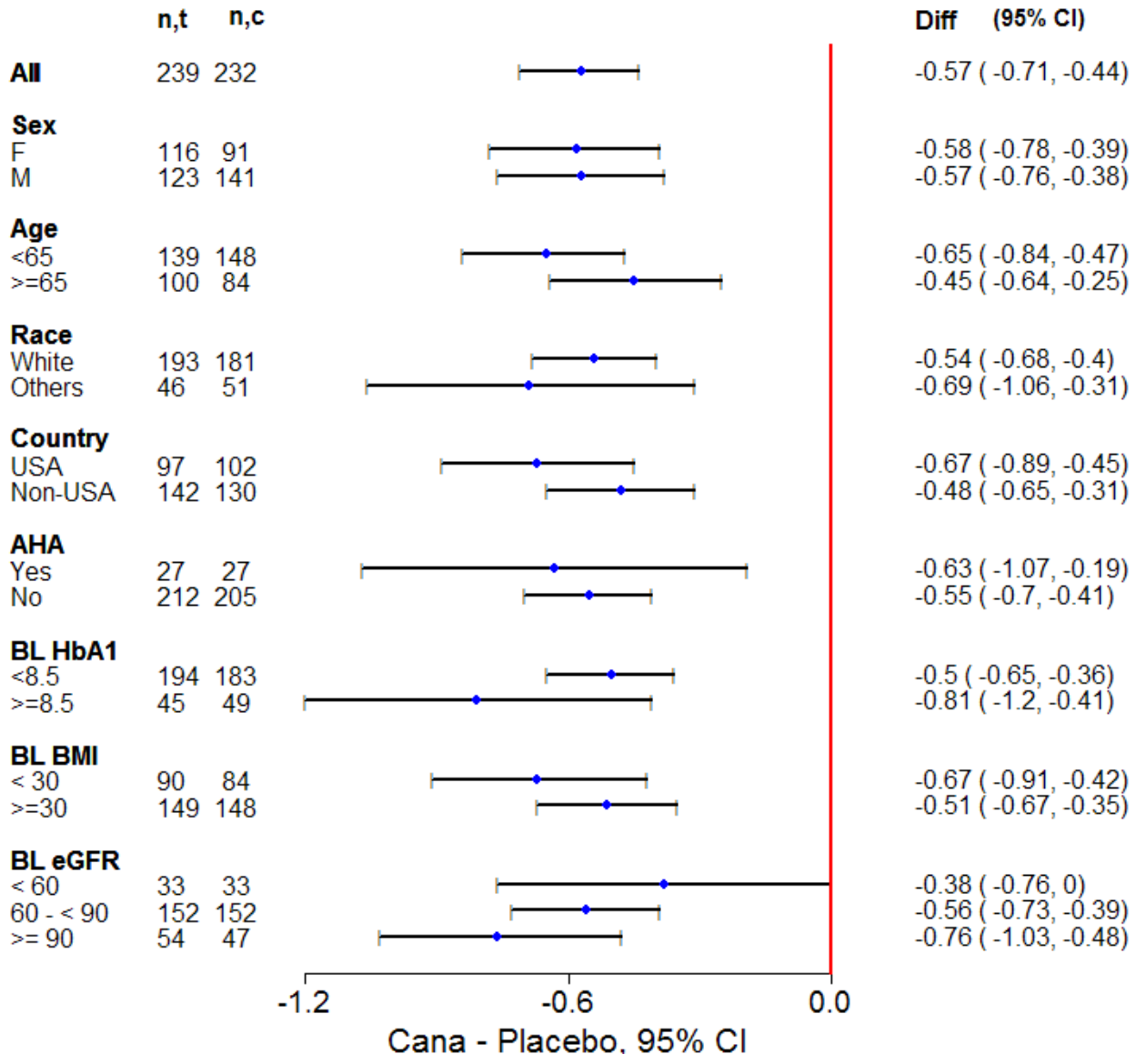


Appendix Figure 11.6. The Forest Plot of HbA1c Changes from Baseline between Canagliflozin 300 mg and Sitaglipiride 100 mg to Week 52 in Study DIA3015 (LOCF).

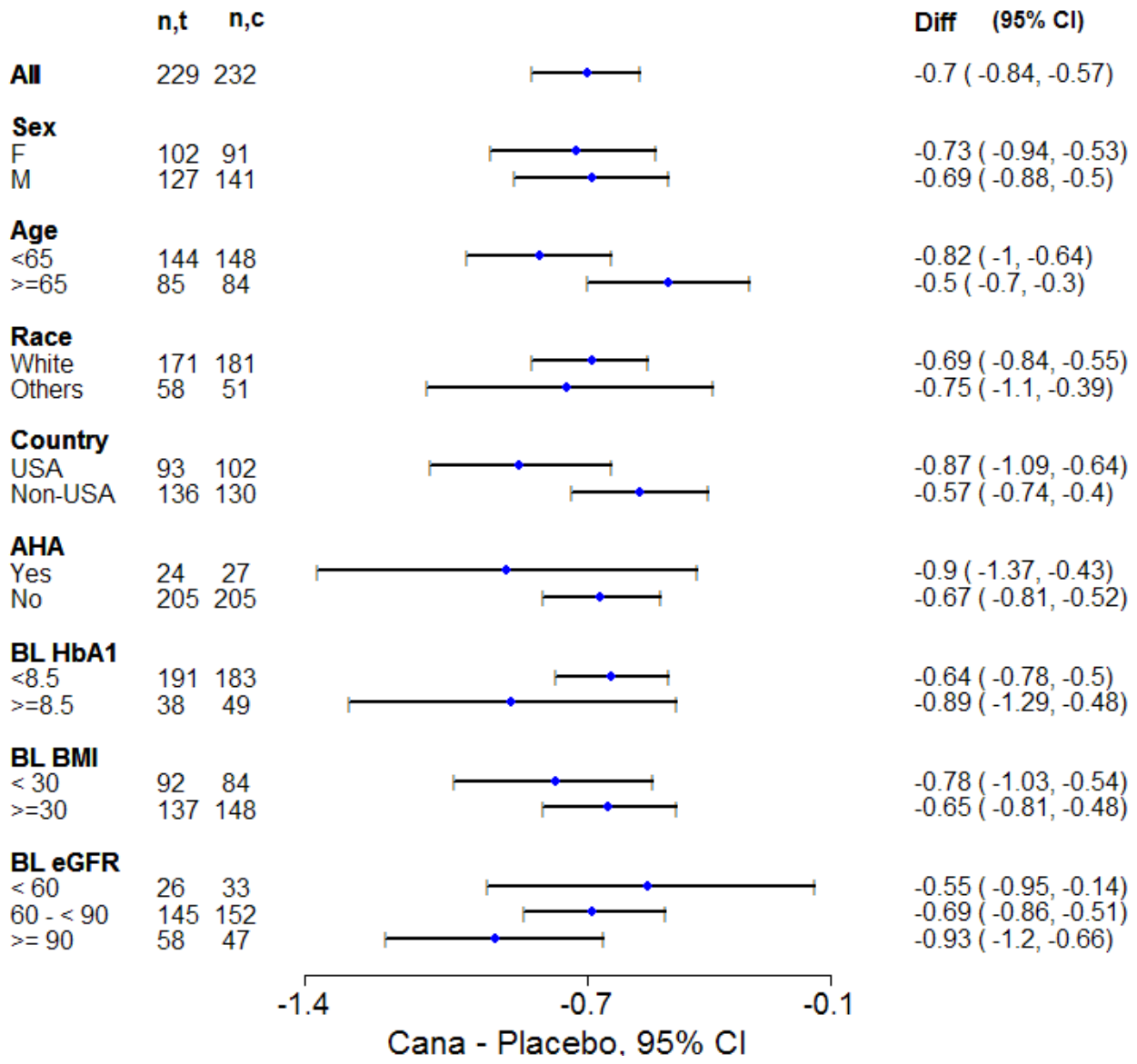


Appendix Figure 11.7. The Forest Plot of HbA1c Changes from Baseline to Week 26 between Canagliflozin and placebo Treatments in Study DIA3010.

CANA 100 mg vs. Placebo

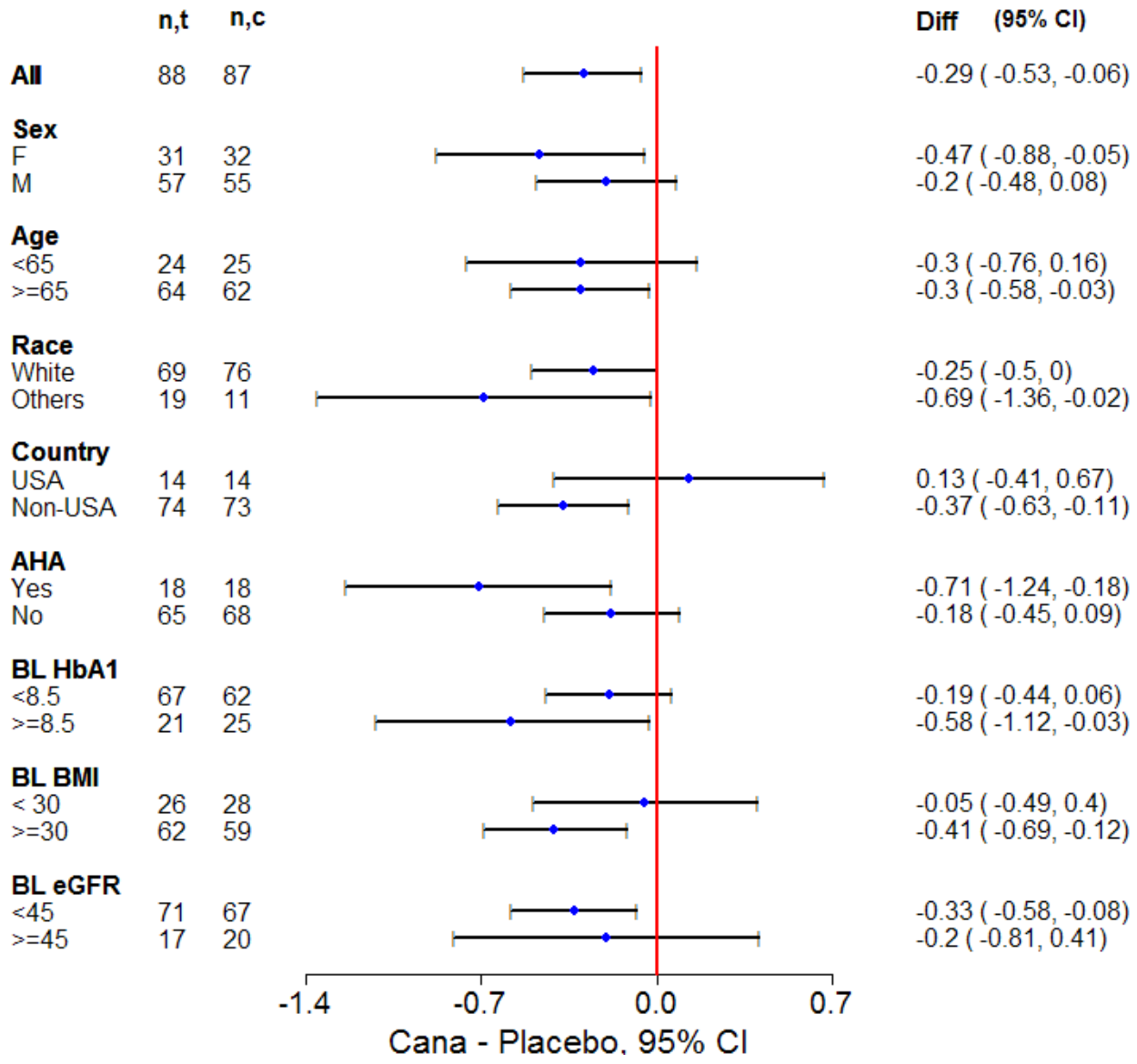


CANA 300 mg vs. Placebo

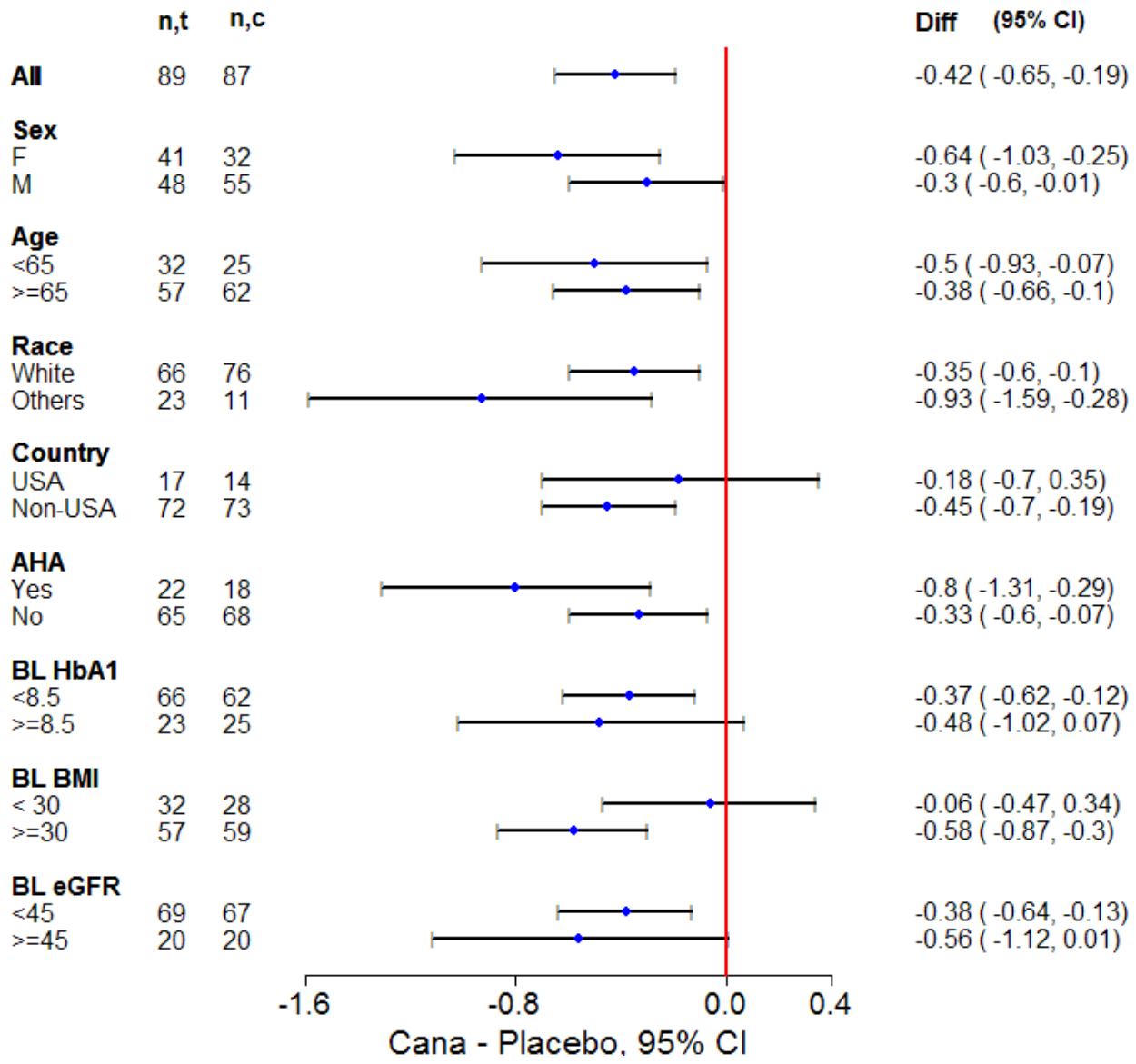


Appendix Figure 11.8. The Forest Plot of HbA1c Changes from Baseline to Week 26 between Canagliflozin and placebo Treatments in Study DIA3004 (LOCF).

CANA 100 mg vs. Placebo

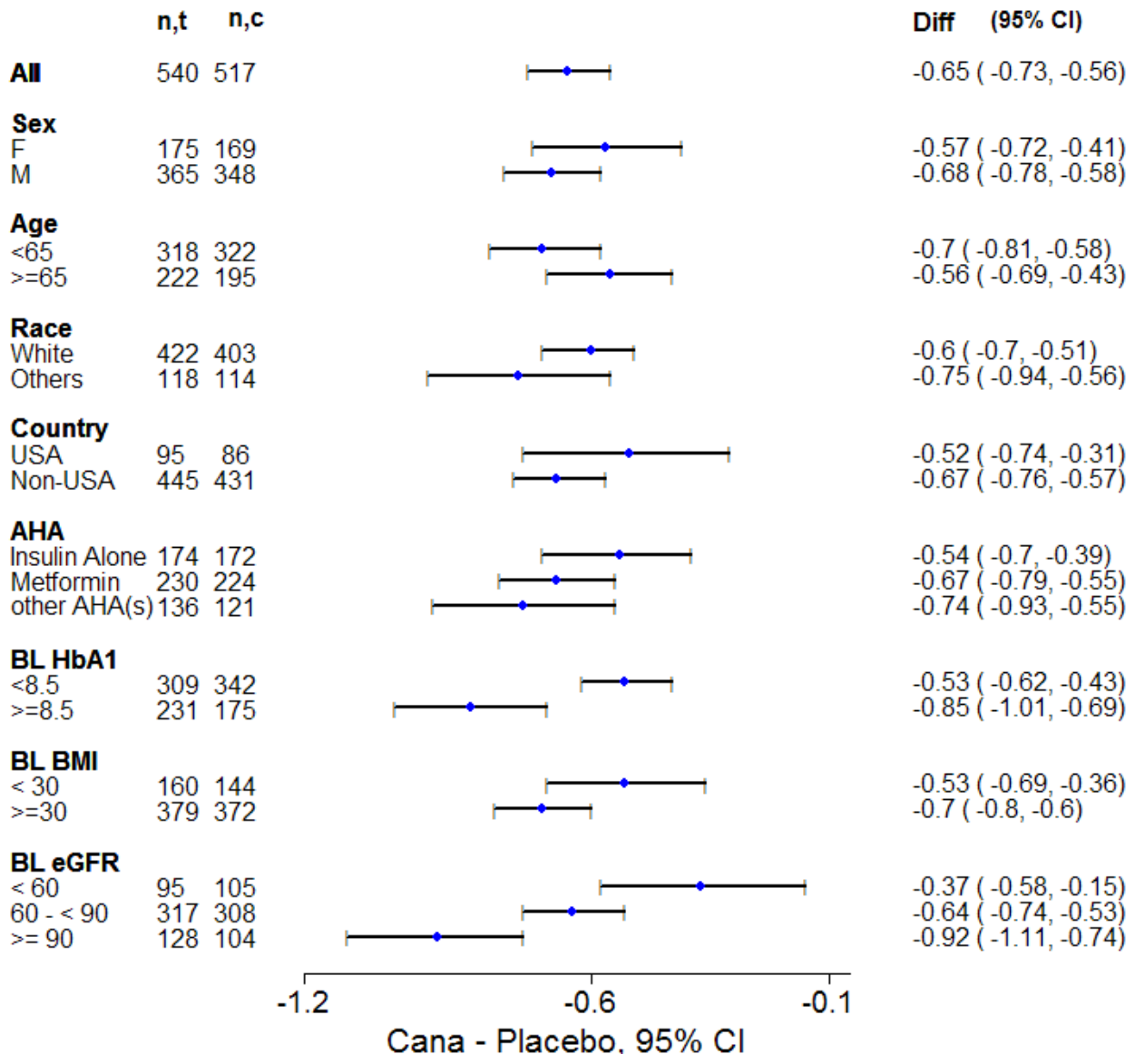


CANA 300 mg vs. Placebo

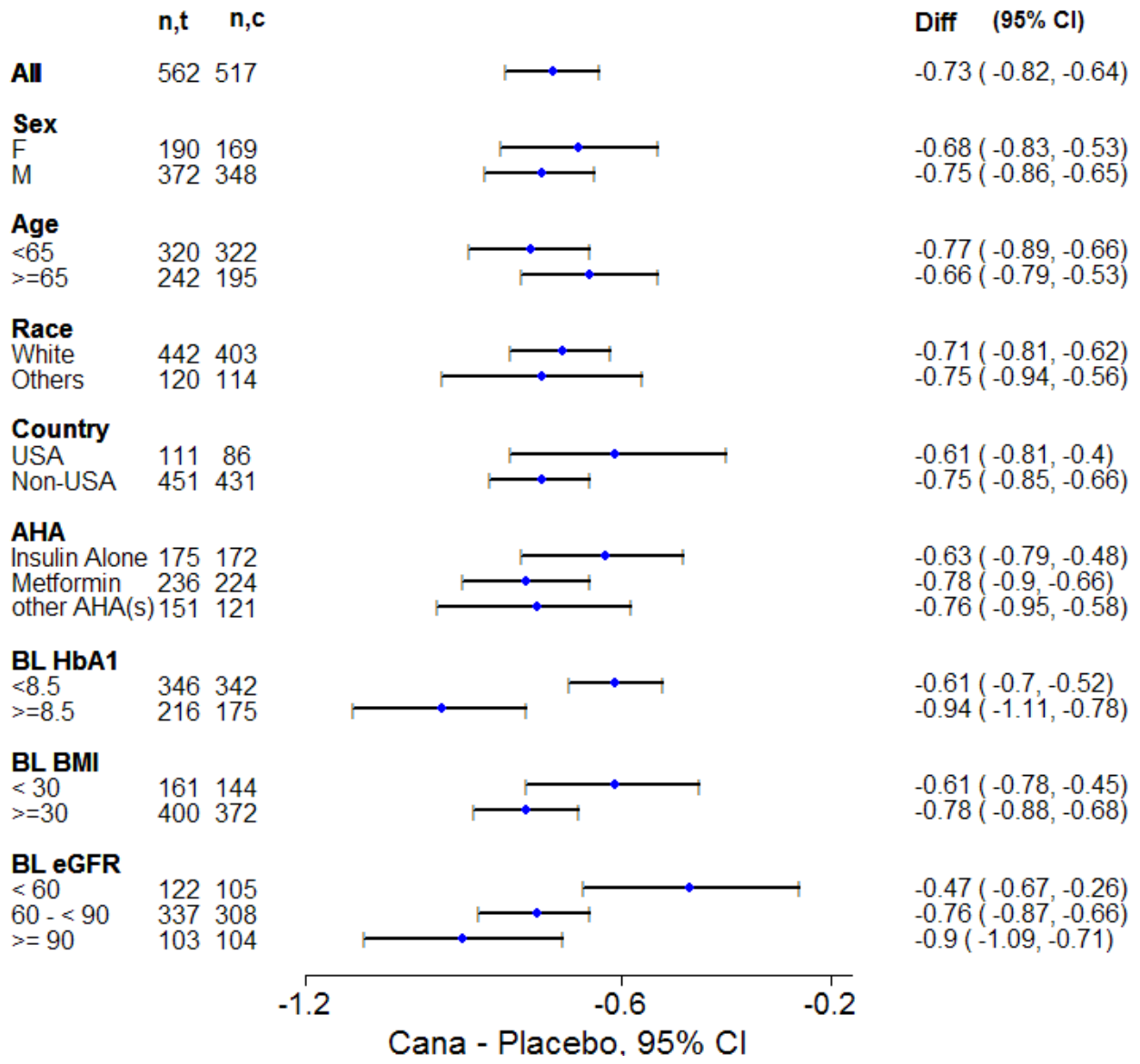


Appendix Figure 11.9. The Forest Plot of HbA1c Changes from Baseline to Week 18 between Canagliflozin and placebo Treatments in Study DIA3008 (INS, pop2, LOCF).

AHA: Insulin alone; Insulin + metformin; Insuline + other AHA(s)
CANA 100 mg vs. Placebo



CANA 300 mg vs. Placebo



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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	204042
Drug Name:	Canagliflozin tablets
Indication(s):	Treatment of type 2 diabetes mellitus
Applicant:	Janssen Research and Development, LLC
Date(s):	Letter date 5/31/2012 PDUFA Goal Date: 03/31/2013
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
Statistical Reviewer:	Eugenio Andraca-Carrera, Ph.D.
Concurring Reviewers:	Mat Soukup, Ph.D. Aloka Chakravarty, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products (DMEP)
Clinical Team:	Medical Officer: Hyon Kwon, MD Medical Team Leader: Jean-Marc Guettier, MD
Project Manager:	Jena M. Weber (DMEP)

Keywords: type 2 diabetes mellitus, cardiovascular safety

1 Executive Summary

The proposed indication of canagliflozin is as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM). The proposed therapeutic dosage is 100 mg or 300 mg, orally, once daily. Per the request of the Division of Metabolism and Endocrinology Products this statistical review evaluates the cardiovascular (CV) safety of canagliflozin in 9 Phase 2 and Phase 3 randomized clinical trials (trials 2001, 3002, 3004, 3005, 3006, 3008/CANVAS, 3009, 3010 and 3012). This review focuses on the pre-marketing evaluation of cardiovascular safety of canagliflozin. A separate statistical review addressing the efficacy and glycemic control of canagliflozin is being conducted by Dr. Wei Liu.

1.1 Conclusions and Recommendations

The Sponsor evaluated the CV safety of canagliflozin through a meta-analysis of 9 randomized, controlled Phase 2 and Phase 3 trials, including a dedicated cardiovascular outcomes trial, Study 3008, also known as CANVAS. The 9 trials had different inclusion and exclusion criteria as described in Section 3.1.1 of this review. Notably, CANVAS enrolled subjects with higher baseline cardiovascular risk than the other trials.

The agreed upon population of interest in the meta-analysis consisted of all randomized subjects in the 9 trials who took at least 1 dose of the double-blind study medication. The comparator group in the meta-analysis was comprised of all non-canagliflozin randomized groups and included glimepiride (n=482), sitagliptin (n=366) and placebo (n=2479).The primary agreed upon safety endpoint of interest was major adverse cardiovascular events plus (MACE-plus), a composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and hospitalizations due to unstable angina. An Endpoint Adjudication Committee reviewed and adjudicated all possible cardiovascular events in the 9 trials.

There were 130 MACE-plus observed among 6396 subjects in the canagliflozin treatment group and 71 MACE-plus observed among 3327 subjects in the comparator group in the 9 trials utilized in the meta-analysis. The dedicated cardiovascular outcomes trial CANVAS contributed 108 MACE-plus among 2886 subjects in the canagliflozin treatment group and 53 MACE-plus among 1441 in the placebo group. The pre-specified Cox proportional hazards model with two strata (CANVAS and non-CANVAS trials) including all 9 trials yielded an estimated hazard ratio of canagliflozin vs. all comparators of **0.91** with 95% confidence interval **(0.68, 1.21).** The upper bound of this 95% confidence interval is below the risk margin of 1.8 necessary to show adequate cardiovascular safety of new antidiabetic products in accordance to the FDA Diabetes Guidance for assessing cardiovascular safety (2008). However, the data showed some evidence to suggest that the assumption of proportional hazards necessary to interpret the pre-specified Cox proportional hazards model may not have been met.

An imbalance of MACE-plus was observed during the first 30 days in CANVAS. During that time, 13 MACE-plus were observed among 2886 subjects on canagliflozin and 1 MACE-plus was observed among 1441 subjects on placebo. The estimated hazard ratio and 95% confidence

interval comparing canagliflozin to placebo during the first 30 days of CANVAS was 6.49 (0.85, 49.64). Based on the small number of events observed during this early period of CANVAS, it is not possible to determine whether the observed imbalance of MACE-plus during the first 30 days of CANVAS may be attributable to chance. This issue is discussed in more detail in Section 3.1.6.4 of this document.

The estimated hazard ratio of MACE-plus comparing canagliflozin to placebo in CANVAS after the first 30 days was 0.89 (0.64, 1.25). The estimated hazard ratio of MACE-plus in the 8 trials excluding CANVAS was 0.64 (0.34, 1.19). Both upper bounds of these 95% confidence intervals meet the risk margin of 1.8 set forth in the FDA Diabetes Guidance for assessing cardiovascular safety. A summary of these findings is shown in Table 1.

Table 1. Primary and Secondary Analyses of MACE-plus

	Canagliflozin (events / N)	Comparators (events / N)	Hazard Ratio (95% CI)
Primary Analysis (including all 9 trials)	**130 / 6396**	**71 / 3327**	**0.91 (0.68, 1.21)**
Secondary Analyses			
First 30 Days in CANVAS	13 / 2886	1 / 1441	6.49 (0.85, 49.64)
After first 30 Days in CANVAS	95 / 2867	52 / 1435	0.89 (0.64, 1.25)
Non-CANVAS trials	22 / 3510	18 / 1886	0.64 (0.34, 1.19)

Source: Created by reviewer. Dataset: adttecv.xpt

Subgroup analyses were consistent with the results shown in Table 1. There was no evidence of an interaction between the use of canagliflozin and any of the following variables in terms of risk of MACE-plus: gender, race, age, country of randomization, BMI, prior cardiovascular disease, baseline statin use or baseline eGFR.

The upper bound of the 95% confidence interval for the hazard ratio of MACE-plus comparing canagliflozin to comparators based on the primary pre-specified Cox model met the 1.8 hazard ratio margin set forth in the FDA Diabetes Guidance. This margin was also met in secondary analyses excluding CANVAS, and in CANVAS after the first 30 days post-randomization.

However, the data showed some evidence of non-proportional hazards due primarily to an early imbalance of MACE-plus observed during the first 30 days of CANVAS. We recommend that the higher rate of MACE-plus associated with canagliflozin observed during the first 30 days of CANVAS be interpreted with consideration to the clinical plausibility of this finding in a population with high baseline cardiovascular risk. We recommend that future clinical trials for canagliflozin in populations with high baseline cardiovascular risk are designed not only to evaluate long-term cardiovascular risk, but also to collect clinically relevant information to better understand the mechanism of early events.

1.2 Brief Overview of Clinical Studies

Janssen submitted data for one Phase 2 trial (Study 2001), seven Phase 3 trials (Studies 3002, 3004, 3005, 3006, 3009, 3010 and 3012) and one dedicated cardiovascular safety trial, CANVAS, in support of this application. All trials, except for CANVAS, were designed to evaluate the change in glycosylated hemoglobin (HbA1c) from baseline associated with canagliflozin in subjects with type 2 diabetes. CANVAS was designed to compare the cardiovascular safety of canagliflozin to placebo. The background therapy and inclusion criteria were not consistent across the 9 trials: trial 3004 enrolled subjects with moderate renal impairment, trial 3009 enrolled older subjects, and CANVAS enrolled subjects with cardiovascular risk factors. A detailed discussion of the design of these trials is provided in Section 3.1.1.

1.3 Statistical Issues and Findings

In the Statistical Analysis Plan (SAP) to assess Cardiovascular Safety submitted to IND 76479 on 13 July 2010 and agreed upon by the FDA, it was determined that the CV safety of canagliflozin would be evaluated through a meta-analysis of Phase 2 and Phase 3 clinical trials for canagliflozin, including the dedicated cardiovascular trial CANVAS.

The meta-analysis was designed to demonstrate that the hazard ratio of MACE-plus associated with canagliflozin relative to all comparators is smaller than the risk margin of 1.8 set forth in the FDA Diabetes Guidance for assessing cardiovascular safety. The pre-specified primary model was a Cox proportional hazards model with two strata: CANVAS and non-CANVAS trials. The estimated hazard ratio was **0.91** with 95% confidence interval **(0.68, 1.21)** as discussed in Section 1.1.

A test to rule out a hazard ratio of MACE-plus larger than 1.3 with a two-sided α=0.001 was planned to be conducted at the same time as the pre-specified meta-analysis assessment of the HR risk margin of 1.8. The estimated 99.9% confidence interval for the hazard ratio of MACE-plus based on the primary Cox model was (0.56, 1.48), and therefore the upper bound of the 99.9% confidence interval did not rule out a hazard ratio of 1.3 at this time as pre-specified. Based on the agreed-upon SAP, the Sponsor plans to conduct future analyses to rule out a hazard ratio risk margin of 1.3 after 500 and 700 MACE-plus have been observed in the canagliflozin development program. Section 3.1.3.1 discusses the proposed plan in more detail.

Secondary analyses assessed the hazard ratio of MACE and individual components of MACE-plus associated with canagliflozin. A summary of these findings is shown in Table 2. The estimated hazard ratio and 95% confidence interval for MACE, cardiovascular death, myocardial infarction, and hospitalized unstable angina show no statistical evidence of increased risk associated with canagliflozin. The only secondary endpoint with estimated hazard ratio larger than 1 was stroke: 1.46 (0.83, 2.58). Detailed results are provided in Section 3.1.6.

Table 2. Components of MACE-plus in All Trials in the Meta-analysis

	Canagliflozin N= 6396	Comparators N = 3327	Hazard Ratio (95% CI)
MACE	104	53	0.98 (0.70, 1.36)
CV Death	21	16	0.65 (0.34, 1.24)
MI	45	27	0.83 (0.51, 1.34)
Stroke	47	16	1.46 (0.83, 2.58)
Hospitalized unstable angina	26	18	0.71 (0.39, 1.30)

Source: Created by reviewer. Dataset: adttecv.xpt

2 Introduction

2.1 Product Description and Regulatory Background

Canagliflozin is a subtype 2 sodium-glucose transport protein (SGLT2) inhibitor. The proposed indication of canagliflozin is as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM). The proposed dosage is 100 mg or 300 mg, orally, once daily.

On 31 May 2012, Janssen submitted a meta-analysis of cardiovascular events conducted in nine randomized clinical trials for canagliflozin as part of their application package for NDA 204042. The meta-analysis included one Phase 2 trial (Study 2001), seven Phase 3 trials (Studies 3002, 3004, 3005, 3006, 3009, 3010 and 3012) and one dedicated cardiovascular safety trial, Study 3008, also referred to as CANVAS. The development program for canagliflozin was designed to observe a sufficient number of cardiovascular events in order to assess the risk criteria set forth in the FDA Diabetes Guidance for evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes (2008)[1]. The criteria set forth in the Guidance reads:

> *For completed studies, before submission of the new drug application (NDA)/biologics license application (BLA):*
>
> - *Sponsors should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8.*

This review addresses Janssen's submission of NDA 204042 on 31 May 2012.

2.2 Clinical Trial Overview

Janssen conducted analyses to assess the cardiovascular safety of canagliflozin through a meta-analysis of 9 randomized, controlled, clinical trials. Table 3 summarizes the design, duration and sample size of these trials. The datasets provided in the NDA submission for CANVAS were locked on January 31, 2012. At that time, all trials in the meta-analysis except for DIA2001 were ongoing.

2.3 Data Sources

The applicant submitted electronic documents and datasets for 9 trials: DIA2001, DIA3002, DIA3004, DIA3005, DIA3006, DIA3008/CANVAS, DIA3009, DIA3010 and DIA3012. Baseline characteristics of subjects randomized in these nine trials were collected in dataset ADSL. Subjects' clinical trial disposition data were collected in dataset ADDS. The applicant

compiled the data necessary to conduct time to event analyses of cardiovascular endpoints across these nine trials in datasets ADTTECV and ADTTECVM. The time to event data for individual components of the composite cardiovascular endpoint were collected in dataset ADTTEVNT.

Clinical study reports (CSRs) of each individual trial were reviewed to evaluate trial protocols.

The following file folder available within the CDER Electronic Document Room (EDR) was used in this review:

\\Cdsesub1\evsprod\NDA204042\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus

The format, content and documentation of the data submitted in support of this application was adequate to conduct a statistical review of the cardiovascular risk associated with canagliflozin.

Table 3. List of Trials Included in the CV Meta-Analysis, mITT Population

Trial ID	Phase	Duration of Treatment	Total Sample Size	Canagliflozin (N)		Control (N)		
				100 mg	300 mg	Placebo	Glimepiride	Sitagliptin
DIA2001	2	12 weeks	193	64	64	65	-	-
DIA3002	3	52 weeks	469	157	156	156	-	-
DIA3004	3	52 weeks	269	90	89	90	-	-
DIA3005	3	52 weeks	675	242	241	192	-	-
DIA3006	3	52 weeks	1284	368	367	183	-	366
CANVAS	3	Not fixed	4327	1445	1441	1441	-	-
DIA3009	3	104 weeks	1450	483	485	0	482	-
DIA3010	3	104 weeks	714	241	236	237	-	-
DIA3012	3	52 weeks	342	113	114	115	-	-

Source: Created by reviewer from Integrated Summary of Safety and dataset adttecv.xpt

3 Statistical Evaluation

This review focuses on the analysis of cardiovascular risk in the nine trials included in the pre-specified meta-analysis, and the analysis of cardiovascular risk in CANVAS alone. For a complete statistical evaluation of efficacy results, please refer to the review authored by Dr. Wei Liu.

3.1 Evaluation of Safety

3.1.1 Trial Designs

Nine trials were included in the meta-analysis of cardiovascular events: DIA2001, DIA3002, DIA3004, DIA3005, DIA3006, DIA3008/CANVAS, DIA3009, DIA3010 and DIA3012.

Datasets for these trials were locked on 31 January 2012. At that time, study DIA2001 had been completed. Studies DIA3002, 3004, 3005, 3006, 3009, 3010 and 3012 had completed their core treatment period to evaluate efficacy (varying between 26 and 52 weeks) and were following subjects in pre-specified double-blind extension periods to evaluate the safety and tolerability of canagliflozin. Study DIA3008/CANVAS has completed recruiting subjects at the time of database lock and continues to follow subjects to assess cardiovascular safety.

A description of the 9 trials used in the meta-analysis of MACE-plus is provided below.

DIA2001 is a Phase 2 trial titled: "A Randomized, Double-Blind, Placebo-Controlled, Double-Dummy, Parallel-Group, Multicenter, Dose-Ranging Study in Subjects With Type 2 Diabetes Mellitus to Evaluate the Efficacy, Safety, and Tolerability of Orally Administered SGLT2 Inhibitor JNJ-28431754 With Sitagliptin as a Reference Arm". The primary objective of this trial was to compare the effects of canagliflozin to placebo on the change in glycosylated hemoglobin (HbA1c) from baseline to week 12 in subjects with T2DM. The trial included seven treatment arms: placebo, sitagliptin 100 mg qd, and canagliflozin doses: 50 mg qd, 100 mg qd, 200 mg qd, 300 mg qd and 300 mg bid. The trial had the following inclusion criteria: men or women aged 18 to 65, with HbA1c levels ≥7% and ≤10.5% at screening, stable daily does of metformin, a BMI between 25 and 45 kg/m² and with a serum creatinine concentration <1.5 mg/dL (137 μmol/L) for men and <1.4 mg/dL (128 μmol/L) for women. This trial was conducted between March 2008 and January 2009.

***Reviewer Comment**: The meta-analysis reviewed in this document only includes subjects in Trial DIA2001 who were randomized to placebo (n=65), canagliflozin 100 mg qd (n=64) and canagliflozin 300 mg qd (n=64).*

DIA3002 is a Phase 3 trial titled: "A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicenter Study, to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate

Glycemic Control on Metformin and Sulphonylurea Therapy". The trial had a 26-week core treatment period and a 26-week double-blinded extension period. The primary objectives of this trial were to assess the effect of canagliflozin relative to placebo on HbA1c after 26 weeks of treatment and to assess the safety and tolerability of canagliflozin. A total of 469 subjects were randomized in a 1:1:1 ratio to once daily canagliflozin 100 mg (n=157), canagliflozin 300 mg (n=156) or placebo (n=156). The trial had the following inclusion criteria: men or women age 18 to 80 with T2DM, HbA1c levels ≥7% and ≤10.5% on the combination of metformin and sulphonylurea (SU). This trial was started on April 2010. According to clinicaltrials.gov, the study's completion date was March 2012. The NDA submission reviewed in this document includes data up to January 31, 2012.

DIA3004 is a Phase 3 trial titled: "A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, 26-Week, Multicenter Study With a 26-Week Extension, to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Compared in the Treatment of Subjects With Type 2 Diabetes Mellitus Who Have Moderate Renal Impairment". The trial had a 26-week core treatment period and a 26-week double-blinded extension period. The primary objective of this trial was to assess the effect of canagliflozin relative to placebo on HbA1c after 26 weeks of treatment. A total of 272 subjects were randomized to placebo (n=91), canagliflozin 100 mg (n=90) and canagliflozin 300 mg (n=91). The trial had the following inclusion criteria: men or women of at least 25 years of age with T2DM, HbA1c levels ≥7% and ≤10.5% at screening, moderate renal impairment defined as eGFR values ≥30 and <50 mL/min/1.73m² with generally stable renal function, not on antihyperglycemic agent (AHA) therapy, and fasting plasma glucose (FPG) ≤ 270 mg/dL (15 mmol/L) at screening. This trial was started on March 2010. According to clinicaltrials.gov, the study's completion date was August 2012. The NDA submission reviewed in this document includes data up to January 31, 2012.

DIA3005 is a Phase 3 trial titled: "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin as Monotherapy in the Treatment of Subjects With Type 2 Diabetes Mellitus Inadequately Controlled With Diet and Exercise". This trial was composed of a main study and a high glycemic substudy. Only the main study is included in the CV meta-analysis and therefore only the main study is described here. The main study had a 26-week core treatment period and a 26-week double-blinded extension period. The primary objective of the main study was to assess the effect of canagliflozin relative to placebo on HbA1c after 26 weeks of treatment. A total of 587 subjects were randomized to placebo (n= 194), canagliflozin 100 mg (n= 196) and canagliflozin 300 mg (n=197). The trial had the following inclusion criteria: men or women age 18 to 80 with T2DM who met one of the following two criteria: 1. not on an AHA at screening with HbA1c levels ≥7% and ≤10%, or 2. on an oral AHA in monotherapy, or a low dose combination therapy of metformin and SU, with HbA1c levels ≥7% and ≤10% and FPG <270 mg/dL. This trial was started on February 2010. According to clinicaltrials.gov, the study's completion date was March 2012. The NDA submission reviewed in this document includes data up to January 31, 2012.

DIA3006 is a Phase 3 trial titled: "A Randomized, Double-Blind, Placebo- and Active-Controlled, 4-Arm, Parallel Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 (Canagliflozin) Compared with Sitagliptin and Placebo in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on

Metformin Monotherapy". The trial had a 26-week core treatment period and a 26-week double-blinded extension period. The primary objective of this trial was to assess the effect of canagliflozin relative to placebo on HbA1c after 26 weeks of treatment. A total of 1284 subjects were randomized to placebo (n=183), canagliflozin 100 mg (n=368), canagliflozin 300 mg (n=367), and sitagliptin 100 mg (n=366). The trial had the following inclusion criteria: men or women, age 18 to 80, with T2DM, HbA1c levels ≥7% and ≤10.5% at screening, who were on one of four allowed metformin regimens at screening. This trial was conducted between April 2010 and May 2012. The NDA submission reviewed in this document includes data up to January 31, 2012.

DIA3009 is a Phase 3 trial titled: "A Randomized, Double-Blind, 3-Arm Parallel-Group, 2-Year (104-Week), Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 100 mg and JNJ 28431754 300 mg Compared With Glimepiride in the Treatment of Subjects With Type 2 Diabetes Mellitus Not Optimally Controlled on Metformin Monotherapy". The primary objective of this trial was to assess the effect of canagliflozin relative to glimepiride on HbA1c after 52 weeks of treatment. The double blind treatment phase lasted 104 weeks. A total of 1452 subjects were randomized to canagliflozin 100 mg (n=483), canagliflozin 300 mg (n=485), and glimepiride (n=484). The trial had the following inclusion criteria: men or women, age 18 to 80, with T2DM, who were on one of four allowed metformin regimens at screening with different HbA1c level requirements. This trial was started on August 2009. According to clinicaltrials.gov, the estimated completion date for this trial is January 2013. The NDA submission reviewed in this document includes data up to January 31, 2012.

DIA3010 is an ongoing Phase 3 trial titled: "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Compared With Placebo in the Treatment of Older Subjects With Type 2 Diabetes Mellitus Inadequately Controlled on Glucose Lowering Therapy". The trial had a 26-week core treatment period and a 78-week double-blinded extension period. The primary objective of this trial was to assess the effect of canagliflozin relative to placebo on HbA1c after 26 weeks of treatment in older subjects (55 to 80 years of age, inclusive). A total of 716 subjects were randomized to placebo (n=239), canagliflozin 100 mg (n=241), and canagliflozin 300 mg (n=236). The trial had the following inclusion criteria: men or women aged 55 to 80, with T2DM, HbA1c levels ≥7% and ≤10.0% at screening, BMI between 20 and 40 kg/m², and either not on AHA therapy or on stable AHA regimen with any approved agent. This trial was started on April 2010. According to clinicaltrials.gov, the estimated completion date for this trial is June 2013. The NDA submission reviewed in this document includes data up to January 31, 2012.

DIA3012 is a Phase 3 trial titled: "A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, 26-Week Multicenter Study with a 26-Week Extension to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 (Canagliflozin) Compared with Placebo in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Pioglitazone Therapy". The trial had a 26-week core treatment period and a 26-week double-blind extension period. The primary objective of this study was to assess the effect of canagliflozin relative to placebo on HbA1c after 26 weeks of treatment. A total of 344 subjects were randomized to placebo (n=115), canagliflozin 100 mg (n=115), and canagliflozin 300 mg (n=114). The trial had the following inclusion criteria: men or women aged 18 to 80,

with T2DM, HbA1c levels ≥7% and ≤10.5% at screening on dual combination of metformin and pioglitazone. This trial was started on April 2010. According to clinicaltrials.gov, the study's completion date was July 2012. The NDA submission reviewed in this document includes data up to January 31, 2012.

DIA3008/CANVAS (CANagliflozin cardioVascular Assessment Study) is a Phase 3 trial titled: "A Randomized, Multicenter, Double-Blind, Parallel, Placebo- Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects with Type 2 Diabetes Mellitus". The primary objective of CANVAS is to demonstrate that canagliflozin is not associated with increased risk of MACE-plus compared to placebo. A total of 4330 subjects have been randomized to placebo (n=1442), canagliflozin 100 mg (n=1445), and canagliflozin 300 mg (n=1443). Enrollment in CANVAS has completed, but subjects are being followed to assess cardiovascular risk. The trial had the following inclusion criteria: men or women with a diagnosis of T2DM, HbA1c levels ≥7% and ≤10.5% at screening, either (1) not on AHA therapy or (2) on AHA monotherapy or combination therapy with any approved agent., history or high risk of CV disease defined as either (1) age ≥ 30 with documented symptomatic atherosclerotic CV disease or (2) age ≥ 50 with 2 or more risk factors for CV disease at the time of screening. The first subject in CANVAS was enrolled on November 2009. The last subjects enrolled in CANVAS received their first dose of randomized treatment on March 2011. The NDA submission reviewed in this document includes data up to January 31, 2012.

***Reviewer's Comments**: MACE-plus observed in CANVAS represent approximately 80% of the events in the meta-analysis submitted to rule out a hazard ratio of MACE-plus greater than 1.8 associated with the use of canagliflozin. Post-marketing analyses are planned to rule out a hazard ratio greater than 1.3. A more detailed discussion of future analyses in CANVAS and across all trials in the meta-analysis is found in Section 3.1.3.*

3.1.2 Endpoints and Adjudication Methods

3.1.2.1 Primary Composite Endpoint

The primary endpoint of the meta-analysis is the time until first Major Adverse Cardiovascular Event–plus (MACE-plus), defined as any of the following adjudicated events: cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke, or hospitalization due to unstable angina.

The time to event analysis is calculated from the time of a subject's first dose of randomized treatment to the occurrence of MACE-plus. Subjects without an observed MACE-plus are censored 30 days after their last recorded dose. The dataset submitted for the meta-analysis of CV events was locked on January 31, 2012. All trials in the meta-analysis were ongoing at that date, except for DIA2001. All subjects who were being followed and had not experienced an event on January 31, 2012 are censored at this date.

3.1.2.2 Secondary Composite Endpoint

The secondary endpoint is the time until first Major Adverse Cardiovascular Event (MACE), a composite event including cardiovascular death, nonfatal myocardial infarction and nonfatal stroke, but excluding hospitalization due to unstable angina. Censoring rules for MACE are the same as those implemented for MACE-plus.

3.1.2.3 Adjudication Methods

An Endpoint Adjudication Committee (EAC) was convened to review and adjudicate possible cardiovascular events from all trials in the canagliflozin development program. The EAC is composed of independent physicians and includes no Sponsor representatives. The EAC charter was submitted to the FDA as part of the application package for NDA 204042.

According to the EAC charter, its members adjudicated and classified the following CV events in a blinded manner: cardiovascular death / all deaths, nonfatal myocardial infarction, nonfatal stroke, hospitalized unstable angina, hospitalized congestive heart failure, and venous thromboembolism. The EAC members, procedures and event definitions are detailed in the submitted charter.

Reviewer's comment: *The formation of the EAC addresses the Guidance for Industry recommendation that reads: "Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials." The adjudication process appears adequate from a statistical perspective.*

3.1.3 Statistical Methodologies

Section 3.1.3.1 discusses the pre-specified statistical analysis plan submitted by the Sponsor to rule out a hazard ratio risk margin of MACE-plus greater than 1.8 associated with canagliflozin, as well as the plan to rule out a hazard ratio risk margin greater than 1.3. These margins are set forth in the Diabetes Guidance for assessing cardiovascular risk.

Section 3.1.3.2 discusses the statistical methodology used in the primary meta-analysis of MACE-plus in the nine Phase 2 and Phase 3 trials.

Section 3.1.3.3 discusses secondary pre-specified analyses and post-hoc analyses conducted as a result of an imbalance of early events observed in CANVAS.

Section 3.1.3.4 discusses methods to evaluate trial heterogeneity.

3.1.3.1 Pre-Specified Statistical Analysis Plan to Meet the FDA Diabetes Guidance Requirements

According to the Statistical Analysis Plan (SAP) to assess Cardiovascular Safety submitted to IND 76479 on 13 July 2010, a single meta-analysis will be conducted to rule out a hazard ratio greater than 1.8 if at least 160 MACE-plus have been observed in the canagliflozin development program at the time of the NDA submission. No other analyses will be conducted to rule out a hazard ratio greater than 1.8. The single meta-analysis will successfully rule out a hazard ratio of 1.8 if the upper bound of a one-sided 97.5% confidence interval for the HR of MACE-plus is less than 1.8. Assuming that canagliflozin has no effect on the incidence of MACE-plus (true hazard ratio equal to 1), the pre-specified meta-analysis with 160 events will have approximately 94% power to rule out a hazard ratio greater than 1.8.

If fewer than 160 total events have observed at the time of the NDA submission, 2 pre-specified interim analyses were planned that adequately control for multiplicity.

Analyses designed to rule out a hazard ratio of 1.3 are pre-specified in the SAP using a sequential approach. The first analysis to test against a hazard ratio of 1.3 was pre-specified with a two-sided α=0.001 that was planned to be conducted at the same time as the pre-specified meta-analysis assessment of the HR risk margin of 1.8. If the upper-bound of the 99.9% confidence interval of the HR for MACE-plus in the meta-analysis is less than 1.3, then it will successfully exclude a HR of 1.3. The second pre-planned meta-analysis to test against a HR risk margin of 1.3 will be conducted with a two-sided α=0.015 after approximately 500 events are observed in the canagliflozin program. A final pre-planned meta-analysis will be conducted after approximately 700 events have occurred with a two-sided α=0.045. The alpha-spending function to rule out a hazard ratio of 1.3 corresponds to a Lan-DeMets function with an O'Brien Fleming boundary and a cumulative α=0.05.

According to the SAP, 500 and 700 events are expected to be observed in the canagliflozin program approximately 2 years and 4 years post-approval respectively. The majority of these events will be observed in the ongoing CANVAS trial.

Reviewer's comment 1:
Since a total of 201 MACE-plus have been observed and are included in the current submission, a single meta-analysis was conducted in accordance with the pre-specified SAP to attempt to rule out a hazard ratio risk margin of MACE-plus greater than 1.8 associated with canagliflozin compared to all comparators.

Reviewer's comment 2:
According to an Addendum to the Statistical Analysis Plan to establish cardiovascular safety (submitted by the Sponsor on 13 March 2012), the pooled results of the Phase 3 program showed dose-related increases in LDL-cholesterol associated with canagliflozin relative to placebo. According to the Addendum "the Study Steering Committee and the Sponsor felt that the integrity of CANVAS as an independent CV outcome study could be impacted by the release of this information, which reflects the primary endpoint results for CANVAS".

According to this Addendum, the ongoing CANVAS will continue to follow already enrolled subjects with the objective of demonstrating CV safety, defined as ruling out a hazard ratio for MACE-plus greater than 1.3. At the present time, CANVAS has finished enrolling subjects. According to the Addendum, all subjects enrolled in the trial, site personnel and local Sponsor personnel who are monitoring the study sites will remain blinded to treatment assignment until CANVAS is completed. However, it is possible that trial participants and personnel may be partially unblinded to treatment assignment due to subjects' changes in LDL-cholesterol. In addition, cardiovascular outcome data from CANVAS and the meta-analysis of cardiovascular outcomes were presented by both the sponsor and the Agency in an open public advisory committee meeting held on January 10, 2012.

The ability of the ongoing CANVAS trial and the present meta-analysis to rule out a hazard ratio of MACE-plus greater than 1.8 associated with canagliflozin is not compromised by this potential partial unblinding. However, future analyses designed to rule out a hazard ratio risk margin of 1.3 may be impacted. Therefore, the post-marketing requirements for ruling out a HR risk margin of MACE-plus greater than 1.3 associated with canagliflozin should be discussed in light of these issues.

3.1.3.2 Primary Analysis

The agreed upon primary meta-analysis compares the hazard ratio of MACE-plus in subjects randomized to canagliflozin 100 mg or 300 mg once daily versus subjects randomized to all comparators using a Cox proportional hazards model with two strata: CANVAS and non-CANVAS. The meta-analysis includes the 9 Phase 2 and Phase 3 clinical trials described earlier. Kaplan-Meier curves will be provided to compare the survival functions of MACE-plus in both treatment groups graphically.

The proportional hazards assumption of the primary Cox model will be evaluated graphically by plotting the scaled-Schoenfeld residuals of the model against time. If the assumption of proportional hazards in the pre-specified proportional hazards model is not met, post-hoc analyses will be conducted to evaluate time intervals where proportionality holds.

Reviewer's comment:
The pre-specified Cox proportional hazards model contains only two strata: CANVAS and non-CANVAS. When combining data across trials, it is advisable to stratify by each trial. The review team conducted sensitivity analyses with a Cox proportional hazards model stratified by each of the nine trials in the meta-analysis and found the results to be similar to those of the pre-specified model with two strata. Therefore, we do not discuss stratification further in this review.

3.1.3.3 Secondary Analyses

The following secondary analyses were pre-specified and are discussed in this review:

- Cox proportional hazards model of individual components of MACE-plus in the nine trials in the meta-analysis, stratified by CANVAS and non-CANVAS.
- Cox proportional hazards model for MACE-plus in CANVAS alone.
- Cox proportional hazards model for MACE-plus in non-CANVAS trials.
- Analysis of MACE-plus by subgroups defined by sex, age group, race, geographic region of randomization, baseline eGFR, prior CV disease and baseline statin use.
- Cox proportional hazards model of MACE in the nine trials in the meta-analysis, stratified by CANVAS and non-CANVAS.

The following post-hoc analyses were conducted after observing an imbalance of MACE-plus within the first 30 days of CANVAS and a potential violation of the assumption of proportional hazards in the primary model:

- Cox proportional hazards model for MACE-plus during the first 30 days of CANVAS.
- Cox proportional hazards model for MACE-plus after the first 30 days of CANVAS.

The following additional sensitivity analysis was conducted:

- Cox proportional hazards model for MACE-plus comparing canagliflozin 100 mg versus canagliflozin 300 mg.

3.1.3.4 Evaluation of Heterogeneity between Trials

The stratified Cox model allows for different baseline hazards across strata, but assumes that the effect of treatment, the hazard ratio, is constant across strata. Testing for a difference in hazard ratios is equivalent to testing for an interaction of treatment by strata in the Cox model. Given that only CANVAS was powered to evaluate cardiovascular safety, few MACE-plus are expected to be observed in each of the other trials in the meta-analysis. Therefore a test for interaction of treatment by trial in the primary Cox model would have limited power to detect differences in the hazard ratios between trials. Consequently, we do not test for the interaction of treatment and strata in this review.

Different trials' populations were heterogeneous by design as can be seen from their inclusion criteria. Subjects in CANVAS had higher baseline CV risk on average than subjects in other trials in the meta-analysis. The influence of CANVAS on the meta-analysis is assessed by conducting the primary meta-analysis of all nine trials and secondary analyses of CANVAS alone and non-CANVAS trials alone.

3.1.4 Populations

The meta-analysis was conducted on a modified intent-to-treat (mITT) population consisting of all randomized subjects who took at least 1 dose of the double-blind study medication. Subjects without an observed MACE-plus were censored at 30 days after their last recorded dose or 31

January 2012, whichever occurred first. The mITT population for the 9 trials includes 6,396 subjects randomized to canagliflozin and 3,327 subjects randomized to comparators.

3.1.5 Subject Disposition, Demographics and Baseline Characteristics

3.1.5.1 Characteristics of All Trials in the Meta-Analysis

Table 4 shows that baseline demographic characteristics pooled across the 9 trials were similar between subjects randomized to canagliflozin and subjects randomized to comparators. There were no noticeable imbalances in these characteristics.

Table 5 shows baseline cardiovascular risk factors pooled across the 9 trials included in the meta-analysis. Again, the two treatment groups appear balanced beyond small differences reasonably explained by chance.

Table 4. Baseline Characteristics Pooled across All Trials in Meta-Analysis

	Canagliflozin (*N = 6396*)	**All Comparators** (*N = 3327*)
Percent Female	42.4%	41.2%
Age± SD (years)	59.5 ± 9.5	59.5 ± 9.3
≤ 50 years	16.2%	16.0%
51 – 65 years	57.2%	59.3%
66 - 75 years	22.7%	21.4%
> 75 years	3.9%	3.3%
BMI± SD (kg/m^2)	31.9 ± 6.0	31.8 ± 6.1
≤ 25	10.7%	11.0%
26-30	30.5%	31.0%
> 30	58.8%	58.0%
Race and Ethnicity		
White	72.2%	73.0%
Black	3.9%	3.6%
Asian	16.1%	15.6%
Other / Multiracial	7.8%	7.8%
Region		
North America	36.0%	36.0%
Europe	27.5%	26.6%
Central and South America	6.4%	7.1%
Rest of the World	30.1%	30.4%

Source: Created by reviewer. Dataset: adsl.xpt

Table 5. Baseline Cardiovascular Risk Factors Pooled across All Trials in Meta-Analysis

	Canagliflozin (*N = 6396*)	All Comparators (*N = 3327*)
Baseline eGFR (ml/min)		
< 60	12.4%	13.2%
60-90	54.1%	54.4%
≥ 90	33.5%	32.5%
Daily Cigarette Smoker	14.0%	15.0%
Prior CV Disease	32.5%	32.2%
Statin Use	57.8%	56.4%
SBP > 140 mmHg	38.2%	38.4%
Diabetes Duration ≥ 10 years	49.7%	48.3%

Source: Created by reviewer. Dataset: adsl.xpt

3.1.5.2 Characteristics of CANVAS

Table 6 shows demographic characteristics of subjects in CANVAS. These characteristics are balanced between both treatment arms. Compared to the pooled population of all trials in the meta-analysis in Table 4 (which includes CANVAS), CANVAS enrolled fewer women (34% versus 42%) and slightly older subjects (62.4 versus 59.5 years old).

Table 7 shows baseline cardiovascular risk factors in CANVAS. The risk factors appear balanced between both treatment arms. As expected due to CANVAS' inclusion criteria, subjects enrolled in CANVAS have higher background CV risk than subjects in the pooled population of all trials in the meta-analysis shown in Table 5 (which includes CANVAS). Compared to the other eight trials, subjects in CANVAS were more likely to have prior CV disease (57% versus 32%), use statins (72% versus 57%), have systolic blood pressure greater than 140 mmHg (55% versus 38%), and diabetes duration longer than 10 years (70% versus 49%).

Reviewer's comment:
Overall, the canagliflozin and comparator arms appear balanced in terms of demographic characteristics and cardiovascular risk factors in CANVAS and the pooled non-CANVAS trials.

Table 6. Baseline Characteristics in CANVAS

	Canagliflozin (*N = 2886*)	All Comparators (*N = 1441*)
Percent Female	34.0%	33.7%
Age± SD (years)	62.4 ± 8.1	62.3 ± 7.9
≤ 50 years	6.5%	6.7%
51 – 65 years	58.2%	60.9%
66 - 75 years	30.2%	27.6%
> 75 years	5.2%	4.8%
BMI± SD (kg/m^2)	32.1 ± 6.2	32.1 ± 6.3
≤ 25	11.0%	10.5%

26-30	29.3%	29.9%
> 30	59.8%	59.6%
Race and Ethnicity		
White	73.3%	73.8%
Black	2.4%	2.4%
Asian	18.5%	18.2%
Other / Multiracial	5.9%	5.6%
Region		
North America	28.8%	28.7%
Europe	31.7%	29.2%
Central and South America	3.7%	4.2%
Rest of the World	35.8%	37.9%

Source: Created by reviewer. Dataset: adsl.xpt

Table 7. Baseline Cardiovascular Risk Factors in CANVAS

	Canagliflozin (*N = 2886*)	**All Comparators** (*N = 1441*)
Baseline eGFR (ml/min)		
< 60	15.9%	17.6%
60-90	60.1%	58.5%
≥ 90	24.0%	23.9%
Daily Cigarette Smoker	17.1%	19.4%
Prior CV Disease	57.2%	56.8%
Statin Use	72.2%	71.7%
SBP > 140 mmHg	54.2%	56.1%
Diabetes Duration ≥ 10 years	70.4%	69.6%

Source: Created by reviewer. Dataset: adsl.xpt

3.1.5.3 Follow-up Time by Treatment Arm

At the time of submission, subjects on canagliflozin had been followed for an average of 392 days across all trials, and subjects on comparators had been followed for an average of 381 days. Table 8 shows the average subject follow-up by trial and randomized treatment. Table 9 shows the total number of patient-years used in the meta-analysis by treatment arm and trial. Note that the time of submission all trials except for DIA2001 were still following subjects for cardiovascular outcomes and the information below reflects patient-years of exposure utilizing the 31 January 2012 cutoff date.

Table 8. Mean (SD) Days of Follow-up by Trial

Trial	Canagliflozin	All Comparators
DIA2001	108 (19)	104 (29)
DIA3002	326 (106)	306 (114)
DIA3004	297 (94)	288 (97)
DIA3005	319 (107)	331 (104)
DIA3006	323 (91)	320 (92)
CANVAS	431 (159)	421 (163)
DIA3009	471 (180)	468 (180)
DIA3010	366 (114)	333 (132)
DIA3012	326 (93)	303 (102)
Overall:	392 (158)	381 (160)

Source: Created by reviewer. Dataset: adttecv.xpt

Table 9. Patient-years used in the meta-analysis by Trial

Trial	Canagliflozin	All Comparators
DIA2001	38	19
DIA3002	279	131
DIA3004	145	71
DIA3005	422	174
DIA3006	650	481
CANVAS	3412	1664
DIA3009	1248	618
DIA3010	478	216
DIA3012	203	95
Total:	6876	3470

Source: Created by reviewer. Dataset: adttecv.xpt

Figure 1 shows the percentage of subjects being followed through time in CANVAS by randomized treatment group. Subjects in this plot were censored at the first of the following events: time of first MACE-plus, treatment discontinuation + 30 days, study discontinuation. The plot shows that similar proportions of randomized subjects were being followed at each time point by treatment arm. Based on this plot, we found no evidence to suggest different overall discontinuation rates by randomized treatment in CANVAS.

Figure 2 shows the percentage of subjects being followed through time in the pooled non-CANVAS trials by randomized treatment arm. In a similar fashion to Figure 1, subjects were censored at the earliest of MACE-plus, treatment discontinuation + 30 days or study discontinuation. This plot shows no evidence of differential discontinuation by randomized treatment arm in the pooled non-CANVAS trials.

The reasons for trial discontinuation by trial and treatment arm are given in Table 10. There are no consistent imbalances by reason of discontinuation and treatment arm across trials.

Figure 1. Follow-up time in CANVAS, censored at first MACE-plus, last treatment dose + 30 days or study discontinuation

Source: Created by reviewer. Dataset: adttevnt.xpt

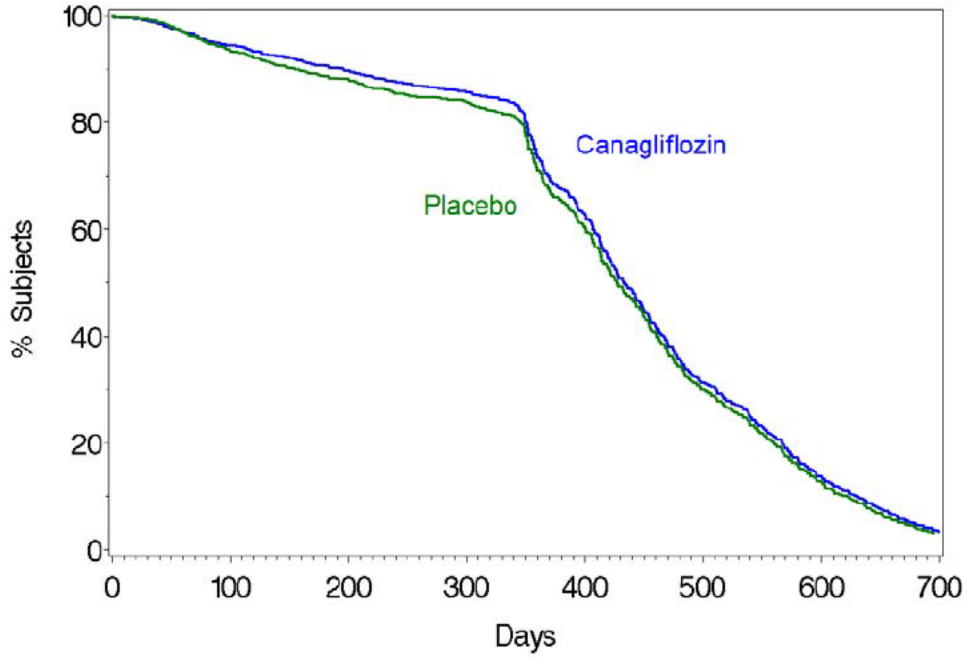


Figure 2. Follow-up time excluding CANVAS, censored at first MACE-plus, last treatment dose + 30 days or study discontinuation

Source: Created by reviewer. Dataset: adttevnt.xpt

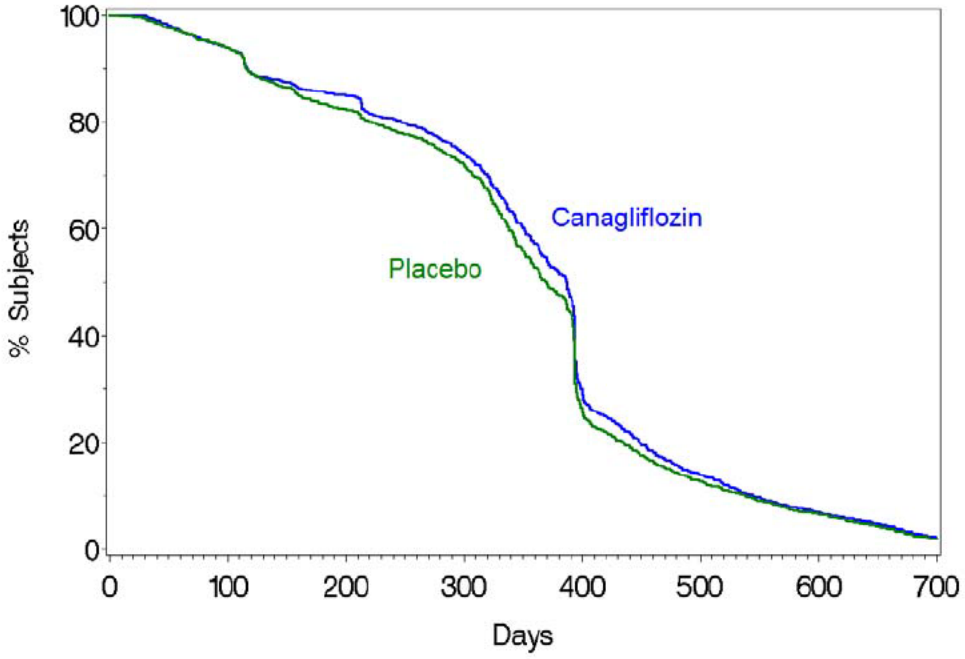


Table 10. Trial Discontinuation Rates by Reason

Trial	Randomized Treatment	Sample Size	Reason for Discontinuation			
			Adverse Event	Lost to Follow-up	Other	Withdrawal of Consent
DIA2001	Canagliflozin	128	5 (3.9%)	0	1 (0.8%)	7 (5.5%)
	Placebo	65	2 (3.1%)	5 (7.7%)	2 (3.1%)	1 (1.5%)
DIA3002	Canagliflozin	313	22 (7.0%)	9 (2.9%)	39 (12.5%)	22 (7.0%)
	Placebo	156	7 (4.5%)	5 (3.2%)	38 (24.4%)	14 (9.0%)
DIA3004	Canagliflozin	179	8 (4.5%)	0	22 (12.3%)	4 (2.2%)
	Placebo	90	5 (5.6%)	1 (1.1%)	13 (14.4%)	5 (5.6%)
DIA3005	Canagliflozin	483	13 (2.7%)	11 (2.3%)	39 (8.1%)	22 (4.6%)
	Placebo	192	2 (1.0%)	5 (2.6%)	31 (16.1%)	19 (9.9%)
DIA3006	Canagliflozin	735	30 (4.1%)	10 (1.4%)	65 (8.8%)	26 (3.5%)
	All Comparators	549	20 (3.6%)	8 (1.5%)	73 (13.3%)	14 (2.6%)
CANVAS	Canagliflozin	2886	172 (6.0%)	22 (0.8%)	249 (8.6%)	64 (2.2%)
	Placebo	1441	54 (3.7%)	22 (1.5%)	183 (12.7%)	52 (3.6%)
DIA3009	Canagliflozin	968	65 (6.7%)	24 (2.5%)	122 (12.6%)	36 (3.7%)
	All Comparators	482	30 (6.2%)	9 (1.9%)	69 (14.3%)	21 (4.4%)
DIA3010	Canagliflozin	477	26 (5.5%)	4 (0.8%)	31 (6.5%)	10 (2.1%)
	Placebo	237	13 (5.5%)	4 (1.7%)	30 (12.7%)	15 (6.3%)
DIA3012	Canagliflozin	227	7 (3.1%)	4 (1.8%)	28 (12.3%)	2 (0.9%)
	Placebo	115	6 (5.2%)	1 (0.9%)	22 (19.1%)	7 (6.1%)
Pooled	Canagliflozin	6396	348 (5.4%)	84 (1.3%)	596 (9.3%)	193 (3.0%)
	All Comparators	3327	139 (4.2%)	60 (1.8%)	461 (13.9%)	148 (4.4%)

Source: Created by reviewer. Dataset: adds.xpt

3.1.6 Analysis Results

3.1.6.1 Descriptive Statistics of Primary Composite MACE-plus

Table 11 shows the number of observed MACE-plus by trial and treatment arm among all randomized subjects in the modified intent-to-treat population in 9 trials in the meta-analysis. There have been 130 MACE-plus observed among 6396 subjects randomized to canagliflozin and 71 MACE-plus among 3327 subjects randomized to comparators. Out of the 201 total events, 161 have been observed in CANVAS.

Table 11. Number of Subjects with MACE-plus by Trial (mITT)

Trial	Canagliflozin 100 mg	Canagliflozin 300 mg	Placebo	Active Comparator
DIA2001	0 /64	0 /64	0 /65	-
DIA3002	1 /157 (0.64%)	0 /156	1 /156 (0.64%)	-
DIA3004	1 /90 (1.11%)	3 /89 (3.37%)	4 /90 (4.44%)	-
DIA3005	0 /242	0 /241	0 /192	-
DIA3006	0 /368	1 /367 (0.27%)	1 /183 (0.55%)	3 /366 (0.82%)
CANVAS	56 /1445 (3.88%)	52 /1441 (3.61%)	53 /1441 (3.68%)	-
DIA3009	5 /483 (1.04%)	4 /485 (0.82%)	-	5 /482 (1.04%)
DIA3010	3 /236 (1.27%)	3 /236 (1.27%)	4 /237 (1.69%)	-
DIA3012	0 /114	1 /114 (0.88%)	0 /115	-
Total:	66 / 3203	64 / 3193	63 / 2479	8 / 848

Source: Created by reviewer. Dataset: adttecv.xpt

Figure 3 shows the time to event for each of the 201 observed MACE-plus. The plot shows a possible imbalance of MACE-plus during the first 30 days in study DIA3008 (CANVAS). During the first 30 days in CANVAS there were 13 MACE-plus observed among 2886 subjects on canagliflozin (0.45%) and 1 event among 1441 subjects on placebo (0.07%) . Table 12 shows a list of these 14 early events. Among the 13 events observed on the canagliflozin arm, 7 occurred among subjects randomized to canagliflozin 100 mg and 6 occurred among subjects randomized to canagliflozin 300 mg. Seven of the 13 events on canagliflozin were observed during the first week after randomization. This early imbalance of MACE-plus in CANVAS is further discussed in Section 3.1.6.4.

Figure 3. Observed Time to MACE-plus by Trial and Treatment

Source: Created by reviewer. Dataset: adttecv.xpt

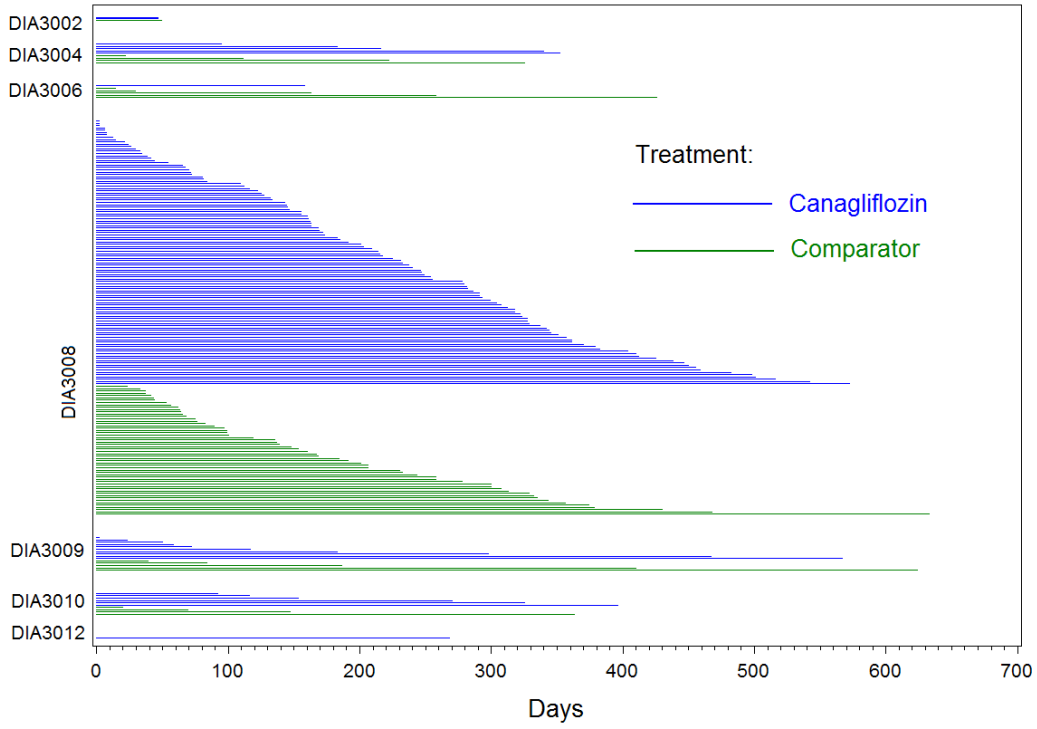


Table 12. MACE-plus observed during the first 30 days in CANVAS

Treatment	Age	Start Date	Event Date	Days to Event	Type of Event
Cana 300 mg	79	(b) (4)	(b) (4)	2	Nonfatal Stroke
Cana 100 mg	65	(b) (4)	(b) (4)	2	Hospitalized Unstable Angina
Cana 100 mg	68	(b) (4)	(b) (4)	2	Nonfatal Stroke
Cana 300 mg	57	(b) (4)	(b) (4)	6	Nonfatal Myocardial Infarction
Cana 300 mg	76	(b) (4)	(b) (4)	6	Nonfatal Myocardial Infarction
Cana 300 mg	54	(b) (4)	(b) (4)	7	Cardiovascular Death
Cana 100 mg	68	(b) (4)	(b) (4)	7	Nonfatal Stroke
Cana 300 mg	37	(b) (4)	3 (b) (4)	12	Nonfatal Myocardial Infarction
Cana 100 mg	57	(b) (4)	(b) (4)	14	Hospitalized Unstable Angina
Cana 100 mg	76	(b) (4)	(b) (4)	21	Nonfatal Myocardial Infarction
Placebo	67	(b) (4)	(b) (4)	23	Nonfatal Myocardial Infarction
Cana 100 mg	61	(b) (4)	(b) (4)	24	Nonfatal Myocardial Infarction
Cana 100 mg	57	(b) (4)	(b) (4)	26	Nonfatal Stroke
Cana 300 mg	56	(b) (4)	(b) (4)	29	Nonfatal Stroke

*Sample size = 2886 on canagliflozin and 1441 on placebo

Source: Created by reviewer. Dataset: adttecv.xpt

Figure 4 shows pooled Kaplan-Meier survival plots and corresponding 95% confidence intervals for MACE-plus for the 9 trials in the meta-analysis. The pooled cumulative probability of MACE-plus appears to be higher in the canagliflozin arm during the first 30 days of the 9 trials. This is consistent with the imbalance in early events observed in Figure 3. After approximately day 40, the cumulative probability of MACE-plus was smaller among subjects randomized to canagliflozin. During the period from approximately 100 days to 250 days, the estimated survival curve for canagliflozin is close to the lower bound of the 95% confidence interval survival curve for the comparators. The survival curves crossed again after approximately 470 days, however at the time of this later crossing, the estimated survival curves have wide confidence intervals due to the smaller number of subjects being followed.

Figure 4. Estimated Probability and 95% CI of MACE-plus by Time in All Trials

Source: Created by reviewer. Dataset: adttecv.xpt

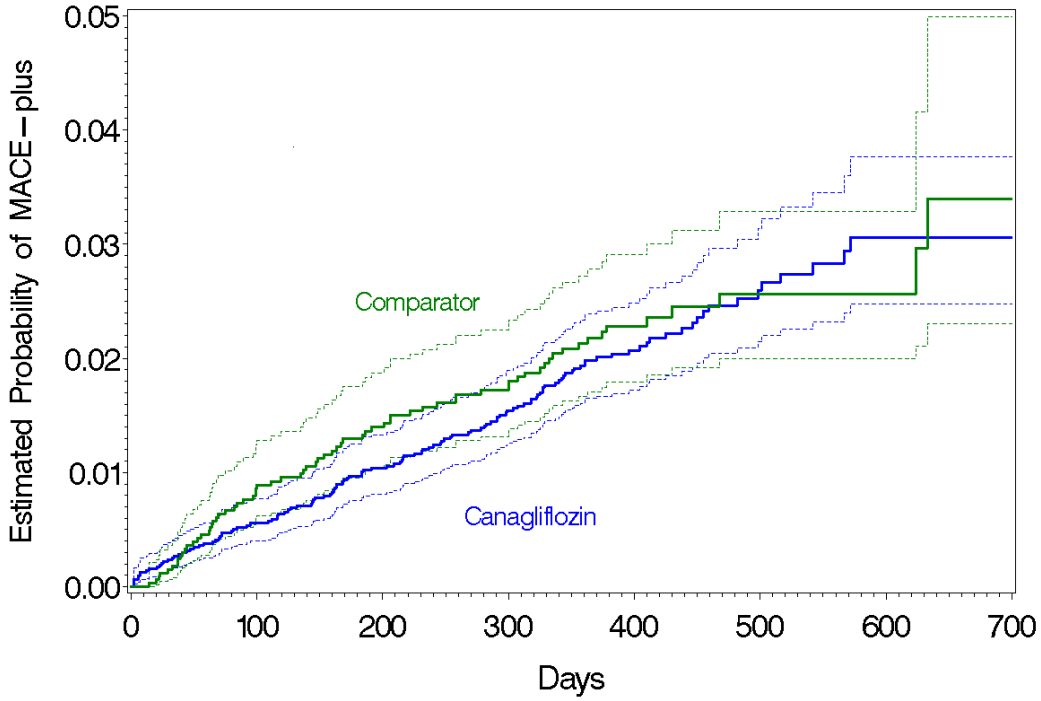


Figure 5 shows survival plots for MACE-plus by treatment arm among subjects in CANVAS. This plot shows that the imbalance of events observed during the first 30 days resulted in a higher observed cumulative probability of MACE-plus associated with canagliflozin up to approximately day 60. Based on this plot, the assumption of proportional hazards through the full duration of CANVAS appears questionable. The assumption of proportionality is discussed in more detail in Section 3.1.6.2.

Figure 6 shows survival plots for all trials in the meta-analysis excluding CANVAS. The observed cumulative probability of MACE-plus associated with canagliflozin was lower than the cumulative probability associated with comparators through the full duration of the trials. The plot shows no imbalance of early events in the pooled trials excluding CANVAS.

Figure 5. Estimated Probability and 95% CI of MACE-plus by Time in CANVAS
Source: Created by reviewer. Dataset: adttecv.xpt

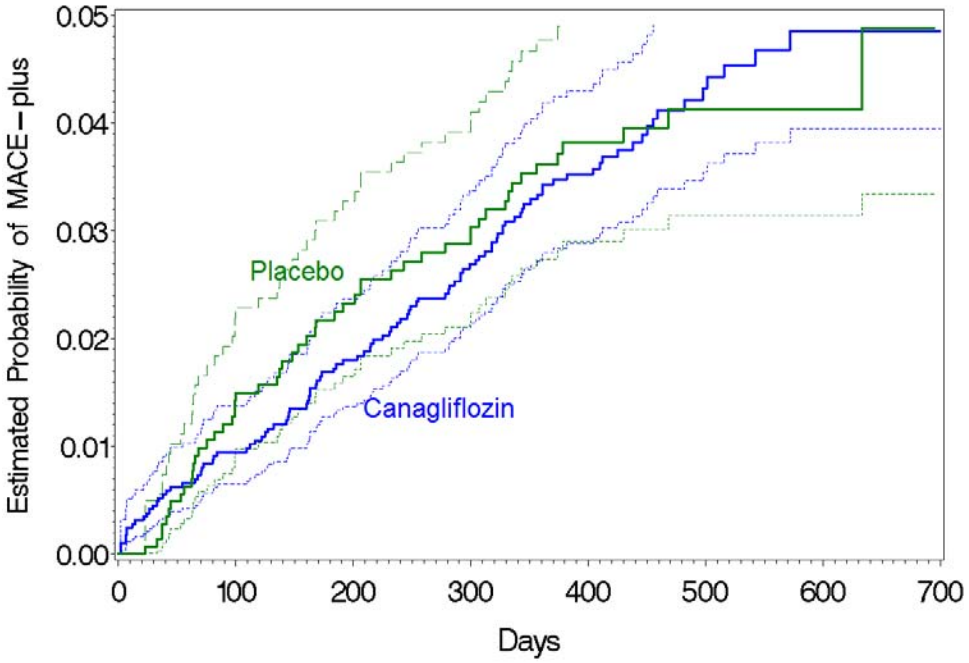
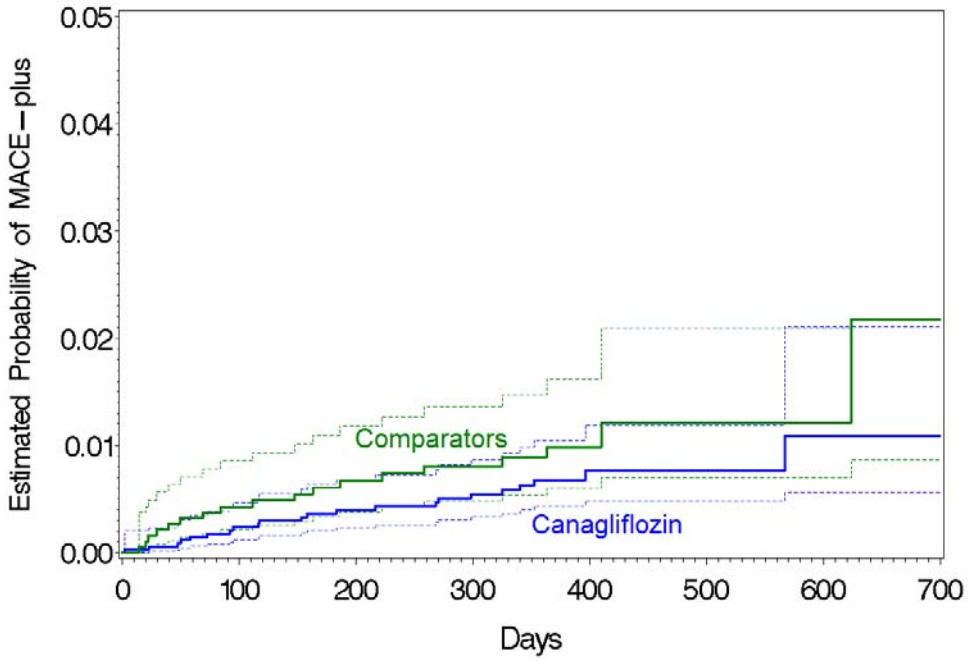


Figure 6. Estimated Probability and 95% CI of MACE-plus by Time in All Trials excluding CANVAS
Source: Created by reviewer. Dataset: adttecv.xpt



3.1.6.2 Primary Analysis of MACE-plus in All Trials

Results of the pre-specified meta-analysis using a stratified Cox proportional hazards model are shown in Table 13. The estimated hazard ratio of MACE-plus based on this model was **0.91** with 95% confidence interval **(0.68, 1.21**). Based on this result alone, the upper bound of the 95% confidence for the hazard ratio successfully ruled out a hazard ratio of MACE-plus greater than 1.8 associated with canagliflozin.

Reviewer's Comment:
The 99.9% confidence interval for the hazard ratio of MACE-plus associated with canagliflozin was (0.56, 1.48), and therefore the upper bound of the 99.9% confidence interval did not rule out a hazard ratio of 1.3 at this time as pre-specified.

Table 13. Primary Analysis of MACE-plus in All Trials

	Canagliflozin N= 6396 PY = 6876	Comparators N = 3327 PY = 3470	Hazard Ratio (95% CI)
Events (rate per 1000 PY)	**130 (18.9)**	**71 (20.5)**	**0.91 (0.68, 1.21)**

Source: Created by reviewer. Dataset: adttecv.xpt

Figure 12 in the Appendix shows the plot of the scaled Schoenfeld residuals corresponding to the primary Cox model discussed above. A plot of the scaled Schoenfeld residuals as a function of time was created to evaluate the assumption of proportional hazards. In this type of plot, a non-zero slope indicates a potential violation of the proportionality assumption. The loess curve corresponding to these residuals shows possible evidence of non-proportional hazards with a steep slope during the early part of the trials. This behavior is consistent with the survival plots shown in Figure 4 through

Figure 6 which suggested possible non-proportional hazards due to the early imbalance of MACE-plus in CANVAS. These deviations from the assumption of proportional hazards complicate the interpretability of the Cox proportional hazards model.

A second approach to test whether hazards are proportional in a Cox model is to include an interaction term of treatment by time in the model. This test for interaction was not significant in these data (p-value = 0.76) and shows no evidence of non-proportional hazards. However, this test is designed to detect non-proportional hazards where the hazard ratio of treatment versus comparator is linearly increasing (or decreasing) in time, which does not appear to be the case in these data based on the survival plots discussed earlier.

In the following sections we estimate the hazard ratio of MACE-plus and evaluate the assumption of proportional hazards in CANVAS and non-CANVAS trials separately.

3.1.6.2.1 Analysis of MACE and Individual Components of MACE-plus in All Trials

Table 14 shows hazard ratio estimates for the secondary MACE and for the individual components of MACE-plus (CV Death, MI, Stroke, Hospitalized unstable angina) based on a Cox proportional hazards model including all trials and stratified by CANVAS and non-CANVAS trials. The estimated hazard ratio and 95% confidence interval for MACE: 0.98 (0.70, 1.36); cardiovascular death: 0.65 (0.34, 1.24); myocardial infarction: 0.83 (0.51, 1.34); and hospitalized unstable angina: 0.71 (0.39, 1.30) show no evidence of increased risk associated with canagliflozin. The only secondary endpoint with estimated hazard ratio larger than 1 was stroke: 1.46 (0.83, 2.58). Table 30 and Table 31 in the Appendix show the reported MedDRA v14.1 preferred terms associated with the 63 strokes used in the meta-analysis. The most commonly reported preferred term for strokes was "Cerebrovascular accident" (n=36).

Note that these parameter estimates may suffer from the same interpretability problems as the primary model described in Section 3.1.6.2 if the assumption of proportional hazards in the Cox model is violated. Hazard ratio estimates for MACE and the individual components of MACE-plus are presented separately in Sections 3.1.6.3 and 3.1.6.4 for CANVAS and non-CANVAS trials.

Table 14. Number of Events (Rate per 1000 Patient-Years) in All Trials

	Canagliflozin N= 6396 PY = 6876	Comparators N = 3327 PY = 3470	Hazard Ratio (95% CI)
MACE	104 (5.1)	53 (15.3)	0.98 (0.70, 1.36)
CV Death	21 (3.1)	16 (4.6)	0.65 (0.34, 1.24)
MI	45 (6.5)	27 (7.8)	0.83 (0.51, 1.34)
Stroke	47 (6.8)	16 (4.6)	1.46 (0.83, 2.58)
Hospitalized unstable angina	26 (3.8)	18 (5.2)	0.71 (0.39, 1.30)

Source: Created by reviewer. Dataset: adttecv.xpt

3.1.6.3 Secondary Analysis of MACE-plus in all trials excluding CANVAS

Table 15 shows counts of events and rates of events per 1000 patient-years for MACE-plus, MACE, and the components of MACE-plus in the 8 trials in the meta-analysis excluding CANVAS. Based on the survival plot for MACE-plus shown in

Figure 6 and the plot of the scaled Schoenfeld residuals in Figure 13 in the Appendix, the assumption of proportional hazards appears to hold in these data.

The estimated hazard ratio and 95% confidence interval for the primary endpoint MACE-plus associated with canagliflozin in the 8 trials excluding CANVAS was **0.64 (0.34, 1.19).**

The estimated hazard ratio for the secondary MACE associated with canagliflozin in this data was 0.63 (0.32, 1.25) which is consistent with the estimated hazard ratio of MACE-plus. Hazard ratios for the individual components of MACE-plus in these data are not shown in Table 15 because of the small number of events observed for each component.

These data show no evidence of increased cardiovascular risk associated with canagliflozin in the 8 trials excluding CANVAS. The upper bound of the 95% confidence interval for the hazard ratio of MACE-plus comparing canagliflozin to all comparators based on these data was 1.19, which is below the risk margin of 1.8 set forth in the FDA Diabetes Guidance for assessing cardiovascular safety (2008).

Table 15. Number of Events (Rate per 1000 Patient-Years) in All Trials Excluding CANVAS

	Canagliflozin N=3510 PY = 3464	Comparators N = 1886 PY = 1806	Hazard Ratio (95% CI)
MACE-plus	**22 (6.4)**	**18 (10.0)**	**0.64 (0.34, 1.19)**
MACE	18 (5.2)	15 (8.3)	0.63 (0.32, 1.25)
CV Death	2 (0.6)	2 (1.1)	
MI	7 (2.0)	12 (6.6)	
Stroke	9 (2.6)	1 (0.6)	
Hospitalized unstable angina	4 (1.2)	3 (1.7)	

Source: Created by reviewer. Dataset: adttecv.xpt

3.1.6.4 Secondary Analysis of MACE-plus in CANVAS

CANVAS is an ongoing trial designed to evaluate the cardiovascular safety of canagliflozin compared to placebo. Based on the dataset submitted in support of the current NDA application with data locked on 31 January 2012, 108 MACE-plus have been observed among the 2886 subjects randomized to canagliflozin and 53 MACE-plus among the 1441 subjects randomized to placebo in CANVAS. Section 3.1.6.1 discussed the early imbalance in MACE-plus observed during the first 30 days in CANVAS: 13 events were observed among subjects randomized to canagliflozin and 1 event was observed among subjects on placebo. Table 16 shows a summary of events and corresponding rate per 1000 patient-years of exposure during the first 30 days of CANVAS and during the full duration of the trial.

Table 16. Number of MACE-plus (Rate per 1000 Patient-Years) in CANVAS

	Canagliflozin N = 2886	**Placebo N= 1441**
First 30 Days	13 (54.99)	1 (8.46)
Full CANVAS	108 (31.65)	53 (31.85)

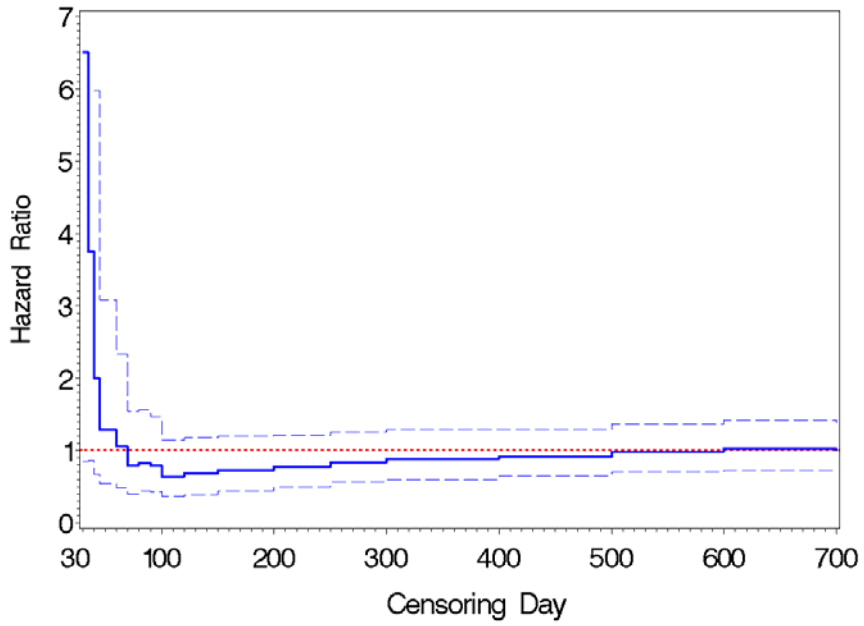
Source: Created by reviewer. Dataset: adttecv.xpt

Figure 5 shows that the imbalance in early events suggests possibly non-proportional hazards in CANVAS. The scaled Schoenfeld residuals plot for the full duration of CANVAS is shown in Figure 14 in the Appendix. The corresponding loess curve also shows possible evidence of non-proportional hazards in these data.
Figure 7 shows the estimated hazard ratio for MACE-plus comparing canagliflozin to placebo in CANVAS using a Cox proportional hazards model using data from time 0 to *t*, where subjects are censored at time *t*. For example, Figure 7 shows that if a Cox model is fit to the period of time from 0 to 30 days, the estimated hazard ratio would be 6.50; however if the same model is fit to the period of time from 0 to 700 days, the estimated hazard ratio would be approximately 1.

Based on the observed data and the plots discussed above, there is evidence to suggest that the hazard ratio of MACE-plus during the first 30 days of CANVAS may be different from the hazard ratio after 30 days due to the imbalance of early MACE-plus. Therefore, it appears reasonable to study the risk of MACE-plus in these two periods of CANVAS separately. Sections 3.1.6.4.1 and 3.1.6.4.2 evaluate the risk of MACE-plus in CANVAS during the first 30 days and after 30 days respectively.

Figure 7. Estimated Hazard Ratio and 95% CI of MACE-plus by Censoring Day in CANVAS

Source: Created by reviewer. Dataset: adttecv.xpt



3.1.6.4.1 Analysis of MACE-plus during the first 30 days in CANVAS

Figure 8 shows a survival plot by treatment for the first 30 days after randomization in CANVAS. The estimated hazard ratio and 95% confidence interval for MACE-plus associated with canagliflozin based on these data is 6.49 (0.85, 49.64).

During the first 30 days of CANVAS there were fewer MACE-plus observed among subjects randomized to placebo than would be expected based on the rate of events observed during the full duration of the trial. Only 1 event was observed during the first 30 days among subjects randomized to placebo, whereas the expected number of events would be 3.76 based on the rate of events per year among subjects on placebo during the full length of the trial. Because of the small number of events observed during the first 30 days in CANVAS, the estimated hazard ratio corresponding to this period of time is highly sensitive to small changes in the number of events. Table 17 shows the effect that 1, 2 and 3 additional events observed among subjects randomized to placebo would have had on the estimated hazard ratio of MACE-plus during the first 30 days of CANVAS. One additional event on placebo would have resulted in a hazard ratio and 95% confidence interval of 3.25 (0.73, 14.38); three additional events would have resulted in a hazard ratio and 95% confidence interval of 1.62 (0.53, 4.97).

Table 16 above shows that the large estimated hazard ratio of MACE-plus associated with canagliflozin during the first 30 days of CANVAS was a result of a higher observed rate of events among subjects on canagliflozin during the first 30 days than during the full duration of the trial (54.99 vs. 31.65 events per 1000 patient-years), and a lower observed rate of events among subjects on placebo during the first 30 days (8.46 vs. 31.85 events per 1000 patient-years).

Since the analysis of the first 30 days of CANVAS was conducted after reviewing the data and because the hazard ratio during this time is derived from small counts of events, it is not possible to determine whether the early imbalance of MACE-plus and corresponding hazard ratio represents a true early increase in risk associated with canagliflozin in CANVAS or whether this early imbalance may be attributable to chance.

Figure 8. Estimated Probability and 95% CI of MACE-plus During the First 30 Days of CANVAS

Source: Created by reviewer. Dataset: adttecv.xpt

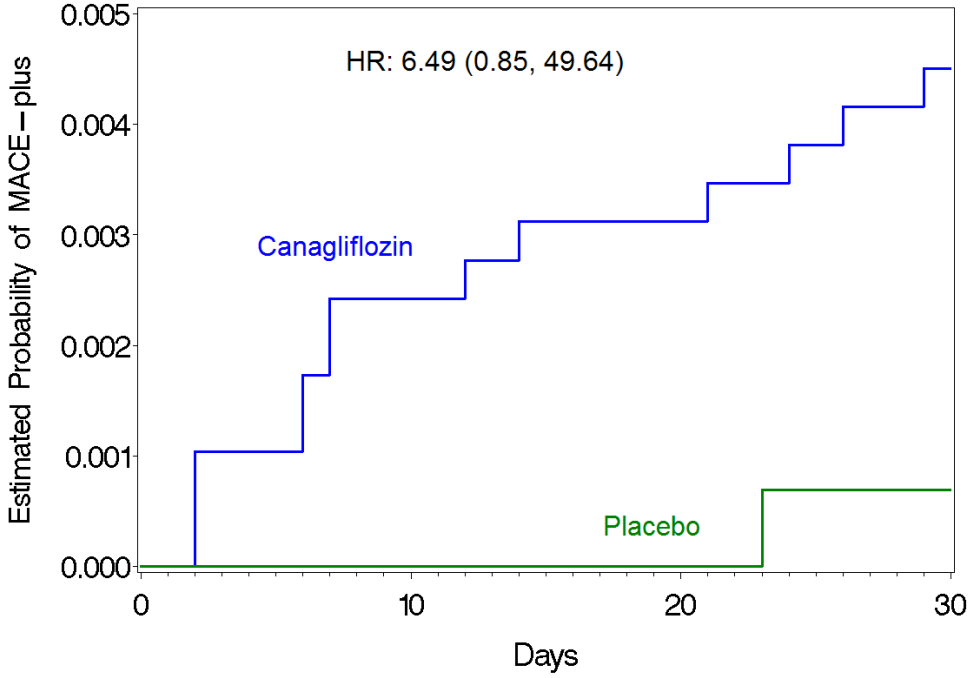


Table 17. Sensitivity of the estimated hazard ratio to additional MACE-plus during the first 30 days of CANVAS

	Canagliflozin N = 2886	Placebo N= 1441	Hazard Ratio
Observed data	13	1	6.49 (0.85, 49.64)
1 additional event on placebo	13	2	3.25 (0.73, 14.38)
2 additional events on placebo	13	3	2.16 (0.62, 7.59)
3 additional events on placebo	13	4	1.62 (0.53, 4.97)

Source: Created by reviewer. Dataset: adttecv.xpt

3.1.6.4.2 Analysis of MACE-plus after 30 days in CANVAS

Figure 9 shows a survival plot by treatment arm among subjects who survived and were being followed past day 30 in CANVAS. The plot shows that after day 30 (origin point in Figure 9), there is graphical evidence of a lower risk of MACE-plus associated with canagliflozin. The survival curves for the two treatment arms cross after approximately day 500; however this may be an artifact of fewer subjects being followed at that time in CANVAS as shown in the bottom two rows of the plot.

The estimated hazard ratio and corresponding 95% confidence interval for MACE-plus associated with canagliflozin after day 30 in CANVAS was **0.89 (0.64, 1.25).** Table 12 shows estimates of the hazard ratio of MACE and the individual components of MACE-plus in

CANVAS after day 30. Overall, the estimated hazard ratios show no evidence of increased cardiovascular risk associated with canagliflozin after day 30 in CANVAS. The upper bound of the 95% confidence interval for the hazard ratio of MACE-plus comparing canagliflozin to placebo based on these data was 1.25, which is below the risk margin of 1.8 set forth in the FDA Diabetes Guidance for assessing cardiovascular safety (2008).

Figure 15 in the Appendix shows a plot of the scaled Schoenfeld residuals for the Cox proportional hazards model for MACE-plus after day 30 in CANVAS. The plot shows evidence of an increasing slope and therefore possibly non-proportional hazards in these data. We fit a Cox proportional hazards model with an interaction term of treatment by time to these data. The interaction term was statistically significant (p-value 0.01) and suggests that the hazard ratio of MACE-plus between canagliflozin and placebo may be changing through time after day 30 in CANVAS. The rapidly decreasing number of subjects being followed through time in CANVAS, limits our ability to model the shape of the hazard functions at the time of this analysis. The behavior of the hazard function through time may be studied more carefully in future analyses of CANVAS when more subjects have been followed for longer periods of time and more total events have been observed.

Figure 9. Estimated Probability and 95% CI of MACE-plus in CANVAS Among Subjects who Survived and were Followed at Day 30

Source: Created by reviewer. Dataset: adttecv.xpt

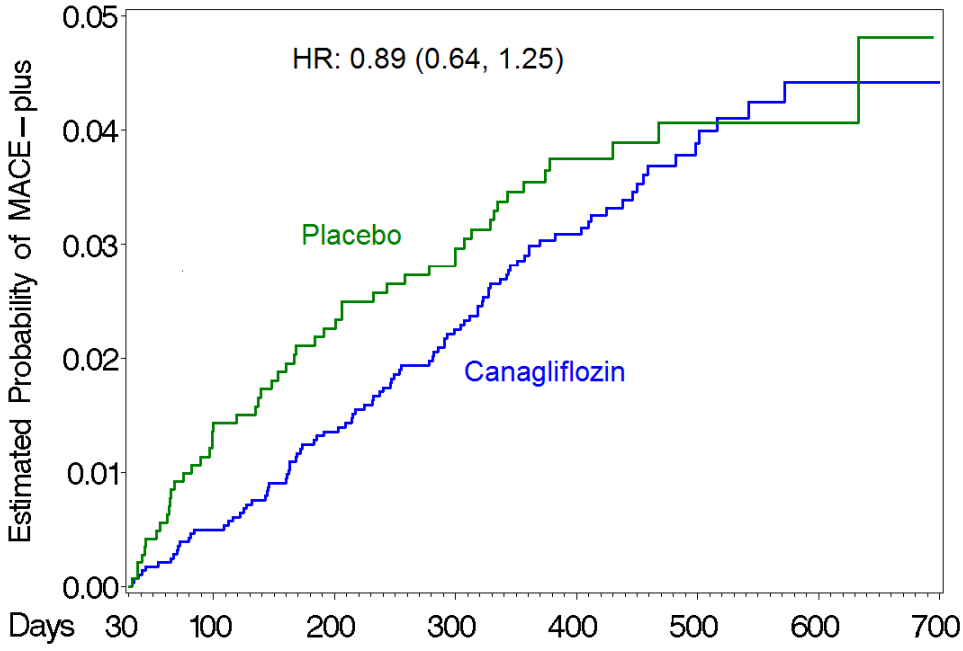


Table 18. Number of Events (Rate per 1000 Patient-Years) in CANVAS after Day 30

	Canagliflozin N=2867 PY = 3175	Comparators N = 1435 PY = 1546	Hazard Ratio (95% CI)
MACE-plus	**95 (29.9)**	**52 (33.6)**	**0.89 (0.64, 1.25)**
MACE	75 (23.6)	37 (23.9)	0.99 (0.67, 1.47)
CV Death	18 (5.7)	14 (9.1)	0.63 (0.31, 1.26)
MI	33 (10.4)	13 (8.4)	1.24 (0.65, 2.35)
Stroke	31 (9.8)	15 (9.7)	1.01 (0.55, 1.87)
Hospitalized unstable angina	20 (6.3)	15 (9.7)	0.65 (0.33, 1.27)

Source: Created by reviewer. Dataset: adttecv.xpt

3.1.6.5 Sensitivity Analysis of MACE-plus by dose of canagliflozin

The submitted data showed no difference in the estimated hazard ratio of MACE-plus (HR=1.00) between the two doses of canagliflozin. Table 19 shows the number of MACE-plus observed among subjects randomized to canagliflozin 100 mg and canagliflozin 300 mg in all trials, trials excluding CANVAS, and CANVAS alone. The table shows that the rate of MACE-plus was comparable between the two canagliflozin doses.

Table 19. MACE-Plus by dose of canagliflozin

	Canagliflozin 300mg	Canagliflozin 100mg	Hazard Ratio
All Trials	64 / 3193	66 / 3203	1.00 (0.71, 1.41)
All trials excluding CANVAS	12 / 1752	10 / 1758	1.21 (0.52, 2.80)
First 30 days in CANVAS	6 / 1441	7 / 1445	0.86 (0.29, 2.56)
CANVAS after 30 days	46 / 1433	49 / 1433	0.97 (0.65, 1.45)

Source: Created by reviewer. Dataset: adttecv.xpt

4 Findings in Special/Subgroup Populations

In the following paragraphs the risk of MACE-plus associated with canagliflozin is evaluated within subgroups defined by gender, race, age and country of randomization. Results are presented for all nine trials, all trials excluding CANVAS, the first 30 days in CANVAS, and CANVAS after 30 days.

4.1 Gender, Race and Age

Gender

Among the 9,723 subjects in the mITT population (6,396 on canagliflozin and 3,327 on comparators), 58% were male and 42% were female. The estimated HR of MACE-plus associated with canagliflozin among males in all trials was 1.05 with 95% CI (0.74, 1.50). Among females, the estimated HR was 0.66 (0.39, 1.10). While the estimated hazard ratio for MACE-plus associated with canagliflozin was lower among females than among males, the test for interaction between gender and canagliflozin was not statistically significant (p-value 0.1482), and consequently there is no statistically significant evidence of differential cardiovascular risk associated with canagliflozin by gender.

Table 20. Number of subjects with MACE-plus / Randomized subjects, by Gender

Gender = Male			
	All Comparators	Canagliflozin	Hazard Ratio
All Trials	46 / 1955	96 / 3683	1.05 (0.74, 1.50)
All trials excluding CANVAS	12 / 1000	17 / 1778	0.79 (0.38, 1.65)
First 30 days in CANVAS	1 / 955	10 / 1895	5.02 (0.64, 39.21)
CANVAS after 30 days	33 / 951	69 / 1892	1.03 (0.68, 1.56)
Gender = Female			
	All Comparators	Canagliflozin	Hazard Ratio
All Trials	25 / 1372	34 / 2713	0.66 (0.39, 1.10)
All trials excluding CANVAS	6 / 886	5 / 1732	0.41 (0.13, 1.35)
First 30 days in CANVAS	0 / 486	3 / 981	-
CANVAS after 30 days	19 / 483	26 / 974	0.66 (0.36, 1.19)

Source: Created by reviewer. Dataset: adttecv.xpt

Race

72.5% of the subjects in the mITT population were White, 15.9% were Asian, 3.8% were Black, and the remaining 7.8% were identified as other races or Multiracial. The estimated HR of MACE-plus associated with canagliflozin among Whites including all trials was 0.87 with corresponding 95% confidence interval (0.64, 1.19). Among Asians, it was 0.99 (0.49, 2.46) and among Blacks, Multiracial and subjects of other races it was 1.52 (0.41, 5.61). There is no clear evidence of differential risk of MACE-plus associated with canagliflozin between subgroups defined by race.

Table 21. Number of subjects with MACE-plus / Randomized subjects, by Race

Race= White			
	All Comparators	Canagliflozin	Hazard Ratio
All Trials	61 / 2429	107 / 4620	0.87 (0.64, 1.19)
All trials excluding CANVAS	13 / 1366	18 / 2506	0.73 (0.36, 1.49)
First 30 days in CANVAS	1 / 1063	9 / 2114	4.53 (0.57, 35.73)
CANVAS after 30 days	47 / 1058	80 / 2100	0.83 (0.58, 1.19)

Race = Asian			
	All Comparators	Canagliflozin	Hazard Ratio
All Trials	7 / 519	14 / 1028	0.99 (0.49, 2.46)
All trials excluding CANVAS	2 / 257	2 / 495	0.50 (0.07, 3.58)
First 30 days in CANVAS	0 / 262	3 / 533	-
CANVAS after 30 days	5 / 261	9 / 528	0.89 (0.30, 2.65)
Race = Black, Other, and Multiracial			
	All Comparators	Canagliflozin	Hazard Ratio
All Trials	3 / 379	9 / 748	1.52 (0.41, 5.61)
All trials excluding CANVAS	3 /263	2 / 509	0.35 (0.06, 2.07)
First 30 days in CANVAS	0 / 116	1 / 239	-
CANVAS after 30 days	0 / 115	6 / 238	-

Source: Created by reviewer. Dataset: adttecv.xpt

Age at Baseline

51.5% of the subjects in the mITT population were 60 years old or younger at the time of randomization, and 48.5% were older than 60 years. The estimated HR of MACE-plus associated with canagliflozin including all trials was 1.03 with 95% CI (0.63, 1.69) in the younger group and 0.85 (0.59, 1.21) in the older group. Neither group showed evidence of increase cardiovascular risk associated with canagliflozin.

Table 22. Number of subjects with MACE-plus / Randomized subjects, by Age at Baseline

Age ≤ 60			
	All Comparators	Canagliflozin	Hazard Ratio
All Trials	24 / 1730	49 / 3280	1.03 (0.63, 1.69)
All trials excluding CANVAS	8 / 1142	10 / 2138	0.66 (0.26, 1.67)
First 30 days in CANVAS	0 / 588	6 / 1136	-
CANVAS after 30 days	16 / 585	33 / 1132	1.03 (0.57, 1.87)
Age > 60			
	All Comparators	Canagliflozin	Hazard Ratio
All Trials	47 / 1597	81 / 3116	0.85 (0.59, 1.21)
All trials excluding CANVAS	10 / 744	12 / 1372	0.62 (0.27, 1.44)
First 30 days in CANVAS	1 / 853	7 / 1737	3.42 (0.42, 27.82)
CANVAS after 30 days	36 / 849	62 / 1734	0.83 (0.55, 1.26)

Source: Created by reviewer. Dataset: adttecv.xpt

Country of Randomization

Approximately 25.0% of the subjects in the mITT population have been randomized in the United States. This proportion is smaller in CANVAS alone, approximately 16.8%. The estimated hazard ratio of MACE-plus associated with canagliflozin including all trials was

higher among subjects randomized in the USA: HR 1.16 with 95% CI (0.61, 1.22); than among subjects randomized outside the USA: HR 0.85 (0.62, 1.18). The difference in hazard ratios between subjects randomized in the USA and outside the USA was not significantly different (p-value 0.3825).

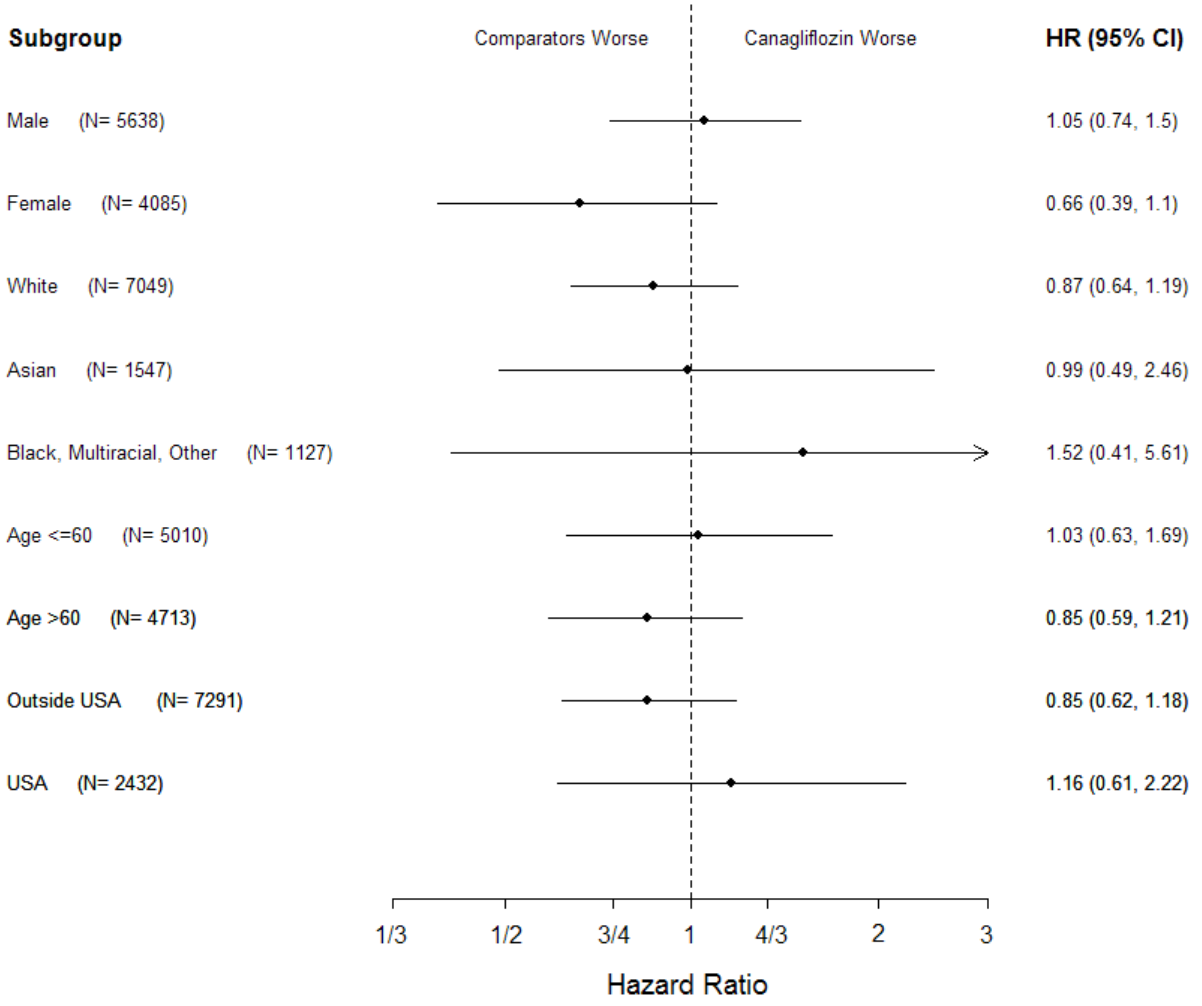
Table 23. Number of subjects with MACE-plus / Randomized subjects, by Country of Randomization

Country = USA			
	All Comparators	Canagliflozin	Hazard Ratio
All Trials	13 / 844	31 / 1588	1.16 (0.61, 2.22)
All trials excluding CANVAS	3 / 604	6 / 1102	1.05 (0.26, 4.19)
First 30 days in CANVAS	1 / 240	2 / 486	0.99 (0.09, 10.86)
CANVAS after 30 days	9 / 238	23 / 482	1.21 (0.56, 2.62)
Country ≠ USA			
	All Comparators	Canagliflozin	Hazard Ratio
All Trials	58 / 2483	99 / 4808	0.85 (0.62, 1.18)
All trials excluding CANVAS	15 / 1282	16 / 2408	0.56 (0.28, 1.13)
First 30 days in CANVAS	0 / 1201	11 / 2400	-
CANVAS after 30 days	43 / 1196	72 / 2384	0.82 (0.56, 1.20)

Source: Created by reviewer. Dataset: adttecv.xpt

The data showed no statistically significant differences in the risk of MACE-plus associated with canagliflozin among subgroups defined by gender, race, age or country of randomization. Figure 10 summarizes the results of these subgroups analyses conducted in the 9 trials in the meta-analysis.

Figure 10. Hazard Ratio of MACE-plus by Subgroups in All Trials



4.2 Other Special/Subgroup Populations

The following paragraphs discuss the HR of MACE associated with the use of canagliflozin versus all comparators in subgroups defined by baseline cardiovascular risk categories of: BMI, prior cardiovascular disease, statin use and eGFR. Results are presented for all nine trials, all trials excluding CANVAS, the first 30 days in CANVAS, and CANVAS after 30 days.

BMI at Baseline

Baseline BMI was not recorded for 9 subjects in the mITT population. Approximately 41.4% of all subjects with measured BMI had a baseline BMI less than 30 kg/m². The remaining 58.6% had a baseline BMI greater than or equal to 30 kg/m². The estimated hazard ratios for MACE-plus associated with canagliflozin across all trials were comparable among subjects with BMI < 30 kg/m², HR 0.83 (0.52, 1.34), and subjects with BMI ≥ 30 kg/m², HR 0.96 (0.66, 1.38).

Table 24. Number of subjects with MACE-plus / Randomized subjects, by Baseline BMI

BMI < 30 kg/m²			
	All Comparators	Canagliflozin	Hazard Ratio
All Trials	28 / 1395	46 / 2631	0.83 (0.52, 1.34)
All trials excluding CANVAS	9 / 816	11 / 1472	0.67 (0.28, 1.61)
First 30 days in CANVAS	0 / 579	6 / 1159	-
CANVAS after 30 days	19 / 576	29 / 1148	0.75 (0.42, 1.35)
BMI ≥ 30 kg/m²			
	All Comparators	Canagliflozin	Hazard Ratio
All Trials	43 / 1929	84 / 3759	0.96 (0.66, 1.38)
All trials excluding CANVAS	9 / 1070	11 / 2037	0.62 (0.26, 1.51)
First 30 days in CANVAS	1 / 859	7 / 1722	3.49 (0.43, 28.36)
CANVAS after 30 days	33 / 855	66 / 1713	0.97 (0.64, 1.47)

Source: Created by reviewer. Dataset: adttecv.xpt

Prior Cardiovascular Disease at Baseline

67.6% of subjects in the mITT population were reported to have prior cardiovascular disease at baseline. The estimated hazard ratios for MACE-plus associated with canagliflozin across all trials were comparable among subjects with no prior CV disease, HR 0.99 with 95% CI (0.57, 1.71), and subjects with prior CV disease, HR 0.89 with 95% CI (0.63, 1.25).

Table 25. Number of subjects with MACE-plus / Randomized subjects, by Prior Cardiovascular Disease at Baseline

No Prior Cardiovascular Disease			
	All Comparators	Canagliflozin	Hazard Ratio
All Trials	19 / 2255	37 / 4316	0.99 (0.57, 1.71)
All trials excluding CANVAS	11 / 1633	13 / 3081	0.61 (0.28, 1.37)
First 30 days in CANVAS	0 / 622	4 /1235	-
CANVAS after 30 days	8 / 618	20 / 1227	1.24 (0.54, 2.80)
Prior Cardiovascular Disease			
	All Comparators	Canagliflozin	Hazard Ratio
All Trials	52 / 1072	93 / 2080	0.89 (0.63, 1.25)
All trials excluding CANVAS	7 / 253	9 / 429	0.75 (0.28, 2.02)
First 30 days in CANVAS	1 / 819	9 / 1651	4.47 (0.57, 35.29)
CANVAS after 30 days	44 / 816	75 / 1639	0.83 (0.57, 1.20)

Source: Created by reviewer. Dataset: adttecv.xpt

Statin Use at Baseline

42.7% of subjects in the mITT population were using statins at baseline. The estimated hazard ratios for MACE-plus associated with canagliflozin across all trials were comparable among statin users, HR 0.87 with 95% CI (0.61, 1.24), and non-users, HR 0.99 with 95% CI (0.59, 1.66).

Table 26. Number of subjects with MACE-plus / Randomized subjects, by Statin Use at Baseline

No Statin Use at Baseline			
	All Comparators	Canagliflozin	Hazard Ratio
All Trials	22 / 1450	43 / 2702	0.99 (0.59, 1.66)
All trials excluding CANVAS	5 / 1042	10 / 1900	1.09 (0.37, 3.18)
First 30 days in CANVAS	0 / 408	4 / 802	-
CANVAS after 30 days	17 / 404	29 / 796	0.85 (0.47, 1.54)
Statin Use at Baseline			
	All Comparators	Canagliflozin	Hazard Ratio
All Trials	49 / 1877	87 / 3694	0.87 (0.61, 1.24)
All trials excluding CANVAS	13 / 844	12 / 1610	0.46 (0.21, 1.01)
First 30 days in CANVAS	1 / 1033	9 / 2084	4.47 (0.57, 35.27)
CANVAS after 30 days	35 / 1030	66 / 2070	0.92 (0.61, 1.38)

Source: Created by reviewer. Dataset: adttecv.xpt

Baseline eGFR

Table 27 shows that 12.6% of the subjects in the mITT population had eGFR < 60 ml/min at baseline. The estimated hazard ratio for MACE-plus associated with canagliflozin across all trials among subjects with eGFR < 60 ml/min was 0.56 with 95% CI (0.31, 1.02). The estimated hazard ratio among subjects with eGFR ≥ 60 ml/min was 1.06 with 95% CI (0.76, 1.48). The test for interaction between eGFR and canagliflozin on the effect of MACE-plus was borderline statistically significant (p-value 0.0635); however this test is not corrected for multiplicity and does not account for the multiple subgroup comparisons conducted in this review.

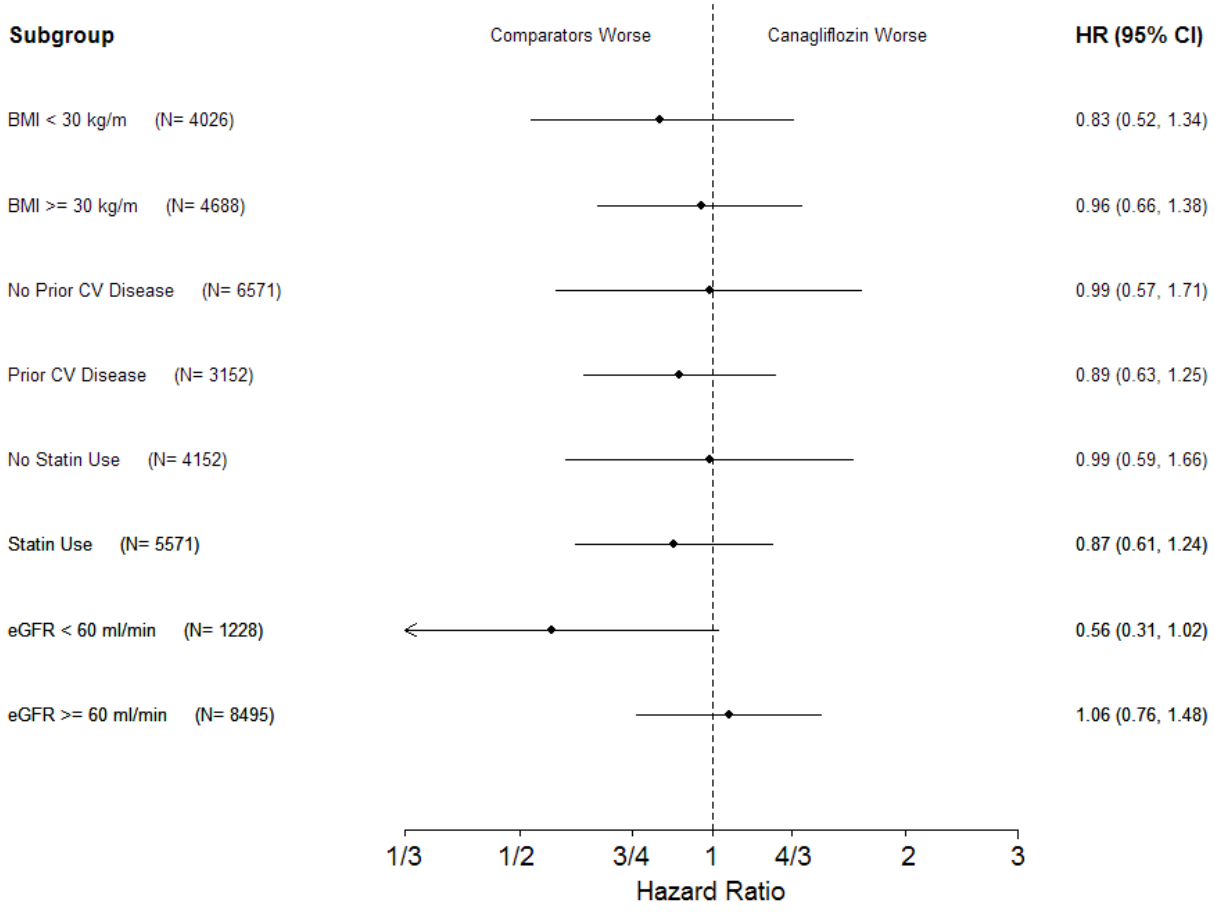
Table 27. Number of subjects with MACE-plus / Randomized subjects, by Baseline eGFR

Baseline eGFR < 60 ml/min			
	All Comparators	Canagliflozin	Hazard Ratio
All Trials	21 / 437	22 / 791	0.56 (0.31, 1.02)
All trials excluding CANVAS	5 / 184	4 / 333	0.46 (0.12, 1.72)
First 30 days in CANVAS	0 / 253	2 / 458	-
CANVAS after 30 days	16 / 252	16 / 455	0.52 (0.26, 1.04)
Baseline eGFR ≥ 60 ml/min			
	All Comparators	Canagliflozin	Hazard Ratio
All Trials	50 / 2890	108 / 5605	1.06 (0.76, 1.48)
All trials excluding CANVAS	13 / 1702	18 / 3159	0.72 (0.35, 1.47)
First 30 days in CANVAS	1 / 1188	11 / 2428	5.39 (0.70, 41.71)
CANVAS after 30 days	36 / 1182	79 / 2411	1.06 (0.71, 1.57)

Source: Created by reviewer. Dataset: adttecv.xpt

The data showed no statistically significant differences in the risk of MACE-plus associated with canagliflozin among subgroups defined by BMI, prior cardiovascular disease or statin use at baseline. Among subjects with baseline eGFR < 60 ml/min, canagliflozin showed borderline statistically significant CV benefit before correcting for multiple comparisons. Figure 11 summarizes the results of these subgroups analyses conducted in the 9 trials in the meta-analysis.

Figure 11. Hazard Ratio of MACE-plus by Special/Subgroup Populations in All Trials



5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

Based on the Statistical Analysis Plan (SAP) to assess Cardiovascular Safety submitted to IND 76479 on 13 July 2010 and agreed upon by the FDA, it was determined that the CV safety of canagliflozin would be evaluated through a meta-analysis of Phase 2 and Phase 3 clinical trials for canagliflozin, including the dedicated cardiovascular outcomes trial CANVAS. The agreed

upon population of interest in the meta-analysis consisted of all subjects randomized in the 9 trials who took at least 1 dose of the double-blind study medication. The comparator group in the meta-analysis was comprised of all non-canagliflozin randomized groups. The primary agreed upon safety endpoint of interest was major adverse cardiovascular events plus (MACE-plus), a composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and hospitalizations due to unstable angina.

The meta-analysis was designed to demonstrate that the hazard ratio of MACE-plus associated with canagliflozin relative to all comparators is smaller than the risk margin of 1.8 set forth in the FDA Diabetes Guidance for assessing cardiovascular safety. The pre-specified primary analysis used a Cox proportional hazards model with two strata, CANVAS and non-CANVAS trials, to estimate the hazard ratio of MACE-plus associated with canagliflozin.

There were 130 MACE-plus observed among 6396 subjects in the canagliflozin treatment group and 71 MACE-plus observed among 3327 subjects in the comparator group in the 9 trials utilized in the meta-analysis. The dedicated cardiovascular outcomes trial CANVAS contributed 108 MACE-plus among 2886 subjects in the canagliflozin treatment group and 53 MACE-plus among 1441 in the placebo group. The pre-specified Cox proportional hazards model obtained an estimated hazard ratio of canagliflozin vs. all comparators of **0.91** with 95% confidence interval **(0.68, 1.21).** The upper bound of this 95% confidence interval is below the risk margin of 1.8 necessary to show adequate cardiovascular safety of new antidiabetic products in accordance to the FDA Diabetes Guidance. A test to rule out a hazard ratio of MACE-plus larger than 1.3 with a two-sided α=0.001 was planned to be conducted at the same time as the pre-specified meta-analysis assessment of the HR risk margin of 1.8. The estimated 99.9% confidence interval for the hazard ratio of MACE-plus based on the primary Cox model was (0.56, 1.48), and therefore the upper bound of the 99.9% confidence interval did not rule out a hazard ratio of 1.3 at this time.

The data showed some evidence to suggest that the assumption of proportional hazards necessary to interpret the pre-specified Cox proportional hazards model may not have been met. An imbalance of MACE-plus was observed during the first 30 days in CANVAS. During that time, 13 MACE-plus were observed among 2886 subjects on canagliflozin and 1 MACE-plus was observed among 1441 subjects on placebo. The estimated hazard ratio and 95% confidence interval comparing canagliflozin to placebo during the first 30 days of CANVAS was 6.49 (0.85, 49.64). The estimated hazard ratio of MACE-plus comparing canagliflozin to placebo in CANVAS after the first 30 days was 0.89 (0.64, 1.25). The estimated hazard ratio of MACE-plus in the 8 trials excluding CANVAS was 0.64 (0.34, 1.19). These finding are summarized in Table 28. Note that except for the first 30 days of CANVAS, the upper bound of the other 95% confidence intervals for the hazard ratio of MACE-plus met the hazard ratio risk margin of 1.8 set forth in the FDA Diabetes Guidance for assessing cardiovascular safety.

Table 28. Primary and Secondary Analyses of MACE-plus

	Canagliflozin (events / N)	Comparators (events / N)	Hazard Ratio (95% CI)
Primary Analysis (including all 9 trials)	**130 / 6396**	**71 / 3327**	**0.91 (0.68, 1.21)**
Secondary Analyses			
First 30 Days in CANVAS	13 / 2886	1 / 1441	6.49 (0.85, 49.64)
After first 30 Days in CANVAS	95 / 2867	52 / 1435	0.89 (0.64, 1.25)
Non-CANVAS trials	22 / 3510	18 / 1886	0.64 (0.34, 1.19)

Source: Created by reviewer. Dataset: adttecv.xpt

Subgroup analyses were consistent with the results shown in Table 28. There was no evidence of an interaction between the use of canagliflozin and any of the following variables in terms of risk of MACE-plus: gender, race, age, country of randomization, BMI, prior cardiovascular disease, baseline statin use or baseline eGFR.

Secondary analyses estimated the hazard ratio of MACE and individual components of MACE-plus associated with canagliflozin. A summary of these findings is shown in Table 29. The estimated hazard ratio and 95% confidence interval for MACE, cardiovascular death, myocardial infarction, and hospitalized unstable angina show no statistical evidence of increased risk associated with canagliflozin. The only secondary endpoint with estimated hazard ratio larger than 1 was stroke: 1.46 (0.83, 2.58). Detailed results are provided in Section 3.1.6.

Table 29. Components of MACE-plus in All Trials in the Meta-analysis

	Canagliflozin N= 6396	Comparators N = 3327	Hazard Ratio (95% CI)
MACE	104	53	0.98 (0.70, 1.36)
CV Death	21	16	0.65 (0.34, 1.24)
MI	45	27	0.83 (0.51, 1.34)
Stroke	47	16	1.46 (0.83, 2.58)
Hospitalized unstable angina	26	18	0.71 (0.39, 1.30)

Source: Created by reviewer. Dataset: adttecv.xpt

5.2 Conclusions and Recommendations

Janssen evaluated the cardiovascular safety of canagliflozin through a meta-analysis of Phase 2 and Phase 3 trials including one dedicated cardiovascular outcomes trial, CANVAS. The pre-specified primary Cox model for this meta-analysis obtained an estimated hazard ratio of MACE-plus associated with canagliflozin relative to all comparators of **0.91** with corresponding 95% confidence interval **(0.68, 1.21).** The upper bound of this 95% confidence interval was smaller than 1.8 and therefore met the hazard ratio risk margin set forth in the FDA Guidance to establish cardiovascular safety of new antidiabetic products.

The data showed some evidence of non-proportional hazards due primarily to an early imbalance of MACE-plus observed during the first 30 days of CANVAS. This imbalance may limit the ease of interpretation of the primary analysis that utilizes the full duration of time in the 9 trials. Given that the findings within the first 30 days of treatment are sensitive to the few number of events observed during this time period, we recommend that the higher rate of MACE-plus associated with canagliflozin observed during the first 30 days of CANVAS be interpreted with consideration to the clinical plausibility of this finding in a population with high baseline cardiovascular risk. Since chance cannot be ruled out as the cause of this early imbalance, we recommend that future clinical trials for canagliflozin in populations with high baseline cardiovascular risk are designed not only to evaluate long-term cardiovascular risk, but also to collect clinically relevant information to better understand the mechanism of early events.

Based on the agreed-upon SAP, the Sponsor plans to conduct future analyses to rule out a hazard ratio risk margin of 1.3 after 500 and 700 MACE-plus have been observed in the canagliflozin development program. These analyses may be impacted by the partial unblinding of CANVAS due to an observed increase in LDL-cholesterol among subjects treated with canagliflozin and the results of the meta-analysis of cardiovascular outcomes discussed by both the Sponsor and the Agency in an open public advisory committee meeting held on January 10, 2012. Therefore, we recommend that the post-marketing requirements for ruling out a HR risk margin of MACE-plus greater than 1.3 associated with canagliflozin should be discussed in light of these issues.

6 References

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

7 Appendix

A.1 Assessment of Proportional Hazards

Figure 12. Assessment of Proportional Hazards: Schoenfeld Residuals Plot in All Trials
Source: Created by reviewer. Dataset: adttecv.xpt

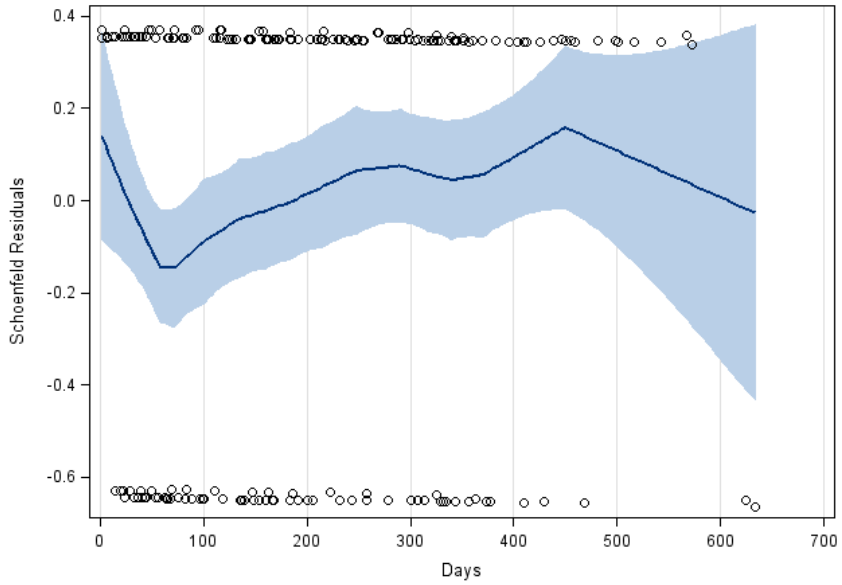


Figure 13. Assessment of Proportional Hazards: Schoenfeld Residuals Plot in Trials Excluding CANVAS
Source: Created by reviewer. Dataset: adttecv.xpt

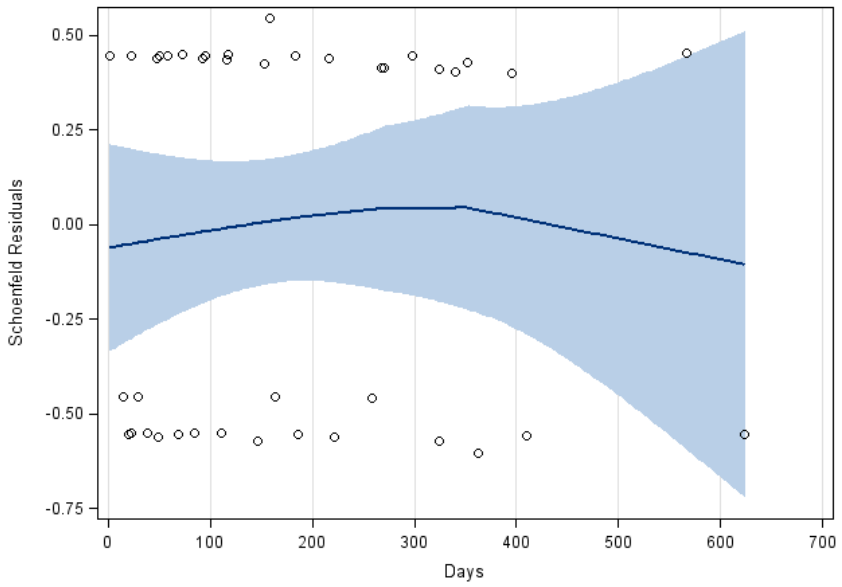


Figure 14. Assessment of Proportional Hazards: Schoenfeld Residuals Plot in CANVAS
Source: Created by reviewer. Dataset: adttecv.xpt

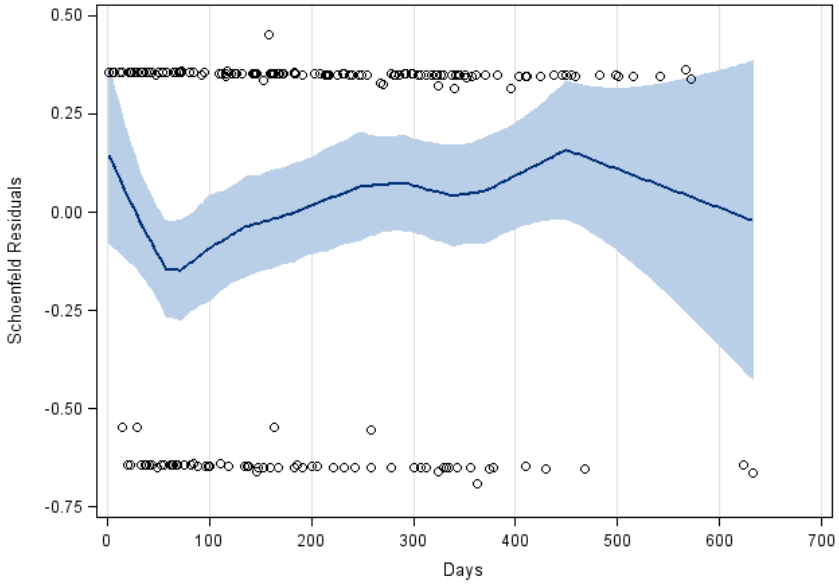
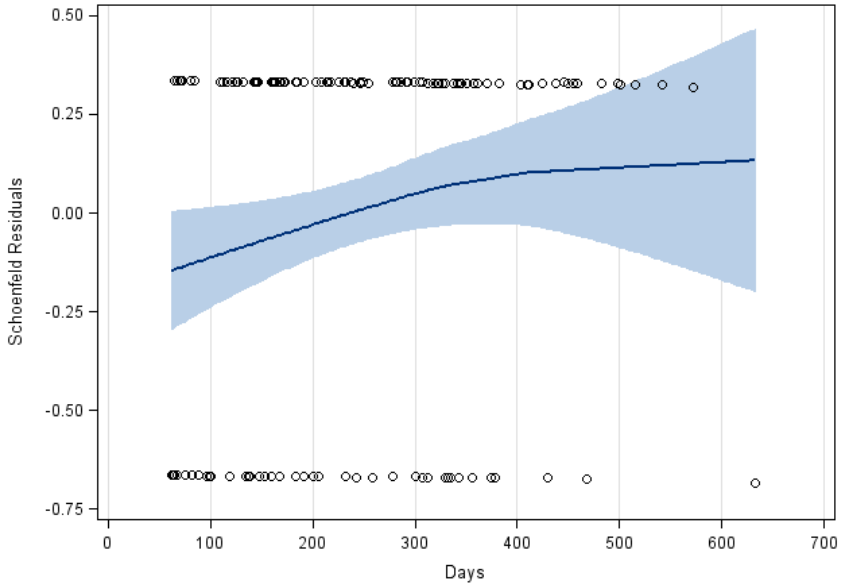


Figure 15. Assessment of Proportional Hazards: Schoenfeld Residuals Plot in CANVAS after Day 30
Source: Created by reviewer. Dataset: adttecv.xpt



A.2 Categorization of Strokes in All Trials in the Meta-Analysis

Table 30. Categorization of Fatal Strokes

	Canagliflozin N= 6396	Comparators N= 3327
Brain stem haemorrhage	0	1
Cerebral infarction	1	0
Cerebrovascular accident	2	0
Haemorrhage intracranial	1	0
Haemorrhagic stroke	0	1
Ischaemic stroke	1	1
Vertebrobasilar insufficiency	1	0
Total	6	3

Source: Created by reviewer. Datasets: adttevnt.xpt, adcvevnt.xpt

Table 31. Categorization of Non-Fatal Strokes

	Canagliflozin N= 6396	Comparators N= 3327
Carotid artery stenosis	1	0
Cerebral infarction	2*	1
Cerebrovascular accident	27	7
Haemorrhagic stroke	2	1
Ischaemic stroke	4	0
Lacunar infarction	1	1
Paraesthesia	1	0
Transient ischaemic attack	3*	2
Vascular encephalophaty	0	1
Vertebrobasilar insufficiency	1	0
Total	41	13
*One subject had one stroke recorded as both "cerebral infarction" and "transient ischaemic attack"		

Source: Created by reviewer. Datasets: adttevnt.xpt, adcvevnt.xpt

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Eugenio Andraca-Carrera
Date:

Concurring Reviewers: Mat Soukup, Aloka Chakravarty

Statistical Team Leader: Mat Soukup

Biometrics VII Division Director: Aloka Chakravarty

cc:
HFD-750
Aloka Chakravarty (Director, Division of Biometrics VII)
Mat Soukup (Division of Biometrics VII)
Eugenio Andraca-Carrera (Division of Biometrics VII)
Lillian Patrician (Office of Biostatistics)

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/s/

EUGENIO ANDRACA-CARRERA
02/04/2013

MATTHEW J SOUKUP
02/04/2013
Concur with review

ALOKA G CHAKRAVARTY
02/04/2013

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 204042 **Applicant:** Janssen Research & Development, LLC **Stamp Date:** 5/31/2012

Drug Name: Canagliflozin **NDA/BLA Type:** 505(b)(1). **Type of review:** Safety (CV) Meta-analysis

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	**X**			eCTD
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	**X**			Study report for meta-analysis and for studies included in meta-analysis are available
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	**X**			MACE+ was analyzed by sex, gender, race, region and other subgroups
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	**X**			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES

The NDA is fileable from a statistics perspective.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter: no potential review issues have been identified at this time.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	**X**			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	**X**			
The primary composite endpoint consists of adjudicated CV events including CV death, MI, Stroke and Hospitalization for unstable angina (i.e. traditional MACE)	**X**			MACE+ agreed upon with FDA
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	**X**			Interim analysis was pre-specified.
Appropriate references for novel statistical methodology (if present) are included.			**X**	

File name: Statistics Filing Checklist for NDA 204042

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Safety data organized to permit analyses across clinical trials in the NDA/BLA.	**X**			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			**X**	

File name: Statistics Filing Checklist for NDA 204042

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Brief summary of MACE events in controlled clinical trials

Table copied from ISS dated 18 May 2012

Table 206 MACE-Plus Events by Study (All Phase 2/3 Studies: mITT Analysis Set)

	Non-Cana[a] n/N (%)	Cana 100 mg n/N (%)	Cana 300 mg n/N (%)	All Cana n/N (%)	Total n/N (%)	Hazard ratio (95% CI)
All studies[a]	71/ 3327 (2.1)	66/ 3156 (2.1)	64/ 3149 (2.0)	130/ 6305 (2.1)	201/ 9632 (2.1)	0.91 (0.68, 1.22)
CANVAS	53/ 1441 (3.7)	56/ 1445 (3.9)	52/ 1441 (3.6)	108/ 2886 (3.7)	161/ 4327 (3.7)	1.00 (0.72, 1.39)
Other than CANVAS	18/ 1886 (1.0)	10/ 1711 (0.6)	12/ 1708 (0.7)	22/ 3419 (0.6)	40/ 5305 (0.8)	0.65 (0.35, 1.21)
DIA2001	0/ 65	0/ 64	0/ 64	0/ 128	0/ 193	
DIA3002	1/ 156 (0.6)	1/ 157 (0.6)	0/ 156	1/ 313 (0.3)	2/ 469 (0.4)	
DIA3004	4/ 90 (4.4)	1/ 90 (1.1)	3/ 89 (3.4)	4/ 179 (2.2)	8/ 269 (3.0)	
DIA3010	4/ 237 (1.7)	3/ 241 (1.2)	3/ 236 (1.3)	6/ 477 (1.3)	10/ 714 (1.4)	
DIA3005	0/ 192	0/ 195	0/ 197	0/ 392	0/ 584	
DIA3012	0/ 115	0/ 113	1/ 114 (0.9)	1/ 227 (0.4)	1/ 342 (0.3)	
DIA3006	4/ 549 (0.7)	0/ 368	1/ 367 (0.3)	1/ 735 (0.1)	5/ 1284 (0.4)	
DIA3009	5/ 482 (1.0)	5/ 483 (1.0)	4/ 485 (0.8)	9/ 968 (0.9)	14/ 1450 (1.0)	

Denominators include all treated subjects in that study.
[a] Stratified by CANVAS/studies other than CANVAS for all studies

Eugenio Andraca-Carrera 08/17/2012
Reviewing Statistician Date

Mat Soukup, Ph.D.
Supervisor/Team Leader Date

File name: Statistics Filing Checklist for NDA 204042

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/s/

EUGENIO ANDRACA-CARRERA
08/17/2012

STATISTICS FILING CHECKLIST FOR NDA/BLA

NDA Number: 204042/0000 **Applicant:** Janssen **Stamp Date: 5/31/2012**

Drug Name: Canagliflozin **NDA/BLA Type: New NDA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	✓			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	✓			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	✓			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	✓			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	✓			
Appropriate references for novel statistical methodology (if present) are included.			✓	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	✓			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	✓			LOCF method

Comment: No statistical review issues to be forwarded to the Applicant for the 74-day letter.

File name: 5_Statistics Filing Checklist for a New NDA_BLA

STATISTICS FILING CHECKLIST FOR NDA/BLA

Wei Liu **7/31/2012**

Reviewing Statistician Date

Supervisor/Team Leader Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA

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/s/

WEI LIU
07/31/2012

JON T SAHLROOT
08/03/2012