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Canagliflozin: Clinical Efficacy and Safety

Endocrinologic and Metabolic Drugs Advisory Committee Meeting
January 10, 2013

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Outline

- Efficacy
  - Renal impairment
- Safety
  - Volume depletion events
  - Renal safety
  - Bone safety
  - Genital mycotic infections
  - Cardiovascular safety
- Summary

Canagliflozin: Mechanism of Action

- Canagliflozin is an SGLT-2 inhibitor
- SGLT-2 inhibition lowers the renal glucose threshold
  - The renal glucose threshold is **the plasma glucose concentration** which exceeds the maximum glucose reabsorption capacity of the kidney
- Lowering the renal glucose threshold results in **increased urinary glucose excretion**
- The glucose lowering effect of SGLT-2 inhibition is thus dependent on both plasma glucose level and renal function

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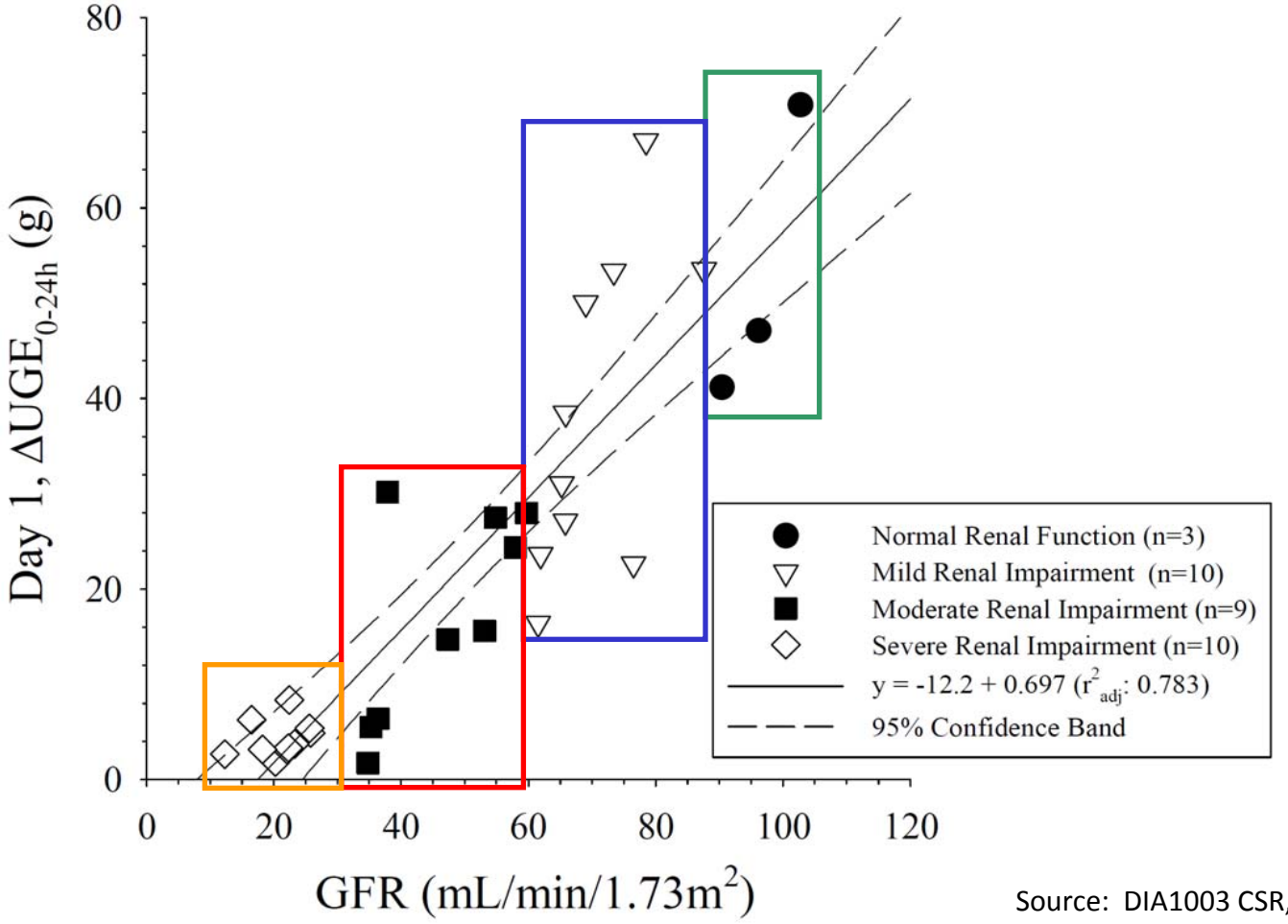
Canagliflozin: Renal Function and Efficacy

Effect of Renal Impairment on Urinary Glucose Excretion



Source: DIA1003 CSR, Figure 4

Canagliflozin: Renal Function and Efficacy

Pooled data to explore the impact of renal function on efficacy

Moderate Renal Impairment
(eGFR ≥30 to <60 mL/min/1.73m^2)

Trial ID	Time of Primary Efficacy Endpoint	Total Subjects
DIA3005	26 Weeks	32
DIA3008	18 Weeks	706
DIA3004	26 Weeks	253
DIA3010	26 Weeks	94
Total		1085

Placebo-Controlled Studies:
Normal to Mild Renal Function

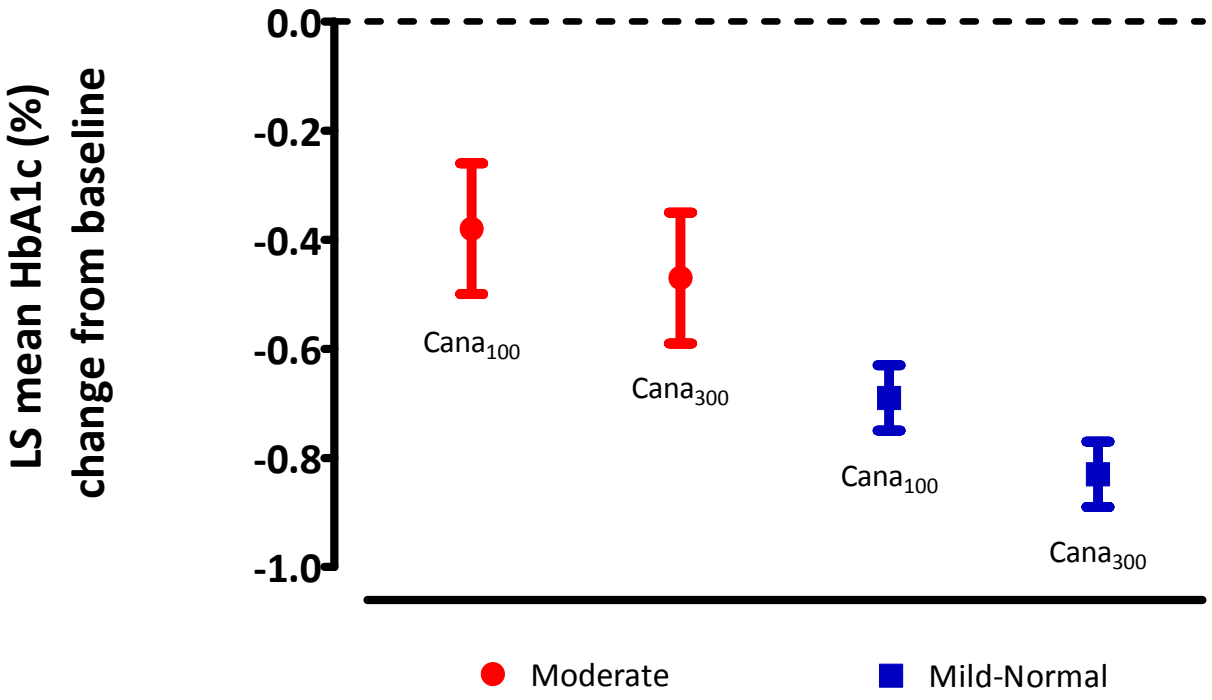
Trial ID	Time of Primary Efficacy Endpoint	Total Subjects
DIA3005	26 Weeks	584
DIA3006	26 Weeks	918
DIA3008	18 Weeks	1845
DIA3002	26 Weeks	469
DIA3012	26 Weeks	342
Total		4158

Canagliflozin: Renal Function and Efficacy

Baseline Characteristics for Pooled Efficacy Datasets

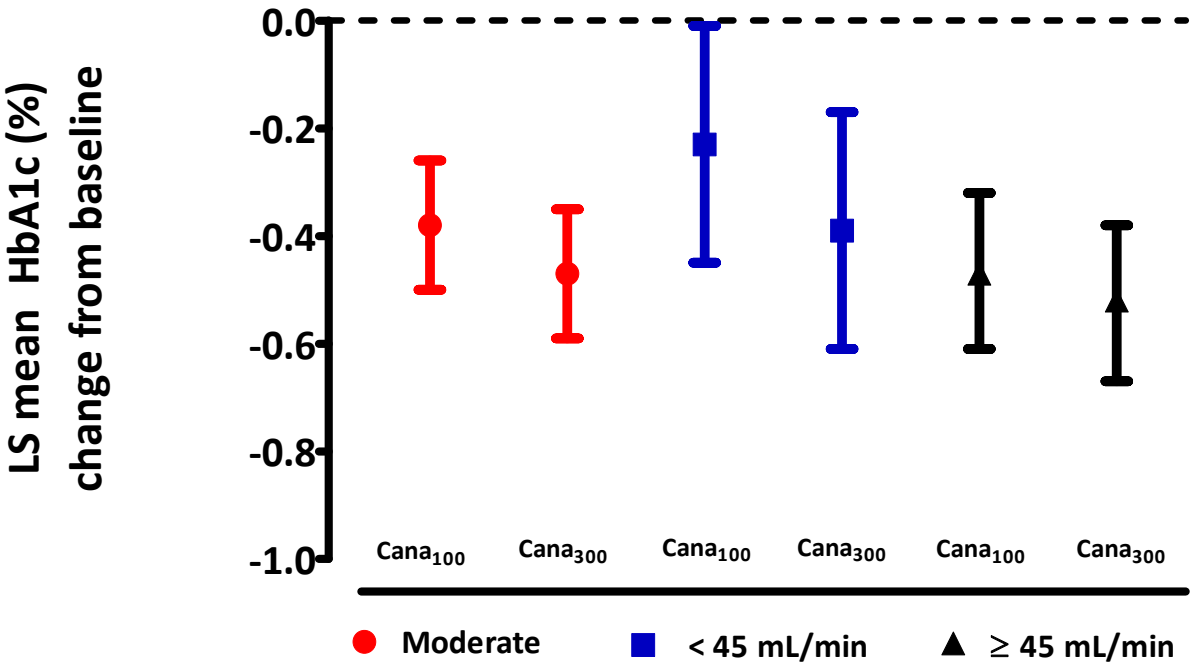
	Moderate Renal Impairment		Normal to Mild Renal Function	
	Canagliflozin (N=703)	Placebo (N=382)	Canagliflozin (N=2902)	Placebo (N=1256)
Mean Age (years)	67.1	66.9	58.9	59.4
Male (%)	58%	59%	56%	59%
Mean BMI (kg/m^2)	32.3	33.0	32.7	32.6
Mean HbA1c (%)	8.0	7.9	8.1	8.1
Mean duration of diabetes (years)	15.2	15.0	11.1	11.6
Mean eGFR (mL/min/1.73m^2)	47.9	48.8	82	80.7
<60 mL/min/1.73m^2, n (%)	703 (100)	382 (100)	323 (11)	167 (13)
60 - <90 mL/min/1.73m^2, n (%)			1587 (55)	708 (56)
≥90 mL/min/1.73m^2, n (%)			989 (34)	380 (30)

Canagliflozin: Renal Function and Efficacy



	Moderate Renal Impairment		Normal to Mild Renal Function	
	Cana 100 (N=326)	Cana 300 (N=354)	Cana 100 (N=1404)	Cana 300 (N=1419)
PBO adjusted LS mean HbA1c (%) change from baseline (95% CI)	-0.4 (-0.50,-0.26)	-0.5 (-0.59,-0.35)	-0.7 (-0.75,-0.63)	-0.8 (-0.89,-0.77)

Canagliflozin: Renal Function and Efficacy



	Moderate Renal Impairment ≥30 to 60 mL/min/1.73m²		eGFR <45 mL/min/1.73 m²		eGFR ≥45 mL/min/1.73 m²	
	Cana 100 (N=326)	Cana 300 (N=354)	Cana 100 (N=118)	Cana 300 (N=122)	Cana 100 (N=208)	Cana 300 (N=232)
PBO adjusted LS mean HbA1c (%) change from baseline (95% CI)	-0.4 (-0.50,-0.26)	-0.5 (-0.59,-0.35)	-0.2 (-0.45,-0.01)	-0.4 (-0.61,-0.17)	-0.5 (-0.61,-0.32)	-0.5 (-0.67,-0.38)

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Safety Data

Name of Pooled Dataset	Dataset Description	Pooled Trials	Pooled Treatment Groups	Exposure Duration Data Cutoff Date
Placebo-controlled 26-Week Studies Dataset (DS1)	4 placebo controlled 26-week studies	DIA3002 DIA3005* DIA3006** DIA3012	Placebo Cana 100 Cana 300	26 weeks
Moderate Renal Impairment Dataset (DS2)	Pool of subjects with eGFR $\geq$ 30 to <60 mL/min/1.73m^2 at baseline	DIA3004 Sub-DIA3005 Sub-DIA3008 Sub-DIA3010	Placebo Cana 100 Cana 300	September 15, 2011 for DIA3008 26 weeks for other trials
Broad Dataset (DS3)	Pool of all active- and placebo-controlled trials (excluding DIA3015)	DS1 plus DIA3004 DIA3008 DIA3009 DIA3010	All Non-Cana Cana 100 Cana 300	September 15, 2011 for DIA3008 52 weeks for DIA3009 26 weeks for all other trials

*excludes High Glycemic substudy; **excludes sitagliptin group

Sub=Subgroups; Non-Cana = placebo, sitagliptin, or glimepiride

Safety Data

Baseline Characteristics: Pooled Safety Data

	DS1	DS2	DS3
Mean Age (years)	57	67	60
Proportion of subjects age 75 or older	2.3%	17.2%	5.2%
Male (%)	50%	58%	58%
Caucasian (%)	72%	78%	73%
Mean BMI (kg/m^2)	32	33	32
Mean HbA1c (%)	8.0	8.1	8.0
Mean duration of diabetes (years)	7.3	15	10.6
Microvascular complications (%)	19%	59%	33%
Mean eGFR ($mL/min/1.73m^2$)	88.1	48.2	81.3
Proportion with moderate renal impairment (%)	4.2%	100%	13%

Safety Data

Mean Exposure for Pooled Safety Datasets (Original Cutoff Dates)

	DS1		DS2		DS3	
	All Cana	Placebo	All Cana	Placebo	All Cana	All Non-Cana
Total (N)	1667	646	714	387	6177	3262
Mean exposure (patient-years)	772	274	508	263	4466	2273
Mean exposure (weeks)	24	22	37	35	38	36

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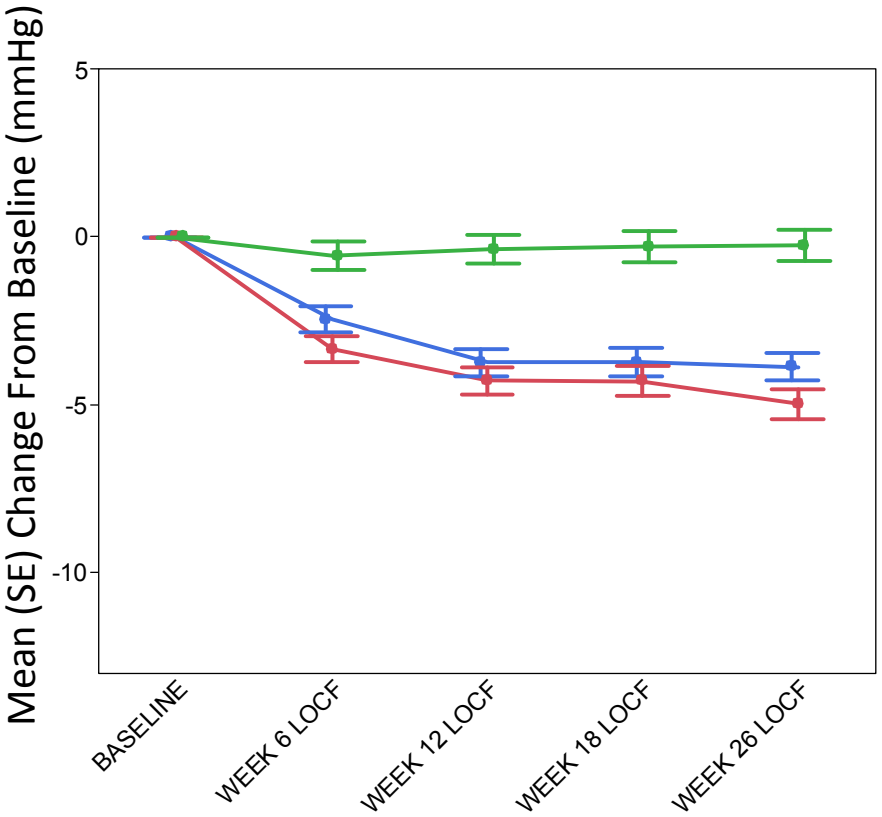
Volume Depletion Events: Effects on Systolic Blood Pressure

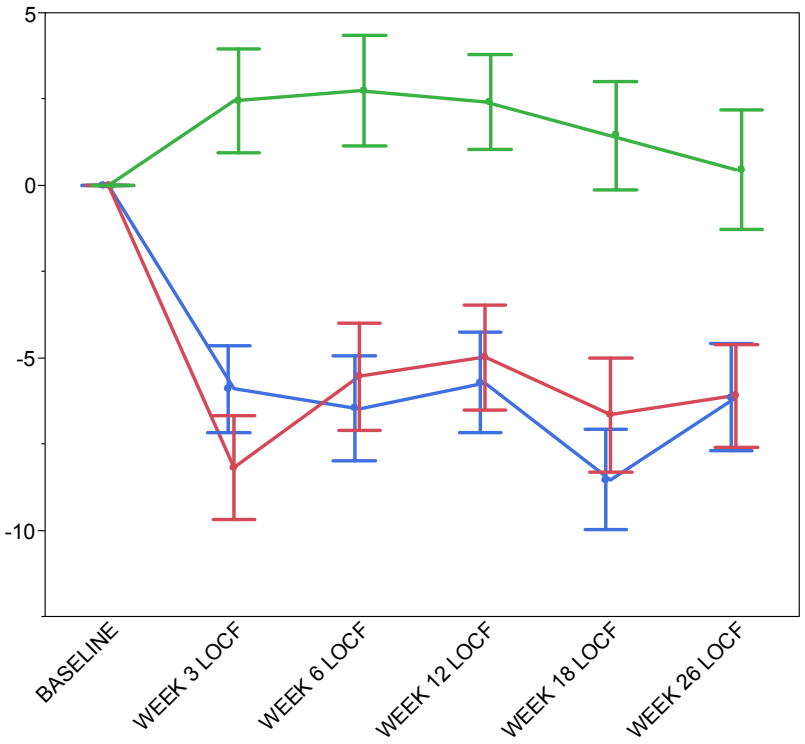
DS-1: Placebo Controlled 26-Week Studies

(mean eGFR at baseline 88 mL/min/1.73 m²)



DIA3004: Moderate Renal Impairment

(mean eGFR at baseline 39 mL/min/1.73 m2)

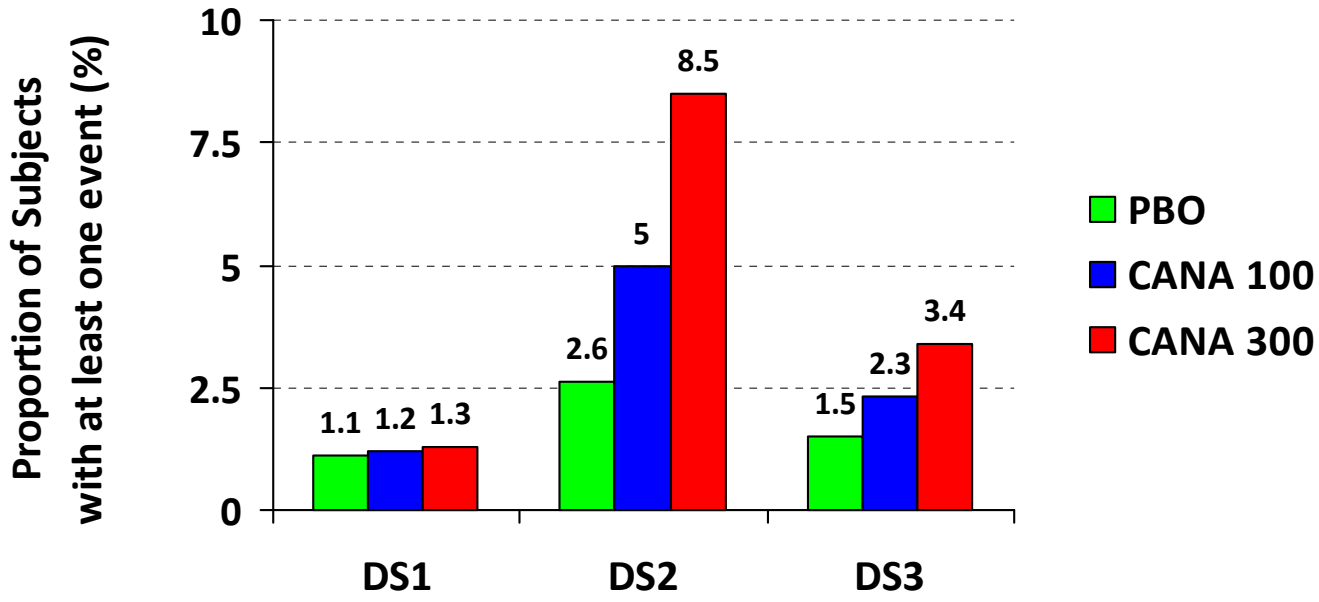


PBO Cana 100 Cana 300

Volume Depletion Events: Search Terms

- Blood pressure decreased
- Dehydration
- Diastolic hypotension
- Dizziness postural
- Hypotension
- Hypovolemia
- Hypovolemic shock
- Orthostatic blood pressure decreased
- Orthostatic hypotension
- Orthostatic intolerance
- Postural orthostatic tachycardia syndrome
- Presyncope
- Shock
- Syncope
- Urine output decreased

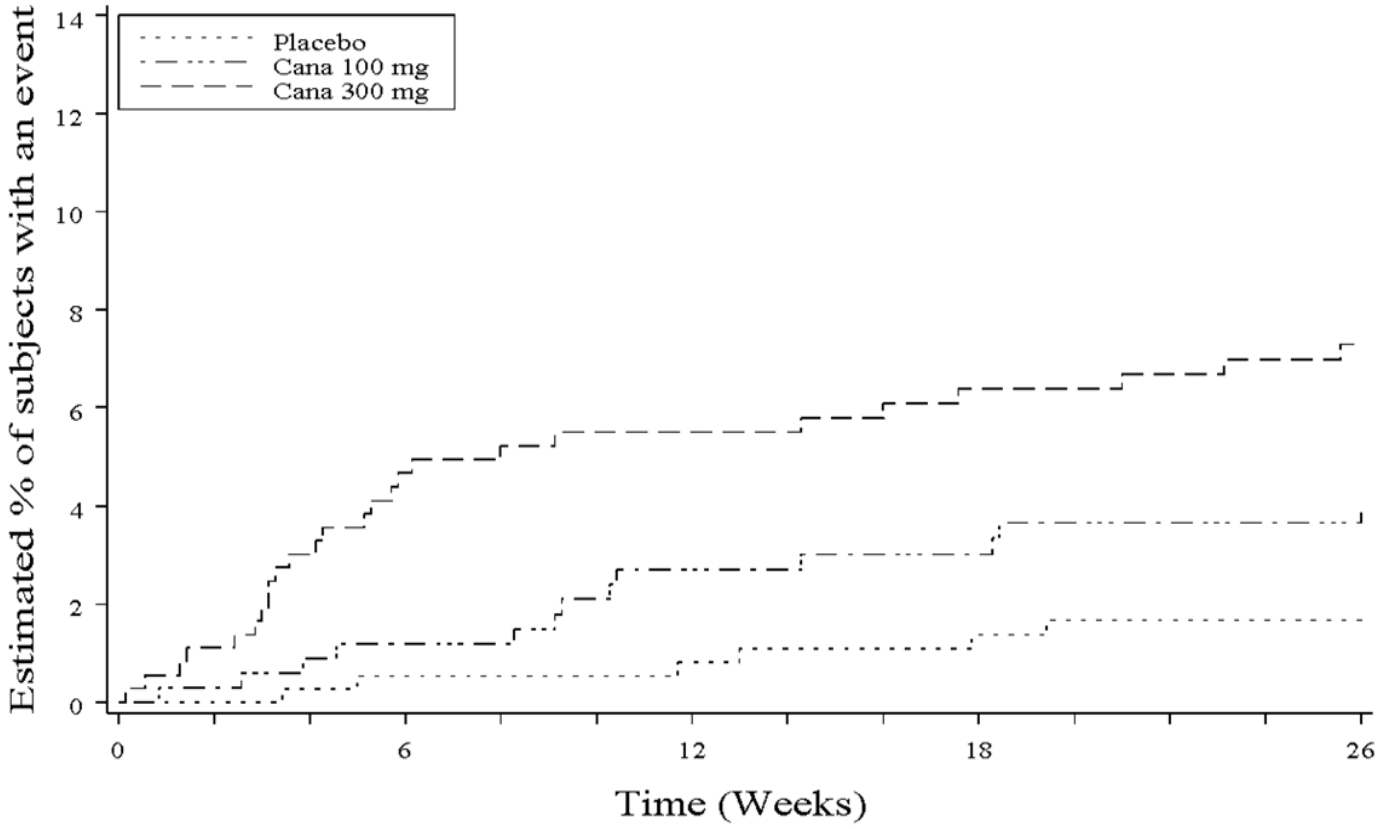
Volume Depletion Events: Incidence



	Placebo/Non-Cana	Cana 100	Cana 300
Placebo-controlled 26-Week Studies Dataset (DS1)	1.1% N=646	1.2% N=833	1.3% N=834
Moderate Renal Impairment Dataset (DS2)	2.6% N=382	5.0% N=338	8.5% N=365
Broad Dataset (DS3)	1.5% N=3262	2.3% N=3092	3.4% N=3085

Volume Depletion Events: Time to First Event

Time to First Volume Depletion Events:
Moderate Renal Impairment Dataset (DS2)



No. Subjects at Risk					
Placebo	382	376	356	343	295
Cana 100 mg	338	330	318	305	259
Cana 300 mg	365	348	329	317	266

Source: NDA 204042

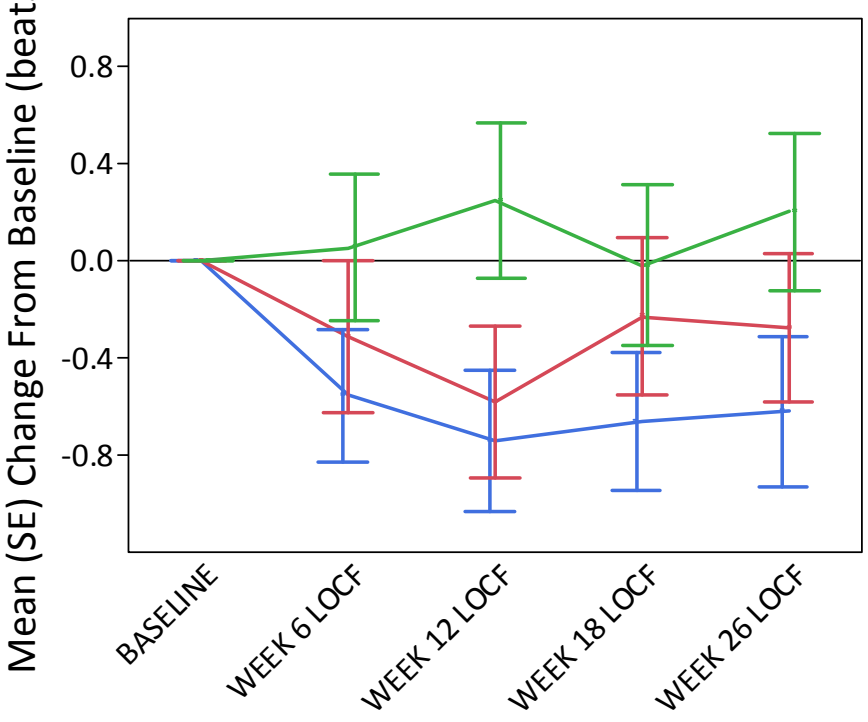
Volume Depletion Events: Baseline Predictors in DS-3

Subgroup Category	N (%) in population	All Non-Cana	Cana 100	Cana 300
eGFR <60 mL/min/1.72m^2	1223 (13%)	2.5%	4.7%	8.1%
Male	5493 (58%)	1.6%	2.6%	4.3%
Age:				
≥65 years	2930 (31%)	1.8%	4.1%	4.8%
≥75 years	490 (5.2%)	2.6%	4.9%	8.7%
Use of Diuretics	3321 (35.2%)	2.1%	2.7%	5.4%
Use of Loop Diuretics	722 (7.6%)	4.7%	3.2%	8.8%
Use of ACE/ARB:	6478 (68.6%)	1.7%	2.8%	4.3%
Use of ACE/ARB only	3507 (37.2%)	1.3%	2.8%	3.1%
Use with diuretics	2971 (31.5%)	2.2%	2.8%	5.6%
Systolic BP ≤ 110 mmHg	575 (6.1%)	2.3%	4.5%	6.0%
Baseline HbA1c > 7.9%	4540 (48%)	1.4%	2.2%	3.9%
10+ years of diabetes	4734 (50%)	1.9%	2.8%	4.8%

Volume Depletion Events: Effects on Heart Rate

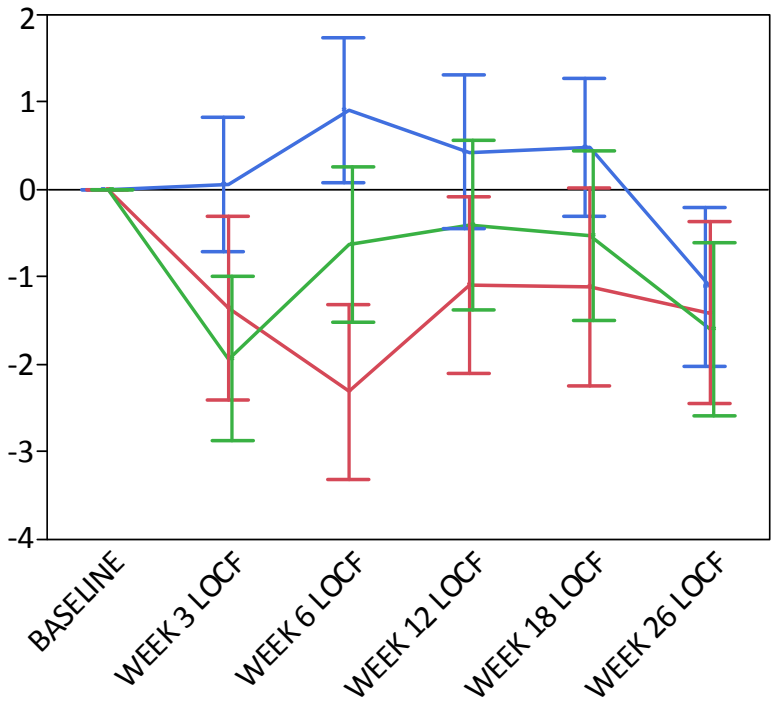
DS-1: Placebo Controlled 26-Week Studies

(mean eGFR at baseline 88 mL/min/1.73 m²)



DIA3004: Moderate Renal Impairment

(mean eGFR at baseline 39 mL/min/1.73 m2)



PBO Cana 100 Cana 300

Arrhythmia/Palpitation Adverse Events: Broad Search Terms

- Atrial fibrillation
- Palpitations
- Tachycardia
- Atrioventricular block first degree
- Bradycardia
- Arrhythmia
- Ventricular extrasystoles
- Bundle branch block left
- Sinus bradycardia
- Bundle branch block right
- Extrasystoles
- Sinus tachycardia
- Supraventricular tachycardia
- Atrial flutter
- Atrioventricular block second degree
- Supraventricular extrasystoles
- Ventricular fibrillation
- Cardiac flutter
- Sinus arrhythmia
- Atrioventricular block
- Atrioventricular block complete
- Reperfusion arrhythmia
- Tachycardia paroxysmal
- Ventricular arrhythmia
- Ventricular tachycardia

Arrhythmia: Incident Cases Broad Search Results

197 cases were identified to have at least one broad treatment-emergent "arrhythmia or palpitation" adverse event in **DS-3**

	All Cana (N=6177)	All Non-Cana (N=3262)
% (n)	2.2 (134)	1.9 (63)

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Renal Function Changes

Phase 1 trials

Early observed changes

- ↑ urine volume
- ↑ serum creatinine
- ↑ BUN levels
- ↓ blood pressure

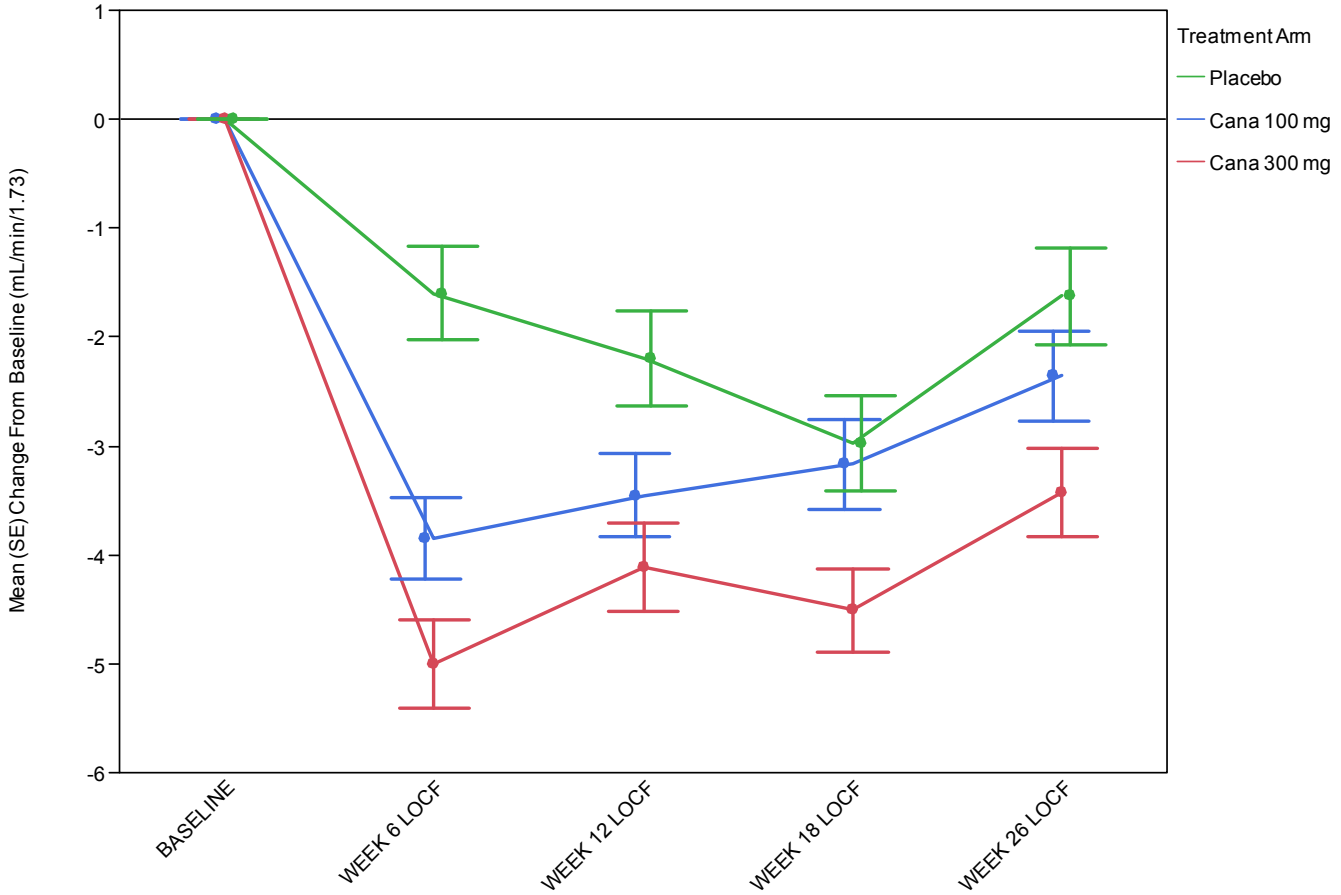
Phase 3 trials

Early and dose-dependent

- ↓ eGFR
- corresponding early and persistent ↑ BUN and serum creatinine

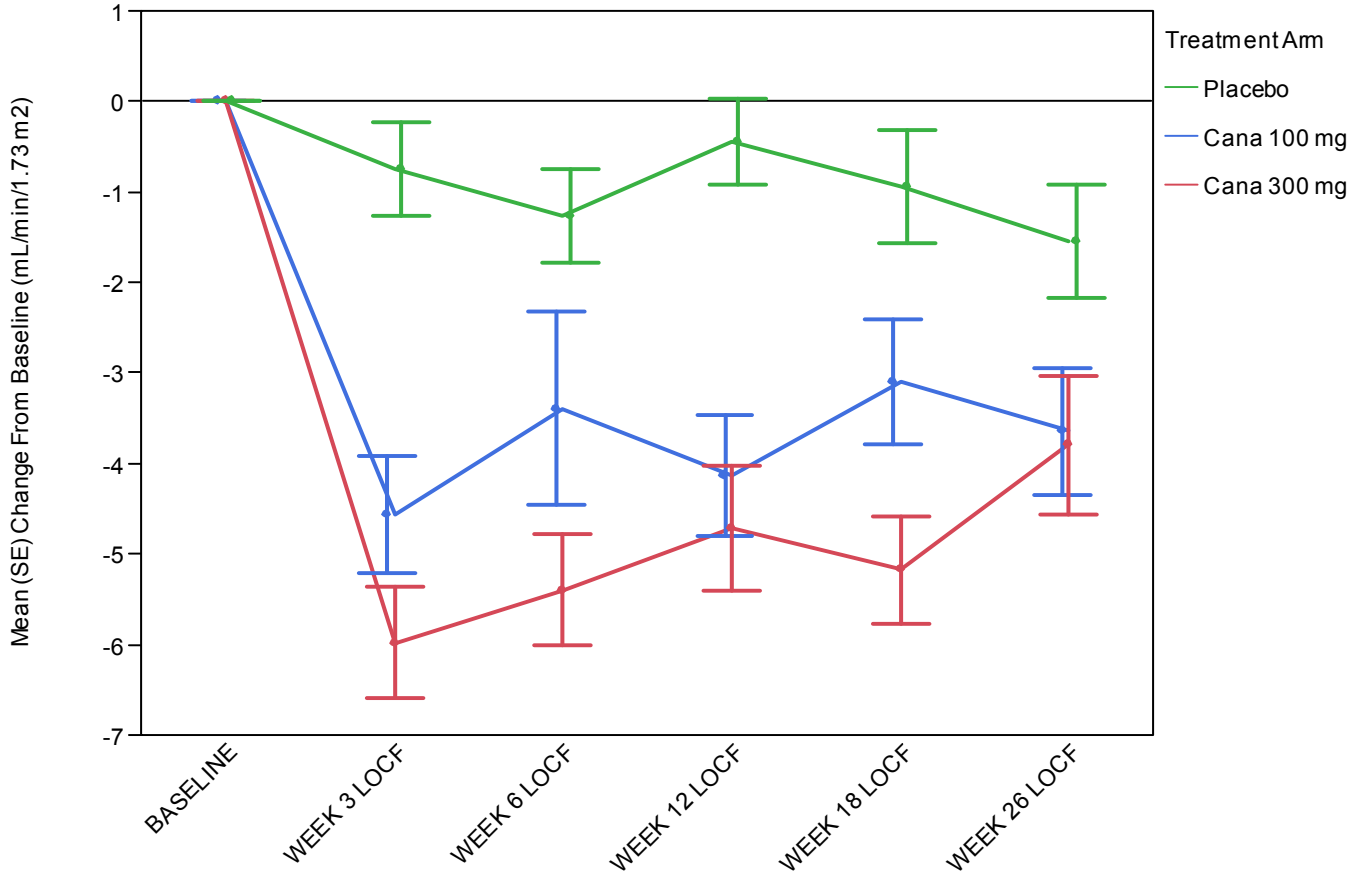
Renal Function Changes: Mild or Normal Function at Baseline

Mean change in eGFR from baseline over time in **DS1**
(mean eGFR at baseline 88 mL/min/1.73 m2)



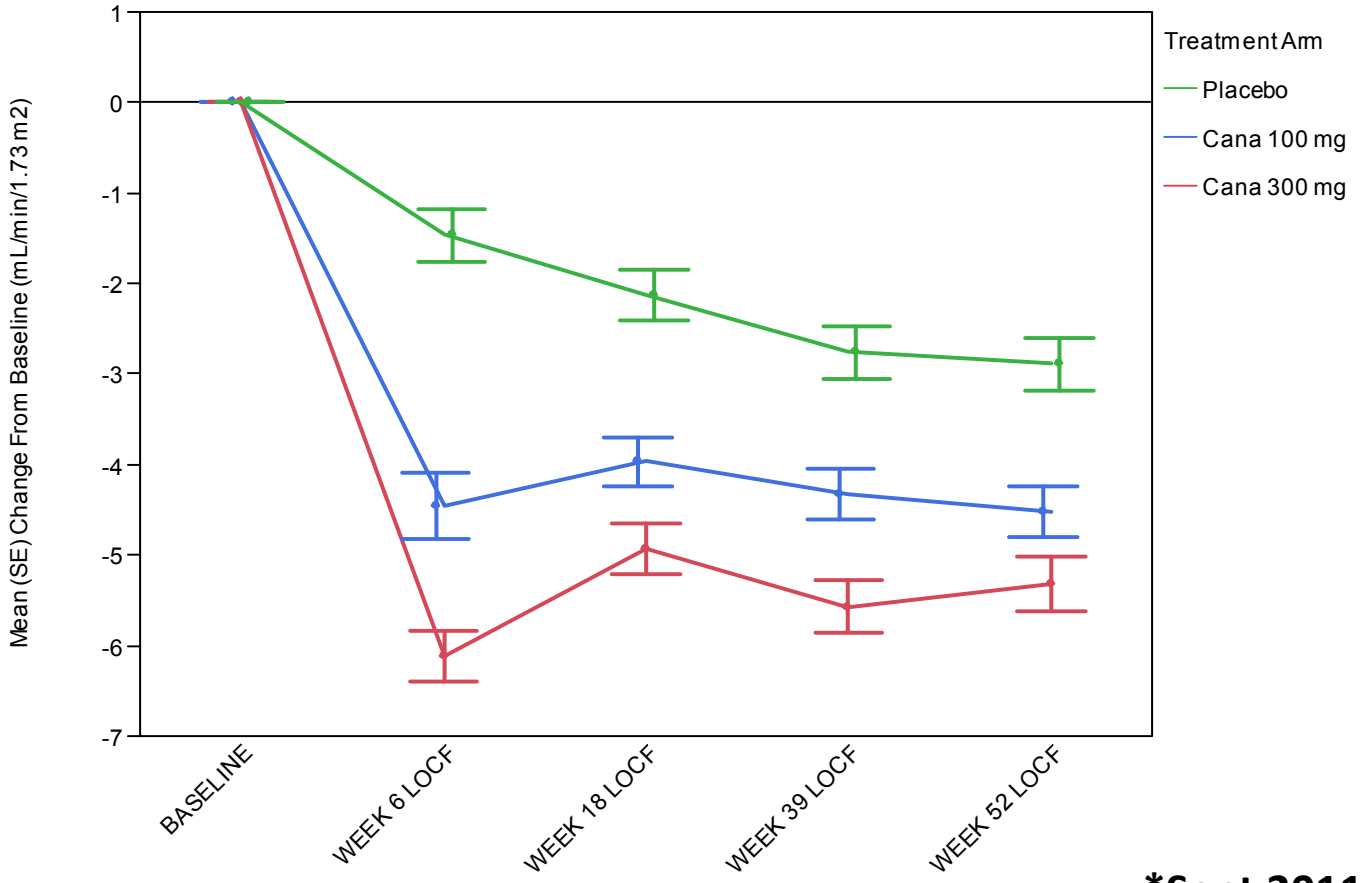
Renal Function Changes: Moderate Function at Baseline

Mean change in eGFR from baseline over time in **Trial DIA3004**
(Mean baseline eGFR 39 mL/min/1.73 m^2)



Renal Function Changes: Long Term in High CV Risk Individuals

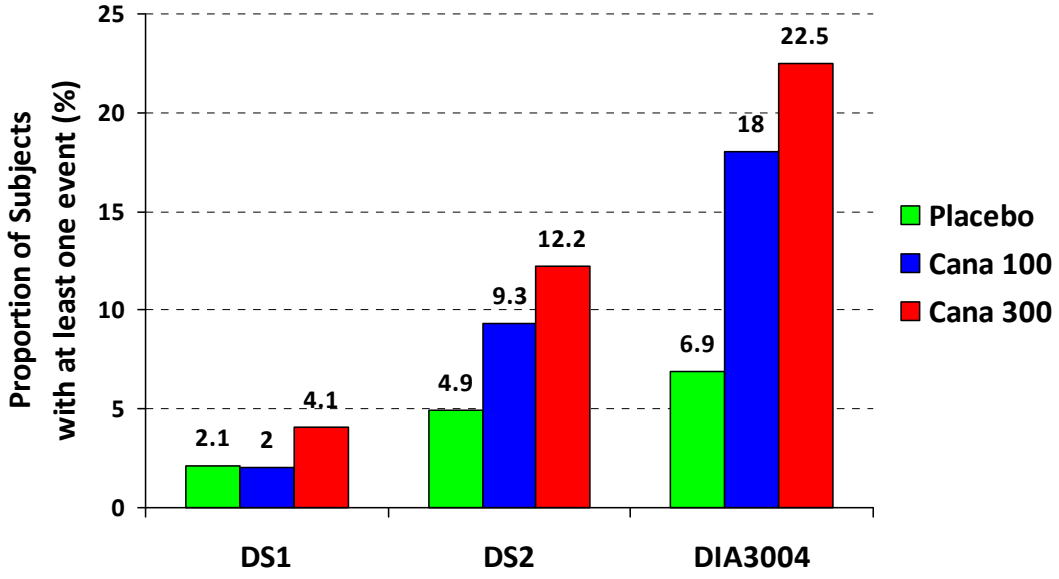
Mean change in eGFR from baseline over time in **Trial DIA3008***
(Mean baseline eGFR 77 mL/min/1.73 m^2)



***Sept 2011 Cutoff**

Significant Renal Function Changes: Incidence

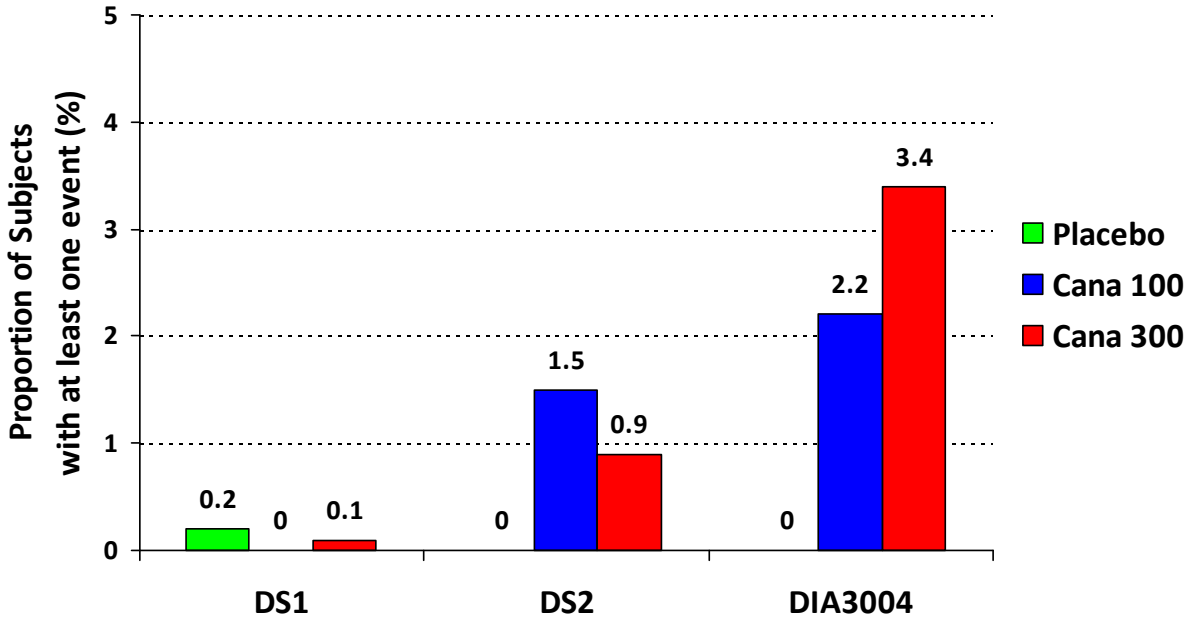
Proportion of subjects with a baseline eGFR <80 mL/min/1.73 m^2 who had an eGFR reduction of >30% from baseline at any time



	Placebo	Cana 100	Cana 300
Placebo-Controlled 26-Week Studies Dataset (DS1)	2.1%	2.0%	4.1%
Moderate Renal Impairment Dataset (DS2)	4.9%	9.3%	12.2%
Moderate Renal Impairment Trial (DIA3004)	6.9%	18.0%	22.5%

Significant Renal Function Changes: Incidence

Proportion of subjects with an eGFR reduction of >50% from baseline at any time



	Placebo	Cana 100	Cana 300
Placebo-Controlled 26-Week Studies Dataset (DS1)	0.2%	0	0.1%
Moderate Renal Impairment Dataset (DS2)	0	1.5%	0.9%
Moderate Renal Impairment Trial (DIA3004)	0	2.2%	3.4%

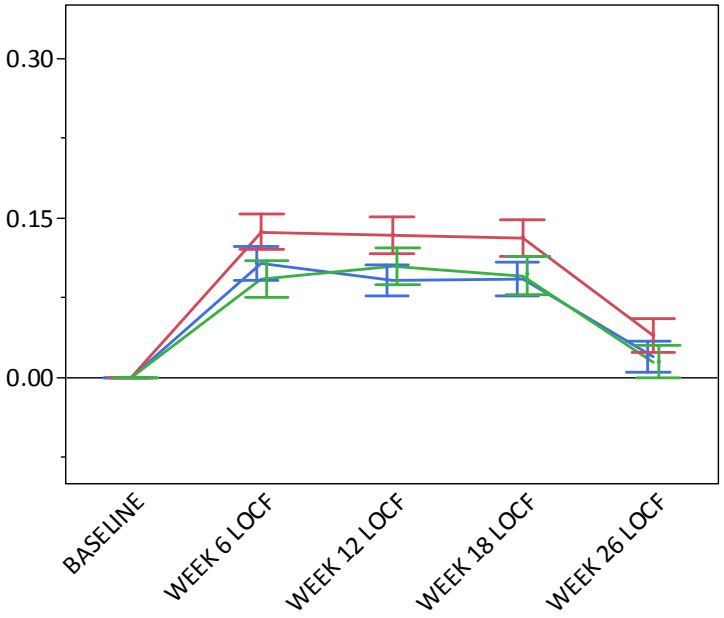
Renal Function Changes: Potassium Handling

Mean Serum Potassium Changes by Visit

Mean (SE) Change From Baseline (mEq/L)

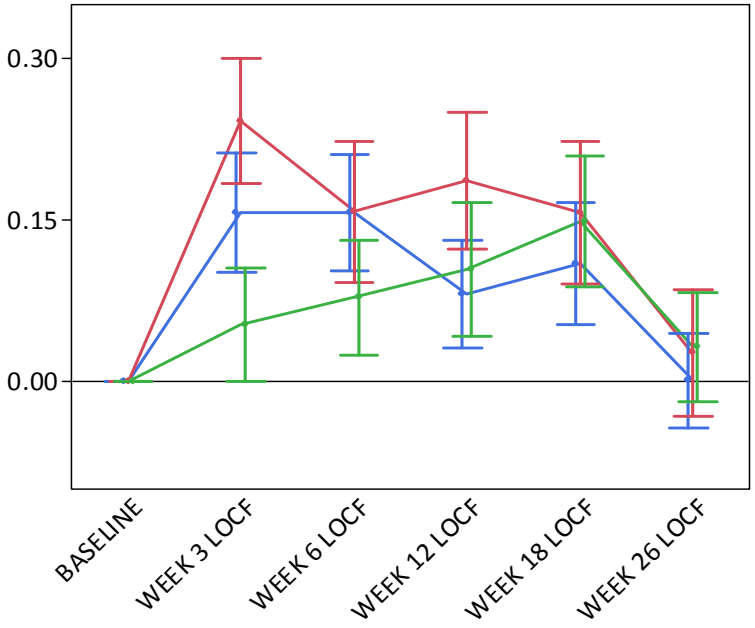
DS-1: Placebo Controlled 26-Week Studies

(mean eGFR at baseline 88 mL/min/1.73 m^2)



DIA3004: Moderate Renal Impairment

(mean eGFR at baseline 39 mL/min/1.73 m2)

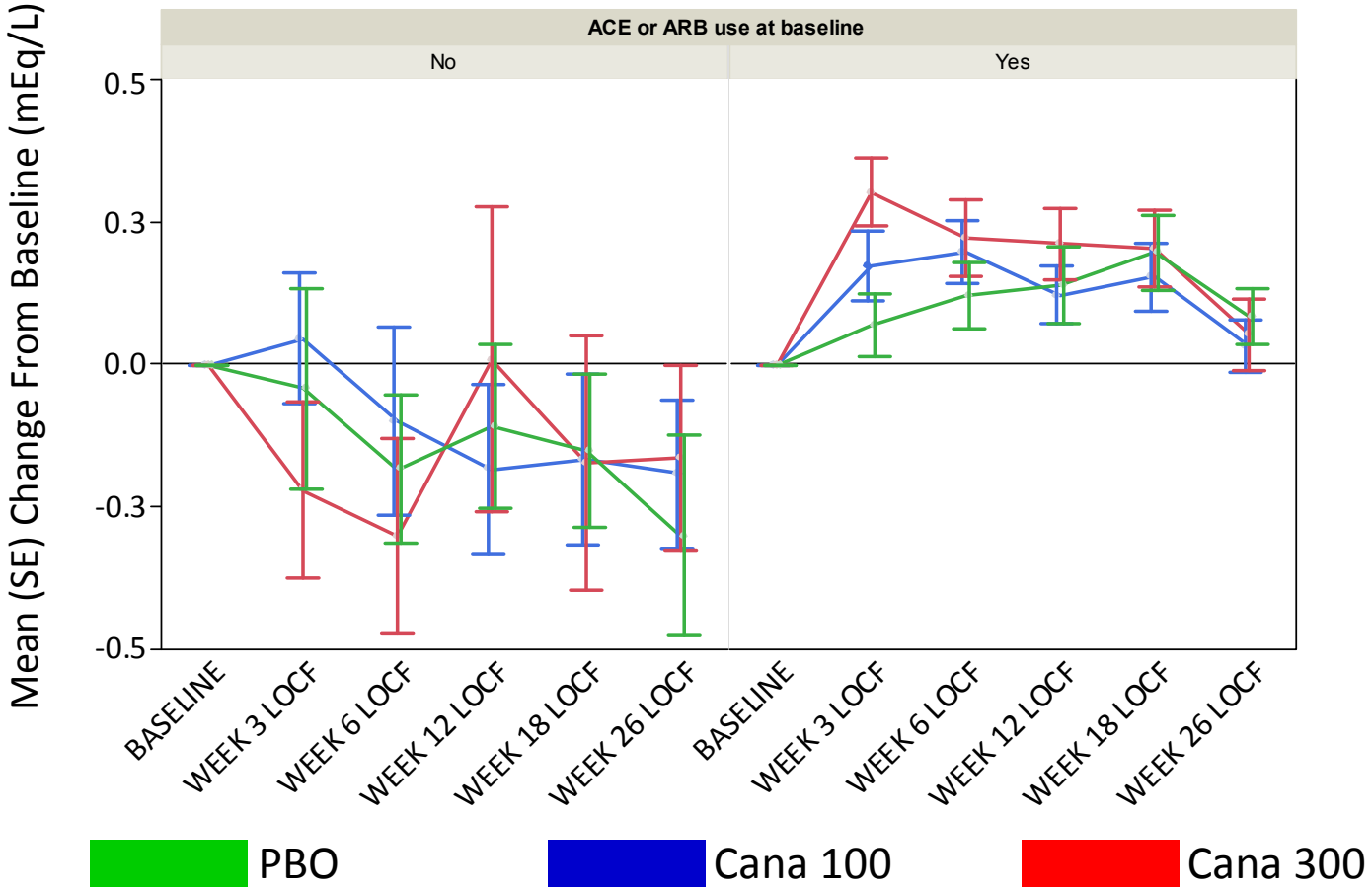


PBO Cana 100 Cana 300

Renal Function Changes: Potassium Handling

Baseline Use of **ACE inhibitor or ARB** on Mean Change in Serum Potassium

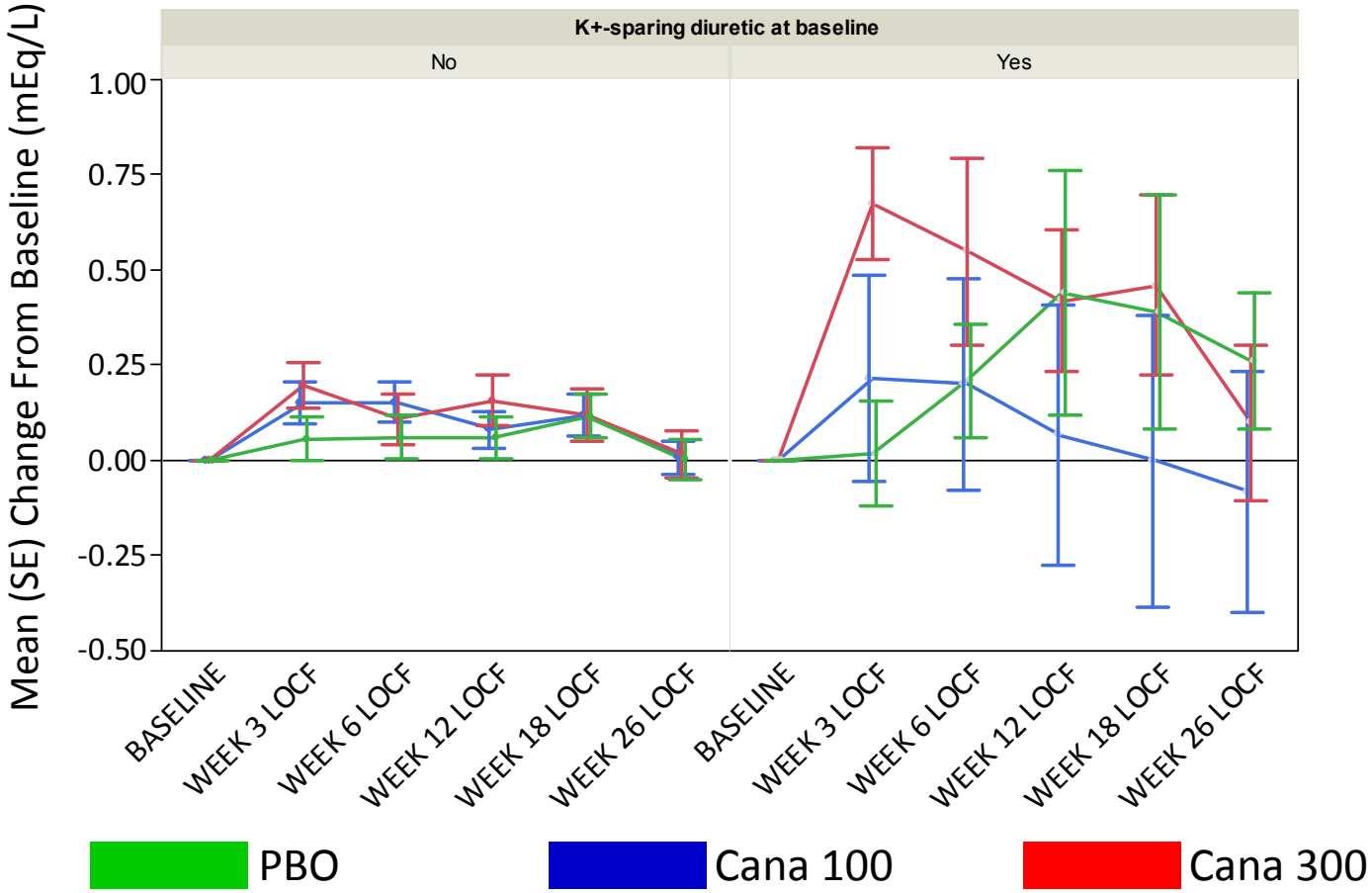
DIA3004: Moderate Renal Impairment (mean eGFR at baseline 39 mL/min/1.73 m^2)



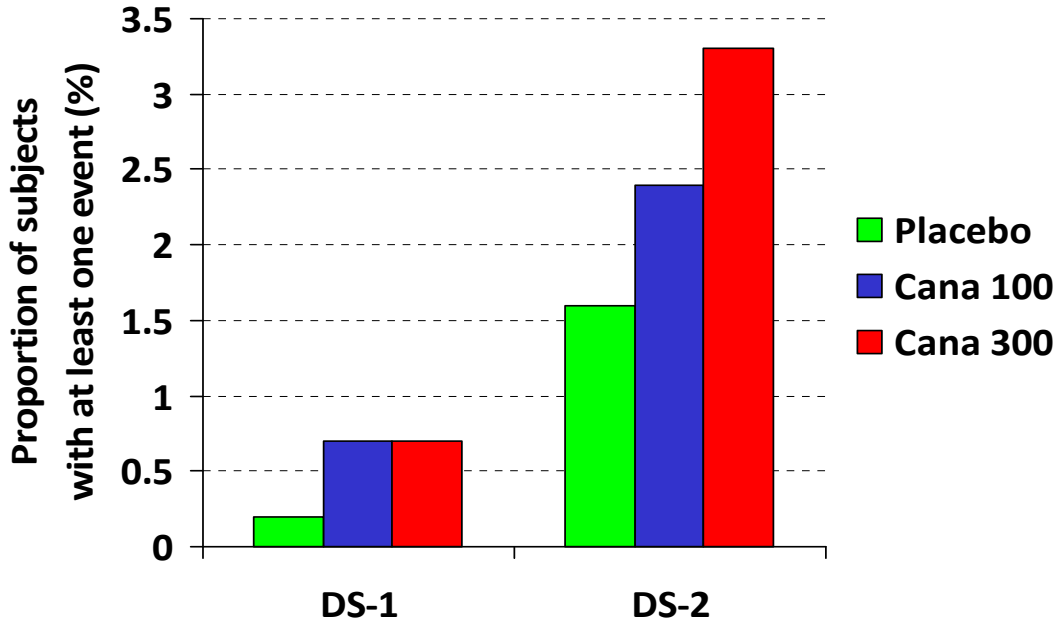
Renal Function Changes: Potassium Handling

Baseline Use of **Potassium Sparing Diuretic** on Mean Change in Serum Potassium

DIA3004: Moderate Renal Impairment (mean eGFR at baseline 39 mL/min/1.73 m^2)



Hyperkalemia-related Adverse Events: Incidence



	Placebo	Cana 100	Cana 300
Placebo-controlled 26-Week Studies Dataset (DS1)	0.2% N=646	0.7% N=833	0.7% N=0.7
Moderate Renal Impairment Dataset (DS2)	1.6% N=382	2.4% N=338	3.3% N=365

Renal-related Adverse Events

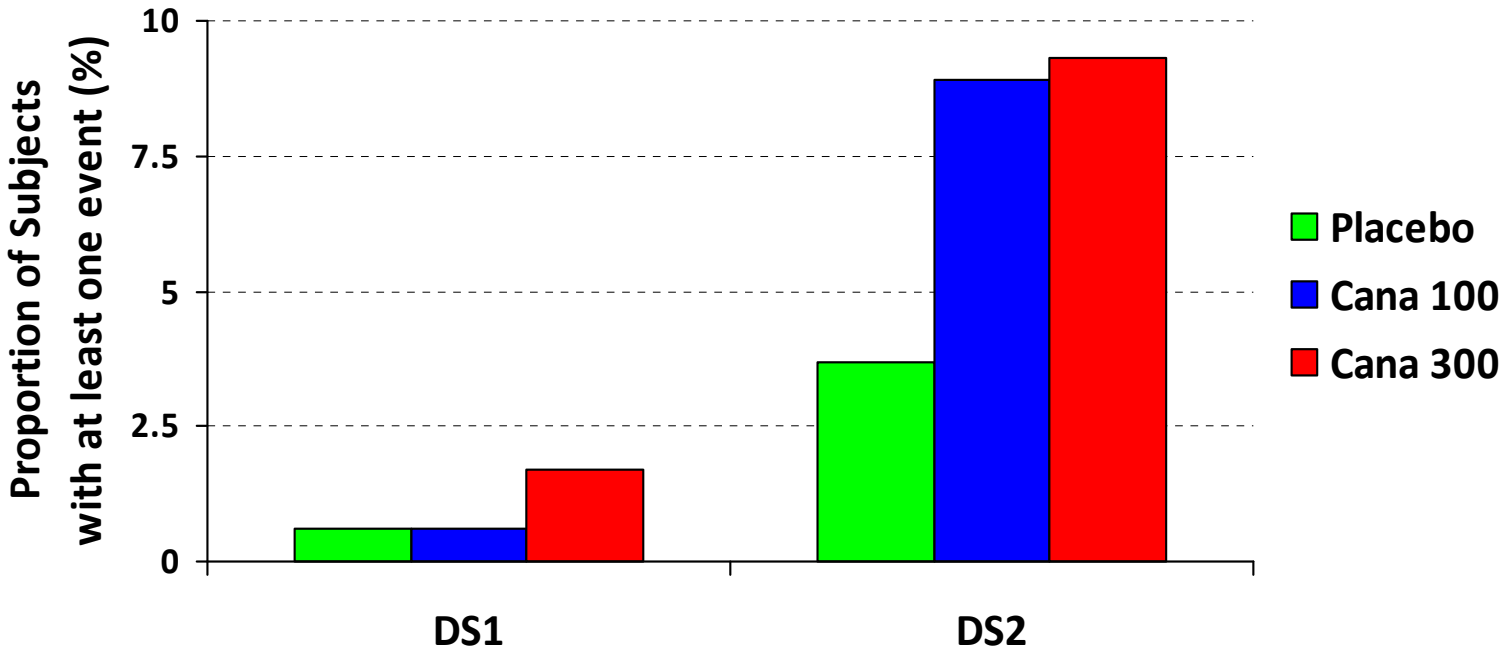
- No systematic prospective approach to ensure capture of renal-related adverse events in Phase 3 trials
- Potential renal-related adverse events were identified from the larger pool of investigator reported adverse events retrospectively
- Datasets were queried for all preferred term using the **Standardized MedDRA Query (SMQ) for acute renal failure** and the Preferred Terms (PT) **'blood creatinine increased'** and **'glomerular filtration rate decrease'**

Renal-related Adverse Events: SMQ Search Terms

SMQ for acute renal failure includes the following PTs:

- Acute phosphate nephropathy
- Acute prerenal failure
- Anuria
- Azotemia
- Continuous hemodiafiltration
- Dialysis
- Hemodialysis
- Neonatal anuria
- Nephropathy toxic
- Oliguria
- Peritoneal dialysis
- Renal failure
- Renal failure acute
- Renal failure neonatal
- Renal impairment
- Renal impairment neonatal

Renal-related Adverse Events



	Placebo	Cana 100	Cana 300
Placebo-controlled 26-Week Studies Dataset (DS1)	0.6%	0.6%	1.7%
Moderate Renal Impairment Dataset (DS2)	3.7%	8.9%	9.3%

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Bone Safety:
Nonclinical Bone-Related Findings Rats

- ↑ metaphyseal trabecular bone (hyperostosis)
  - Dose-dependent
- ↑ in urinary calcium excretion
- ↓ in serum parathyroid hormone (PTH)
- ↓ in 1,25-OH vitamin D
- ↓ bone turnover markers

Bone Safety:
Phase-2 Bone Related Findings

Trial DIA2001

- ↑ bone resorption marker: collagen type 1 beta-carboxy-telopeptide (CTX)
  - **23-37%** rise in canaglifozin dose groups
  - **9%** rise in placebo group
  - Non-dose dependent above 50 mg
  - Observed by Week 3 and persists to end of study (Week 12)
- No consistent changes in bone formation markers
- ↑ in PTH
  - Non-dose dependent
  - Observed by Week 3 returns towards baseline by Week 6 to 12
- Slight ↓ in
  - 25-OH vitamin D
  - 1,25-OH vitamin D levels at high doses
- No consistent increase in urine calcium

Bone Safety:
DS-1 Calcium and Phosphate Findings

Mean (%) change from baseline to end of trial

	Placebo (N=526)	Cana 100 (N=715)	Cana 300 (N=720)
Serum Calcium	0.2	0.8	1.1
Serum Phosphate	1.5	3.6	5.1

Bone Safety:
DIA3004 Calcium Regulatory Axis

Mean (%) change from baseline to end of trial

	Placebo (N=90)	Cana 100 (N=90)	Cana 300 (N=89)
Serum 25-OH vitamin D	1.1	10.2	6.8
Serum 1,25-OH vitamin D	-3.1	-0.4	-8.1
Serum Parathyroid Hormone	6.8	8.3	-10.5
Serum Calcium	-0.4	1.3	7.2
Serum Phosphate	0	3.4	7.8

Source: CSR DIA3004, Table 39

Bone Safety:
Mean Serum Calcium Changes

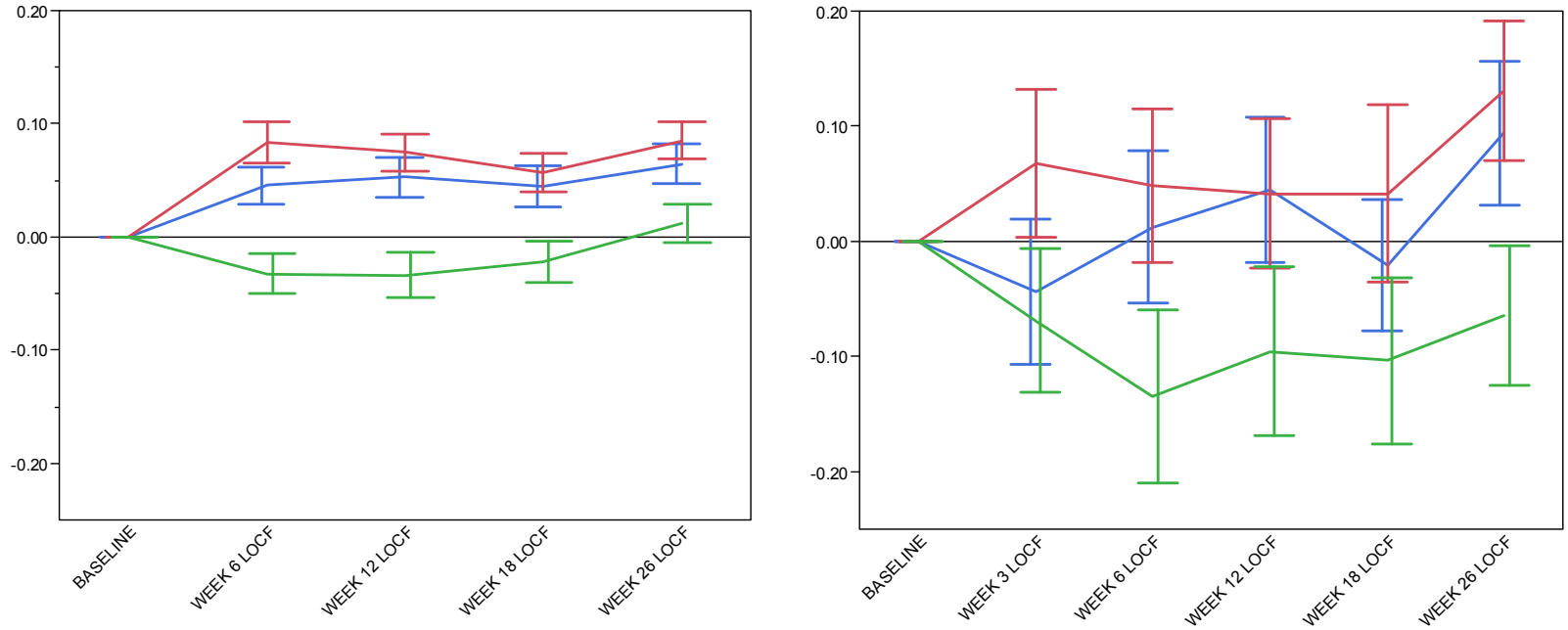
DS-1: Placebo Controlled 26-Week Studies

(mean eGFR at baseline 88 mL/min/1.73 m^2)

DIA3004: Moderate Renal Impairment

(mean eGFR at baseline 39 mL/min/1.73 m2)

Mean (SE) Change From Baseline (mg/dL)

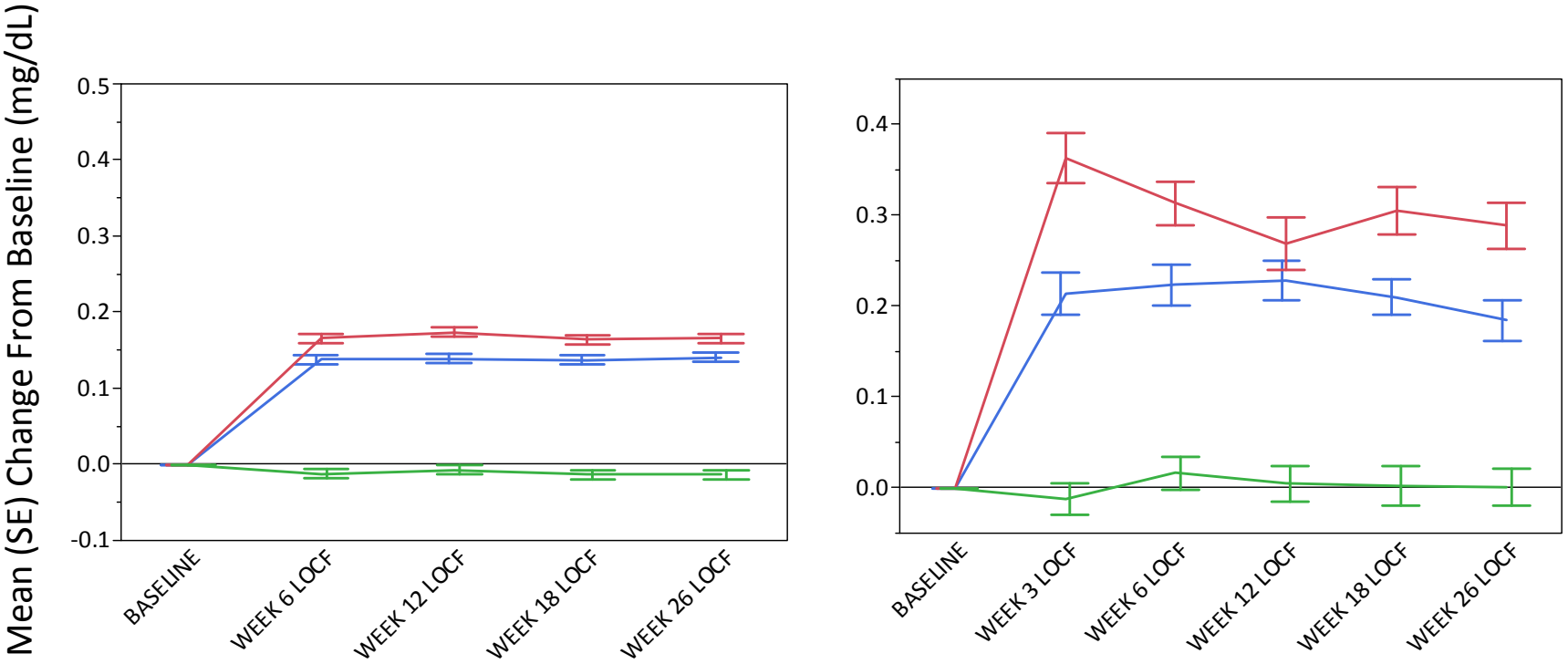


PBO Cana 100 Cana 300

Bone Safety:
Mean Serum Magnesium Changes

DS-1: Placebo Controlled 26-Week Studies
(mean eGFR at baseline 88 mL/min/1.73 m²)

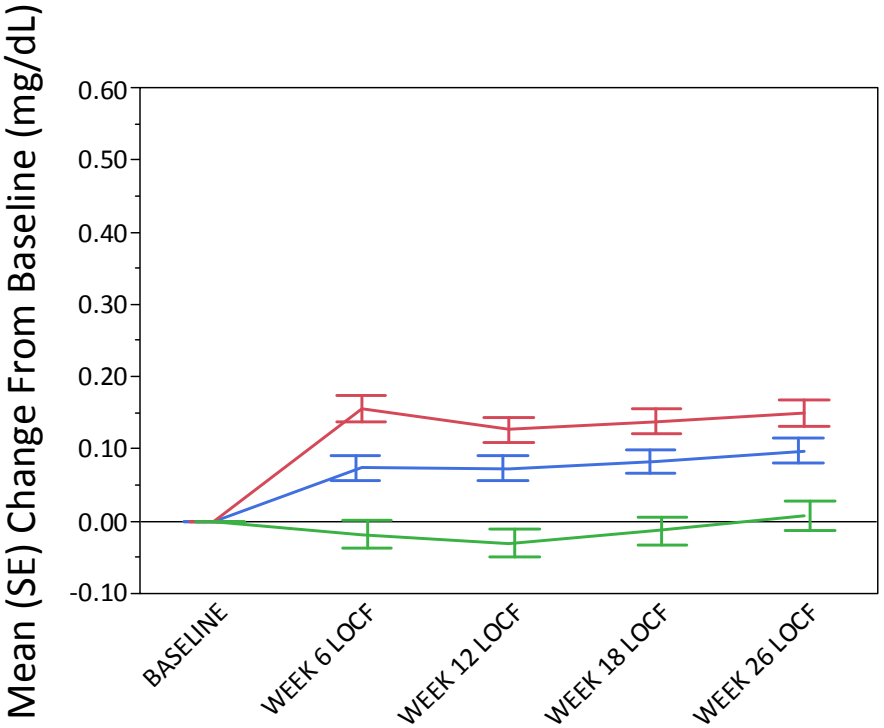
DIA3004: Moderate Renal Impairment
(mean eGFR at baseline 39 mL/min/1.73 m2)



Bone Safety:
Mean Serum Phosphate Changes

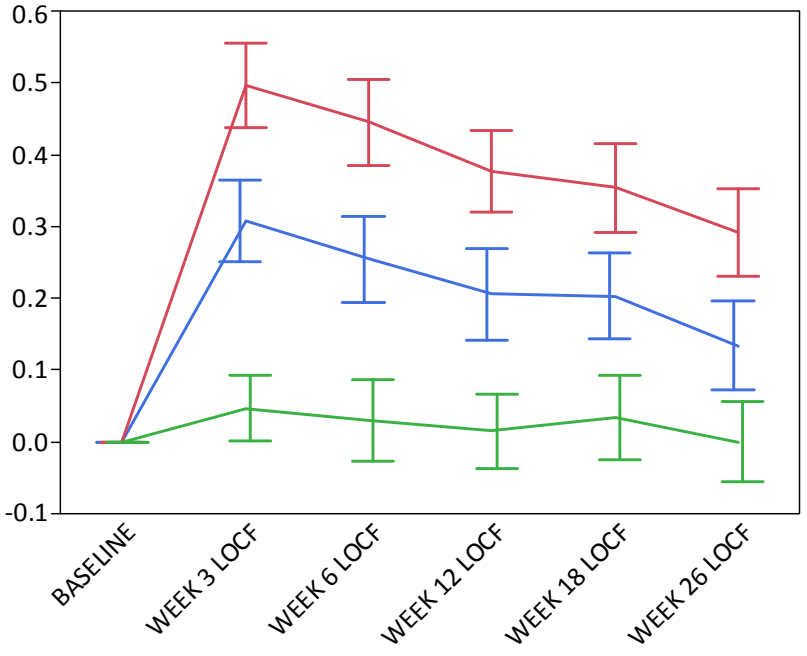
DS-1: Placebo Controlled 26-Week Studies

(mean eGFR at baseline 88 mL/min/1.73 m²)



DIA3004: Moderate Renal Impairment

(mean eGFR at baseline 39 mL/min/1.73 m2)



PBO Cana 100 Cana 300

Bone Safety: Trial in Older Adults: DIA3010

- Ongoing 104-week trial evaluates
  - Bone turnover markers
  - Bone mineral density
- Inclusion
  - Age 55 to 80 years inclusive
  - Osteopenia
  - Women at least 3 years post-menopause
- Exclusion criteria based on
  - Disorders or medications that could confound outcome
- Randomization
  - 714 subjects randomized 1:1:1 ratio to
    - Canagliflozin 100 mg
    - Canagliflozin 300 mg
    - Placebo
- 26-week core double-blind period, followed by 78-week double-blind extension
- 26-week results available at NDA submission;
  - 52-week interim data received November 30th 2012

Bone Safety: Trial in Older Adults: DIA3010

Placebo-adjusted changes in bone **resorption** and bone **formation** markers

Placebo adjusted LS Mean **percent change** from baseline to Week-26 and Week-52

	26 Weeks		52 Weeks	
	Cana 100	Cana 300	Cana 100	Cana 300
Serum beta-CTX	↑17.1*	↑ 24.9 *	↑ 10.3 *	↑ 22.0 *
Serum P1NP	↓ -5.7	↓ -6.9		
Serum osteocalcin	↑ 3.2	↑ 4.3	↑ 9.4 *	↑ 10.1 *
Serum estradiol	↓ -4.4	↓ -13.7	↓-14.2	↓-21.0 *
Serum PTH	↑ 7.0	↑ 2.0	↑ 6.2	↑ 1.5

Beta-CTX = Collagen type 1 beta-carboxy-telopeptide

P1NP=Propeptide amino-term type 1 procollagen

*** 95% CI excludes zero**

Bone Safety: Trial in Older Adults: DIA3010

Changes to **bone mineral density** by DXA

Placebo-adjusted LS Mean percent change (95% CI) from Baseline to Week 52

	Cana 100 (N=241)	Cana 300 (N=236)
Lumbar spine	-0.4 (-1.0, 0.3)	-0.7 (-1.4, -0.1) *
Distal forearm	0.5 (-0.1, 1.2)	0.1 (-0.6, 0.7)
Femoral neck	0.1 (-0.6, 0.8)	0.6 (-0.1, 1.4)
Total hip	-0.4 (-1.0, 0.1)	-0.7 (-1.3, -0.2) *

*** 95% CI excludes zero**

Bone Safety: Trial in Older Adults: DIA3010

Changes to **bone mineral density** by Quantitative-CT

Placebo-adjusted LS Mean percent change (95% CI) from Baseline to Week 52

	Cana 100 (N=241)	Cana 300 (N=236)
Lumbar spine	-0.8 (-2.7, 1.1)	-1.9 (-3.8, -0.0)*
Femoral neck	0.8 (-1.7, 3.3)	-1.9 (-4.4, 0.6)
Total hip	-0.5 (-1.0, 1.1)	-1.6 (-3.1, -0.0)*

*** 95% CI excludes zero**

Fractures

- Prospectively adjudicated across all Phase 3 trials by a blinded adjudication committee
- Adjudicated fractures were classified as:
  - High trauma fracture:
    - resulting from severe trauma (i.e., motor vehicle crashes) or fall from greater than standing height
  - Low trauma fracture:
    - Resulting from falls from standing height or less; falls on stairs, steps, or curbs; moderate trauma other than fall; minimal trauma other than fall
  - Pathological fracture:
    - Fractures resulting from another disease process such as tumor, metastatic cancer of bone, etc
  - Stress fracture:
    - Identifiable fractures caused by repetitive stress
  - Other fracture:
    - Fractures not defined above

Fractures: Incidence

Total fractures (regardless of adjudication)
across Phase 3 Program: Data cutoff July 1st 2012

	All Cana (N=6177)	All Non-Cana (N=3262)	Difference: Cana-Non Cana [95% CI]
Subjects with Fractures	2.4%	1.7%	0.6% [0.0, 1.2]
Exposure adjusted incidence per 1000 PYE	18.1	14.2	3.9 [-0.79, 8.68]

Adjudicated Fractures: Incidence

Adjudicated fractures by location and trauma classification across Phase 3 Program: Data cutoff July 1st 2012

	All Cana (N=6177)	All Non-Cana (N=3262)
All Adjudicated Fractures	2.1%	1.6%
Upper Limb	0.9%	0.5%
Lower Limb	0.8%	0.8%
All High Trauma	0.4%	0.3%
All Low Trauma	1.6%	1.2%
Upper Limb	0.7%	0.3%
Lower Limb	0.6%	0.7%
Spine*	0.1%	0

(* n=6 versus 0)

Fragility* Fractures: Incidence

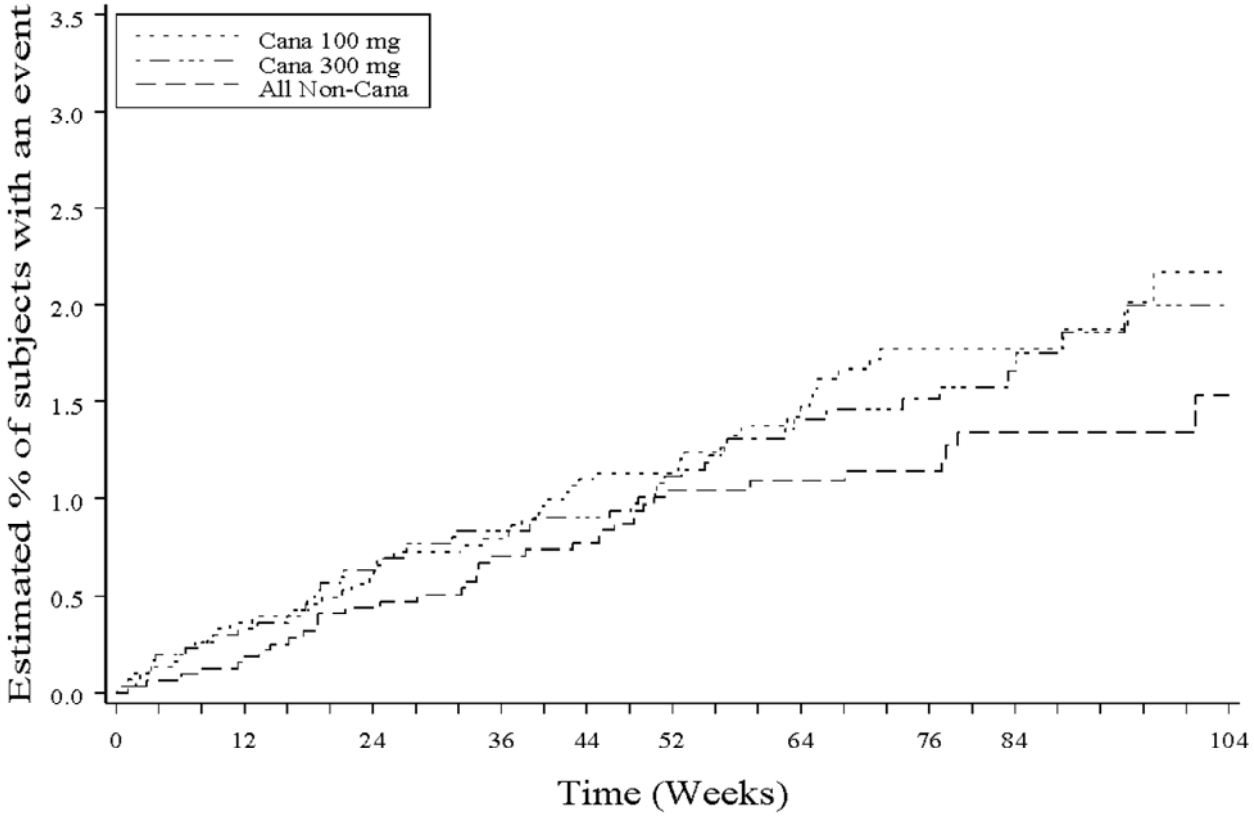
Fragility fractures (regardless of adjudication)
Across Phase 3 Program: Data cutoff January 31, 2012

	All Cana (N=6177)	All Non-Cana (N=3262)
Total	1.30 % (n=80)	1.10 % (n=36)
Upper Limb	0.53 % (n=33)	0.28 % (n=9)
Humerus	0.18 % (n=11)	0.06 % (n=2)
Wrist	0.15 % (n=9)	0.06 % (n=2)
Spine (thoracic/lumbar)	0.11 % (n=7)	0.03 % (n=1)

*Excludes fractures of hand/fingers, foot/toes, skull, facial bones, scapula and patella

Fractures: Low Trauma Time to First Event

Time to first **low trauma** adjudicated fracture event across Phase 3 Program: Data cutoff July 1st 2012



No. Subjects at Risk

Cana 100 mg	3092	3042	2983	2931	2882	2840	2021	1621	1166	421
Cana 300 mg	3085	3020	2940	2870	2844	2801	1983	1601	1125	413
All Non-Cana	3262	3192	3095	3011	2964	2877	1932	1537	1113	413

Source: NDA 204042

Falls: Incident Cases Narrow Search

35 cases reported to have at least one treatment-emergent adverse event coded to the **preferred term** "FALL" in DS-3

	All Cana (N=6177)	All Non-Cana (N=3262)
% (n)	0.34 (21)	0.43 (14)

This search and analysis strategy suggests that falls in the CANA group occurred **less commonly** (i.e., 21% relative reduction) than in the Non-Cana group

Falls: Incident Cases Broad Search

The narrow search strategy was limited to adverse events coded to the **preferred term** "FALL"

Fall events can be "lost" in the process of transforming investigator reported adverse event terms (i.e., **verbatim terms**) to **preferred term** (examples in table)

Verbatim Term	Preferred Term
Painful left wrist from **fall**	Arthralgia
Facial Bruising after **fall**	Contusion
Patient had a **fall**, wound on the back of his head.	Head injury
Right shoulder trauma after **fall**	Joint injury
Swollen left index finger, from **fall**	Oedema peripheral
Hematoma right hip (after **fall**)	Haematoma

A broad search strategy identifying adverse event with **verbatim terms** containing the words "**FALL, FELL, or COLLAPSE**" in DS-3 was performed

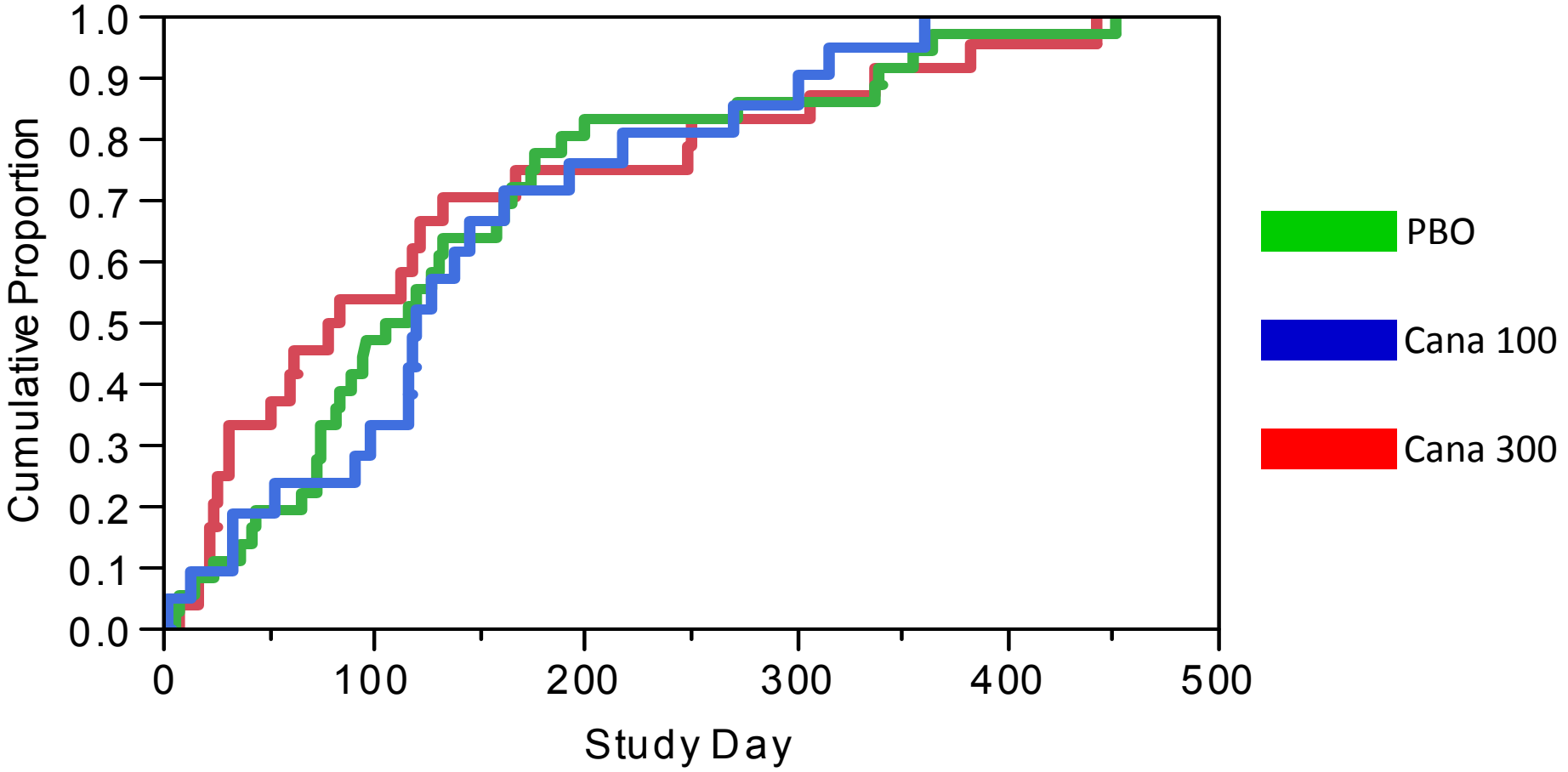
Falls: Incident Cases Broad Search

84 cases reported to have at least one treatment emergent fall event where the **verbatim term** contained the modifier "**FALL, FELL or COLLAPSE**" in DS-3

	All Cana (N=6177)	All Non-Cana (N=3262)
% (n)	0.97 (60)	0.74 (24)

This search and analysis strategy suggests that falls in the CANA group occurred **more commonly** (i.e., 31% relative increase) than in the Non-Cana group

Falls: Time to First Fall Event
Broad Search DS3



Glimeperide (n=2 events) and Sitagliptin (n=1 event) arms excluded

Outline

- Efficacy
  - Renal impairment
- Safety
  - Volume depletion events
  - Renal safety
  - Bone safety
  - Genital mycotic infections
  - Cardiovascular safety
- Summary

Female Genital Mycotic Infections: Search Terms

- Genital candidiasis
- Genital infection fungal
- Urogenital infection fungal
- Vaginal infection
- Vaginal inflammation
- Vulvitis
- Vulvovaginal candidiasis
- Vulvovaginal mycotic infection
- Vulvovaginitis

Female Genital Mycotic Infections: Incidence

	Placebo	Cana 100	Cana 300
Placebo-controlled Dataset (DS1)	3.2%	10.4%	11.4%
	N=312	N=425	N=430
Incidence rate per 100 PYE	7	22	25
Moderate Renal Impaired (DS-2)	1.9%	11.4%	9.6%
	N=156	N=140	N=155
DIA3010	2.1%	15.4%	11.2%
	N=94	N=117	N=107
DIA3008	2.3%	14.9%	13.1%
	N=486	N=484	N=497

Female Genital Mycotic Infections: Description and Outcome

- **Most commonly reported preferred terms**
  - **Vulvovaginal candidiasis**
  - **Vulvovaginal mycotic infections**
- **Recurrence rate was higher with canagliflozin in DS1:**
  - **22%** of subjects in the combined canagliflozin group had a recurrent event
  - **10%** of subjects in the placebo arm had a recurrent event
- **Use of antifungal therapy to treat genital mycotic infection was higher with canagliflozin in DS1:**
  - **82%** of subjects in the combined canagliflozin group
  - **64%** of subjects in the placebo group
- **Use of dual antifungal and antibacterial therapy for vulvovaginal events was higher with canagliflozin in DS1:**
  - **8%** of subjects in the combined canagliflozin group
  - **0%** in the placebo group
- **The overall mean duration of vulvovaginitis was longer with canagliflozin in DIA3008:**
  - **38 days** in the combined canagliflozin group
  - **16 days** in the placebo group

Male Genital Mycotic Infections: Search Terms

- Balanitis
- Balanitis candida
- Balanoposthitis
- Balanoposthitis infective
- Erosive balanitis
- Gangrenous balanitis
- Genital candidiasis
- Genital infection
- Genital infection fungal
- Penile candida
- Penile infection
- Posthitis

Male Genital Mycotic Infections: Incidence

	Placebo	Cana 100	Cana 300
Placebo-controlled Dataset (DS1)	0.6% N=334	4.2% N=408	3.7% N=404
Incidence rate per 100 PYE	1	9	9
Moderate-Renal Impaired (DS2)	1.3% N=226	2.0% N=198	4.6% N=210
DIA3010	0 N=143	3.2% N=124	6.2% N=129
DIA3008	1.4% N=995	6.8% N=961	10.2% N=944

Male Genital Mycotic Infections: Description and Outcome

- **Most commonly reported in:**
  - **Uncircumcised men**
  - **Men with prior history of balanitis/balanoposthitis**
- **Recurrence rate was higher with canagliflozin in DS1:**
  - **22%** of subjects in the combined canagliflozin group had a recurrent event
  - **0%** of subjects in the placebo arm had a recurrent event
- **Use of antifungal therapy to treat genital mycotic infection was higher with canagliflozin in DS1:**
  - **83%** of subjects in the combined canagliflozin group
  - **50%** of subjects in the placebo group
- **The overall mean duration of balanitis was longer with canagliflozin in DS1:**
  - **40** days in the combined canagliflozin group
  - **16** days in the placebo group
- **An imbalance in the number of subjects on canagliflozin reporting phimosis or acquired phimosis was observed in DIA3008:**
  - **9** subjects in the canagliflozin group
    - 4 events were serious
    - 1 event required circumcision
  - **0** subjects in the placebo group

Outline

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Lipid Parameter Changes: LDL-cholesterol

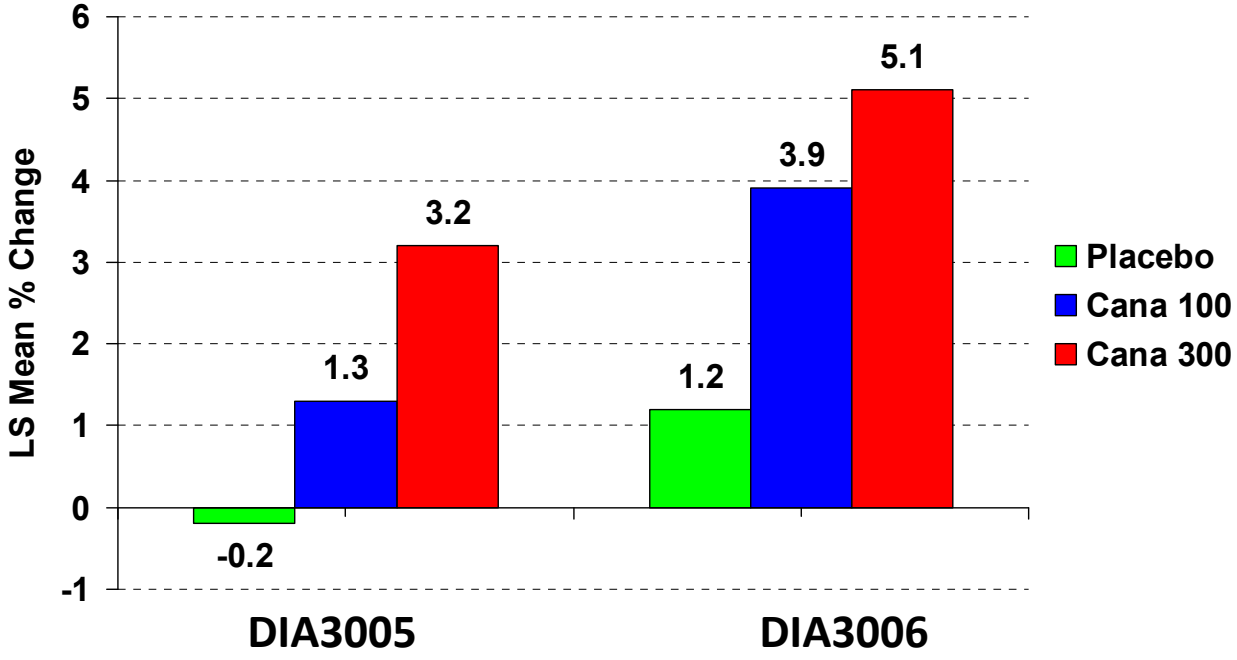
Canagliflozin use was associated with

- A **dose-dependent increase** in LDL cholesterol (LDL-C)
- Comparator subtracted **LS mean percent change in LDL-C from baseline to primary efficacy assessment time point** across all Phase 3 trials ranged from:
  - **-2.0%** to **+8.5%** for Cana 100
  - **+2.8%** to **+12.0%** for Cana 300
- The changes were seen at **Week 18** and persisted at **Week 52**
- The changes observed for **calculated LDL concentration (Friedewald)** were consistent with **directly measured LDL concentration** in **DIA3005** and **DIA3006**
- The proportion of subjects who **initiated statin therapy** during the core trial period was small and balanced:
  - Cana 100: **2.0%**
  - Cana 300: **1.6%**
  - PBO: **1.9%**

Lipid Parameter Changes: LDL-cholesterol Particle Number

Measurement of Apolipoprotein B (Apo B) concentration in **DIA3005** and **DIA3006** suggests LDL-C increase is due to an increase in particle numbers

LS Mean Percent Change in Apo B from Baseline to Week 26



Lipid Parameter Changes: LDL-cholesterol Particle Size

Measurement of LDL-C particle size by **Nuclear Magnetic Resonance Spectroscopy** in **DIA3006** suggests LDL-C rise is due predominantly to an increase in amount of large LDL particles

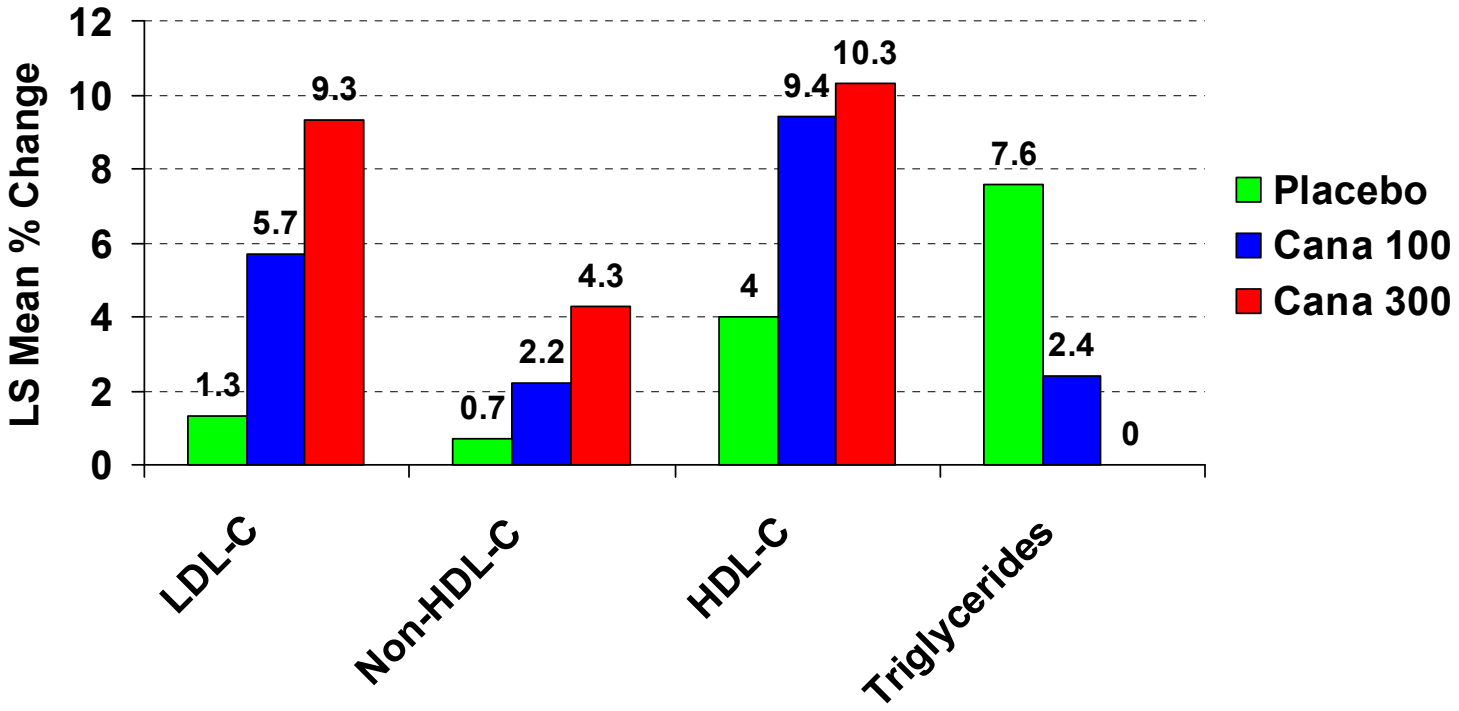
Placebo-adjusted LS Mean percent change [95% CI] from baseline to Week 26

	Cana 100 (N=368)	**Cana 300 (N=367)**
Plasma LDL-C particles	3.2 [-1.4, 7.9]	5.0 [0.3, 9.7]
Plasma Large LDL Particles	41.4 [-2.9, 85.7]	22.2 [-22.4, 66.8]
Plasma Small LDL Particles	-1.4 [-19.7, 16.9]	5.7 [-12.8, 24.1]

Lipid Parameter Changes: LDL-C, Non-HDL-C, HDL-C and Triglycerides

Placebo-controlled 26-Week Studies Dataset (DS1)

LS Mean % change in lipids parameters from baseline to Week 26



Cardiovascular Safety: Meta-analysis

Number of subjects (%) with MACE-Plus events
Break-down of MACE-Plus events by individual components

	Canagliflozin N=6305	Comparators N=3327	Hazard Ratio (95% CI)
MACE-plus	130 (2.1)	71 (2.1)	0.91 (0.68, 1.22)
CV Death	21 (0.3)	16 (0.5)	0.65 (0.34, 1.24)
Fatal or non-fatal MI	45 (0.7)	27 (0.8)	0.83 (0.51, 1.34)
Fatal or non-fatal stroke	47 (0.7)	16 (0.5)	**1.46** (0.83, 2.58)
Ischemic stroke	37	9	
Hospitalization for UA	26 (0.4)	18 (0.5)	0.71 (0.39, 1.30)

Cardiovascular Safety: Early Events in DIA3008-CANVAS

- In the first 30 days after randomization:
  - **13** MACE+ events occurred on **canagliflozin**
    - 7 on canagliflozin 100 mg
    - 6 on canagliflozin 300 mg
  - **1** MACE+ event occurred on **placebo**
- The 13 events on canagliflozin were:
  - 6 stroke (1 fatal due to ischemic stroke)
  - 5 MI
  - 2 hospitalization for unstable angina
- Provided narratives for these 13 events were not sufficiently detailed to allow assessment of volume status before or concurrent with these CV events

Cardiovascular Safety: Early Events in DIA3008-CANVAS

Baseline Characteristics For Subjects with CV Events in **DIA3008-CANVAS**

	Cana within 30 days (N=13)	Cana after 30 days (N=95)	Placebo All Subjects with CV event (N=53)
Mean age, years	62.4	63.2	64.4
Male, %	77%	73%	64%
Mean Baseline HbA1c (%)	8.3	8.2	8.2
Mean Baseline eGFR	77.3	75.1	73.5
Mean Baseline LDL-C (mg/dL)	101	100	94
Baseline BMI (kg/m2)	31	33	33
Previous history of CV, %:	69%	79%	85%
History of HTN	92%	88%	83%
History of MI	54%	44%	45%
History of dyslipidemia	46%	63%	72%
CV Risk Factor, %:			
Current smoker	31%	18%	13%
Diabetes ≥10 years	77%	63%	72%
HDL-C (<39 mg/dL)	31%	33%	42%
Micro or macro-albuminuria	54%	36%	34%
SBP >140 mmHg at Screening	46%	43%	43%

Outline

- Efficacy
  - Renal impairment
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  - Renal safety
  - Bone safety
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Canagliflozin: Summary – Renal Impairment

- The **glucose lowering efficacy** of canagliflozin **decreased with deteriorating renal function**
- Canagliflozin was associated with a **decrease in renal function** as measured by estimated GFR
- In subjects with moderate renal impairment, canagliflozin was associated with an increased risk of **significant renal function changes, renal-related adverse events,** and **hyperkalemia events**
- In subjects with moderate renal impairment, **elevation** in the mean **serum potassium** with canagliflozin was more pronounced at the earliest time point
  - Subjects on ACEi/ARB and potassium sparing diuretic appeared most susceptible

Canagliflozin: Summary – Volume Depletion Events

- Canagliflozin was associated with an increased risk for **volume depletion events** (most commonly hypotension)
- Patients with **moderate renal impairment**, **advanced age**, **advanced disease stage** and on **therapies to treat co-morbid conditions** (i.e., ACEi and diuretic) appeared to be particularly susceptible to volume depletion events with canagliflozin
- The timing of volume depletion events coincided with **reductions** in **systolic** and **diastolic blood pressure** observed at the earliest ascertained time point in Phase 3 trials

Canagliflozin: Summary – Bone

- Canagliflozin was associated with a **rise** in markers **of bone turnover**
- Canagliflozin was associated with a **consistent, dose-dependent, small increase in mean serum phosphate and magnesium** and a relative small increase in **mean serum calcium** levels
- An imbalance not favoring canagliflozin was seen **in the incidence of overall fractures**
  - An imbalance not favoring canagliflozin was seen **in the incidence of upper limb fractures**

Canagliflozin: Summary continued

- Canagliflozin was associated with a **4 to 7 fold increase** in the incidence of **genital mycotic infections.** This resulted in:
  - Increased use of antifungal therapy
  - Phimosis in male requiring surgical intervention
- Canagliflozin was associated with an **increase** in **LDL-C**, **non-HDL-C levels** and **HDL-C** levels
- In contrast to placebo, canagliflozin was not associated with a rise in serum triglyceride levels
- An imbalance in early CV events not favoring canagliflozin was observed in a population of subjects at increased risk for CV events

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Canagliflozin: Statistical Assessment of CV Safety

January 10, 2013

Mat Soukup, PhD

Division of Biometrics 7

Office of Biostatistics

Office of Translational Sciences

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Outline

- **Trial Database**
- Statistical Methods
- Results
- Summary

Trial Listing

Trial ID	Duration (weeks)	Canagliflozin		Control		
		N	Patient Years	Placebo (N)	Active (N)	Patient Years
DIA3008 (CANVAS)	**Not fixed**	**2886**	**3412**	**1441**	**-**	**1664**
DIA2001	12	128	38	65	-	19
DIA3002	52	313	279	156	-	131
DIA3004	52	179	145	90	-	71
DIA3005	52	483	422	192	-	174
DIA3006	52	735	650	183	366	481
DIA3009	104	968	1248	-	482	618
DIA3010	104	477	478	237	-	216
DIA3012	52	227	203	115	-	95

All trials except for DIA2001 were ongoing at the time of database lock: 31 January 2012

CANVAS Population

CANVAS enrolled subjects from a high CV risk population

- **Age ≥ 30** with documented symptomatic atherosclerotic CV disease (stroke, MI), hospital admission for unstable angina, coronary artery bypass graft, percutaneous coronary intervention, peripheral revascularization, symptomatic with hemodynamically-significant carotid or peripheral vascular disease, or amputation secondary to vascular disease
- **Age ≥ 50** with 2 or more of the following risk factors present at screening:
  - duration of TD2M of ≥10 years, SBP >140 mmHg while on at least 1 BP-lowering treatment, current daily cigarette smoker, documented micro- or macro-albuminuria, or documented high-density lipoprotein cholesterol (HDL-C) of <1 mmol/L (<39 mg/dL)

Demographics

	Non-CANVAS		CANVAS	
	Canagliflozin (*N= 3510*)	**Comparators** (*N= 1886*)	**Canagliflozin** (*N= 2886*)	**Placebo** (*N= 1441*)
Mean Age (years)	57.2	57.4	62.4	62.3
Female	49.3%	47.0%	34.0%	33.7%
Race/Ethnicity				
White	71.4%	72.4%	73.3%	73.8%
Black	5.1%	4.5%	2.4%	2.4%
Asian	14.1%	13.6%	18.5%	18.2%
Other	9.4%	9.6%	5.9%	5.6%
Mean BMI (kg/m^2)	31.7	31.7	32.1	32.1
US Sites	31.4%	32.0%	16.8%	16.7%

Baseline CV Risk Factors

	Non-CANVAS		CANVAS	
	Canagliflozin (*N= 3510*)	Comparators (*N= 1886*)	Canagliflozin (*N= 2886*)	Placebo (*N= 1441*)
eGFR < 60 ml/min	9.5%	9.8%	15.9%	17.6%
Daily Cigarette Smoker	11.5%	11.6%	17.1%	19.4%
Prior CV Disease	12.2%	13.4%	57.2%	56.8%
Statin Use	45.9%	44.8%	72.2%	71.7%
SBP > 140 mmHg	27.1%	26.8%	54.2%	56.1%
Diabetes Duration ≥ 10 years	32.6%	32.0%	70.4%	69.6%

Outline

- Trial Database
- **Statistical Methods**
- Results
- Summary

Pre-Specified Analysis

- **Objective**
  - Rule *out risk margin of 1.8* (assessed using a 95% CI)
- **Primary analysis population**
  - mITT: All randomized subjects who took at least one dose of the double-blind medication
  - Nine trials: *N* = 6396 canagliflozin, *N* = 3327 comparators
- **Comparison**
  - ***Canagliflozin vs. All Comparators*** (placebo, glimepiride, sitagliptin)

Composite Endpoints

- Definitions of Major Adverse Cardiovascular Event Endpoint
  - **MACE+**: ***pre-specified*** primary composite endpoint
    - *Cardiovascular death*
    - *Non-fatal myocardial infarction*
    - *Non-fatal stroke*
    - *Hospitalized for unstable angina*
  - **MACE:** ***secondary*** composite endpoint
    - *Excludes hospitalized for unstable angina*
- All events **prospectively** collected and adjudicated

Pre-Specified Analysis Methods

- Primary analysis: **Time-to-event** (Hazard Ratio)
  - *Cox proportional hazards model with 2 strata: CANVAS and non-CANVAS trials*
- Secondary analyses:
  - *Time to event in CANVAS alone*
  - *Time to event in non-CANVAS trials*

Sensitivity Analysis Methods

- **Assessment of proportional hazards** in primary model: interaction test, Schoenfeld residuals
- Due to some evidence of **non-proportional hazards** in CANVAS:
  - Time to event during first 30 days of CANVAS
  - Time to event after 30 days in CANVAS

Outline

- Trial Database
- Statistical Methods
- **Results**
- Summary

MACE+ Event Rates by Trial

Trial	Canagliflozin	All Comparators
CANVAS	**108 / 2886 (3.7%)**	**53 /1441 (3.7%)**
DIA2001	0 / 128 (0%)	0 /65 (0%)
DIA3002	1 / 313 (0.3%)	1 /156 (0.6%)
DIA3004	4 / 179 (2.2%)	4 /90 (4.4%)
DIA3005	0 / 483 (0%)	0 /192 (0%)
DIA3006	1 / 735 (0.1%)	4 /549 (0.7%)
DIA3009	9 / 968 (0.9%)	5 /482 (1.0%)
DIA3010	6 / 472 (1.3%)	4 /237 (1.7%)
DIA3012	1 / 228 (0.4%)	0 /115 (0%)
Total	**130 / 6396 (2.0%)**	**71 / 3327 (2.1%)**

Primary Analysis Results*

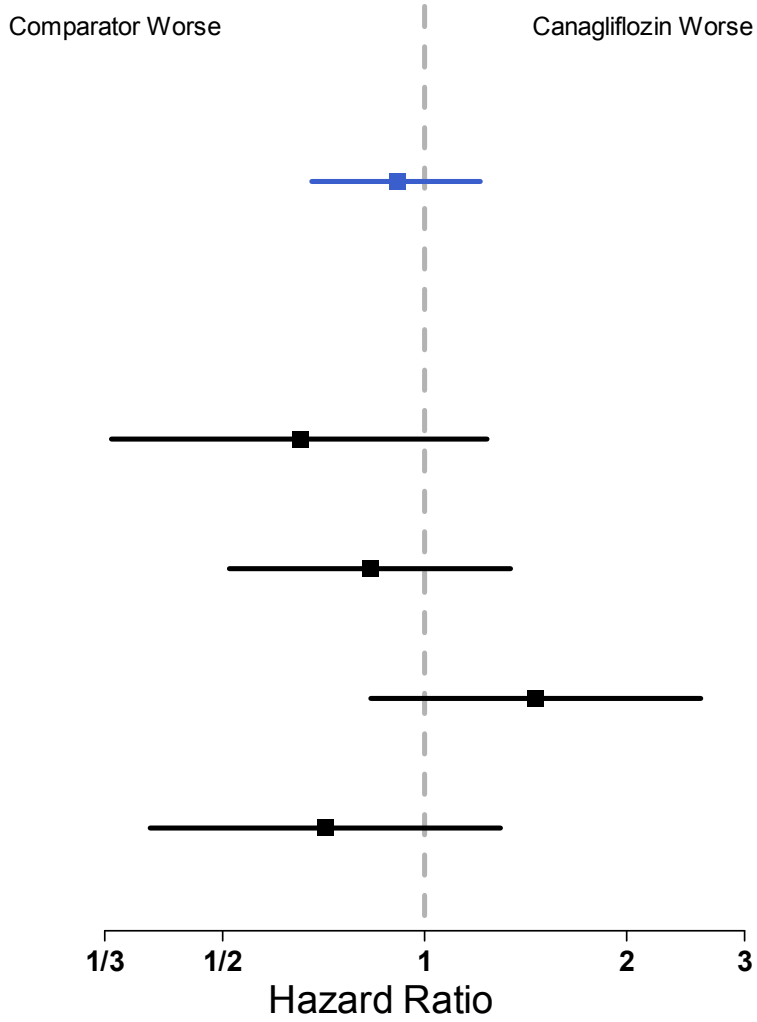
	Canagliflozin	Comparators	
	N = 6396	*N = 3327*	**Hazard Ratio**
	PY = 6876	*PY = 3470*	(95% CI)
MACE+	**130 (18.9)**	**71 (20.5)**	**0.91 (0.68, 1.21)**
MACE	104 (15.1)	53 (15.3)	0.98 (0.70, 1.36)

(incidence rate per 1000 person-years)

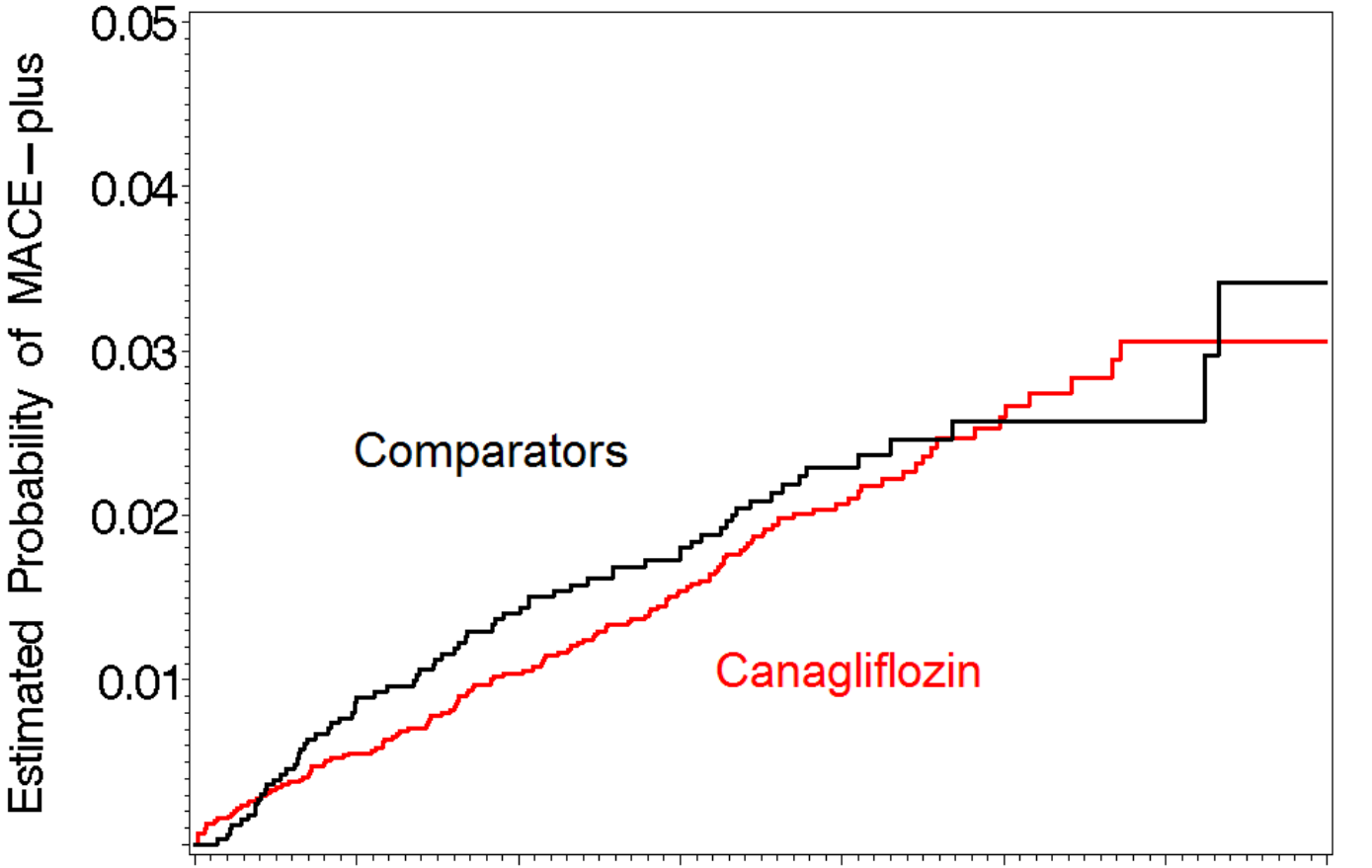
* All 9 Phase 2/3 trials

MACE+ Components

	Canagliflozin (N = 6396) Events (%)	Comparators (N = 3327) Events (%)	Hazard Ratio (95% CI)
MACE+	**130 (2)**	**71 (2.1)**	**0.9 (0.7, 1.2)**
CV Death	21 (0.3)	16 (0.5)	0.6 (0.3, 1.2)
FNF MI	45 (0.7)	27 (0.8)	0.8 (0.5, 1.3)
FNF Stroke	47 (0.7)	16 (0.5)	1.5 (0.8, 2.6)
Hosp. UAP	26 (0.4)	18 (0.5)	0.7 (0.4, 1.3)



K-M of MACE+ (All Trials)

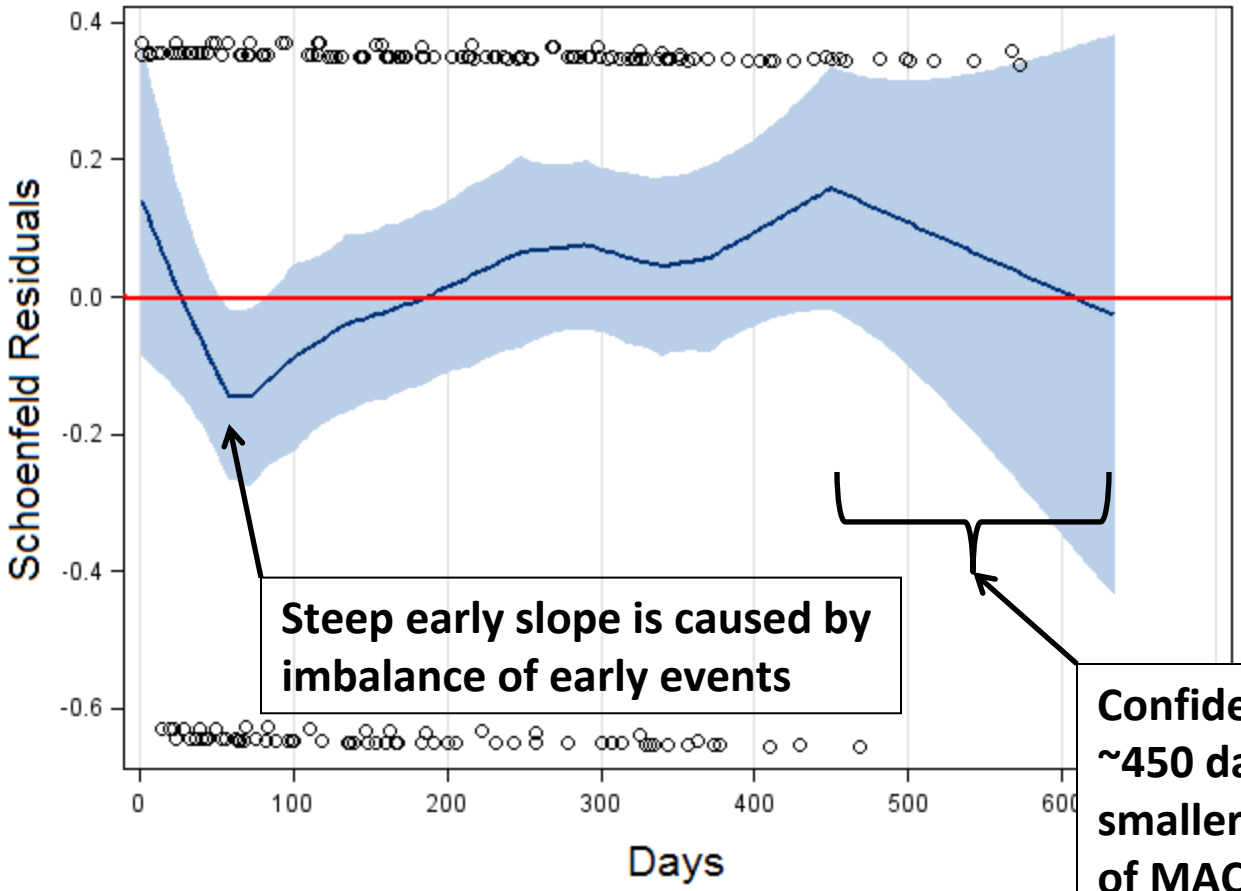


At risk:

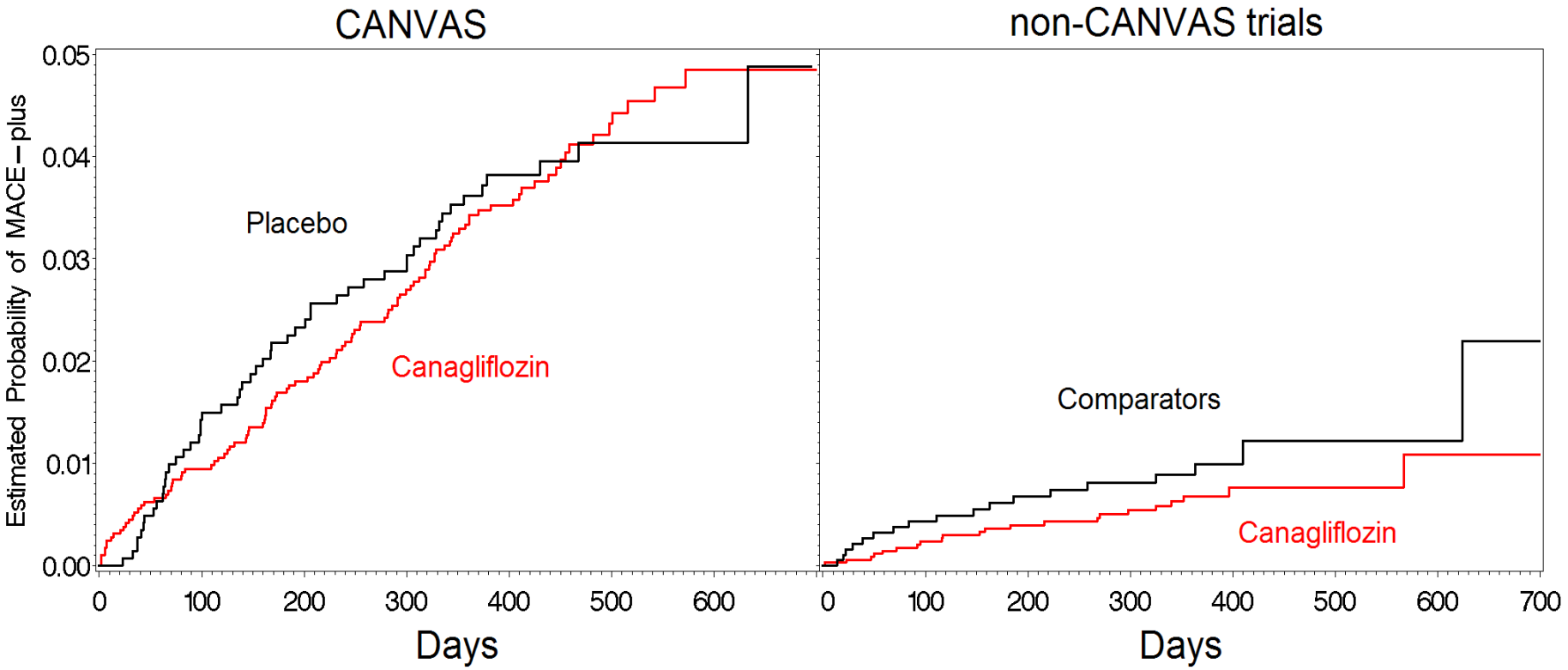
Canagliflozin:	6396	6027	5572	5079	2873	1392	643	180
Comparators:	3327	3117	2821	2567	1370	671	309	82

Some Evidence of Non-Proportional Hazards

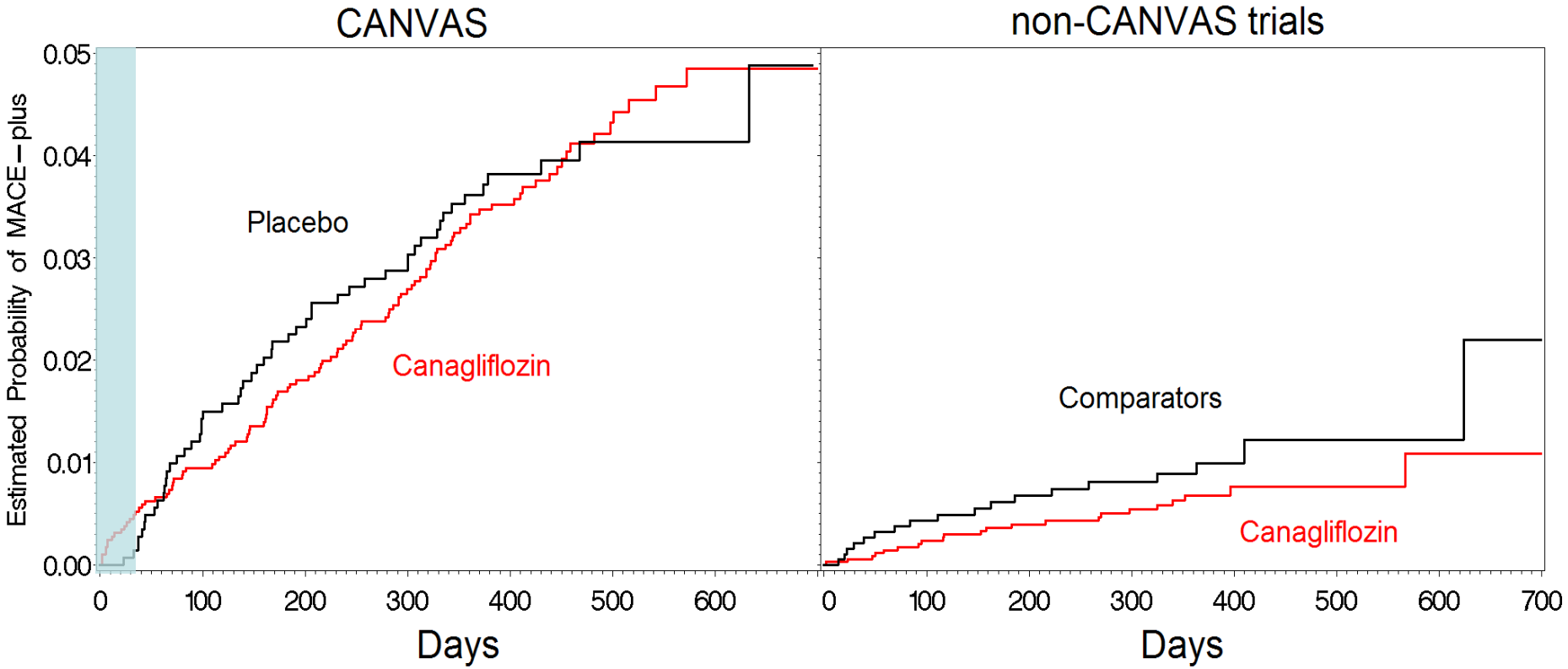
Under proportional hazards, the blue line should resemble approximately a horizontal line through 0 (red line)



K-M of MACE+ by Stratum



MACE+ Results by Stratum



	Cana	Comp	HR (95% CI)
≤ 30 days	13/2886	1/1441	6.49 (0.85, 49.64)
> 30 days	95/2867	52/1435	0.89 (0.64, 1.25)

Cana	Comp	HR (95% CI)
22/3510	18/1886	0.64 (0.34, 1.19)

MACE+ During the First 30 Days in CANVAS

Treatment	Age	Day of Event	Type of Event
Cana 300 mg	79	2	Nonfatal Stroke
Cana 100 mg	65	2	Hospitalized Unstable Angina
Cana 100 mg	68	2	Nonfatal Stroke
Cana 300 mg	57	6	Nonfatal Myocardial Infarction
Cana 300 mg	76	6	Nonfatal Myocardial Infarction
Cana 300 mg	54	7	Cardiovascular Death
Cana 100 mg	68	7	Nonfatal Stroke
Cana 300 mg	37	12	Nonfatal Myocardial Infarction
Cana 100 mg	57	14	Hospitalized Unstable Angina
Cana 100 mg	76	21	Nonfatal Myocardial Infarction
Placebo	67	23	Nonfatal Myocardial Infarction
Cana 100 mg	61	24	Nonfatal Myocardial Infarction
Cana 100 mg	57	26	Nonfatal Stroke
Cana 300 mg	56	29	Nonfatal Stroke

Sample size = 2886 on canagliflozin and 1441 on placebo

Sensitivity Analyses at 30 Days

- Fewer MACE+ were observed on placebo during the first 30 days in CANVAS than would be expected given the event rate on placebo during the full trial:

1 observed vs. **3.76 expected**

- HR estimates during the first 30 days are sensitive to few events

	Canagliflozin (*N = 2886*)	Placebo (*N= 1441*)	Hazard Ratio (95% CI)
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)

Outline

- Trial Database
- Statistical Methods
- Results
- **Summary**

Summary of Findings

- Pre-specified meta-analysis of MACE+ **HR: 0.91 (0.68, 1.21)**
- Evidence of non-proportional hazards suggests the pre-specified Cox model may not be appropriate,
  - Imbalance of early events in CANVAS (proportionality holds in non-CANVAS trials)

Secondary/Sensitivity Analyses of MACE+:

- Non-CANVAS trials **HR: 0.64 (0.34, 1.19)**
- CANVAS after 30 days **HR: 0.89 (0.64, 1.25)**
- CANVAS first 30 days **HR: 6.49 (0.85, 49.64)**
  - 13 events among 2886 subjects on canagliflozin (7 in first week)
  - 1 event among 1441 subjects on placebo
  - Hazard ratio highly sensitive to small changes in number of events

Acknowledgement

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