Introduction

Jacqueline Coelln-Hough, R.Ph.
Janssen Research & Development, LLC
Canagliflozin
Drug Class and Indication

- **New Class**
  - Sodium glucose co-transporter 2 (SGLT2) inhibitor
  - Insulin independent mechanism

- **Proposed Indication**
  - an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

- **Proposed dose and administration**
  - 100 or 300 mg tablet once daily
    - With specific recommendations for patients who should start with 100 mg
Canagliflozin
Clinical Development Program

- **Largest T2DM program submitted to Health Authorities to date**
  - 10,301 subjects enrolled in Phase 3

- **Long duration of treatment**
  - > 2800 subjects treated with canagliflozin ≥ 18 months
    (as of 01 July 2012)

- **Studies at each step of the treatment paradigm**

- **Significant experience in vulnerable populations (> 50 % Phase 3)**
  - Long standing diabetes: mean 10.6 years
  - Age
    - ≥ 65 years: >3000 subjects
    - ≥ 75 years: >500 subjects
  - Renal impairment: > 1000 subjects
  - CV disease: >4000 subjects
Canagliflozin

The totality of the data supports that canagliflozin:

• Provides substantial glucose control with the added benefits of weight loss and BP reduction

• Has a safety profile that is characterized across the full continuum of patients with T2DM

• Has adverse drug reactions that can be managed

• Both the 100 and 300 mg doses provide a valuable additional treatment option to address the unmet medical need
## Sponsor Presentation Agenda

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<th>Section</th>
<th>Presenter</th>
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<tr>
<td>Introduction</td>
<td>Jacqueline Coelln-Hough, RPh</td>
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<td></td>
<td>Janssen Research &amp; Development, LLC</td>
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<tr>
<td></td>
<td>Senior Director, Global Regulatory Affairs</td>
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<tr>
<td>Medical Landscape &amp; Unmet Need</td>
<td>Edward Horton, MD</td>
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<tr>
<td></td>
<td>Senior Investigator, Joslin Diabetes Center, Boston</td>
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<td>Professor of Medicine, Harvard Medical School</td>
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<td>Past-President ADA</td>
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<tr>
<td>Mechanism of Action, Phase 3 Program Overview &amp; Efficacy</td>
<td>Gary Meininger, MD</td>
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<td>Franchise Medical Leader</td>
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<td>Safety &amp; Tolerability</td>
<td>Peter Stein, MD</td>
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<td>Head of Metabolism Development</td>
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<td>Benefit-Risk Review</td>
<td>John Gerich, MD</td>
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<td></td>
<td>Professor Emeritus, University of Rochester, New York</td>
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# Consultants Available to the Committee

<table>
<thead>
<tr>
<th>Participant</th>
<th>Expertise and Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>George Bakris, MD</td>
<td>Nephrology</td>
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<tr>
<td></td>
<td>Professor of Medicine, University of Chicago</td>
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<tr>
<td>John Bilezikian, MD</td>
<td>Metabolic Bone Disease</td>
</tr>
<tr>
<td></td>
<td>Professor of Medicine &amp; Pharmacology</td>
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<tr>
<td></td>
<td>Columbia University College of Physicians and Surgeons</td>
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<tr>
<td>Samuel Cohen, MD, PhD</td>
<td>Oncology</td>
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<tr>
<td></td>
<td>Professor, Department of Pathology &amp; Microbiology, University of Nebraska Medical Center</td>
</tr>
<tr>
<td>Greg Fulcher, MD</td>
<td>Chairman of the Endpoint Adjudication Committee</td>
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<tr>
<td></td>
<td>Clinical Professor of Medicine</td>
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<td></td>
<td>University of Sydney</td>
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<tr>
<td>Peter Kowey, MD</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td></td>
<td>Professor of Medicine &amp; Clinical Pharmacology, Thomas Jefferson University</td>
</tr>
<tr>
<td>David Matthews, MD</td>
<td>Chairman of the CANVAS Steering Committee</td>
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<tr>
<td></td>
<td>Professor of Diabetes</td>
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<td></td>
<td>Oxford Center for Diabetes, Endocrinology &amp; Metabolism</td>
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<tr>
<td>Paul Watkins, MD</td>
<td>Hepatology</td>
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<tr>
<td></td>
<td>Professor of Medicine</td>
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<tr>
<td></td>
<td>University of North Carolina Health Care System</td>
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</tbody>
</table>
Medical Landscape

Edward Horton, MD
Joslin Diabetes Center, Harvard Medical School, Boston
Global Projections for the Diabetes Epidemic: 2011–2030

**World**
- 2011 = 366 M
- 2030 = 552 M
- ↑ >51%

**Europe**
- 2011 = 52.8 M
- 2030 = 64.2 M
- ↑ 22%

**North America and Caribbean**
- 2011 = 37.7 M
- 2030 = 51.2 M
- ↑ 36%

**South and Central America**
- 2011 = 14.7 M
- 2030 = 28.0 M
- ↑ 90%

**Africa**
- 2011 = 25.1 M
- 2030 = 39.9 M
- ↑ 59%

**Middle East and North Africa**
- 2011 = 32.6 M
- 2030 = 59.7 M
- ↑ 83%

**South-East Asia**
- 2011 = 71.4 M
- 2030 = 121 M
- ↑ 69%

**Western Pacific**
- 2011 = 112.8 M
- 2030 = 187.9 M
- ↑ 60%

M = million

Increased Obesity has Led to Increased Type 2 Diabetes

**Obesity (BMI ≥30 kg/m²)**

- **1994**
- **2000**
- **2009**

**Diabetes**

- **1994**
- **2000**
- **2009**

The Dual Epidemic: Obesity and Diabetes

- 65% of adult Americans are overweight (BMI >25) and 32% are obese (BMI >30)
- There are now an estimated 25.8 million people with DM in the USA (11.3% of adults) and 79 million with pre-diabetes (IFG/IGT)
- The lifetime risk of developing DM for people born in 2000 is 33% for men and 39% for women
Economic Costs of Diabetes

• Total direct and indirect costs of diabetes in the USA (2007): $174 billion*. Direct costs $116 billion, indirect costs $58 billion

• Diabetes is the leading cause of blindness in adults, the leading cause of kidney failure and of non-traumatic lower limb amputations.

• 60-70% of people with diabetes have mild to severe neuropathy

• The risk of heart disease and stroke is 2-4x greater in people with diabetes than without

*Diabetes Care March 2008 vol. 31 no. 3 596-615
# Lowering HbA$_{1c}$ Reduces Complications in Type 1 and Type 2 Diabetes

<table>
<thead>
<tr>
<th></th>
<th>DCCT  9.1% → 7.3%</th>
<th>Kumamoto 9.4% → 7.1%</th>
<th>UKPDS  7.9% → 7.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>↓ 63%</td>
<td>↓ 69%</td>
<td>↓ 17%–21%</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>↓ 54%</td>
<td>↓ 70%</td>
<td>↓ 24%–33%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>↓ 60%</td>
<td>Significantly improved</td>
<td>—</td>
</tr>
<tr>
<td>Macrovascular disease</td>
<td>↓ 41%*</td>
<td>—</td>
<td>↓ 16%*</td>
</tr>
</tbody>
</table>

*Not statistically significant*


Glycemia in Relation to Microvascular Disease and Myocardial Infarction

## Glycemic Goals for Diabetes Management

<table>
<thead>
<tr>
<th>AMERICAN DIABETES ASSOCIATION</th>
<th>NORMAL</th>
<th>GOAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA$_{1c}$ (%)</td>
<td>&lt; 6</td>
<td>&lt; 7*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/AMERICAN COLLEGE OF ENDOCRINOLOGY (AACE/ACE)</th>
<th>NORMAL</th>
<th>GOAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA$_{1c}$ (%)</td>
<td>&lt; 6</td>
<td>≤ 6.5</td>
</tr>
</tbody>
</table>

*HbA$_{1c}$ goal for individual patient is as close to normal (<6%) as possible without significant hypoglycemia

The Need for Individualization of Treatment Approaches and Goals

• Intensive management – with tight glycemic control – can have dramatic and long-term benefits

• *However*, late introduction of tight control in older patients with CVD (as in ACCORD), may have risks

• The key is **individualization** of therapy – based upon age, life expectancy, presence of complications, co-morbidities (including CVD), other patient factors, risks/impact of hypoglycemia, all must be considered
Glycemic Control Has Improved – But Many Patients Still Not at Goal HbA$_{1c}$ <7%

N=1334
NHANES=National Health and Nutrition Examination Survey
UKPDS Head to Head Therapy Comparison: Progressive Deterioration with All Agents

Progressive HbA1c deterioration – due to progressive loss of insulin secretion

Overweight patient cohort
Body mass index 31.4 kg/m²

UKPDS 34. Lancet 1998; 352: 837-853
Natural History of Type 2 Diabetes

Glucose (mg/dL)

Fasting glucose

Postmeal glucose

Insulin resistance

β-cell function

Onset of Diabetes

Years

Prediabetes (IFG, IGT)
Clinical diagnosis
Metabolic syndrome

Kendall DM, Bergenstal RM ©2003  International Diabetes Center, Minneapolis, MN. All rights reserved.

126 mg/dl
7.0 mM
Pathophysiology and Pharmacotherapy of Hyperglycemia in Type 2 Diabetes

- **Pancreas β-cell**
  - Decreased Insulin Secretion
  - Sulfonylureas
  - Meglitinides
  - GLP-1/DPP4 inhibitors

- **Pancreas α-cell**
  - Increased Glucagon Secretion
  - GLP-1/DPP4 inhibitors

- **Liver**
  - Increased Glucose Production
  - Metformin
  - TZDs

- **Gut**
  - CHO digestion and absorption
  - a-glucosidase inhibitors
  - GLP-1 / DPP4 inhibitors

- **Adipose Tissue**
  - Decreased Glucose Uptake
  - Increased Lipolysis
  - TZDs

- **Kidney**
  - Increased Glucose Re-absorption
  - SGLT-2 inhibitors

- **Peripheral Tissue**
  - Decreased Glucose Uptake
  - TZDs
  - Metformin

- **Neurotransmitter Dysfunction**
  - Bromocriptine

Adapted from DeFronzo RA. *Diabetes*. 2009;58:773-795.
Limitations of Current Treatments for Patients with T2DM

- 5 classes of oral agents – 2 classes of SQ agents are recommended by ADA/EASD
- Limitations of currently available classes
  - Limited efficacy or durability: sulphonylurea (SU) agents, DPP-4 inhibitors
  - Hypoglycemia: SU agents, insulin
  - Weight gain: SU agents, PPARγ agents, insulin
  - GI side effects: metformin, GLP-1 agonists
  - Fluid retention: SU agents, PPARγ agents, insulin

Conclusion: there is a need for new agents / new options
Imperative for New AHAs

• Diabetes is a rapidly advancing epidemic
  – Failure to adequately control hyperglycemia can have devastating consequences on affected individuals and on society

• Currently available AHAs have limitations (wt gain, GI side effects, limited efficacy and/or long-term durability)
  – Many patients not achieving or maintaining HbA1c goal of < 7%
Mechanism of Action

Gary Meininger, MD
Franchise Medical Leader - Metabolism
Janssen Research and Development
Sodium-glucose Transporter-2 (SGLT2): Key Renal Transporter Reabsorbing Filtered Glucose Back into Systemic Circulation

**SGLT2**
- Primarily expressed in kidney
- Responsible for majority of renal glucose reabsorption

**SGLT1**
- Responsible for small portion of renal glucose reabsorption
- Prominent role in intestinal glucose absorption

Glucose is Filtered in the Glomerulus

Glucose Reabsorbed to Systemic Circulation

No Glucose in Urine
Canagliflozin: SGLT2 Inhibition Leads to Improved Glucose Control in T2DM

- CANA is potent, selective inhibitor of SGLT2
- UGE ~ 80-100 grams/day, thereby reducing plasma glucose
- Additional contributors to glucose control
  - Reduction in body weight due to 300-400 kcal/day loss to UGE
  - Improved beta-cell function
- Mechanism of action independent of insulin
There is a Threshold Relationship Between Plasma Glucose and UGE

Healthy Subjects
RT$_G^*$~180 mg/dL

*Renal threshold for glucose
Renal Glucose Reabsorption and RT<sub>G</sub> are Elevated in T2DM

*Renal threshold for glucose
Canagliflozin Lowers $RT_G$

- T2DM+CANA $RT_G \sim 70-90 \text{ mg/dL}$
- T2DM mean $RT_G \sim 240 \text{ mg/dL}$

*Renal threshold for glucose*
Canagliflozin: Pharmacokinetics and Pharmacodynamics

Pharmacokinetics

• Half-life of 11-13 hrs supports once-daily dosing
• Balanced renal and biliary excretion
• Glucuronidation is major metabolic pathway
  – No active metabolites
• No clinically meaningful drug-drug interactions observed

Pharmacodynamics

24-Hour Profile for $RT_G$ in Subjects With T2DM Treated with Canagliflozin

Profiles shown were obtained from PK/PD model developed using pooled Phase 1 dataset. (N=242)
Canagliflozin Treatment Lowers Plasma Glucose Concentrations Throughout the Entire Day

Example: CANA 100 mg treatment in subjects with T2DM

Canagliflozin lowers fasting, postprandial, and 24-h mean plasma glucose

Data shown are mean values from NAP1002
Canagliflozin Treatment Improves Indices of Beta-cell Function

Data from DIA3002 (Week 26)

HOMA2-%B (Fasting-based index)

- Similar results observed in all studies in subjects with T2DM where these indices have been assessed
- Effects believed to be secondary to improved glucose control rather than direct effects of SGLT inhibition

Data shown are mean ± s.e.
## Summary of Pharmacodynamic Effects of CANA 100 mg and 300 mg

<table>
<thead>
<tr>
<th>Effect</th>
<th>CANA 100 mg</th>
<th>CANA 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased UGE</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Maximal $RT_G$ lowering during daytime</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Maximal $RT_G$ lowering for full 24 h</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Reduced fasting and postprandial glucose</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Delayed intestinal glucose absorption (only after dosing with meal)</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Improved indices of beta-cell function</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>
# Phase 3 Clinical Development Program: 9 Studies Conducted

## Monotherapy
- **Monotherapy** (DIA3005)
  - 26 / 26 wks N=587

## Dual Combination
- **Combo with MET** (DIA3006)
  - 26 / 26 wks N=1284

## Triple Combination
- **Combo with MET/PIO** (DIA3012)
  - 26 / 26 wks N=344
- **Combo with INSULIN** (Substudy DIA3008)
  - 18 wks N=1718

## Insulin +/- oral(s)
- **Combo with MET vs GLIM** (DIA3009)
  - 52 / 52 wks N=1452
- **Combo with MET/SU vs SITA** (DIA3015)
  - 52 wks N=756

### Pbo-control
- **Combo with MET** (DIA3006)
  - 26 / 26 wks N=1284

### Active-control
- **Combo with MET/PIO vs GLIM**
  - 52 / 52 wks N=1452
- **Combo with MET/SU vs SITA**
  - 52 wks N=756

## Studies in Special T2DM Populations
- **Placebo-controlled studies / add-on to current diabetes treatment**

### Older Subjects - Bone Safety and Body Comp (DIA3010)
- 26 / 78 wks N=716

### Renal Impairment (DIA3004)
- 26 / 26 wks N=272

### CV Safety Study (DIA3008: CANVAS)
- Event-driven N=4330
Distribution of Subjects Phase 3

North America
Canada, Mexico, USA
3743 (36%)

EU/EEA/EFTA
2681 (26%)

Central/South America
795 (8%)

Rest of the world
3082 (30%)
Baseline Characteristics – Worldwide and US
All Randomized Subjects from Phase 3 Studies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Worldwide N=10301</th>
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<th>US N=2634</th>
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<tbody>
<tr>
<td><strong>Age, y</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>59.5 (9.46)</td>
<td></td>
<td>58.8 (9.86)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>5965 (58)</td>
<td></td>
<td>1523 (58)</td>
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<tr>
<td>Female</td>
<td>4336 (42)</td>
<td></td>
<td>1111 (42)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>7411 (72)</td>
<td></td>
<td>2158 (82)</td>
</tr>
<tr>
<td>Black or African-American</td>
<td>452 (4)</td>
<td></td>
<td>359 (14)</td>
</tr>
<tr>
<td>Asian</td>
<td>1643 (16)</td>
<td></td>
<td>50 (2)</td>
</tr>
<tr>
<td>Other a</td>
<td>795 (8)</td>
<td></td>
<td>67 (3)</td>
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<tr>
<td><strong>Ethnicity, n (%)</strong></td>
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<tr>
<td>Hispanic or Latino</td>
<td>1699 (16)</td>
<td></td>
<td>444 (17)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>8563 (83)</td>
<td></td>
<td>2177 (83)</td>
</tr>
<tr>
<td>Not provided</td>
<td>39 (&lt;1)</td>
<td></td>
<td>13 (&lt;1)</td>
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a Includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple, and Other
Overview of Efficacy

• Results from Placebo-controlled Studies
• Results from Active-controlled Studies
• Results in Subjects with Renal Impairment (Stage 3 CKD)
• HbA$_{1c}$ Subgroup Analyses
Placebo-controlled Studies

- HbA$_{1c}$
- Body weight
- Systolic blood pressure
HbA$_{1c}$ Change from Baseline
Placebo-controlled Phase 3 Studies

**Add-on Combinations with**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Monotherapy (DIA3005)</th>
<th>Metformin (DIA3006)</th>
<th>SU (DIA3008)</th>
<th>Met/SU (DIA3002)</th>
<th>Met/Pio (DIA3012)</th>
<th>Insulin (DIA3008)</th>
<th>Current Therapy in Older Subjects (DIA3010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>584</td>
<td>1284</td>
<td>127</td>
<td>469</td>
<td>342</td>
<td>1718</td>
<td>714</td>
</tr>
<tr>
<td>BL Mean HbA$_{1c}$ (%)</td>
<td>8.0</td>
<td>7.9</td>
<td>8.4</td>
<td>8.1</td>
<td>7.9</td>
<td>8.3</td>
<td>7.7</td>
</tr>
<tr>
<td>Placebo-subtracted</td>
<td>-0.91*</td>
<td>-0.77*</td>
<td>-0.83*</td>
<td>-0.71*</td>
<td>-0.62*</td>
<td>-0.65*</td>
<td>-0.57*</td>
</tr>
<tr>
<td>LS Mean Change in HbA$_{1c}$ (%) (95% CI)</td>
<td>-1.16*</td>
<td>-0.74*</td>
<td>-0.83*</td>
<td>-0.92*</td>
<td>-0.76*</td>
<td>-0.73*</td>
<td>-0.70*</td>
</tr>
</tbody>
</table>

All at 26 weeks except 18 weeks DIA3008 Insulin, SU sub-studies

* p<0.001

Based on ANCOVA models, data prior to rescue (LOCF)
HbA$_{1c}$ Change from Baseline at Week 18
Placebo-controlled Add-on to Insulin Substudy (DIA3008 Insulin)

N=1718

Mean age (y): 62.8
Mean duration of T2DM (y): 16.6
BL insulin dose (IU/day): 83
BL Mean HbA$_{1c}$ (%): 8.3

Based on ANCOVA model, data prior to rescue (LOCF)

* p <0.001

Placebo-subtracted LS Mean % Change from Baseline (95% CI) HbA$_{1c}$

- CANA 100 mg: -0.65*
- CANA 300 mg: -0.73*

* p <0.001

CC-40
Subjects with HbA\textsubscript{1c} <7\% at Primary Endpoint
Placebo-controlled Phase 3 Studies

Add-on combinations with

<table>
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<tr>
<th>Monotherapy (DIA3005) N =584</th>
<th>Metformin (DIA3006) N = 1284</th>
<th>SU (DIA3008) N = 127</th>
<th>Met/SU (DIA3002) N = 469</th>
<th>Met/Pio (DIA3012) N = 342</th>
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<th>Current Therapy in Older Subjects (DIA3010) N = 714</th>
</tr>
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<tbody>
<tr>
<td>BL Mean HbA\textsubscript{1c} (%)</td>
<td>8.0</td>
<td>7.9</td>
<td>8.4</td>
<td>8.1</td>
<td>7.9</td>
<td>8.3</td>
</tr>
<tr>
<td>% Subjects Achieving HbA\textsubscript{1c} &lt;7%</td>
<td>44.5</td>
<td>45.5</td>
<td>57.8</td>
<td>56.6</td>
<td>64.3</td>
<td>47.7</td>
</tr>
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Data prior to rescue (LOCF);
Body Weight Percent Change from Baseline
Placebo-controlled Phase 3 Studies

Based on ANCOVA models, data prior to rescue (LOCF)

Add-on combinations with

<table>
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<tr>
<th>Monotherapy (DIA3005) N = 584</th>
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<th>Current Therapy in Older Subjects (DIA3010) N = 714</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL Mean Weight (kg)</td>
<td>86.8</td>
<td>87.2</td>
<td>83.0</td>
<td>92.8</td>
<td>94.1</td>
<td>97.0</td>
</tr>
<tr>
<td>Placebo-subtracted LS Mean</td>
<td>% Change in Body Weight (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CANA 100 mg</td>
<td>-2.2*</td>
<td>-2.5*</td>
<td>-2.9*</td>
<td>-1.4*</td>
<td>-2.0*</td>
<td>-1.9*</td>
</tr>
<tr>
<td>CANA 300 mg</td>
<td>-3.3*</td>
<td>-3.0*</td>
<td>-2.9*</td>
<td>-1.8†</td>
<td>-2.7*</td>
<td>-2.4*</td>
</tr>
</tbody>
</table>

* p <0.001; † p <0.05

Based on ANCOVA models, data prior to rescue (LOCF)
Percent of Subjects with Weight Reduction ≥5%
Placebo-controlled Phase 3 Studies

Add-on combinations with

<table>
<thead>
<tr>
<th>Add-on combinations with</th>
<th>Monotherapy (DIA3005) N=584</th>
<th>Metformin (DIA3006) N=1284</th>
<th>SU (DIA3008) N=127</th>
<th>Met/SU (DIA3002) N=469</th>
<th>Met/Pio (DIA3012) N=342</th>
<th>Insulin (DIA3008) N=1718</th>
<th>Current Therapy in Older Subjects (DIA3010) N=714</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL Mean Weight (kg)</td>
<td>86.8</td>
<td>87.2</td>
<td>83.0</td>
<td>92.8</td>
<td>94.1</td>
<td>97.0</td>
<td>89.5</td>
</tr>
<tr>
<td>% Subjects with ≥5% Body Weight Reduction</td>
<td>22.1</td>
<td>32.5</td>
<td>29.6</td>
<td>11.9</td>
<td>15.9</td>
<td>15.5</td>
<td>24.1</td>
</tr>
</tbody>
</table>

Data prior to rescue (LOCF)
Systolic Blood Pressure Change from Baseline
Placebo-controlled Phase 3 Studies

Add-on combinations with

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy (DIA3005)</td>
<td>584</td>
</tr>
<tr>
<td>Metformin (DIA3006)</td>
<td>1284</td>
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<td>1718</td>
</tr>
<tr>
<td>Current Therapy in Older Subjects (DIA3010)</td>
<td>714</td>
</tr>
</tbody>
</table>

**Placebo-subtracted LS Mean Change in Systolic BP (mmHg) (95% CI)**

- **CANA 100 mg**
  - Monotherapy: -3.7*, -5.4*, -5.4*, -6.6*
  - Metformin: -0.1, -2.2, -1.6
  - SU: -1.8
  - Met/SU: -4.1†, -3.5†
  - Met/Pio: -2.6*, -4.4*
  - Insulin: -4.6*, -4.6*
  - Current Therapy in Older Subjects: -7.9*

- **CANA 300 mg**
  - Monotherapy: -4.03, -3.75
  - Metformin: -0.16, -0.53
  - SU: -0.16
  - Met/SU: -1.11, -0.22
  - Met/Pio: -1.18, 0.22

* p<0.001; † p<0.05

Based on ANCOVA models, data prior to rescue (LOCF)

No clinically meaningful changes in pulse rate

Pulse rate (bpm) LS mean change
-1.33 -0.70 -0.95 -0.24 -4.03 -3.75 -0.16 -0.53 1.02 -0.08 -1.11 -0.22 -1.18 0.22
Results from Active-controlled Studies

- HbA$_{1c}$
- Body weight
- Systolic blood pressure
HbA1c Change from Baseline Over Time
Active (Glimepiride)-controlled Add-on to Metformin Study (DIA3009)

Baseline Mean HbA1c (%): 7.8
N = 1450

Glimepiride dose:
- Mean (median) of highest dose reached - 5.6 mg (6.0 mg)
- 82% of subjects on ≥4 mg/day

Based on ANCOVA model, data prior to rescue (LOCF)
Body Weight Percent Change from Baseline Over Time
Active (Glimepiride)-controlled Add-on to Metformin Study (DIA3009)

-5.7%* (-4.7 kg)
-5.2%* (-4.4 kg)

* p < 0.001
Based on ANCOVA model, data prior to rescue (LOCF)
**Changes in Body Composition and Weight**

Active (Glimepiride)-controlled Add-on to Metformin Study (DIA3009)

**Weight Loss Over Time**

BL Mean Body Weight (kg): 86.6
N = 1450

<table>
<thead>
<tr>
<th>Week</th>
<th>BL</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>18</th>
<th>26</th>
<th>36</th>
<th>44</th>
<th>52</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS Mean % Change from Baseline ± SE Body Weight</td>
<td>-5.7%* (-4.7 kg)</td>
<td>-5.2%* (-4.4 kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Change in Body Composition (DXA Analysis Subgroup)**

N = 312

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Lean Mass (kg)</th>
<th>Fat Mass (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glimepiride</td>
<td>-5.2%* (-4.4 kg)</td>
<td>-5.7%* (-4.7 kg)</td>
</tr>
<tr>
<td>CANA 100 mg</td>
<td>-0.89</td>
<td>-1.06</td>
</tr>
<tr>
<td>CANA 300 mg</td>
<td>-2.89</td>
<td>-2.51</td>
</tr>
</tbody>
</table>

Weight changes relative to glimepiride in DXA analysis subgroup (-5.3 kg and -5.0 kg for CANA 100 mg and 300 mg, respectively) were similar to overall cohort.

* p < 0.001

Based on ANCOVA model, data prior to rescue (LOCF)
Systolic Blood Pressure Change From Baseline at Week 52
Active (Glimepiride)-controlled Add-on to Metformin Study (DIA3009)

N=1450

BL Mean Systolic BP (mmHg): 129.8

SBP endpoint was not included in the prespecified testing sequence, however CI excluded 0.
Based on ANCOVA model, data prior to rescue (LOCF)
**HbA₁c Change from Baseline Over Time**
Active (Sitagliptin)-controlled Add-on to Metformin + SU Study (DIA3015)

- **LS Mean Change from Baseline ±SE**
- **HbA₁c (%)**
  - BL Mean HbA₁c (%): 8.1
  - N = 755

Weeks:
- BL
- 6
- 12
- 18
- 26
- 34
- 42
- 52

**SITA 100 mg**
**CANA 300 mg**

Based on ANCOVA model (LOCF)

(95% CI: -0.500; -0.250)
Body Weight Percent Change from Baseline Over Time
Active (Sitagliptin)-controlled Add-on to Metformin + SU Study (DIA3015)

BL Body Weight (kg): 88.3
N = 755

-2.8%* (-2.4 kg)

* p < 0.001
Based on ANCOVA model (LOCF)
Systolic Blood Pressure Change From Baseline at Week 52
Active (Sitagliptin)-controlled Add-on to Metformin + SU Study (DIA3015)

N=755

BL Mean Systolic BP (mmHg): 130.7

Difference from Sitagliptin

* p <0.001
Based on ANCOVA model (LOCF)
Results in Subjects with Renal Impairment

- HbA1c
- Body weight
- Systolic blood pressure
HbA$_{1c}$ Change from Baseline
Renal Impairment Study (DIA3004) and Pooled Population (DS2)

Study in T2DM Subjects with Renal Impairment
(eGFR 30 to <50) (DIA3004)
(N=269)

- BL Mean HbA$_{1c}$ (%) 8.0
- BL Mean eGFR (mL/min/1.73m$^2$) 39.4

Pooled Renal Impairment Population §
(eGFR 30 to <60)
(N=1085)

- BL Mean HbA$_{1c}$ (%) 8.1
- BL Mean eGFR (mL/min/1.73m$^2$) 48.2

<table>
<thead>
<tr>
<th>Drug</th>
<th>LS Mean Change from Baseline (± 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.03</td>
</tr>
<tr>
<td>CANA 100 mg</td>
<td>-0.33*</td>
</tr>
<tr>
<td>CANA 300 mg</td>
<td>-0.44*</td>
</tr>
<tr>
<td>Pbo-subtracted differences</td>
<td></td>
</tr>
</tbody>
</table>

* $p <0.001$; † $p <0.05$

§Data from monotherapy study (DIA3005), renal impairment study (DIA3004), study in older subjects (DIA3010), and CV study (DIA3008)
Subjects Achieving HbA$_{1c}$ <7.0%
Renal Impairment Study (DIA3004) and Pooled Population (DS2)

DIA3004 (eGFR* 30 to <50)

BL Mean HbA$_{1c}$ 8.0%
N  = 269

Proportion Achieving Goal (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>CANA 100 mg</th>
<th>CANA 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion</td>
<td>17.2</td>
<td>27.3</td>
<td>32.6</td>
</tr>
</tbody>
</table>

Pooled Renal Impairment Population (eGFR* 30 to <60)

BL Mean HbA$_{1c}$ 8.1%
N  = 1085

Proportion Achieving Goal (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>CANA 100 mg</th>
<th>CANA 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion</td>
<td>17.4</td>
<td>24.5</td>
<td>31.9</td>
</tr>
</tbody>
</table>

*eL/min/1.73m$^2$
Body Weight Percent Change from Baseline at Endpoint
Pooled Renal Impairment Population (eGFR 30 to <60)

N=1085
BL Body Weight (kg): 90.9

LS Mean % Change from Baseline (±95% CI)

- Placebo
- CANA 100 mg
- CANA 300 mg

-1.6%* (-1.4 kg)
-1.9%* (-1.8 kg)

Pbo-subtracted differences

* p <0.001
Based on ANCOVA model, data prior to rescue (LOCF)
Systolic BP Change from Baseline at Endpoint
Pooled Renal Impairment Population (eGFR 30 to <60)

N=1085
BL Mean Systolic BP (mmHg): 135.3

LS Mean Change from Baseline (95%CI)

Systolic Blood Pressure (mmHg)

- Placebo
- CANA 100 mg
- CANA 300 mg

-6.0
-4.4
-1.6

-2.77†
-4.38*

* p <0.001; † p <0.05
Based on ANCOVA model, data prior to rescue (LOCF)
HbA$_{1c}$ Subgroup Analyses
HbA\textsubscript{1c} Change from Baseline by Subgroup Factors
Pooled Placebo-controlled Studies for Efficacy

*includes: monotherapy, dual therapy, triple therapy, and insulin
Summary of Canagliflozin Efficacy Data

• HbA1c
  – Consistent improvement across Phase 3 studies, with more subjects achieving HbA1c goal
  – Sustained response over 52 weeks
  – Meaningful, albeit lesser, reductions in HbA1c in subjects with renal impairment

• Other efficacy parameters
  – Consistent reductions in body weight
  – Consistent reductions in systolic blood pressure

• Additional efficacy with 300 mg relative to 100 mg
Overview of Safety and Tolerability

Peter Stein, MD
Head of Development, Metabolism
Janssen Research and Development, LLC
Agenda

• Pooled datasets for safety: definition, characteristics, exposure
  – Placebo-controlled 26 week studies dataset
  – “Broad Dataset”

• Review of adverse drug reactions (ADRs)
  – Overview of identified ADRs
  – Review of specific ADRs: UTIs, related to reduced intravascular volume

• Additional safety assessments
  – LDL-C changes and CV meta-analysis (including events in 1st 30 days in CANVAS)
  – Renal safety and safety in stage 3 CKD subjects
  – Bone
### Phase 3 Clinical Development Program: 9 Studies Conducted

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Dual Combination</th>
<th>Triple Combination</th>
<th>Insulin +/- oral(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy (DIA3005)</strong></td>
<td><strong>Combo with MET (DIA3006)</strong></td>
<td><strong>Combo with MET/PIO (DIA3012)</strong></td>
<td><strong>Combo with INSULIN (Substudy DIA3008)</strong></td>
</tr>
<tr>
<td>26 / 26 wks N=587</td>
<td>26 / 26 wks N=1284</td>
<td>26 / 26 wks N=344</td>
<td>18 wks N=1784</td>
</tr>
<tr>
<td><strong>Combo with SU (Substudy DIA3008)</strong></td>
<td><strong>Combo with MET/SU (DIA3002)</strong></td>
<td><strong>Combo with MET/SU vs SITA (DIA3015)</strong></td>
<td></td>
</tr>
<tr>
<td>18 wks N=127</td>
<td>26 / 26 wks N=469</td>
<td>52 wks N=756</td>
<td></td>
</tr>
<tr>
<td><strong>Combo with MET vs GLIM (DIA3009)</strong></td>
<td><strong>Combo with MET/SU vs SITA (DIA3015)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>52 / 52 wks N=1452</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Studies in Special T2DM Populations
- Placebo-controlled studies / add-on to current diabetes treatment

- **Older Subjects - Bone Safety and Body Comp (DIA3010)**
  - 26 / 78 wks N=716

- **Renal Impairment (DIA3004)**
  - 26 / 26 wks N=272

- **CV Safety Study (DIA3008: CANVAS)**
  - Event-driven N=4330
### Phase 3 Pooled Safety Populations: Placebo-controlled Studies Dataset (DS1)

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Dual Combination</th>
<th>Triple Combination</th>
<th>Insulin +/- oral(s)</th>
</tr>
</thead>
<tbody>
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<td><strong>Combo with MET/PIO (DIA3012)</strong></td>
<td></td>
</tr>
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<td>26 / 26 wks N=587</td>
<td>26 / 26 wks N=1284</td>
<td>26 / 26 wks N=344</td>
<td></td>
</tr>
<tr>
<td><strong>Combo with MET/PIO (DIA3012)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 / 26 wks N=469</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**4 Phase 3 studies / 2313 subjects**  
**26 week double-blind duration**
## Phase 3 Pooled Safety Populations: Broad Dataset (DS3)

### Monotherapy
- **Monotherapy (DIA3005)**
  - 26 / 26 wks N=587

### Dual Combination
- **Combo with MET (DIA3006)**
  - 26 / 26 wks N=1284
- **Combo with SU (Substudy DIA3008)**
  - 18 wks N=127

### Triple Combination
- **Combo with MET/PIO (DIA3012)**
  - 26 / 26 wks N=344
- **Combo with MET/SU (DIA3002)**
  - 26 / 26 wks N=469

### Insulin +/- oral(s)
- **Combo with INSULIN (Substudy DIA3008)**
  - 18 wks N=1784

### Studies in Special T2DM Populations
- **Older Subjects - Bone Safety and Body Comp (DIA3010)**
  - 26 / 78 wks N=716
- **Renal Impairment (DIA3004)**
  - 26 / 26 wks N=272
- **CV Safety Study (DIA3008: CANVAS)**
  - Event-driven N=4330

---

**Total:** 8 Phase 3 Studies
9439 subjects
- PBO/comparators pooled (=“Non-CANA” group)
## Baseline Characteristics

### Pooled Datasets

<table>
<thead>
<tr>
<th></th>
<th>Placebo-controlled Studies Dataset N=2313</th>
<th>Broad Dataset N=9439</th>
<th>CANVAS N=4,327</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>49.5</td>
<td>58.2</td>
<td>66.1</td>
</tr>
<tr>
<td>Female</td>
<td>50.5</td>
<td>41.8</td>
<td>33.9</td>
</tr>
<tr>
<td><strong>Age (y), Mean (SD)</strong></td>
<td>56.0 (9.81)</td>
<td>59.9 (9.35)</td>
<td>62.4 (8.02)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>72.2</td>
<td>72.6</td>
<td>73.4</td>
</tr>
<tr>
<td>Black or African-American</td>
<td>5.1</td>
<td>3.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Asian</td>
<td>12.3</td>
<td>15.8</td>
<td>18.4</td>
</tr>
<tr>
<td>Other</td>
<td>10.4</td>
<td>7.8</td>
<td>5.8</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m², Mean (SD)</strong></td>
<td>32.1 (6.42)</td>
<td>31.9 (6.06)</td>
<td>32.1 (6.24)</td>
</tr>
<tr>
<td><strong>HbA₁c (%), Mean (SD)</strong></td>
<td>8.0 (0.93)</td>
<td>8.0 (0.90)</td>
<td>8.2 (0.92)</td>
</tr>
<tr>
<td><strong>Duration of diabetes (y), Mean (SD)</strong></td>
<td>7.3 (6.04)</td>
<td>10.6 (7.53)</td>
<td>13.4 (7.52)</td>
</tr>
<tr>
<td><strong>eGFR, Mean</strong></td>
<td>88</td>
<td>81</td>
<td>77</td>
</tr>
<tr>
<td>≥ 1 Microvascular Complications (%)</td>
<td>18.9</td>
<td>33.1</td>
<td>44.2</td>
</tr>
</tbody>
</table>
# Exposure

**Placebo-controlled Studies Dataset and Broad Dataset through 01 Jul 2012**

<table>
<thead>
<tr>
<th>Category, %</th>
<th>Placebo N=646</th>
<th>CANA 100 mg N=833</th>
<th>CANA 300 mg N=834</th>
<th>Broad Dataset through 01 Jul 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50 weeks</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>77.7</td>
</tr>
<tr>
<td>≥ 76 weeks</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>40.6</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td>64.4 (30.2)</td>
</tr>
<tr>
<td>Median</td>
<td>26.0</td>
<td>26.1</td>
<td>26.1</td>
<td>65.9</td>
</tr>
<tr>
<td>Total Exposure (subject-years)</td>
<td>294</td>
<td>387</td>
<td>388</td>
<td>4024</td>
</tr>
</tbody>
</table>

<table>
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<tr>
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<th>Placebo N=646</th>
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<th>CANA 300 mg N=834</th>
<th>Broad Dataset through 01 Jul 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50 weeks</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>83.5</td>
</tr>
<tr>
<td>≥ 76 weeks</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>46.4</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td>68.8 (29.0)</td>
</tr>
<tr>
<td>Median</td>
<td>26.0</td>
<td>26.1</td>
<td>26.1</td>
<td>72.9</td>
</tr>
<tr>
<td>Total Exposure (subject-years)</td>
<td>294</td>
<td>387</td>
<td>388</td>
<td>4075</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category, %</th>
<th>Placebo N=646</th>
<th>CANA 100 mg N=833</th>
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<th>Broad Dataset through 01 Jul 2012</th>
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</thead>
<tbody>
<tr>
<td>≥ 50 weeks</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>81.9</td>
</tr>
<tr>
<td>≥ 76 weeks</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>45.2</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td>67.4 (30.2)</td>
</tr>
<tr>
<td>Median</td>
<td>26.0</td>
<td>26.1</td>
<td>26.1</td>
<td>72.4</td>
</tr>
<tr>
<td>Total Exposure (subject-years)</td>
<td>294</td>
<td>387</td>
<td>388</td>
<td>3987</td>
</tr>
</tbody>
</table>

Note: Total duration = Treatment duration = last dose date - first dose date + 1 (in days).

*Broad dataset does not include DIA3015*
## Summary of Adverse Events

**Broad Dataset through 01 Jul 2012**

<table>
<thead>
<tr>
<th></th>
<th>Non-CANA N=3262 %</th>
<th>CANA 100 mg N=3092 %</th>
<th>CANA 300 mg N=3085 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events</td>
<td>75.8</td>
<td>76.6</td>
<td>77.0</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>5.0</td>
<td>5.6</td>
<td>7.3</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>13.6</td>
<td>13.5</td>
<td>13.2</td>
</tr>
<tr>
<td>Serious AEs leading to discontinuation</td>
<td>2.2</td>
<td>2.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Deaths</td>
<td>1.1</td>
<td>0.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>

- Genital mycotic infections: male and female
- Osmotic diuresis-related (pollakiuria, thirst)
- Other: UTI, renal-related
Adverse Drug Reactions

• Overview of ADRs
• Discussion of specific ADRs:
  • Urinary tract infections
  • Reduced intravascular volume-related AEs
## Summary of Adverse Drug Reactions

≥ 2% and > Placebo in the Placebo-controlled Studies Dataset

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=646 n (%)</th>
<th>CANA 100 mg N=833 n (%)</th>
<th>CANA 300 mg N=834 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>6 (0.9)</td>
<td>15 (1.8)</td>
<td>19 (2.3)</td>
</tr>
<tr>
<td>Thirst</td>
<td>1 (0.2)</td>
<td>23 (2.8)</td>
<td>19 (2.3)</td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyuria or pollakiuria</td>
<td>5 (0.8)</td>
<td>44 (5.3)</td>
<td>38 (4.6)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>26 (4.0)</td>
<td>49 (5.9)</td>
<td>36 (4.3)</td>
</tr>
<tr>
<td><strong>Reproductive System and Breast Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balanitis or balanoposthitis</td>
<td>2 (0.6)</td>
<td>17 (4.2)</td>
<td>15 (3.7)</td>
</tr>
<tr>
<td>Vulvovaginal candidiasis</td>
<td>10 (3.2)</td>
<td>44 (10.4)</td>
<td>49 (11.4)</td>
</tr>
</tbody>
</table>
Additional ADRs Identified

In *Broad Dataset*

- Reduced intravascular volume-related AEs (eg, postural dizziness)
- Less common (< 2%): rash/urticaria

In *individual* Phase 3 studies

- Hypoglycemia in patients on insulin or sulphonylurea agent
  - Low rate of hypoglycemia in studies of subjects not on agents associated with hypoglycemia
Adverse Drug Reactions

Urinary tract infections

Adverse events related to reduced intravascular volume
## Incidence of Urinary Tract Infection Adverse Events

**Broad Dataset through 01 Jul 2012**

<table>
<thead>
<tr>
<th></th>
<th>Non-CANA N=3262</th>
<th>CANA 100 mg N=3092</th>
<th>CANA 300 mg N=3085</th>
<th>All CANA N=6177</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events</td>
<td>218 (6.7)</td>
<td>254 (8.2)</td>
<td>250 (8.1)</td>
<td>504 (8.2)</td>
</tr>
<tr>
<td>Upper UTI AE</td>
<td>11 (0.3)</td>
<td>20 (0.6)</td>
<td>10 (0.3)</td>
<td>30 (0.5)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>4 (0.1)</td>
<td>11 (0.4)</td>
<td>6 (0.2)</td>
<td>17 (0.3)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>12 (0.4)</td>
<td>16 (0.5)</td>
<td>8 (0.3)</td>
<td>24 (0.4)</td>
</tr>
</tbody>
</table>
## Reduced Intravascular Volume-Related AEs
### Broad Dataset through 01 Jul 2012

<table>
<thead>
<tr>
<th></th>
<th>Non-CANA N=3262 n (%)</th>
<th>CANA 100 mg N=3092 n (%)</th>
<th>CANA 300 mg N=3085 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events</td>
<td>78 (2.4)</td>
<td>99 (3.2)</td>
<td>141 (4.6)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>4 (0.1)</td>
<td>2 (0.1)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>11 (0.3)</td>
<td>12 (0.4)</td>
<td>8 (0.3)</td>
</tr>
</tbody>
</table>

### Specific AE Terms

- **Blood pressure decreased**: 1 (<0.1), 2 (0.1), 2 (0.1)
- **Dehydration**: 13 (0.4), 6 (0.2), 13 (0.4)
- **Dizziness postural**: 24 (0.7), 26 (0.8), 33 (1.1)
- **Hypotension**: 20 (0.6), 47 (1.5), 60 (1.9)
- **Orthostatic hypotension**: 6 (0.2), 8 (0.3), 27 (0.9)
- **Orthostatic intolerance**: 1 (<0.1), 1 (<0.1), 1 (<0.1)
- **Presyncope**: 9 (0.3), 4 (0.1), 3 (0.1)
- **Syncope**: 13 (0.4), 12 (0.4), 20 (0.6)
- **Urine output decreased**: 1 (<0.1), 0, 0
Time to Event: Reduced Intravascular Volume AE
Broad Dataset through 01 Jul 2012

KM estimate

Estimated % of Subjects with an Event vs Time (Weeks)

Subjects at Risk
- Non CANA: 3262, 3097, 2861, 2679, 2580, 2506, 1639, 1303, 995, 344
- CANA 100 mg: 3092, 2954, 2791, 2666, 2582, 2532, 1750, 1395, 1060, 369
- CANA 300 mg: 3085, 2866, 2692, 2564, 2491, 2442, 1671, 1345, 1014, 370

Time (Weeks): 0, 12, 24, 36, 44, 52, 64, 76, 84, 104

Non-CANA

CANA 100 mg

CANA 300 mg
### Risk Factors: Reduced Intravascular Volume AEs

**Broad Dataset Core Period**

<table>
<thead>
<tr>
<th></th>
<th>Non-CANA % (n/N)</th>
<th>CANA 100 mg % (n/N)</th>
<th>CANA 300 mg % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>eGFR (mL/min/1.73m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>2.8 (12/436)</td>
<td>5.0 (19/382)</td>
<td><strong>8.1 (33/405)</strong></td>
</tr>
<tr>
<td>60 to &lt;90</td>
<td>1.5 (26/1788)</td>
<td>2.4 (40/1686)</td>
<td>2.9 (48/1680)</td>
</tr>
<tr>
<td>≥90</td>
<td>1.2 (12/1035)</td>
<td>1.3 (13/1021)</td>
<td>2.4 (24/999)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>1.5 (46/3107)</td>
<td>2.2 (64/2929)</td>
<td><strong>3.1 (90/2913)</strong></td>
</tr>
<tr>
<td>≥75</td>
<td>2.6 (4/155)</td>
<td>4.9 (8/163)</td>
<td><strong>8.7 (15/172)</strong></td>
</tr>
<tr>
<td><strong>Use of loop diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.2 (37/3006)</td>
<td>2.3 (65/2876)</td>
<td><strong>2.9 (83/2835)</strong></td>
</tr>
<tr>
<td>Yes</td>
<td>5.1 (13/256)</td>
<td>3.2 (7/216)</td>
<td><strong>8.8 (22/250)</strong></td>
</tr>
<tr>
<td><strong>Age &lt;75, not on loop diuretics and with eGFR ≥60 mL/min/1.73m²</strong></td>
<td>1.1 (29/2604)</td>
<td>1.8 (45/2491)</td>
<td>2.2 (54/2434)</td>
</tr>
</tbody>
</table>
Summary: Reduced Intravascular Volume Related Adverse Events

• Dose-related increase in events
  – No increase in AEs leading to discontinuation or SAEs
  – Generally mild-moderate in intensity, short duration
  – Manageable, often with adjustment in concomitant BP-lowering regimen

• Risk factors for dose-related increase identified
  – eGFR < 60 mL/min/1.73 m², age ≥ 75 yrs, on loop diuretics
  – Supports dosing recommendations to initiate therapy at 100 mg in patients with any 1 of 3 risk factors
Additional Key Safety Assessments

- CV Meta-analysis Results
- Renal Safety Evaluations
- Bone Safety
Additional Key Safety Assessments

CV Safety
- Changes in LDL-C
- CV Meta-analysis results
Fasting Lipids: Absolute Change
Placebo-controlled Studies Dataset

**LS Mean placebo-subtracted absolute change from baseline at Week 26**

- **LDL-C**: 4.4 mg/dL (95% CI), -2.1 mg/dL
- **Non-HDL-C**: 8.2 mg/dL (95% CI), 2.8 mg/dL
- **HDL-C**: 5.1 mg/dL (95% CI), 2.3 mg/dL
- **LDL-C/HDL-C**: 0.0, 0.1
- **Triglycerides**: -9.2 mg/dL, -19.1 mg/dL

Increases in Apo B and NMR measured LDL particle number approximately half as large as increases in LDL-C.
CV Risk Factor Changes with Canagliflozin

• Changes in fasting lipids
  – Increases in LDL-C
    • Smaller increases in non-HDL-C, Apo B, LDL particle number
  – Increases in HDL-C
  – No change in LDL-C/HDL-C ratio
  – Decreases in TG

• Decreases in systolic and diastolic blood pressure
• Improved glycemic control
• Decrease in body weight
Pre-specified Cardiovascular Meta-analyses Procedures

- Predefined composite endpoint of “MACE-plus”: CV death, nonfatal MI, nonfatal stroke, hospitalized unstable angina
- Stepwise CV meta-analyses (based upon FDA DM CV guidance, 2008)
  - Current step 1 to meet upper bound < 1.8 planned when 200 events
  - Step 2 to meet upper bound < 1.3 planned when 500 events
- Step 1 meta-analysis included 201 events from all Phase 2 and 3 studies completed prior to 02 FEB 2012
  - Events from CANVAS (161) and non-CANVAS studies (40)
- Blinded, independent adjudication committee operating under committee charter
Time to Event Analysis for MACE-plus
All Phase 2/3 Studies

Probability of a MACE-plus Event

HR=0.91 (95% CI: 0.68, 1.22)
HR=1.00 (0.72, 1.39) CANVAS
HR=0.65 (0.35, 1.21) non-CANVAS

Number of Subjects at Risk
Non-CANA 3327 3282 3161 2991 2848 2650 1985 931 508 213 42
All CANA 6305 6224 6000 5715 5539 5227 4065 1935 1039 462 91

Note: includes all studies with data base lock prior to 31-Jan-12; mITT analysis set; events within 30 days of last dose
Incidence and HR for Adjudicated CV Events
All Phase 2/3 Studies

<table>
<thead>
<tr>
<th></th>
<th>Non-CANA</th>
<th>All CANA</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/PYs (per 100 patient-yrs)</td>
<td>Events/PYs (per 100 patient-yrs)</td>
<td>Favors CANA</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>71/3467 (2.05)</td>
<td>130/6821 (1.91)</td>
<td>0.91 (0.68, 1.22)</td>
</tr>
<tr>
<td>CV Death</td>
<td>16/3496 (0.46)</td>
<td>21/6888 (0.30)</td>
<td>0.65 (0.34, 1.24)</td>
</tr>
<tr>
<td>FNF MI</td>
<td>27/3484 (0.78)</td>
<td>45/6864 (0.66)</td>
<td>0.83 (0.52, 1.34)</td>
</tr>
<tr>
<td>FNF Stroke</td>
<td>16/3489 (0.46)</td>
<td>47/6859 (0.69)</td>
<td>1.47 (0.83, 2.59)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>18/3484 (0.52)</td>
<td>26/6874 (0.38)</td>
<td>0.71 (0.39, 1.30)</td>
</tr>
</tbody>
</table>
CV Meta-analysis – Further Assessments

Early Imbalance in CANVAS
HR Differences by Event Type
Issue: imbalance in 1\textsuperscript{st} 30 days in CANVAS: 13 events in All CANA groups vs 1 event in PBO (2:1 rand)

**Assessment**

- Imbalance not seen in overall CV meta-analysis (pre-specified): 15 vs 5 in All CANA vs PBO (~2:1 rand)
- Considerable month-to-month variability in frequency of events
- Low rate in PBO group in 1\textsuperscript{st} 30 days not typical in T2DM outcome studies
- Lack of association with volume depletion-related adverse events – time course or dose-relationship
- Subjects with “early” MACE+ events not more susceptible subset
Estimated Hazard Function
MACE-Plus CANVAS Study, mITT Analysis Set

Hazard Rate vs. Months on Treatment

- Placebo
- All CANA

CC-87
Initial Imbalance in Events in CANVAS Assessment

Plausibility of association of MACE-plus and volume depletion:

• Volume-related AEs increased over 1st ~ 90-120 days
  – vs MACE-plus events - higher rate in CANA group in 1st 30 days
    – then lower rate in next 60 days

• Volume-related AEs notably dose-related (300 mg > 100 mg)
  – vs MACE-plus events: 7 in 100 mg group / 6 in 300 mg group

• No reports of reduced intravascular volume-related AEs in subjects
  with MACE-plus events – or suggestive descriptions in narratives

Conclusions

• No evident relationship of MACE-plus to reduced intravascular-
  related AEs

• Early imbalance reflects the marked month-to-month variability
Incidence and HR for Adjudicated CV Events
All Phase 2/3 Studies

<table>
<thead>
<tr>
<th></th>
<th>Non-CANA</th>
<th>All CANA</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/PYs (per 100 patient-yrs)</td>
<td>Events/PYs (per 100 patient-yrs)</td>
<td>Favors CANA</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>71/3467 (2.05)</td>
<td>130/6821 (1.91)</td>
<td></td>
</tr>
<tr>
<td><strong>CV Endpoint</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV Death</td>
<td>16/3496 (0.46)</td>
<td>21/6888 (0.30)</td>
<td></td>
</tr>
<tr>
<td>FNF MI</td>
<td>27/3484 (0.78)</td>
<td>45/6864 (0.66)</td>
<td></td>
</tr>
<tr>
<td>FNF Stroke</td>
<td>16/3489 (0.46)</td>
<td>47/6859 (0.69)</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>18/3484 (0.52)</td>
<td>26/6874 (0.38)</td>
<td></td>
</tr>
</tbody>
</table>
Assessment of Observed HR for Stroke

- Pre-specified composite provides most robust assessment
  - Variability expected in individual event types with smaller event number

- Assessment of plausibility of association with CANA due to dehydration with hypercoagulability
  - Minimal overlap with volume-related AEs, and decreases in SBP/increases in hemoglobin not notably different in subjects with stroke
  - Different time-course, lack of dose-relationship (vs volume-related AEs)
  - No difference in other events in stroke continuum: TIA HR 0.99
  - No evidence of hypercoagulability
  - No reported increase in strokes with diuretics

- Assessment: reflects a chance difference, with further assessment of stroke HR over time appropriate
Additional Key Safety Assessments

Renal Safety Evaluations

• eGFR change from baseline
• Albumin / Creatinine Ratio (ACR)
Mean Change in eGFR from Baseline Over Time
Placebo-controlled Studies Dataset

Mean Change +/- SE

<table>
<thead>
<tr>
<th>Group</th>
<th>BL</th>
<th>Wk 6</th>
<th>Wk 12</th>
<th>Wk 18</th>
<th>Wk 26</th>
<th>Wk 26 LOCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>87.0</td>
<td>620</td>
<td>590</td>
<td>560</td>
<td>526</td>
<td>624</td>
</tr>
<tr>
<td>CANA 100 mg</td>
<td>88.3</td>
<td>796</td>
<td>765</td>
<td>748</td>
<td>715</td>
<td>809</td>
</tr>
<tr>
<td>CANA 300 mg</td>
<td>88.8</td>
<td>795</td>
<td>758</td>
<td>744</td>
<td>720</td>
<td>805</td>
</tr>
</tbody>
</table>

eGFR (mL/min/1.73m²)
eGFR Mean Change from Baseline Over Time
Active (Glimepiride)-controlled Add-on to Metformin Study (DIA3009) and
Active (Sitagliptin)-controlled Add-on to Metformin + SU Study (DIA3015)

**DIA3009**
- **Glimepiride** (BL: 89.5)
- **CANA 100 mg** (BL: 89.7)
- **CANA 300 mg** (BL: 91.4)

**DIA3015**
- **SITA 100 mg** (BL: 87.76)
- **CANA 300 mg** (BL: 87.17)
Mean Change in eGFR from Baseline Over Time
Study in Subjects with T2DM and Renal Impairment (DIA3004)

Placebo
BL: 40.1 mL/min/1.73m²

CANA 100 mg
BL: 39.7 mL/min/1.73m²

CANA 300 mg
BL: 38.5 mL/min/1.73m²

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Wk 3</th>
<th>Wk 6</th>
<th>Wk 12</th>
<th>Wk 18</th>
<th>Wk 26</th>
<th>Wk 26 LOCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>90</td>
<td>86</td>
<td>83</td>
<td>82</td>
<td>80</td>
<td>75</td>
<td>87</td>
</tr>
<tr>
<td>CANA 100 mg</td>
<td>90</td>
<td>86</td>
<td>84</td>
<td>79</td>
<td>77</td>
<td>72</td>
<td>89</td>
</tr>
<tr>
<td>CANA 300 mg</td>
<td>89</td>
<td>84</td>
<td>83</td>
<td>83</td>
<td>83</td>
<td>80</td>
<td>89</td>
</tr>
</tbody>
</table>
Mean Percent Change in eGFR After Drug Discontinuation
CV Safety Study (DIA3008 July 2012 Dataset)

Baseline eGFR (mL/min/1.73m²): 77

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>CANA 100 mg</th>
<th>CANA 300 mg</th>
<th>All CANA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median days on drug</td>
<td>130</td>
<td>184</td>
<td>128</td>
<td>134</td>
</tr>
<tr>
<td>Median days since last dose</td>
<td>68.0</td>
<td>66.0</td>
<td>60.5</td>
<td>64.0</td>
</tr>
</tbody>
</table>

Mean Percent Change +/- SE
Change from Baseline in Albumin/Creatinine Ratio
CV Safety Study (DIA3008) through 01 Jul 2012

Within 2 Days After Last Study Medication
Safety in Subjects with Stage 3 CKD (eGFR 30 to <60 mL/min/1.73 m²)
## Baseline Characteristics
### Renal Impairment Dataset (eGFR 30 to <60)

<table>
<thead>
<tr>
<th></th>
<th>Placebo-controlled Study N = 2313</th>
<th>Renal Impairment Dataset N = 1085</th>
<th>Broad Dataset N = 9439</th>
<th>CANVAS N = 4327</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td>Male 49.5</td>
<td>58.4</td>
<td>58.2</td>
<td>66.1</td>
</tr>
<tr>
<td></td>
<td>Female 50.5</td>
<td>41.6</td>
<td>41.8</td>
<td>33.9</td>
</tr>
<tr>
<td>Age (y), Mean (SD)</td>
<td>56.0 (9.81)</td>
<td>67.1 (7.67)</td>
<td>59.9 (9.35)</td>
<td>62.4 (8.02)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>White 72.2</td>
<td>78.2</td>
<td>72.6</td>
<td>73.4</td>
</tr>
<tr>
<td></td>
<td>Black or African-American 5.1</td>
<td>2.9</td>
<td>3.8</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>Asian 12.3</td>
<td>13.0</td>
<td>15.8</td>
<td>18.4</td>
</tr>
<tr>
<td></td>
<td>Other 10.4</td>
<td>5.9</td>
<td>7.8</td>
<td>5.8</td>
</tr>
<tr>
<td>Body mass index, kg/m², Mean (SD)</td>
<td>32.1 (6.42)</td>
<td>32.5 (6.12)</td>
<td>31.9 (6.06)</td>
<td>32.1 (6.24)</td>
</tr>
<tr>
<td>HbA1c (%), Mean (SD)</td>
<td>8.0 (0.93)</td>
<td>8.1 (0.93)</td>
<td>8.0 (0.90)</td>
<td>8.2 (0.92)</td>
</tr>
<tr>
<td>Duration of diabetes (y), Mean (SD)</td>
<td>7.3 (6.04)</td>
<td>15.1 (8.40)</td>
<td>10.6 (7.53)</td>
<td>13.4 (7.52)</td>
</tr>
<tr>
<td>eGFR, Mean</td>
<td>88</td>
<td>48</td>
<td>81</td>
<td>77</td>
</tr>
<tr>
<td>≥ 1 Microvascular Complication, %</td>
<td>18.9</td>
<td>59.1</td>
<td>33.1</td>
<td>44.2</td>
</tr>
</tbody>
</table>

Renal impairment dataset: subjects from DIA3004, DIA3005, DIA3008, and DIA3010 with baseline eGFR 30 to < 60 mL/min/1.73 m²
## Summary of Adverse Events
### Renal Impairment Dataset (eGFR 30 to <60)

<table>
<thead>
<tr>
<th></th>
<th>Placebo 382 N</th>
<th>CANA 100 mg 338 N</th>
<th>CANA 300 mg 365 N</th>
<th>All CANA 703 N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any Adverse Events</strong></td>
<td>269 (70.4%)</td>
<td>250 (74.0%)</td>
<td>275 (75.3%)</td>
<td>525 (74.7%)</td>
</tr>
<tr>
<td>AEs leading to</td>
<td>22 (5.8%)</td>
<td>19 (5.6%)</td>
<td>28 (7.7%)</td>
<td>47 (6.7%)</td>
</tr>
<tr>
<td>discontinuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serious AEs</strong></td>
<td>75 (19.6%)</td>
<td>45 (13.3%)</td>
<td>54 (14.8%)</td>
<td>99 (14.1%)</td>
</tr>
<tr>
<td>Serious AEs leading to</td>
<td>14 (3.7%)</td>
<td>9 (2.7%)</td>
<td>12 (3.3%)</td>
<td>21 (3.0%)</td>
</tr>
<tr>
<td>discontinuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>6 (1.6%)</td>
<td>3 (0.9%)</td>
<td>5 (1.4%)</td>
<td>8 (1.1%)</td>
</tr>
</tbody>
</table>
## Incidence of Adverse Drug Reactions
### Renal Impairment Dataset (eGFR 30 to <60)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo N=382 n (%)</th>
<th>CANA 100 mg N=338 n (%)</th>
<th>CANA 300 mg N=365 n (%)</th>
<th>All CANA N=703 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmotic diuresis-related AEs</td>
<td>14 (3.7)</td>
<td>14 (4.1)</td>
<td>14 (3.8)</td>
<td>28 (4.0)</td>
</tr>
<tr>
<td>Reduced intravascular volume-related AEs</td>
<td>10 (2.6)</td>
<td>17 (5.0)</td>
<td>31 (8.5)</td>
<td>48 (6.8)</td>
</tr>
<tr>
<td>Urinary tract infection AEs</td>
<td>23 (6.0)</td>
<td>21 (6.2)</td>
<td>27 (7.4)</td>
<td>48 (6.8)</td>
</tr>
</tbody>
</table>

### Female Subjects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo N=156 n (%)</th>
<th>CANA 100 mg N=140 n (%)</th>
<th>CANA 300 mg N=155 n (%)</th>
<th>All CANA N=295 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital mycotic infection AEs</td>
<td>3 (1.9)</td>
<td>15 (10.7)</td>
<td>15 (9.7)</td>
<td>30 (10.2)</td>
</tr>
</tbody>
</table>

### Male Subjects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo N=226 n (%)</th>
<th>CANA 100 mg N=198 n (%)</th>
<th>CANA 300 mg N=210 n (%)</th>
<th>All CANA N=408 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital mycotic infection AEs</td>
<td>3 (1.3)</td>
<td>5 (2.5)</td>
<td>15 (7.1)</td>
<td>20 (4.9)</td>
</tr>
</tbody>
</table>
Renal Function and Electrolyte Changes in Subjects with Stage 3 CKD

• Renal function
  – Larger initial percentage decrease in eGFR, then rise in eGFR towards baseline
    • Reversibility after discontinuation (DIA3008)
  – Outlier analyses shows similar pattern as seen in Broad Dataset
  – No increase in renal-related SAEs or AEs leading to D/C
  – Decrease in the urinary albumin creatinine ratio (DIA3004)

• Electrolytes
  – Modest mean increases in serum phosphate and magnesium
    • Low incidence of values meeting outlier criteria (> 25% above ULN), and no AEs reported
  – No relevant mean changes in serum potassium
    • Infrequent hyperkalemia – generally related to multiple factors including CKD + ACE inhibitors/ARBs + other agents (eg, aliskerin)
Additional Key Safety Assessments

Bone Safety

• Calcium, phosphate, 1-25 dihydroxy-vitamin D, and PTH
• Bone density assessment (DXA)
• Incidence of fractures
Changes in Calcium Axis

- No meaningful mean changes in serum calcium or urine calcium excretion
- Small mean increases in serum phosphate and magnesium (5-10%) – stable over time
- Transient increase in PTH at Week 3 with no substantive changes at Week 12 (Phase 2), or at Weeks 26 or 52 (Phase 3)
  - No increase in PTH in Stage 3 CKD subjects (DIA3004) – small decrease relative to placebo over 26 weeks
- Variable, but overall not meaningful changes in 1,25-dihydroxyvitamin D levels
Percent Change in BMD Results at Week 52 by DXA Study in Older Subjects with T2DM (DIA3010)

<table>
<thead>
<tr>
<th>Site</th>
<th>CANA 100 mg Pbo-subtracted Mean (95% CI) N=241</th>
<th>CANA 300 mg Pbo-subtracted Mean (95% CI) N=236</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td>-0.4 (-1.0, 0.3)</td>
<td>-0.7 (-1.4, -0.1)</td>
</tr>
<tr>
<td>Total hip</td>
<td>-0.4 (-1.0, 0.1)</td>
<td>-0.7 (-1.3, -0.2)</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.1 (-0.6, 0.8)</td>
<td>0.6 (-0.1, 1.4)</td>
</tr>
<tr>
<td>Distal forearm</td>
<td>0.5 (-0.1, 1.2)</td>
<td>0.1 (-0.6, 0.7)</td>
</tr>
</tbody>
</table>
## Adjudicated Fractures
### Broad Dataset through 01 Jul 2012

<table>
<thead>
<tr>
<th>Subjects with adjudicated fracture event n (%)</th>
<th>Non-CANA N=3262</th>
<th>CANA 100 mg N=3092</th>
<th>CANA 300 mg N=3085</th>
<th>All CANA N=6177</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence rate/1000 person years exposure (SE)</td>
<td>13.17 (1.83)</td>
<td>16.69 (2.04)</td>
<td>15.30 (1.98)</td>
<td>16.00 (1.41)</td>
</tr>
<tr>
<td>Between group (vs Non-CANA) difference in incidence rate (95% CI)</td>
<td>-</td>
<td>3.5 (-1.85; 8.88)</td>
<td>2.1 (-3.14; 7.4)</td>
<td>2.8 (-1.7; 7.36)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects with adjudicated low trauma fracture n (%)</th>
<th>Non-CANA N=3262</th>
<th>CANA 100 mg N=3092</th>
<th>CANA 300 mg N=3085</th>
<th>All CANA N=6177</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence rate/1000 person years exposure</td>
<td>9.44 (1.55)</td>
<td>12.51 (1.77)</td>
<td>12.04 (1.76)</td>
<td>12.28 (1.24)</td>
</tr>
<tr>
<td>Between group (vs Non-CANA) difference in incidence rate (95% CI)</td>
<td>-</td>
<td>3.1 (-1.54; 7.68)</td>
<td>2.6 (-2.00; 7.19)</td>
<td>2.8 (-1.06; 6.73)</td>
</tr>
</tbody>
</table>
Summary of Safety and Tolerability

- Large Phase 3 program with >10,000 subjects randomized
  - Substantial proportion of vulnerable individuals studied
- Overall well tolerated at both doses of canagliflozin
  - Low rate of discontinuations due to adverse events
  - Incidence of SAEs and deaths comparable to control
  - Safety and tolerability profile similar across range of eGFR
    (> 30 mL/min/1.73 m²)
Summary of Safety and Tolerability (cont.)

- Specific adverse drug reactions characterized
  - Genital mycotic infections and UTIs
  - Osmotic diuresis-related (thirst, polyuria, frequency)
  - Reduced intravascular volume AEs higher at 300 mg than at 100 mg, with risk factors identified
  - Hypoglycemia with insulin or sulphonylurea agents
  - Other including constipation and uncommon events of urticaria/rash

- Specific safety assessments performed showed
  - Increase in LDL-C; CV HR 0.91 with upper bound of 1.22 (<1.8)
  - Small, transient, and reversible decreases in eGFR consistent with the hemodynamic effect of canagliflozin
  - Small decrease in BMD (likely related to weight loss), small numerical imbalance in fractures
Summary of Efficacy

• Consistent and sustained dose-related improvements in glucose control with a low incidence of hypoglycemia
  – Reductions in HbA$_1^c$, demonstrated non-inferior to glimepiride and sitagliptin and superior at 300 mg to both agents
  – Greater proportion to HbA$_1^c$ goals
  – Fasting and post-meal glucose

• Improvements in beta-cell function (fasting and post-meal)

• Reductions in systolic blood pressure and in body weight
Canagliflozin: Dosing Recommendations

In patients with T2DM (with an eGFR of $>30 \text{ mL/min/1.73m}^2$) who need improved glycemic control

- Canagliflozin 100 mg or 300 mg
  - Starting dose of 100 mg in patients with eGFR $<60 \text{ mL/min/1.73m}^2$, loop diuretics, or age $\geq 75$ years
  - If inadequate response in patients started on 100 mg, increase to 300 mg dose
Canagliflozin
Benefit/Risk Assessment

John Gerich, MD
Professor Emeritus
University of Rochester Medical Center
Reduction in HbA$_{1c}$ Reduces Risk of Microvascular Disease


37% decrease per 1% reduction in HbA$_{1c}$
Glycemic Control Has Improved – But Many Patients Still Not at Goal HbA$_{1c}$ $<$7%

N=1334
NHANES=National Health and Nutrition Examination Survey
Limitations of Current Treatments for Patients with T2DM

- 5 classes of oral agents – 2 classes of SQ agents are recommended by ADA/EASD
- Limitations of currently available classes
  - Limited efficacy or durability: sulphonylurea (SU) agents, DPP-4 inhibitors
  - Hypoglycemia: SU agents, insulin
  - Weight gain: SU agents, PPARγ agents, insulin
  - GI side effects: metformin, GLP-1 agonists
  - Fluid retention: SU agents, PPARγ agents, insulin

Conclusion: there is a need for new agents / new options
# Benefit/Risk Profile of Canagliflozin

<table>
<thead>
<tr>
<th><strong>Benefits</strong></th>
<th><strong>Risks</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Robust, consistent, and sustained HbA1c-lowering, with low incidence of hypoglycemia</td>
<td>Increase in genital mycotic infections</td>
</tr>
<tr>
<td>Unique MOA – combinable/complementary with other AHAs</td>
<td>Small increase in UTIs without increase in upper UTIs or SAEs</td>
</tr>
<tr>
<td>Improves beta-cell function</td>
<td>Dose-related higher incidence of reduced volume-related events</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Dose-related increase in LDL-C</td>
</tr>
<tr>
<td>Reduction in blood pressure</td>
<td>Small reduction in BMD</td>
</tr>
<tr>
<td>Simple to administer, with once-daily oral dosing</td>
<td></td>
</tr>
<tr>
<td>Flexible dosing (100 mg and 300 mg)</td>
<td></td>
</tr>
</tbody>
</table>
Canagliflozin Summary

- Flexible dosing (100 and 300 mg) to meet the needs of different patients
- Favorable Benefit/Risk profile
- Valuable addition to address the unmet medical need of patients with type 2 diabetes