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An Efficacy, Safety, and Tolerability Study of Canagliflozin in the Treatment of Patients With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Monotherapy

This study has been completed.

Sponsor:
Janssen Research & Development, LLC

Information provided by (Responsible Party):
Janssen Research & Development, LLC

ClinicalTrials.gov Identifier:
NCT01340664

First received: April 21, 2011
Last updated: September 5, 2014
Last verified: September 2014
History of Changes

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Results First Received: August 20, 2014

Study Type:	Interventional
Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Treatment
Condition:	Diabetes Mellitus, Type 2
Interventions:	Drug: Canagliflozin 50 mg Drug: Placebo Drug: Canagliflozin 150 mg Drug: Metformin

Participant Flow

Hide Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
This study evaluated the efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus with inadequate control despite treatment with metformin. The study was conducted between 27 June 2011 and 20 April 2012 and recruited patients from 60 study centers located in 7 countries worldwide.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
A total of 279 patients were randomly allocated to the 3 treatment arms in the study. All 279 patients received at least 1 dose of study drug and were included in the modified intent-to-treat analysis set which was used for the efficacy and safety analyses.

Reporting Groups

	Description
Placebo	Each patient received matching placebo twice daily for 18 weeks.
Canagliflozin 50 mg Bid	Each patient received 50 mg canagliflozin twice daily for 18 weeks.

Canagliflozin 150 mg Bid	Each patient received 150 mg canagliflozin twice daily for 18 weeks.

Participant Flow: Overall Study

	Placebo	Canagliflozin 50 mg Bid	Canagliflozin 150 mg Bid
STARTED	**93**	**93**	**93**
COMPLETED	**86**	**85**	**80**
NOT COMPLETED	**7**	**8**	**13**
Adverse Event	**0**	**1**	**7**
Lost to Follow-up	**2**	**0**	**2**
Withdrawal by Subject	**2**	**4**	**0**
Glycemic withdrawal criteria	**2**	**0**	**0**
Creatinine or eGFR withdrawal criteria	**0**	**1**	**2**
Not specified	**1**	**2**	**2**

Baseline Characteristics

Hide Baseline Characteristics

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
No text entered.

Reporting Groups

	Description
Placebo	Each patient received matching placebo twice daily for 18 weeks.
Canagliflozin 50 mg Bid	Each patient received 50 mg canagliflozin twice daily for 18 weeks.
Canagliflozin 150 mg Bid	Each patient received 150 mg canagliflozin twice daily for 18 weeks.
Total	Total of all reporting groups

Baseline Measures

	Placebo	Canagliflozin 50 mg Bid	Canagliflozin 150 mg Bid	Total
Number of Participants [units: participants]	**93**	**93**	**93**	**279**
Age [units: participants]				
<=18 years	**0**	**0**	**0**	**0**
Between 18 and 65 years	**79**	**69**	**75**	**223**
>=65 years	**14**	**24**	**18**	**56**
Age [units: years] Mean (Standard Deviation)	**57 (9.32)**	**58.6 (8.88)**	**56.7 (10.33)**	**57.4 (9.53)**
Gender [units: participants]				
Female	**47**	**53**	**49**	**149**
Male	**46**	**40**	**44**	**130**

Region Enroll [units: participants]				
CANADA	17	11	12	40
CZECH REPUBLIC	2	4	6	12
MEXICO	10	12	10	32
ROMANIA	13	15	9	37
RUSSIAN FEDERATION	18	17	20	55
SLOVAKIA	10	9	11	30
UNITED STATES	23	25	25	73

Outcome Measures

Hide All Outcome Measures

1. Primary: Change in HbA1c From Baseline to Week 18 [Time Frame: Day 1 (Baseline) and Week 18]

Measure Type	Primary
Measure Title	Change in HbA1c From Baseline to Week 18
Measure Description	The table below shows the least-squares (LS) mean change in HbA1c from Baseline to Week 18 for each treatment group. The statistical analyses show the treatment differences (ie, each canagliflozin group minus placebo) in the LS mean change.
Time Frame	Day 1 (Baseline) and Week 18
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
This analysis used the modified intent-to-treat analysis set (all patients who were randomly assigned to a treatment group and received at least 1 dose of study drug). The last-observation-carried-forward method was applied when Week 18 values were missing. The table includes only patients with both baseline and post baseline values.

Reporting Groups

	Description
Placebo	Each patient received matching placebo twice daily for 18 weeks.
Canagliflozin 50 mg Bid	Each patient received 50 mg canagliflozin twice daily for 18 weeks
Canagliflozin 150 mg Bid	Each patient received 150 mg canagliflozin twice daily for 18 weeks

Measured Values

	Placebo	Canagliflozin 50 mg Bid	Canagliflozin 150 mg Bid
Number of Participants Analyzed [units: participants]	**92**	**90**	**91**
Change in HbA1c From Baseline to Week 18 [units: Percent] Least Squares Mean (Standard Error)	**-0.01 (0.069)**	**-0.45 (0.070)**	**-0.61 (0.069)**

Statistical Analysis 1 for Change in HbA1c From Baseline to Week 18

Groups [1]	Placebo vs. Canagliflozin 50 mg Bid

Method [2]	ANCOVA
P Value [3]	<0.001
Least-Squares Mean Difference [4]	-0.44
Standard Error of the mean	(0.098)
95% Confidence Interval	-0.637 to -0.251

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 2 for Change in HbA1c From Baseline to Week 18

Groups [1]	Placebo vs. Canagliflozin 150 mg Bid
Method [2]	ANCOVA
P Value [3]	<0.001
Least-Squares Mean Difference [4]	-0.60
Standard Error of the mean	(0.098)
95% Confidence Interval	-0.792 to -0.407

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

2. Secondary: Change in Fasting Plasma Glucose (FPG) From Baseline to Week 18 [Time Frame: Day 1 (Baseline) and Week 18]

Measure Type	Secondary
Measure Title	Change in Fasting Plasma Glucose (FPG) From Baseline to Week 18
Measure Description	The table below shows the least-squares (LS) mean change in FPG from Baseline to Week 18 for each treatment group. The statistical analyses show the treatment differences (ie, each canagliflozin group minus placebo) in the LS mean change.
Time Frame	Day 1 (Baseline) and Week 18

Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
This analysis used the modified intent-to-treat analysis set (all patients who were randomly assigned to a treatment group and received at least 1 dose of study drug). The last-observation-carried-forward method was applied when Week 18 values were missing. The table includes only patients with both baseline and post baseline values.

Reporting Groups

	Description
Placebo	Each patient received matching placebo twice daily for 18 weeks.
Canagliflozin 50 mg Bid	Each patient received 50 mg canagliflozin twice daily for 18 weeks
Canagliflozin 150 mg Bid	Each patient received 150 mg canagliflozin twice daily for 18 weeks

Measured Values

	Placebo	Canagliflozin 50 mg Bid	Canagliflozin 150 mg Bid
Number of Participants Analyzed [units: participants]	**92**	**90**	**91**
Change in Fasting Plasma Glucose (FPG) From Baseline to Week 18 [units: mg/dL] Least Squares Mean (Standard Error)	**8.1 (3.291)**	**-15.5 (3.327)**	**-15.9 (3.313)**

Statistical Analysis 1 for Change in Fasting Plasma Glucose (FPG) From Baseline to Week 18

Groups [1]	Placebo vs. Canagliflozin 50 mg Bid
Method [2]	ANCOVA
P Value [3]	<0.001
Least-Sqaures Mean Difference [4]	-23.6
Standard Error of the mean	(4.673)
95% Confidence Interval	-32.78 to -14.38

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 2 for Change in Fasting Plasma Glucose (FPG) From Baseline to Week 18

Groups [1]	Placebo vs. Canagliflozin 150 mg Bid
Method [2]	ANCOVA

P Value [3]	<0.001
Least-Sqaures Mean Difference [4]	-24.0
Standard Error of the mean	(4.661)
95% Confidence Interval	-33.18 to -14.83

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

3. Secondary: Percent Change in Body Weight From Baseline to Week 18 [Time Frame: Day 1 (Baseline) and Week 18]

Measure Type	Secondary
Measure Title	Percent Change in Body Weight From Baseline to Week 18
Measure Description	The table below shows the least-squares (LS) mean percent change in body weight from Baseline to Week 18 for each treatment group. The statistical analyses show the treatment differences (ie, each canagliflozin group minus placebo) in the LS mean percent change.
Time Frame	Day 1 (Baseline) and Week 18
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
This analysis used the modified intent-to-treat analysis set (all patients who were randomly assigned to a treatment group and received at least 1 dose of study drug). The last-observation-carried-forward method was applied when Week 18 values were missing. The table includes only patients with both baseline and post baseline values.

Reporting Groups

	Description
Placebo	Each patient received matching placebo twice daily for 18 weeks.
Canagliflozin 50 mg Bid	Each patient received 50 mg canagliflozin twice daily for 18 weeks
Canagliflozin 150 mg Bid	Each patient received 150 mg canagliflozin twice daily for 18 weeks

Measured Values

	Placebo	**Canagliflozin 50 mg Bid**	**Canagliflozin 150 mg Bid**
Number of Participants Analyzed [units: participants]	**92**	**90**	**91**
Percent Change in Body Weight From Baseline to Week 18 [units: Percent change] Least Squares Mean (Standard Error)	**-0.6 (0.3)**	**-2.8 (0.3)**	**-3.2 (0.3)**

Statistical Analysis 1 for Percent Change in Body Weight From Baseline to Week 18

Groups [1]	Placebo vs. Canagliflozin 50 mg Bid
Method [2]	ANCOVA
P Value [3]	<0.001
Least-Squares Mean Difference [4]	-2.2
Standard Error of the mean	(0.5)
95% Confidence Interval	-3.1 to -1.3

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 2 for Percent Change in Body Weight From Baseline to Week 18

Groups [1]	Placebo vs. Canagliflozin 150 mg Bid
Method [2]	ANCOVA
P Value [3]	<0.001
Least-Squares Mean Difference [4]	-2.6
Standard Error of the mean	(0.5)
95% Confidence Interval	-3.5 to -1.7

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

4. Secondary: Percentage of Patients With HbA1c <7% at Week 18 [Time Frame: Week 18]

Measure Type	Secondary
Measure Title	Percentage of Patients With HbA1c <7% at Week 18

Measure Description	The table below shows the percentage of patients with HbA1c <7% at Week 18 in each treatment group. The statistical analyses show the treatment differences (ie, each canagliflozin group minus placebo) in the percentage.
Time Frame	Week 18
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
This analysis used the modified intent-to-treat analysis set (all patients who were randomly assigned to a treatment group and received at least 1 dose of study drug). The last-observation-carried-forward method was applied when Week 18 values were missing. The table includes only patients with both baseline and post baseline values.

Reporting Groups

	Description
Placebo	Each patient received matching placebo twice daily for 18 weeks.
Canagliflozin 50 mg Bid	Each patient received 50 mg canagliflozin twice daily for 18 weeks
Canagliflozin 150 mg Bid	Each patient received 150 mg canagliflozin twice daily for 18 weeks

Measured Values

	Placebo	**Canagliflozin 50 mg Bid**	**Canagliflozin 150 mg Bid**
Number of Participants Analyzed [units: participants]	**92**	**90**	**91**
Percentage of Patients With HbA1c <7% at Week 18 [units: Percentage of Participants]	**31.5**	**47.8**	**57.1**

Statistical Analysis 1 for Percentage of Patients With HbA1c <7% at Week 18

Groups [1]	Placebo vs. Canagliflozin 50 mg Bid
Method [2]	Regression, Logistic
P Value [3]	0.013
Odds Ratio (OR) [4]	2.43
95% Confidence Interval	1.21 to 4.90

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 2 for Percentage of Patients With HbA1c <7% at Week 18

Groups [1]	Placebo vs. Canagliflozin 150 mg Bid
Method [2]	Regression, Logistic

P Value [3]	<0.001
Odds Ratio (OR) [4]	3.38
95% Confidence Interval	1.68 to 6.81

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	Adverse events were reported for the duration of the study; each patient participated in the study for approximately 18 weeks.
Additional Description	Only patients who had at least one of the treatment-emergent adverse events listed in the "Other (non-Serious) Adverse Event" table are included in the total number of patients with non-serious adverse Events.

Reporting Groups

	Description
Placebo	Each patient received matching placebo twice daily for 18 weeks
Canagliflozin 50 mg Bid	Each patient received 50 mg canagliflozin twice daily for 18 weeks.
Canagliflozin 150 mg Bid	Each patient received 150 mg canagliflozin twice daily for 18 weeks

Serious Adverse Events

	Placebo	**Canagliflozin 50 mg Bid**	**Canagliflozin 150 mg Bid**
Total, serious adverse events			
# participants affected / at risk	**1/93 (1.08%)**	**0/93 (0.00%)**	**3/93 (3.23%)**
Gastrointestinal disorders			
Oroantral fistula [*1]			
# participants affected / at risk	**0/93 (0.00%)**	**0/93 (0.00%)**	**1/93 (1.08%)**
Infections and infestations			
Pyelonephritis [*1]			
# participants affected / at risk	**0/93 (0.00%)**	**0/93 (0.00%)**	**1/93 (1.08%)**
Injury, poisoning and procedural complications			
Postoperative wound complication [*1]			
# participants affected / at risk	**0/93 (0.00%)**	**0/93 (0.00%)**	**1/93 (1.08%)**
Neoplasms benign, malignant and unspecified (incl cysts and			

polyps)			
Colon cancer * 1			
# participants affected / at risk	**0/93 (0.00%)**	**0/93 (0.00%)**	**1/93 (1.08%)**
Renal and urinary disorders			
Nephrolithiasis * 1			
# participants affected / at risk	**0/93 (0.00%)**	**0/93 (0.00%)**	**1/93 (1.08%)**
Reproductive system and breast disorders			
Dysfunctional uterine bleeding * 1			
# participants affected / at risk	**1/93 (1.08%)**	**0/93 (0.00%)**	**0/93 (0.00%)**

* Events were collected by non-systematic assessment
1 Term from vocabulary, MEDDRA 15.0

Other Adverse Events

Hide Other Adverse Events

Time Frame	Adverse events were reported for the duration of the study; each patient participated in the study for approximately 18 weeks.
Additional Description	Only patients who had at least one of the treatment-emergent adverse events listed in the "Other (non-Serious) Adverse Event" table are included in the total number of patients with non-serious adverse Events.

Frequency Threshold

Threshold above which other adverse events are reported	5%

Reporting Groups

	Description
Placebo	Each patient received matching placebo twice daily for 18 weeks
Canagliflozin 50 mg Bid	Each patient received 50 mg canagliflozin twice daily for 18 weeks.
Canagliflozin 150 mg Bid	Each patient received 150 mg canagliflozin twice daily for 18 weeks

Other Adverse Events

	Placebo	**Canagliflozin 50 mg Bid**	**Canagliflozin 150 mg Bid**
Total, other (not including serious) adverse events			
# participants affected / at risk	**0/93 (0.00%)**	**0/93 (0.00%)**	**0/93 (0.00%)**

Limitations and Caveats

Hide Limitations and Caveats

Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data
No text entered.

More Information

Hide More Information

Certain Agreements:

Principal Investigators are **NOT** employed by the organization sponsoring the study.

There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The agreement is:

☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed.

☑ **Restriction Description:** If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application.

Results Point of Contact:

Name/Title: Vice President, Franchise Medical Leader, Cardiovascular & Metabolism Franchise
Organization: Janssen Research & Development, LLC
phone: 1 908 927-5775

Responsible Party:	Janssen Research & Development, LLC
ClinicalTrials.gov Identifier:	NCT01340664 History of Changes
Other Study ID Numbers:	CR017914 **28431754DIA2003** (Other Identifier: Janssen Research & Development, LLC) 2010-024256-28 (EudraCT Number)
Study First Received:	April 21, 2011
Results First Received:	August 20, 2014
Last Updated:	September 5, 2014
Health Authority:	United States: Food and Drug Administration

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