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CANagliflozin Treatment And Trial Analysis-Sulfonylurea (CANTATA-SU) SGLT2 Add-on to Metformin Versus Glimepiride

This study has been completed.

Sponsor:
Janssen Research & Development, LLC

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

ClinicalTrials.gov Identifier:
NCT00968812

First received: August 28, 2009
Last updated: April 3, 2014
Last verified: April 2014
History of Changes

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Results First Received: April 17, 2013

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: Glimepiride Drug: Canagliflozin (JNJ-28431754) 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 (JNJ-28431754) compared with glimepiride in participants with type 2 diabetes mellitus with inadequate glycemic control despite metformin treatment. The study was conducted between 28 August 2009 and 25 January 2013 and included 157 study centers in 19 countries worldwide.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
1,452 participants were randomly allocated to the 3 treatment arms. 1450 participants received at least 1 dose of study drug and were included in the modified intent-to-treat (mITT) analysis set and safety analysis set. Participant flow is presented for Baseline to Week 104.

Reporting Groups

	Description
Canagliflozin 100 mg: Baseline to Week 104	Each patient received 100 mg of canagliflozin (JNJ-28431754) once daily with protocol-specified doses of metformin for 104 weeks.
Canagliflozin 300 mg: Baseline to Week 104	Each patient received 300 mg of canagliflozin (JNJ-28431754) once daily with protocol-specified doses of metformin for 104 weeks.

Glimepiride: Baseline to Week 104	Each patient received glimepiride, at protocol-specified doses, once daily in combination with protocol-specified doses of metformin for 104 weeks.

Participant Flow: Overall Study

	Canagliflozin 100 mg: Baseline to Week 104	Canagliflozin 300 mg: Baseline to Week 104	Glimepiride: Baseline to Week 104
STARTED	483	485	482
COMPLETED	343	323	314
NOT COMPLETED	140	162	168
Adverse Event	30	46	33
Death	2	2	1
Lack of Efficacy	9	7	16
Lost to Follow-up	17	12	11
Physician Decision	8	5	9
Protocol Violation	7	4	3
Withdrawal by Subject	17	23	25
Creatinine or eGFR withdrawal criteria	9	13	7
Noncompliance with study drug	4	1	6
Unable to take rescue therapy	12	12	17
Not specified	25	37	40

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
Canagliflozin 100 mg	Each patient received 100 mg of canagliflozin (JNJ-28431754) once daily with protocol-specified doses of metformin for 104 weeks.
Canagliflozin 300 mg	Each patient received 300 mg of canagliflozin (JNJ-28431754) once daily with protocol-specified doses of metformin for 104 weeks.
Glimepiride	Each patient received glimepiride, at protocol-specified doses, once daily in combination with protocol-specified doses of metformin for 104 weeks.
Total	Total of all reporting groups

Baseline Measures

	Canagliflozin 100 mg	Canagliflozin 300 mg	Glimepiride	Total
Number of Participants [units: participants]	483	485	482	1450
Age				

[units: participants]				
<=18 years	0	0	0	0
Between 18 and 65 years	397	411	399	1207
>=65 years	86	74	83	243
Age [units: years] Mean (Standard Deviation)	56.4 (9.49)	55.8 (9.17)	56.3 (9.01)	56.2 (9.22)
Gender [units: participants]				
Female	231	244	219	694
Male	252	241	263	756
Region Enroll [units: participants]				
ARGENTINA	18	18	18	54
BULGARIA	7	7	7	21
CANADA	19	20	19	58
COSTA RICA	10	9	9	28
DENMARK	24	25	25	74
FINLAND	18	17	19	54
GERMANY	6	7	6	19
INDIA	55	55	56	166
ISRAEL	14	15	14	43
MEXICO	24	25	24	73
NORWAY	9	9	9	27
PHILIPPINES	14	13	13	40
POLAND	14	15	15	44
ROMANIA	43	43	44	130
RUSSIAN FEDERATION	23	22	22	67
SLOVAKIA	15	14	13	42
SOUTH KOREA	31	32	31	94
UKRAINE	22	22	22	66
UNITED STATES	117	117	116	350

Outcome Measures

Hide All Outcome Measures

1. Primary: Change in HbA1c From Baseline to Week 52 [Time Frame: Day 1 (Baseline) and Week 52]

Measure Type	Primary
Measure Title	Change in HbA1c From Baseline to Week 52
Measure Description	The table below shows the least-squares (LS) mean change in HbA1c from Baseline to Week 52 for each treatment group. The statistical analyses show the treatment differences (ie, each canagliflozin group minus glimepiride) in the LS mean change.
Time Frame	Day 1 (Baseline) and Week 52

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.
Analysis used mITT analysis set (all randomized patients who received at least 1 dose of study drug). Last-observation-carried-forward method used for missing Week 52 values. Measurements taken pre-rescue used as last observation in patients receiving glycemic rescue therapy. Table includes only patients with both baseline and post baseline values.

Reporting Groups

	Description
Canagliflozin 100 mg	Each patient received 100 mg of canagliflozin (JNJ-28431754) once daily with protocol-specified doses of metformin for 104 weeks.
Canagliflozin 300 mg	Each patient received 300 mg of canagliflozin (JNJ-28431754) once daily with protocol-specified doses of metformin for 104 weeks.
Glimepiride	Each patient received glimepiride, at protocol-specified doses, once daily in combination with protocol-specified doses of metformin for 104 weeks.

Measured Values

	Canagliflozin 100 mg	Canagliflozin 300 mg	Glimepiride
Number of Participants Analyzed [units: participants]	**478**	**474**	**473**
Change in HbA1c From Baseline to Week 52 [units: Percent] Least Squares Mean (Standard Error)	**-0.82 (0.039)**	**-0.93 (0.039)**	**-0.81 (0.039)**

Statistical Analysis 1 for Change in HbA1c From Baseline to Week 52

Groups [1]	Canagliflozin 100 mg vs. Glimepiride
Non-Inferiority/Equivalence Test [2]	Yes
Method [3]	ANCOVA
Least-Squares Mean Difference [4]	-0.01
Standard Error of the mean	(0.050)
95% Confidence Interval	-0.109 to 0.085

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	If the hypothesis of non-inferiority of canagliflozin to glimepiride at Week 52 was demonstrated (ie, upper bound of the 95% Confidence Interval of the treatment difference [canagliflozin minus glimepiride] was less than 0.3) and the upper bound was less than 0.0, the superiority of the canagliflozin dose relative to glimepiride would be concluded.
[2]	Details of power calculation, definition of non-inferiority margin, and other key parameters:
	Power calculation: assuming a difference between canagliflozin and glimepiride of 0.0% and a common standard deviation of 1.0%, and using a 2-sample, 1-sided t-test with a Type I error rate of 0.0125, and assuming a drop-out rate of 35% in 52 weeks, it was estimated that approximately 427 patients per group would provide 90% power to demonstrate non-inferiority with the non-inferiority margin of 0.3, comparing canagliflozin with glimepiride.
[3]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 2 for Change in HbA1c From Baseline to Week 52

Groups [1]	Canagliflozin 300 mg vs. Glimepiride
Non-Inferiority/Equivalence Test [2]	Yes
Method [3]	ANCOVA
Least-Squares Mean Difference [4]	-0.12
Standard Error of the mean	(0.050)
95% Confidence Interval	-0.217 to -0.023

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	If the hypothesis of non-inferiority of canagliflozin to glimepiride at Week 52 was demonstrated (ie, upper bound of the 95% Confidence Interval of the treatment difference [canagliflozin minus glimepiride] was less than 0.3) and the upper bound was less than 0.0, the superiority of the canagliflozin dose relative to glimepiride would be concluded.
[2]	Details of power calculation, definition of non-inferiority margin, and other key parameters:
	Power calculation: assuming a difference between canagliflozin and glimepiride of 0.0% and a common standard deviation of 1.0%, and using a 2-sample, 1-sided t-test with a Type I error rate of 0.0125, and assuming a drop-out rate of 35% in 52 weeks, it was estimated that approximately 427 patients per group would provide 90% power to demonstrate non-inferiority with the non-inferiority margin of 0.3, comparing canagliflozin with glimepiride
[3]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

2. Secondary: Percentage of Patients Experiencing at Least 1 Hypoglycemic Event From Baseline to Week 52 [Time Frame: Day 1 (Baseline) and Week 52]

Measure Type	Secondary
Measure Title	Percentage of Patients Experiencing at Least 1 Hypoglycemic Event From Baseline to Week 52
Measure Description	The table below shows the percentage of patients who experienced at least 1 documented hypoglycemic event from Baseline to Week 52 for each treatment group. The statistical analyses show the treatment differences (ie, each canagliflozin group minus glimepiride) in percentages.
Time Frame	Day 1 (Baseline) and Week 52
Safety Issue	Yes

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.
Analysis used mITT analysis set (all randomized patients who received at least 1 dose of study drug). Last-observation-carried-forward method used for missing Week 52 values. Measurements taken pre-rescue used as last observation in patients receiving glycemic rescue therapy. Table includes only patients with both baseline and post baseline values.

Reporting Groups

	Description
Canagliflozin 100 mg	Each patient received 100 mg of canagliflozin (JNJ-28431754) once daily with protocol-specified doses of metformin for 104 weeks.
Canagliflozin 300 mg	Each patient received 300 mg of canagliflozin (JNJ-28431754) once daily with protocol-specified doses of metformin for 104 weeks.

Glimepiride	Each patient received glimepiride, at protocol-specified doses, once daily in combination with protocol-specified doses of metformin for 104 weeks.

Measured Values

	Canagliflozin 100 mg	Canagliflozin 300 mg	Glimepiride
Number of Participants Analyzed [units: participants]	**483**	**485**	**482**
Percentage of Patients Experiencing at Least 1 Hypoglycemic Event From Baseline to Week 52 [units: Percentage of patients]	**5.6**	**4.9**	**34.2**

Statistical Analysis 1 for Percentage of Patients Experiencing at Least 1 Hypoglycemic Event From Baseline to Week 52

Groups [1]	Canagliflozin 100 mg vs. Glimepiride
Method [2]	Regression, Logistic
P Value [3]	<0.001
Odds Ratio (OR) [4]	0.10
95% Confidence Interval	0.06 to 0.16

[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 Experiencing at Least 1 Hypoglycemic Event From Baseline to Week 52

Groups [1]	Canagliflozin 300 mg vs. Glimepiride
Method [2]	Regression, Logistic
P Value [3]	<0.001
Odds Ratio (OR) [4]	0.09
95% Confidence Interval	0.05 to 0.14

[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 52 [Time Frame: Day 1 (Baseline) and Week 52]

Measure Type	Secondary
Measure Title	Percent Change in Body Weight From Baseline to Week 52
Measure Description	The table below shows the least-squares (LS) mean percent change in body weight from Baseline to Week 52 for each treatment group. The statistical analyses show the treatment differences (ie, each canagliflozin group minus glimepiride) in the LS mean percent change.
Time Frame	Day 1 (Baseline) and Week 52
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.
Analysis used mITT analysis set (all randomized patients who received at least 1 dose of study drug). Last-observation-carried-forward method used for missing Week 52 values. Measurements taken pre-rescue used as last observation in patients receiving glycemic rescue therapy. Table includes only patients with both baseline and post baseline values.

Reporting Groups

	Description
Canagliflozin 100 mg	Each patient received 100 mg of canagliflozin (JNJ-28431754) once daily with protocol-specified doses of metformin for 104 weeks.
Canagliflozin 300 mg	Each patient received 300 mg of canagliflozin (JNJ-28431754) once daily with protocol-specified doses of metformin for 104 weeks.
Glimepiride	Each patient received glimepiride, at protocol-specified doses, once daily in combination with protocol-specified doses of metformin for 104 weeks.

Measured Values

	Canagliflozin 100 mg	Canagliflozin 300 mg	Glimepiride
Number of Participants Analyzed [units: participants]	**479**	**480**	**478**
Percent Change in Body Weight From Baseline to Week 52 [units: Percent change] Least Squares Mean (Standard Error)	**-4.2 (0.2)**	**-4.7 (0.2)**	**1.0 (0.2)**

Statistical Analysis 1 for Percent Change in Body Weight From Baseline to Week 52

Groups [1]	Canagliflozin 100 mg vs. Glimepiride
Method [2]	ANCOVA
P Value [3]	<0.001
Least-Squares Mean Difference [4]	-5.2
Standard Error of the mean	(0.3)
95% Confidence Interval	-5.7 to -4.7

[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.

Statistical Analysis 2 for Percent Change in Body Weight From Baseline to Week 52

Groups [1]	Canagliflozin 300 mg vs. Glimepiride
Method [2]	ANCOVA
P Value [3]	<0.001
Least-Squares Mean Difference [4]	-5.7
Standard Error of the mean	(0.3)
95% Confidence Interval	-6.2 to -5.1

[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: Change in HbA1c From Baseline to Week 104 [Time Frame: Baseline, Week 104]

Results not yet reported. **Anticipated Reporting Date:** 01/2014 **Safety Issue:** No

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	Adverse event data were collected for the duration of the study (104 weeks).
Additional Description	The total number of adverse events listed in the "Other (non-Serious) Adverse Events" table are based upon a cut-off of greater than or equal to 5 percent of patients experiencing the adverse event in any treatment arm. MEDDRA 14.1 used for Week 52 / MEDDRA 15.0 for Week 104 results.

Reporting Groups

	Description
Canagliflozin 100 mg: Baseline to Week 52	Each patient received 100 mg of canagliflozin (JNJ-28431754) once daily with protocol-specified doses of metformin for 104 weeks. Data are presented for Baseline to Week 52.
Canagliflozin 300 mg: Baseline to Week 52	Each patient received 300 mg of canagliflozin (JNJ-28431754) once daily with protocol-specified doses of metformin for 104 weeks. Data are presented for Baseline to Week 52.

Glimepiride: Baseline to Week 52	Each patient received glimepiride, at protocol-specified doses, once daily in combination with protocol-specified doses of metformin for 104 weeks. Data are presented for Baseline to Week 52.
Canagliflozin 100 mg: Baseline to Week 104	Each patient received 100 mg of canagliflozin (JNJ-28431754) once daily with protocol-specified doses of metformin for 104 weeks. Data are presented for Baseline to Week 104.
Canagliflozin 300 mg: Baseline to Week 104	Each patient received 300 mg of canagliflozin (JNJ-28431754) once daily with protocol-specified doses of metformin for 104 weeks. Data are presented for Baseline to Week 104.
Glimepiride: Baseline to Week 104	Each patient received glimepiride, at protocol-specified doses, once daily in combination with protocol-specified doses of metformin for 104 weeks. Data are presented for Baseline to Week 104.

Serious Adverse Events

	Canagliflozin 100 mg: Baseline to Week 52	Canagliflozin 300 mg: Baseline to Week 52	Glimepiride: Baseline to Week 52	Canagliflozin 100 mg: Baseline to Week 104	Canagliflozin 300 mg: Baseline to Week 104	Glimepiride: Baseline to Week 104
Total, serious adverse events						
# participants affected / at risk	**24/483 (4.97%)**	**26/485 (5.36%)**	**39/482 (8.09%)**	**47/483 (9.73%)**	**47/485 (9.69%)**	**69/482 (14.32%)**
Blood and lymphatic system disorders						
Anaemia [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Cardiac disorders						
Acute coronary syndrome [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Angina pectoris [*1]						
# participants affected / at risk	**1/483 (0.21%)**	**2/485 (0.41%)**	**2/482 (0.41%)**	**3/483 (0.62%)**	**2/485 (0.41%)**	**3/482 (0.62%)**
Angina unstable [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**1/485 (0.21%)**	**1/482 (0.21%)**	**1/483 (0.21%)**	**1/485 (0.21%)**	**2/482 (0.41%)**
Aortic valve incompetence [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Atrial fibrillation [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**2/482 (0.41%)**
Bundle branch block left [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Cardiac arrest [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Cardiomyopathy [*1]						

# participants affected / at risk	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)
Coronary artery disease [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)	1/483 (0.21%)	0/485 (0.00%)	2/482 (0.41%)
Diabetic cardiomyopathy [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)
Mitral valve incompetence [*1]						
# participants affected / at risk	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)
Myocardial infarction [*1]						
# participants affected / at risk	1/483 (0.21%)	1/485 (0.21%)	0/482 (0.00%)	2/483 (0.41%)	1/485 (0.21%)	1/482 (0.21%)
Myocardial ischaemia [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)
Pericardial effusion [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)
Tachycardia [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)
Ventricular arrhythmia [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)
Acute myocardial infarction [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	0/483 (0.00%)	1/485 (0.21%)	2/482 (0.41%)
Cardiac failure [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)
Coronary artery occlusion [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)
Congenital, familial and genetic disorders						
Arnold-Chiari malformation [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)
Phimosis [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)
Eye disorders						
Angle closure glaucoma						

* 1						
# participants affected / at risk	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)
Cataract * 1						
# participants affected / at risk	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	0/485 (0.00%)	2/482 (0.41%)
Diabetic retinopathy * 1						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)
Vitreous haemorrhage * 1						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)
Gastrointestinal disorders						
Abdominal pain * 1						
# participants affected / at risk	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)
Duodenal ulcer * 1						
# participants affected / at risk	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)
Duodenitis * 1						
# participants affected / at risk	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)
Inguinal hernia * 1						
# participants affected / at risk	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	1/485 (0.21%)	0/482 (0.00%)
Pancreatitis * 1						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)	0/483 (0.00%)	1/485 (0.21%)	1/482 (0.21%)
Small intestinal perforation * 1 [4]						
# participants affected / at risk	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)
Umbilical hernia * 1						
# participants affected / at risk	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)
Abdominal strangulated herina * 1						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)
Gastrointestinal haemorrhage * 1						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)
Pancreatitis acute * 1						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)
Pancreatitis chronic * 1						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)
General disorders						

Asthenia [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Non-cardiac chest pain [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**1/485 (0.21%)**	**2/482 (0.41%)**	**0/483 (0.00%)**	**2/485 (0.41%)**	**3/482 (0.62%)**
Oedema peripheral [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Cyst [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Hepatobiliary disorders						
Cholecystitis acute [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**1/482 (0.21%)**
Cholelithiasis [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**3/482 (0.62%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**4/482 (0.83%)**
Hepatic cyst [*1]						
# participants affected / at risk	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Cholecystitis chronic [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**2/483 (0.41%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Infections and infestations						
Appendicitis [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**2/482 (0.41%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**2/482 (0.41%)**
Endometritis [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Gastroenteritis [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Localised infection [*1] [5]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Lobar pneumonia [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Lower respiratory tract infection [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Lung infection [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**

Pneumonia [*1]						
# participants affected / at risk	**1/483 (0.21%)**	**1/485 (0.21%)**	**2/482 (0.41%)**	**1/483 (0.21%)**	**2/485 (0.41%)**	**2/482 (0.41%)**
Postoperative wound infection [*1]						
# participants affected / at risk	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Respiratory tract infection viral [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Staphylococcal infection [*1]						
# participants affected / at risk	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Urinary tract infection [*1]						
# participants affected / at risk	**1/483 (0.21%)**	**1/485 (0.21%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**2/485 (0.41%)**	**1/482 (0.21%)**
Herpes zoster [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Orchitis [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Pyelonephritis [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Upper respiratory tract infection [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Sepsis [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Infection [*1] [5]						
# participants affected / at risk	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Injury, poisoning and procedural complications						
Eye injury [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Fall [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Femoral neck fracture [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Foot fracture [*1]						
# participants affected / at risk	**1/483 (0.21%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**1/483 (0.21%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Incisional hernia [*1]						

# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)
Injury [*1]						
# participants affected / at risk	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)
Ligament sprain [*1]						
# participants affected / at risk	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)	2/483 (0.41%)	0/485 (0.00%)	0/482 (0.00%)
Lower limb fracture [*1]						
# participants affected / at risk	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)
Meniscus lesion [*1]						
# participants affected / at risk	2/483 (0.41%)	0/485 (0.00%)	0/482 (0.00%)	2/483 (0.41%)	0/485 (0.00%)	0/482 (0.00%)
Muscle injury [*1]						
# participants affected / at risk	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)
Muscle rupture [*1]						
# participants affected / at risk	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)
Overdose [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)
Road traffic accident [*1]						
# participants affected / at risk	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	1/485 (0.21%)	0/482 (0.00%)
Skull fracture [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)
Subdural haematoma [*1]						
# participants affected / at risk	1/483 (0.21%)	0/485 (0.00%)	1/482 (0.21%)	1/483 (0.21%)	0/485 (0.00%)	1/482 (0.21%)
Toxicity to various agents [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)
Ulna fracture [*1]						
# participants affected / at risk	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)
Wrist fracture [*1]						
# participants affected / at risk	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)
Chemical poisoning [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)
Clavicle fracture [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	1/485 (0.21%)	0/482 (0.00%)
Concussion [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)

Contusion [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Femur fracture [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Head injury [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Heat exhaustion [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Humerus fracture [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Joint dislocation [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Procedural complication [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Procedural nausea [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Investigations						
Blood creatinine increased [*1]						
# participants affected / at risk	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Electrocardiogram T wave biphasic [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Metabolism and nutrition disorders						
Dehydration [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Diabetes mellitus inadequate control [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Hyperglycaemia [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Obesity [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Musculoskeletal and connective tissue disorders						

Intervertebral disc protrusion [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Musculoskeletal pain [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Pain in extremity [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Spinal column stenosis [*1]						
# participants affected / at risk	**1/483 (0.21%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**2/483 (0.41%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Arthritis [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Osteoarthritis [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Polyarthritis [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Endometrial cancer [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Renal cancer stage I [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Squamous cell carcinoma of the cervix [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Uterine leiomyoma [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**2/485 (0.41%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**3/485 (0.62%)**	**0/482 (0.00%)**
Breast cancer stage I [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Colon cancer [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Gastrointestinal tract adenoma [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**

Hepatic neoplasm [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Lung neoplasm [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Oesophageal carcinoma [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Prostate cancer [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**1/482 (0.21%)**
Nervous system disorders						
Carotid arterial embolus [*1]						
# participants affected / at risk	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Cerebral infarction [*1]						
# participants affected / at risk	**1/483 (0.21%)**	**1/485 (0.21%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Cerebrovascular accident [*1]						
# participants affected / at risk	**2/483 (0.41%)**	**1/485 (0.21%)**	**0/482 (0.00%)**	**2/483 (0.41%)**	**1/485 (0.21%)**	**2/482 (0.41%)**
Hemiplegic migraine [*1] [6]						
# participants affected / at risk	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Vertebrobasilar insufficiency [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Complex regional pain syndrome [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Dizziness [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Haemorrhage intracranial [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Hemiparesis [*1] [6]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Syncope [*1]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Transient ischaemic attack [*1]						

# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	1/485 (0.21%)	1/482 (0.21%)
Psychiatric disorders						
Confusional state [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)
Stress [*1] [7]						
# participants affected / at risk	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)
Anxiety [*1] [7]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)
Renal and urinary disorders						
Incontinence [*1]						
# participants affected / at risk	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)
Calculus ureteric [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)
Nephrolithiasis [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)
Renal failure acute [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)
Urethral stenosis [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)
Urinary retention [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)
Reproductive system and breast disorders						
Dysfunctional uterine bleeding [*1]						
# participants affected / at risk	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)
Menstrual disorder [*1]						
# participants affected / at risk	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)	0/483 (0.00%)	1/485 (0.21%)	0/482 (0.00%)
Benign prostatic hyperplasia [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	0/485 (0.00%)	1/482 (0.21%)
Prostatitis [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	1/483 (0.21%)	0/485 (0.00%)	0/482 (0.00%)
Prostatomegaly [*1]						
# participants affected / at risk	0/483 (0.00%)	0/485 (0.00%)	0/482 (0.00%)	0/483 (0.00%)	0/485 (0.00%)	1/482 (0.21%)

Respiratory, thoracic and mediastinal disorders						
Allergic bronchitis * 1						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Chronic obstructive pulmonary disease * 1						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**2/482 (0.41%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**2/482 (0.41%)**
Dyspnoea * 1						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**2/482 (0.41%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**2/482 (0.41%)**
Interstitial lung disease * 1						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Pulmonary oedema * 1						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Pulmonary embolism * 1						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Skin and subcutaneous tissue disorders						
Urticaria * 1						
# participants affected / at risk	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Diabetic foot * 1						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Social circumstances						
Familial risk factor * 1						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**0/482 (0.00%)**
Surgical and medical procedures						
Small bowel perforation * 1 [8]						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**
Vascular disorders						
Deep vein thrombosis * 1						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Haematoma * 1						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Hypertension * 1						
# participants affected / at risk	**0/483 (0.00%)**	**1/485 (0.21%)**	**1/482 (0.21%)**	**1/483 (0.21%)**	**1/485 (0.21%)**	**1/482 (0.21%)**

Hypertensive crisis * 2						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**	**0/483 (0.00%)**	**0/485 (0.00%)**	**1/482 (0.21%)**
Intermittent claudication * 1						
# participants affected / at risk	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**1/483 (0.21%)**	**0/485 (0.00%)**	**0/482 (0.00%)**
Hypotension * 1						
# participants affected / at risk	**0/483 (0.00%)**	**0/485 (0.00%)**	**0/482 (0.00%)**	**0/483 (0.00%)**	**1/485 (0.21%)**	**0/482 (0.00%)**

* Events were collected by non-systematic assessment
1 Term from vocabulary, MEDDRA 14.1 / 15.0
2 Term from vocabulary, MEDDRA 14.1
[4] This event was re-coded as "Small bowel perforation"; it was subsequently re-mapped to the "Surgical and medical procedures".
[5] In the Week 52 study report, this event was coded as "infection"; it was subsequently re-coded in the Week 104 study report as "localised infection".
[6] In the Week 52 study report, this event was coded as "Hemiplegic migraine"; it was subsequently re-coded in the Week 104 study report as "Hemiparesis".
[7] In the Week 52 study report, this event was coded as "stress"; it was subsequently re-coded in the Week 104 study report as "anxiety".
[8] In Week 52 study report this event was coded as "small intestinal perforation" and was mapped under "Gastrointestinal disorders ".

Other Adverse Events

Hide Other Adverse Events

Time Frame	Adverse event data were collected for the duration of the study (104 weeks).
Additional Description	The total number of adverse events listed in the "Other (non-Serious) Adverse Events" table are based upon a cut-off of greater than or equal to 5 percent of patients experiencing the adverse event in any treatment arm. MEDDRA 14.1 used for Week 52 / MEDDRA 15.0 for Week 104 results.

Frequency Threshold

Threshold above which other adverse events are reported	5%

Reporting Groups

	Description
Canagliflozin 100 mg: Baseline to Week 52	Each patient received 100 mg of canagliflozin (JNJ-28431754) once daily with protocol-specified doses of metformin for 104 weeks. Data are presented for Baseline to Week 52.
Canagliflozin 300 mg: Baseline to Week 52	Each patient received 300 mg of canagliflozin (JNJ-28431754) once daily with protocol-specified doses of metformin for 104 weeks. Data are presented for Baseline to Week 52.
Glimepiride: Baseline to Week 52	Each patient received glimepiride, at protocol-specified doses, once daily in combination with protocol-specified doses of metformin for 104 weeks. Data are presented for Baseline to Week 52.
Canagliflozin 100 mg: Baseline to Week 104	Each patient received 100 mg of canagliflozin (JNJ-28431754) once daily with protocol-specified doses of metformin for 104 weeks. Data are presented for Baseline to Week 104.
Canagliflozin 300 mg: Baseline to Week 104	Each patient received 300 mg of canagliflozin (JNJ-28431754) once daily with protocol-specified doses of metformin for 104 weeks. Data are presented for Baseline to Week 104.
Glimepiride: Baseline to Week 104	Each patient received glimepiride, at protocol-specified doses, once daily in combination with protocol-specified doses of metformin for 104 weeks. Data are presented for Baseline to Week 104.

Other Adverse Events

	Canagliflozin 100 mg: Baseline	**Canagliflozin 300 mg: Baseline**	**Glimepiride: Baseline to**	**Canagliflozin 100 mg: Baseline**	**Canagliflozin 300 mg: Baseline**	**Glimepiride: Baseline to**

	to Week 52	to Week 52	Week 52	to Week 104	to Week 104	Week 104
Total, other (not including serious) adverse events						
# participants affected / at risk	**138/483 (28.57%)**	**150/485 (30.93%)**	**175/482 (36.31%)**	**198/483 (40.99%)**	**204/485 (42.06%)**	**242/482 (50.21%)**
Gastrointestinal disorders						
Diarrhoea [*1]						
# participants affected / at risk	**24/483 (4.97%)**	**33/485 (6.80%)**	**29/482 (6.02%)**	**25/482 (5.19%)**	**39/485 (8.04%)**	**34/482 (7.05%)**
Nausea [*1]						
# participants affected / at risk	**16/483 (3.31%)**	**25/485 (5.15%)**	**13/482 (2.70%)**	**20/483 (4.14%)**	**27/485 (5.57%)**	**19/482 (3.94%)**
Infections and infestations						
Nasopharyngitis [*1]						
# participants affected / at risk	**33/483 (6.83%)**	**37/485 (7.63%)**	**37/482 (7.68%)**	**47/483 (9.73%)**	**55/485 (11.34%)**	**51/482 (10.58%)**
Upper respiratory tract infection [*1]						
# participants affected / at risk	**17/483 (3.52%)**	**27/485 (5.57%)**	**41/482 (8.51%)**	**36/483 (7.45%)**	**38/485 (7.84%)**	**56/482 (11.62%)**
Urinary tract infection [*1]						
# participants affected / at risk	**26/483 (5.38%)**	**23/485 (4.74%)**	**18/482 (3.73%)**	**44/483 (9.11%)**	**33/485 (6.80%)**	**27/482 (5.60%)**
Influenza [*1]						
# participants affected / at risk	**14/483 (2.90%)**	**17/485 (3.51%)**	**7/482 (1.45%)**	**25/483 (5.18%)**	**23/485 (4.74%)**	**13/482 (2.70%)**
Metabolism and nutrition disorders						
Hypoglycaemia [*1]						
# participants affected / at risk	**15/483 (3.11%)**	**9/485 (1.86%)**	**61/482 (12.66%)**	**17/483 (3.52%)**	**16/485 (3.30%)**	**86/482 (17.84%)**
Musculoskeletal and connective tissue disorders						
Back pain [*1]						
# participants affected / at risk	**29/483 (6.00%)**	**18/485 (3.71%)**	**20/482 (4.15%)**	**34/483 (7.04%)**	**28/485 (5.77%)**	**26/482 (5.39%)**
Arthralgia [*1]						
# participants affected / at	**18/483 (3.73%)**	**13/485 (2.68%)**	**18/482 (3.73%)**	**26/483 (5.38%)**	**16/485 (3.30%)**	**24/482 (4.98%)**

risk						
Nervous system disorders						
Headache * 1						
# participants affected / at risk	**14/483 (2.90%)**	**25/485 (5.15%)**	**24/482 (4.98%)**	**21/483 (4.35%)**	**29/485 (5.98%)**	**33/482 (6.85%)**
Vascular disorders						
Hypertension * 1						
# participants affected / at risk	**8/483 (1.66%)**	**10/485 (2.06%)**	**13/482 (2.70%)**	**15/483 (3.11%)**	**11/485 (2.27%)**	**30/482 (6.22%)**

* Events were collected by non-systematic assessment
1 Term from vocabulary, MEDDRA 14.1 / 15.0

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 notable study limitations were identified by the Sponsor.

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: A copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. If requested in writing, such publication will be withheld for up to an additional 60 days.

Results Point of Contact:

Name/Title: Vice President, Franchise Medical Leader, Cardiovascular & Metabolism Franchise
Organization: Janssen Research & Development, LLC
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Publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):

Watts NB, Bilezikian JP, Usiskin K, Edwards R, Desai M, Law G, Meininger G. Effects of Canagliflozin on Fracture Risk in Patients With Type 2 Diabetes Mellitus. J Clin Endocrinol Metab. 2016 Jan;101(1):157-66. doi: 10.1210/jc.2015-3167. Epub 2015 Nov 18.

Lavalle-González FJ, Eliaschewitz FG, Cerdas S, Chacon Mdel P, Tong C, Alba M. Efficacy and safety of canagliflozin in patients with type 2

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Leiter LA, Yoon KH, Arias P, Langslet G, Xie J, Balis DA, Millington D, Vercruysse F, Canovatchel W, Meininger G. Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. Diabetes Care. 2015 Mar;38(3):355-64. doi: 10.2337/dc13-2762. Epub 2014 Sep 9.

Nyirjesy P, Sobel JD, Fung A, Mayer C, Capuano G, Ways K, Usiskin K. Genital mycotic infections with canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. Curr Med Res Opin. 2014 Jun;30(6):1109-19. doi: 10.1185/03007995.2014.890925. Epub 2014 Feb 21.

Cefalu WT, Leiter LA, Yoon KH, Arias P, Niskanen L, Xie J, Balis DA, Canovatchel W, Meininger G. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet. 2013 Sep 14;382(9896):941-50. doi: 10.1016/S0140-6736(13)60683-2. Epub 2013 Jul 12.

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Health Authority:	United States: Food and Drug Administration Ukraine: State Pharmacological Center - Ministry of Health Philippines: Bureau of Food and Drugs

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