Clinical trial results:
Open-Label, Multicenter, Multiple Oral Dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Canagliflozin in Older Children and Adolescents 10 to <18 years of age with Type 2 Diabetes Mellitus and Currently on a Stable Dose of Metformin

Summary

EudraCT number	2013-005455-32
Trial protocol	Outside EU/EEA
Global end of trial date	01 April 2016

Results information

Result version number	v1 (current)
This version publication date	08 October 2016
First version publication date	08 October 2016

Trial information

Trial identification

Sponsor protocol code	28431754DIA1055

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02000700
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research and Development, LLC
Sponsor organisation address	920 Route 202, Raritan, United States, NJ 08869
Public contact	Clinical Registry Group, Janssen Research and Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research and Development, LLC, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001030-PIP01-10
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the pharmacokinetics of canagliflozin after multiple oral doses of canagliflozin in children and adolescent subjects with type 2 diabetes mellitus (T2DM) who were more than or equal to (>=) 10 to less than (<) 18 years of age and on stable dose of metformin.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety and tolerability evaluations were based upon physical examinations, vital signs, electrocardiogram (ECGs), clinical laboratory tests (hematology, serum chemistry, and urinalysis), Glycemic Control, and adverse events (AEs) /serious adverse events (SAEs) reported throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 April 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	17
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	1
Adolescents (12-17 years)	16
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted from 06 April 2014 to 01 April 2016 in United States of America (USA) and Brazil within a total of 17 subjects enrolled in the trial.

Pre-assignment

Screening details:

A total of 17 subjects received the study treatment and completed the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Canagliflozin 100 milligram

Arm description:

Subjects received 100 milligram (mg)(1 x 100 mg) tablet of canagliflozin administered orally once daily for 14 days.

Arm type	Experimental
Investigational medicinal product name	Canagliflozin
Investigational medicinal product code	JNJ-28431754
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 100 mg tablet (1 x 100 mg) of canagliflozin administered orally once daily for 14 days.

Arm title	Canagliflozin 300 milligram

Arm description:

Subjects received 300 mg (1 x 300 mg) tablet of canagliflozin administered orally once daily for 14 days.

Arm type	Experimental
Investigational medicinal product name	Canagliflozin
Investigational medicinal product code	JNJ-28431754
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 300 mg (1 x 300 mg) tablet of canagliflozin administered orally once daily for 14 days.

Number of subjects in period 1	Canagliflozin 100 milligram	Canagliflozin 300 milligram
Started	8	9
Completed	8	9

Baseline characteristics

Reporting groups	
Reporting group title	Canagliflozin 100 milligram
Reporting group description:	
Subjects received 100 milligram (mg)(1 x 100 mg) tablet of canagliflozin administered orally once daily for 14 days.	
Reporting group title	Canagliflozin 300 milligram
Reporting group description:	
Subjects received 300 mg (1 x 300 mg) tablet of canagliflozin administered orally once daily for 14 days.	

Reporting group values	Canagliflozin 100 milligram	Canagliflozin 300 milligram	Total
Number of subjects	8	9	17
Title for AgeCategorical			
Units: subjects			
Children (2-11 years)	1	0	1
Adolescents (12-17 years)	7	9	16
Title for AgeContinuous			
Units: years			
arithmetic mean	15	14.2	
standard deviation	± 2.07	± 1.56	-
Title for Gender			
Units: subjects			
Female	6	6	12
Male	2	3	5

End points

End points reporting groups

Reporting group title	Canagliflozin 100 milligram
Reporting group description:	
Subjects received 100 milligram (mg)(1 x 100 mg) tablet of canagliflozin administered orally once daily for 14 days.	
Reporting group title	Canagliflozin 300 milligram
Reporting group description:	
Subjects received 300 mg (1 x 300 mg) tablet of canagliflozin administered orally once daily for 14 days.	

Primary: Maximum Observed Plasma Concentration (Cmax) of Canagliflozin

End point title	Maximum Observed Plasma Concentration (Cmax) of Canagliflozin[1]
End point description:	
Cmax is defined as maximum observed plasma concentration of canagliflozin. Pharmacokinetic (PK) population included all evaluable subjects who received at least 1 dose of study medication and with serial PK blood samples.	
End point type	Primary
End point timeframe:	
Up to 72 hours postdose on Day 14	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The descriptive statistics was calculated for this endpoint.

End point values	Canagliflozin 100 milligram	Canagliflozin 300 milligram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)	951 (± 429)	3260 (± 1330)		

Statistical analyses

No statistical analyses for this end point

Primary: Time to Reach Maximum Observed Plasma Concentration (Tmax) of Canagliflozin

End point title	Time to Reach Maximum Observed Plasma Concentration (Tmax) of Canagliflozin[2]
End point description:	
The Tmax is defined as actual sampling time to reach maximum observed concentration of Canagliflozin. PK population included all evaluable subjects who received at least 1 dose of study medication and with serial PK blood samples.	
End point type	Primary
End point timeframe:	
Up to 72 hours postdose on Day 14	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The descriptive statistics was calculated for this endpoint.

End point values	Canagliflozin 100 milligram	Canagliflozin 300 milligram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: hour (h)				
arithmetic mean (full range (min-max))	1.64 (1 to 1.98)	2.44 (1 to 4)		

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Curve From Time Zero to End of Dosing Interval (AUC tau) of Canagliflozin

End point title	Area Under the Curve From Time Zero to End of Dosing Interval (AUC tau) of Canagliflozin[3]

End point description:

The AUCtau is the measure of the plasma drug concentration from time zero to end of dosing interval. It is used to characterize Canagliflozin absorption. PK population included all evaluable subjects who received at least 1 dose of study medication and with serial PK blood samples.

End point type	Primary

End point timeframe:

Up to 72 hours postdose on Day 14

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The descriptive statistics was calculated for this endpoint.

End point values	Canagliflozin 100 milligram	Canagliflozin 300 milligram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: hour*nanogram per milliliter (h*ng/mL)				
arithmetic mean (standard deviation)	6190 (± 1770)	28392 (± 12412)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Decay Half-Life (t1/2) of Canagliflozin

End point title	Plasma Decay Half-Life (t1/2) of Canagliflozin[4]

End point description:

Plasma decay half-life is the time measured for the plasma concentration to decrease by one half of

canagliflozin. PK population included all evaluable subjects who received at least 1 dose of study medication and with serial PK blood samples.

End point type	Primary

End point timeframe:

Up to 72 hours postdose on Day 14

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The descriptive statistics was calculated for this endpoint.

End point values	Canagliflozin 100 milligram	Canagliflozin 300 milligram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: hour (h)				
arithmetic mean (standard deviation)	11.3 (± 2.5)	15.2 (± 6.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Elimination Rate Constant (Lambda[z]) of Canagliflozin

End point title	Elimination Rate Constant (Lambda[z]) of Canagliflozin[5]

End point description:

Lambda(z) is first-order elimination rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the drug concentration-time curve. PK population included all evaluable subjects who received at least 1 dose of study medication and with serial PK blood samples.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 2, 4, 8, 12, 24, 48 and 72 hours postdose on Day 14

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The descriptive statistics was calculated for this endpoint.

End point values	Canagliflozin 100 milligram	Canagliflozin 300 milligram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: 1 per hour(1/h)				
arithmetic mean (standard deviation)	0.0644 (± 0.0151)	0.0528 (± 0.0183)		

Statistical analyses

No statistical analyses for this end point

Primary: Oral Clearance at Steady-State (CLss/F) of Canagliflozin

End point title	Oral Clearance at Steady-State (CLss/F) of Canagliflozin[6]

End point description:

The Oral Clearance at Steady-State (CLss/F) is the steady state oral clearance based on oral bioavailability. PK population included all evaluable subjects who received at least 1 dose of study medication and with serial PK blood samples.

End point type	Primary

End point timeframe:

Up to 72 hours postdose on Day 14

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The descriptive statistics was calculated for this endpoint.

End point values	Canagliflozin 100 milligram	Canagliflozin 300 milligram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: liter per hour(L/h)				
arithmetic mean (standard deviation)	17.5 (± 5.78)	12.3 (± 6.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Plasma Glucose And Fasting Plasma Glucose (FPG) Concentrations

End point title	Mean Plasma Glucose And Fasting Plasma Glucose (FPG) Concentrations

End point description:

FPG is defined as fasting plasma glucose. MPG0-4h is defined as mean concentration of plasma glucose during the 0- to 4-hour (h) interval, calculated as area under curve (AUC) over 0 to 4h divided by the 4-hour time interval. MPG0-24h is the mean concentration for plasma glucose during the 0- to 24-hour interval, calculated as AUC over 0 to 24h divided by the 24-hour time interval. Pharmacodynamic population set included all evaluable subjects who received at least 1 dose of study medication. Here 'n' is defined as number of subjects analysed for the endpoint at specific timepoint.

End point type	Secondary

End point timeframe:

Day-1 (Baseline) and Day 14

End point values	Canagliflozin 100 milligram	Canagliflozin 300 milligram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: milligram per deciliter (mg/dL)				
arithmetic mean (standard deviation)				
Day -1: MPG 0-24h (n= 8,9)	147 (± 59)	110 (± 11)		
Day 14: MPG 0-24h (n= 8,9)	115 (± 23)	96 (± 10)		
Day -1: MPG 0-4h (n= 8,9)	164 (± 69)	119 (± 18)		
Day 14: MPG 0-4h (n= 8,9)	120 (± 32)	104 (± 12)		
Day -1: FPG (n= 7,7)	143 (± 58)	107 (± 10)		
Day 14: FPG (n= 8,8)	110 (± 24)	100 (± 11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Urinary Glucose Excretion (UGE)

End point title	Mean Urinary Glucose Excretion (UGE)

End point description:

Urinary glucose excretion (UGE) is calculated from the measured individual subject urine glucose and urine volume data. UGEt1-t2 is defined as urinary glucose excretion, equal to the amount of urine glucose excreted into the urine over the time intervals 0 to 12 hours and 12 to 24 hours, abbreviated as UGE0-12h and UGE12-24h, respectively, calculated for each interval by multiplying the urinary volume with the urinary glucose concentration. UGE0-24h is defined as cumulative daily urinary glucose excretion, equal to the amount of plasma glucose excreted into the urine over the entire urine collection interval, 0 to 24 hours, calculated as the sum of UGE0-12h and UGE12-24h. Pharmacodynamic population set included all evaluable subjects who received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

Day-1 (Baseline) and Day 14

End point values	Canagliflozin 100 milligram	Canagliflozin 300 milligram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: gram (g)				
arithmetic mean (standard deviation)				
Day -1: UGE 0-12h	4 (± 7.5)	0.1 (± 0.04)		
Day -1: UGE 12-24h	1.3 (± 3.37)	0 (± 0.01)		
Day -1: UGE 0-24h	5.3 (± 10.5)	0.1 (± 0.04)		
Day 14: UGE 0-12h	50.8 (± 29)	43.4 (± 18.4)		
Day 14: UGE 12-24h	23.3 (± 10.3)	25.2 (± 13.1)		
Day 14: UGE 0-24h	74.1 (± 37.4)	68.6 (± 26.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Renal Threshold for Glucose Excretion (RTG)

End point title	Mean Renal Threshold for Glucose Excretion (RTG)

End point description:

RTG is defined as renal threshold for glucose. RTG,t1-t2 is defined as renal threshold for glucose excretion, calculated over the 0-12 and 12-24h time intervals. 24-h mean RTG is defined as 24-h mean renal threshold for glucose excretion, calculated as the average of the values obtained over the 0-12h and 12-24h intervals. Pharmacodynamic population set included all evaluable subjects who received at

least 1 dose of study medication. The numeric value '999' indicates that on Day -1 (prior to treatment), many subjects had virtually no UGE and therefore their RTG values could not be determined. Values on Day -1 are shown only for the 2 subjects who had assessable values on this day.

End point type	Secondary

End point timeframe:

Days -1 (Baseline), and 14

End point values	Canagliflozin 100 milligram	Canagliflozin 300 milligram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: milligram per deciliter (mg/dL)				
arithmetic mean (standard deviation)				
Day -1: RTG 0-12h (n= 2,0)	258.3 (± 27)	999 (± 999)		
Day -1: RTG 12-24h (n= 2,0)	258.3 (± 27)	999 (± 999)		
Day -1: 24-h mean RTG (n= 2,0)	258.3 (± 27)	999 (± 999)		
Day 14: RTG 0-12h (n= 8,9)	74.1 (± 12.3)	66.7 (± 7.5)		
Day 14: RTG 12-24h (n= 8,9)	95.1 (± 16.7)	71.5 (± 14.1)		
Day 14: 24-h mean RTG (n= 8,9)	84.6 (± 13.8)	69.1 (± 9.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Canagliflozin Tablet Acceptability Assessment Scores: Medicine's Taste

End point title	Canagliflozin Tablet Acceptability Assessment Scores: Medicine's Taste

End point description:

The acceptability questionnaire scores involves the general assessments for taste, smell, swallowing the medicine, mouth taste after tablet swallow, Overall about taking the study medication again. For Acceptability Assessment Scores: Medicine's Taste, the subjects were asked to choose one among following options: Tastes bad, Does not taste good, Taste is not good or bad, Tastes OK, Tastes good, There is no taste.

End point type	Secondary

End point timeframe:

Day 14

End point values	Canagliflozin 100 milligram	Canagliflozin 300 milligram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: Number of Subjects				
Tastes bad	0	0		
Does not taste good	0	0		
Taste is not good or bad	0	1		
Tastes OK	1	2		

Tastes good	0	0		
There is no taste	7	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Canagliflozin Tablet Acceptability Assessment Scores: Medicine's Smell

End point title	Canagliflozin Tablet Acceptability Assessment Scores: Medicine's Smell

End point description:

The acceptability questionnaire scores involves the general assessments for taste, smell, swallowing the medicine, mouth taste after tablet swallow, Overall about taking the study medication again. For Acceptability Assessment Scores: Medicine's Smell, the subjects were asked to choose one among following options: Smells bad, Does not smell good, Smell is not good or bad, Smells OK, Smells good, There is no smell.

End point type	Secondary

End point timeframe:

Day 14

End point values	Canagliflozin 100 milligram	Canagliflozin 300 milligram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: Subjects				
Smells bad	0	0		
Does not smell good	0	0		
Smell is not good or bad	0	0		
Smells OK	1	1		
Smells good	0	1		
There is no smell	7	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Canagliflozin Tablet Acceptability Assessment Scores: Medicine's swallowing property

End point title	Canagliflozin Tablet Acceptability Assessment Scores: Medicine's swallowing property

End point description:

The acceptability questionnaire scores involves the general assessments for taste, smell, swallowing the medicine, mouth taste after tablet swallow and Overall about taking the study medication again. For Acceptability Assessment Scores: Medicine's swallowing property, the subjects were asked to choose one among following options: Very hard to swallow, A little hard to swallow, Not hard or easy to swallow, Easy to swallow, Very easy to swallow.

End point type	Secondary

End point timeframe:

Day 14

End point values	Canagliflozin 100 milligram	Canagliflozin 300 milligram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: Number of Subjects				
Very hard to swallow	0	0		
A little hard to swallow	0	1		
Not hard or easy to swallow	0	1		
Easy to swallow	1	5		
Very easy to swallow	7	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Canagliflozin Tablet Acceptability Assessment Scores: Medicine's Taste After Swallowing Tablet

End point title	Canagliflozin Tablet Acceptability Assessment Scores: Medicine's Taste After Swallowing Tablet

End point description:

The acceptability questionnaire scores involves the general assessments for taste, smell, swallowing the medicine, mouth taste after tablet swallow, Overall about taking the study medication again. For Acceptability Assessment Scores: Medicine's taste after swallowing tablet, the subjects were asked to choose one among following options: Tastes bad, Does not taste good, Taste is not good or bad, Tastes OK, Tastes good, There is no taste.

End point type	Secondary

End point timeframe:

Day 14

End point values	Canagliflozin 100 milligram	Canagliflozin 300 milligram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: Number of Subjects				
Tastes bad	0	0		
Does not taste good	0	0		
Taste is not good or bad	1	0		
Tastes OK	1	1		
Tastes good	0	0		
There is no taste	6	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Canagliflozin Tablet Acceptability Assessment Scores: Overall Feel About Taking The Medication Again

End point title	Canagliflozin Tablet Acceptability Assessment Scores: Overall Feel About Taking The Medication Again

End point description:

The acceptability questionnaire scores involves the general assessments for taste, smell, swallowing the medicine, mouth taste after tablet swallow and Overall about taking the study medication again. For Acceptability Assessment Scores: overall feel about taking the medication again, the subjects were asked to choose one among following options: Very unhappy, Not happy, OK, Fine , Happy.

End point type	Secondary

End point timeframe:

Day 14

End point values	Canagliflozin 100 milligram	Canagliflozin 300 milligram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: Number of Subjects				
Very unhappy	0	0		
Not happy	0	0		
OK	0	2		
Fine	5	4		
Happy	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Adverse Events

End point title	Number of Subjects with Adverse Events

End point description:

An Adverse event (AE) is any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An SAE is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; lifethreatening
experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Safety population included all randomized subjects who received at least 1 dose of the study drug.

End point type	Secondary

End point timeframe:

Up to follow up phase (7 to 10 days) after day 17 or whole study duration

End point values	Canagliflozin 100 milligram	Canagliflozin 300 milligram		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: Subjects	4	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to follow up phase (7 to 10 days) after day 17 or whole study duration	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1
Reporting groups	
Reporting group title	Canagliflozin 100 milligram
Reporting group description:	
Subjects received 100 milligram (mg)(1 x 100-mg) tablet of canagliflozin adminstered orally daily for 14 days.	
Reporting group title	Canagliflozin 300 milligram
Reporting group description:	
Subjects received 300 mg (1 x 300-mg) tablet of canagliflozin administered orally daily for 14 days.	

Serious adverse events	Canagliflozin 100 milligram	Canagliflozin 300 milligram	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Canagliflozin 100 milligram	Canagliflozin 300 milligram	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)	5 / 9 (55.56%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Nausea			

subjects affected / exposed	1 / 8 (12.50%)	2 / 9 (22.22%)	
occurrences (all)	1	3	
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Onychoclasis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	4	
Metabolic acidosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 October 2013	The overall reason for the amendment was to address a comment from the United states food drug adminstration (US FDA) regarding the definition of renal function inclusion criteria and general clarifications of admission days and a few procedures. The restriction on male subjects for use of effective birth control method was removed as per this amendment.
30 October 2013	The overall reason for the amendment was to correct a typo defining the value of a non-acceptable estimated glomerular filtration rate (eGFR) and in exclusion criterion 8 Inclusion of contraceptive injection as an effective birth control method.
09 September 2014	The overall reason for the amendment was to adjust and clarify the language of the Inclusion and Exclusion criteria, modify rules related to concomitant medications, and update the calculation of estimated glomerular filtration rate (eGFR; using Schwartz formula).
16 September 2014	The overall reason for the amendment was to ensure protocol consistency with health authority agreements for study design. Administration of antihyperglycemic agent (AHAs) for up to 7 days in the 8 to 2 weeks prior to the screening visit was not permitted as per this amendment.
21 September 2015	The overall reason for the amendment was to enhance study recruitment. The window period for screening safety assessments was widened from 7 days to 10 days. Updated information on diabetic ketoacidosis and handling of subjects surrounding this event was added. Subjects who were on metformin XR for at least 8 weeks prior to screening and switched to metformin immediate release (IR; at the same total daily dose)which was well tolerated for at least 2 weeks prior to Day 1 were allowed to participate in the study. The concurrent use of insulin with metformin to achieve sufficient glycemic control was allowed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No notable study limitations were identified by the Sponsor.

Notes: