



Clinical trial results:

A Randomized, Multi-Center, Parallel Group, Single-Dose, Pharmacokinetics and Pharmacodynamics Study of Dapagliflozin in Children and Adolescents Aged 10 to 17 Years with Type 2 Diabetes Mellitus

Summary

EudraCT number	2011-005225-40
Trial protocol	Outside EU/EEA
Global end of trial date	13 September 2014

Results information

Result version number	v1 (current)
This version publication date	15 October 2016
First version publication date	15 October 2016

Trial information

Trial identification

Sponsor protocol code	MB102-091
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01525238
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb International, ctt.group@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb International, ctt.group@bms.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000694-PIP01-09
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	13 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 September 2014
Global end of trial reached?	Yes
Global end of trial date	13 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of this study is to evaluate the pharmacokinetics of dapagliflozin in pediatric subjects with T2DM

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 July 2012
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	United States: 44
Country: Number of subjects enrolled	Mexico: 9
Worldwide total number of subjects	53
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)	5
Adolescents (12-17 years)	48
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

53 participants enrolled; 24 randomized; 24 treated with study drug. 29 participants were not randomized due to no longer meeting study criteria (25), withdrawal of consent (2), or other reasons (2).

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Open-label study

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapagliflozin 2.5 mg

Arm description:

Dapagliflozin: Tablet, Oral, 2.5 mg, Single-dose

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	Farxiga, Forxiga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin was administered to each subject at the clinical facility on the morning of Day 1. Subjects were required to fast for at least 8 hours prior to study drug administration and until 2 hours after study drug administration.

Arm title	Dapagliflozin 5 mg
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Arm description:

Dapagliflozin: Tablet, Oral, 5 mg, Single-dose

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	Farxiga, Forxiga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin was administered to each subject at the clinical facility on the morning of Day 1. Subjects were required to fast for at least 8 hours prior to study drug administration and until 2 hours after study drug administration.

Arm title	Dapagliflozin 10 mg
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Arm description:

Dapagliflozin: Tablet, Oral, 10 mg, Single-dose

Arm type	Experimental
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Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	Farxiga, Forxiga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin was administered to each subject at the clinical facility on the morning of Day 1. Subjects were required to fast for at least 8 hours prior to study drug administration and until 2 hours after study drug administration.

Number of subjects in period 1^[1]	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg
Started	8	8	8
Completed	7	8	8
Not completed	1	0	0
Subject withdrew from study for personal reasons	1	-	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Of the 53 participants enrolled, only 24 continued to the treatment period.

Baseline characteristics

Reporting groups

Reporting group title	Dapagliflozin 2.5 mg
Reporting group description:	
Dapagliflozin: Tablet, Oral, 2.5 mg, Single-dose	
Reporting group title	Dapagliflozin 5 mg
Reporting group description:	
Dapagliflozin: Tablet, Oral, 5 mg, Single-dose	
Reporting group title	Dapagliflozin 10 mg
Reporting group description:	
Dapagliflozin: Tablet, Oral, 10 mg, Single-dose	

Reporting group values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg
Number of subjects	8	8	8
Age categorical			
All treated participants			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	1	1
Adolescents (12-17 years)	8	7	7
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	5	5	5
Male	3	3	3

Reporting group values	Total		
Number of subjects	24		
Age categorical			
All treated participants			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	2		
Adolescents (12-17 years)	22		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		

Gender categorical			
Units: Subjects			
Female	15		
Male	9		

End points

End points reporting groups

Reporting group title	Dapagliflozin 2.5 mg
Reporting group description:	
Dapagliflozin: Tablet, Oral, 2.5 mg, Single-dose	
Reporting group title	Dapagliflozin 5 mg
Reporting group description:	
Dapagliflozin: Tablet, Oral, 5 mg, Single-dose	
Reporting group title	Dapagliflozin 10 mg
Reporting group description:	
Dapagliflozin: Tablet, Oral, 10 mg, Single-dose	

Primary: Geometric Mean of Maximum Observed Plasma Concentration (C_{max}) of Dapagliflozin

End point title	Geometric Mean of Maximum Observed Plasma Concentration (C _{max}) of Dapagliflozin ^[1]
End point description:	
Maximum observed plasma concentration (C _{max}) was measured by plasma concentration of Dapagliflozin over time. The geometric means are reported in nanograms per milliliter (ng/mL). All treated subjects with evaluable PK profiles were analyzed.	
End point type	Primary
End point timeframe:	
Day 1 to Day 3	

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: Only descriptive summary statistics were planned for this outcome measure

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8	8	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	24.8 (± 34)	48.4 (± 41)	118 (± 35)	

Statistical analyses

No statistical analyses for this end point

Primary: Median Time of Maximum Observed Plasma Concentration (T_{max}) of Dapagliflozin

End point title	Median Time of Maximum Observed Plasma Concentration (T _{max}) of Dapagliflozin ^[2]
End point description:	
Time of maximum observed plasma concentration (T _{max}) for Dapagliflozin was derived from plasma concentrations versus time data. Medians were reported in hours (h). All treated subjects with evaluable PK profiles were analyzed.	

End point type	Primary
End point timeframe:	
Day 1 to Day 3	
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: Only descriptive summary statistics were planned for this outcome measure	

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8	8	
Units: hours				
median (full range (min-max))	1.5 (0.75 to 2)	0.96 (0.58 to 1.53)	0.875 (0.75 to 4)	

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean of AUC(INF) of Dapagliflozin

End point title	Geometric Mean of AUC(INF) of Dapagliflozin ^[3]
End point description:	Area under the plasma concentration-time curve from time zero extrapolated to infinite time [AUC(INF)] was derived from concentration versus time data. Geometric means are reported in nanogram hours per milliliter (ng*hr/mL). All treated subjects with evaluable PK profiles were analyzed.
End point type	Primary
End point timeframe:	
Day 1 to Day 3	
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: Only descriptive summary statistics were planned for this outcome measure	

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8	8	
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)	101 (± 23)	199 (± 29)	427 (± 31)	

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean of AUC(0-T) of Dapagliflozin

End point title	Geometric Mean of AUC(0-T) of Dapagliflozin ^[4]
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End point description:

Area under the concentration-time curve from time zero to time of the last quantifiable concentration [AUC(0-T)] was measured by plasma concentration of Dapagliflozin over time. The geometric means are reported in nanogram hours per milliliter (ng*h/mL). All treated subjects with evaluable PK profiles were analyzed.

End point type	Primary
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End point timeframe:

Day 1 to Day 3

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: Only descriptive summary statistics were planned for this outcome measure

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8	8	
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	92.3 (± 27)	189 (± 31)	418 (± 31)	

Statistical analyses

No statistical analyses for this end point

Primary: Mean Plasma Half-life (T-HALF) of Dapagliflozin

End point title	Mean Plasma Half-life (T-HALF) of Dapagliflozin ^[5]
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End point description:

Plasma half-life (T-Half) for Dapagliflozin was derived from plasma concentrations versus time data. Means are reported in hours. All treated subjects with evaluable PK profiles were analyzed.

End point type	Primary
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End point timeframe:

Day 1 to Day 3

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: Only descriptive summary statistics were planned for this outcome measure

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8	8	
Units: hours				
arithmetic mean (standard deviation)	14.1 (± 5.59)	10.3 (± 3.72)	10.7 (± 2.16)	

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean of Apparent Clearance After Extravascular Administration (CL/F) of Dapagliflozin

End point title	Geometric Mean of Apparent Clearance After Extravascular Administration (CL/F) of Dapagliflozin ^[6]
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End point description:

Apparent clearance after extravascular administration (CL/F) of Dapagliflozin was derived from plasma concentrations versus time data. Geometric means are reported in milliliters per minute (mL/min). All treated subjects with evaluable PK profiles were analyzed.

End point type	Primary
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End point timeframe:

Day 1 to Day 3

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: Only descriptive summary statistics were planned for this outcome measure

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8	8	
Units: mL/min				
geometric mean (geometric coefficient of variation)	413 (± 26)	418 (± 27)	391 (± 25)	

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean of Apparent Volume of Distribution at Terminal Phase After Extravascular Administration (Vz/F)

End point title	Geometric Mean of Apparent Volume of Distribution at Terminal Phase After Extravascular Administration (Vz/F) ^[7]
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End point description:

Geometric mean of apparent volume of distribution at terminal phase after extravascular administration (Vz/F) of Dapagliflozin was derived from plasma concentration versus time data. Geometric means are reported in Liters (L). All treated subjects with evaluable PK profiles were analyzed.

End point type	Primary
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End point timeframe:

Day 1 to Day 3

Notes:

[7] - 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: Only descriptive summary statistics were planned for this outcome measure

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8	8	
Units: Liters				
geometric mean (geometric coefficient of variation)	468 (± 34)	343 (± 45)	355 (± 34)	

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean of Maximum Observed Plasma Concentration (C_{max}) of Dapagliflozin 3-O-Glucuronide

End point title	Geometric Mean of Maximum Observed Plasma Concentration (C _{max}) of Dapagliflozin 3-O-Glucuronide
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End point description:

Maximum observed plasma concentration (C_{max}) was measured by plasma concentration of Dapagliflozin 3-O-Glucuronide over time. The geometric means are reported in nanograms per milliliter (ng/mL). All treated subjects with evaluable PK profiles were analyzed.

End point type	Secondary
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End point timeframe:

Day 1 to Day 3

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8	8	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	24.6 (± 45)	49 (± 50)	154 (± 27)	

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time of Maximum Observed Plasma Concentration (T_{max}) of Dapagliflozin 3-O-Glucuronide

End point title	Median Time of Maximum Observed Plasma Concentration (T _{max}) of Dapagliflozin 3-O-Glucuronide
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End point description:

Time of maximum observed plasma concentration (T_{max}) for Dapagliflozin 3-O-Glucuronide was derived from plasma concentrations versus time data. Medians were reported in hours (h). All treated subjects with evaluable PK profiles were analyzed.

End point type	Secondary
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End point timeframe:

Day 1 to Day 3

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8	8	
Units: hours				
median (full range (min-max))	1.5 (1 to 4)	1.5 (0.83 to 4)	1.5 (1.47 to 4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean of AUC(INF) of Dapagliflozin 3-O-Glucuronide

End point title	Geometric Mean of AUC(INF) of Dapagliflozin 3-O-Glucuronide
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End point description:

Area under the plasma concentration-time curve from time zero extrapolated to infinite time [AUC(INF)] was derived from concentration versus time data. Geometric means are reported in nanogram hours per milliliter (ng*hr/mL). All treated subjects with evaluable PK profiles were analyzed.

End point type	Secondary
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End point timeframe:

Day 1 to Day 3

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8	8	
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)	105 (± 23)	232 (± 30)	658 (± 21)	

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean of AUC(0-T) of Dapagliflozin 3-O-Glucuronide

End point title	Geometric Mean of AUC(0-T) of Dapagliflozin 3-O-Glucuronide
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End point description:

Area under the concentration-time curve from time zero to time of the last quantifiable concentration [AUC(0-T)] was measured by plasma concentration of Dapagliflozin 3-O-Glucuronide over time. The geometric means are reported in nanogram hours per milliliter (ng*h/mL). All treated subjects with evaluable PK profiles were analyzed.

End point type	Secondary
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End point timeframe:

Day 1 to Day 3

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8	8	
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	95.8 (± 20)	208 (± 32)	612 (± 24)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Plasma Half-life (T-HALF) of Dapagliflozin 3-O-Glucuronide

End point title	Mean Plasma Half-life (T-HALF) of Dapagliflozin 3-O-Glucuronide
End point description: Plasma half-life (T-Half) for Dapagliflozin was derived from plasma concentration versus time data. Means are reported in hours. All treated subjects with evaluable PK profiles were analyzed.	
End point type	Secondary
End point timeframe: Day 1 to Day 3	

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8	8	
Units: hours				
arithmetic mean (standard deviation)	4.62 (± 3.09)	8.71 (± 2.02)	8.37 (± 3.33)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Fasting Plasma Glucose Concentrations at Pre-dose on Day 1 and on Day 2 After an 8-hr Fast

End point title	Mean Fasting Plasma Glucose Concentrations at Pre-dose on Day 1 and on Day 2 After an 8-hr Fast
End point description: Plasma glucose concentrations were evaluated in all treated subjects at Day 1 pre-dose and at Day 2 after fasting for 8 hours. Means are reported in milligrams per deciliter (mg/dL). All treated subjects with evaluable PD profiles were analyzed.	
End point type	Secondary

End point timeframe:

Day 1 (Pre-dose) to Day 2

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	8	8	
Units: mg/dL				
arithmetic mean (standard deviation)				
Day 1 (Pre-Dose) (n= 6, 8, 8)	146.2 (± 72.56)	152.1 (± 49.06)	139.8 (± 39.63)	
Day 2 after 8 hour fast (n= 3, 8, 7)	124 (± 45.21)	119.4 (± 17.18)	119 (± 29.15)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in Fasting Plasma Glucose From Baseline Until Day 2

End point title	Mean Change in Fasting Plasma Glucose From Baseline Until Day 2
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End point description:

Plasma glucose concentrations were evaluated in all treated subjects at Day 1 pre-dose and at Day 2 after fasting for 8 hours. Mean change from baseline to Day 2 is reported in milligrams per deciliter (mg/dL). All treated subjects with evaluable PD profiles were analyzed.

End point type	Secondary
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End point timeframe:

Day 1 (Pre-dose) to Day 2

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	8	7	
Units: mg/dL				
arithmetic mean (standard deviation)	-46.7 (± 60.08)	-32.8 (± 42.41)	-22 (± 27.32)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Total Amount of Glucose Excreted in Urine Over 24 Hours

End point title	Mean Total Amount of Glucose Excreted in Urine Over 24 Hours
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End point description:

The total amount of glucose excreted in urine was measured for 24 hours following administration of Dapagliflozin. Means are reported in grams. All treated subjects with evaluable PD profiles were analyzed.

End point type	Secondary
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End point timeframe:

Day 1 to Day 2

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	8	7	
Units: grams				
arithmetic mean (standard deviation)	52.84 (± 27.18)	62.39 (± 26.55)	89.04 (± 41.25)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Abnormalities in Vital Signs, Electrocardiograms (ECG), or Physical Examinations

End point title	Number of Participants With Abnormalities in Vital Signs, Electrocardiograms (ECG), or Physical Examinations
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End point description:

Participants were followed from dosing on Day 1 until study discharge on Day 3. The number of participants with investigator-assessed clinically-important abnormalities in vital sign measurements, ECGs or physical examinations was reported. All treated participants were analyzed.

End point type	Secondary
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End point timeframe:

Day 1 to Day 3

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	8	
Units: participants				
Vital sign abnormalities	0	0	0	
ECG abnormalities	0	0	0	
Physical exam abnormalities	0	0	0	

Statistical analyses

Secondary: Number of Participants With Marked Hematology Laboratory Abnormalities

End point title	Number of Participants With Marked Hematology Laboratory Abnormalities
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End point description:

LLN=Lower Limit of Normal, ULN=Upper Limit of Normal, Pre-Rx=Value before first dose (Day -1). All treated participants were analyzed. Lab values that met the following criteria were marked as abnormalities:

Hemoglobin (grams per deciliter:g/dL): $<0.85 \times \text{Pre-Rx}$.

Hematocrit (%): $<0.85 \times \text{Pre-Rx}$.

Platelet Count ($\times 10^9$ cells per liter:c/L): $<0.85 \times \text{LLN}$ or $>1.5 \times \text{ULN}$ (if $\text{Pre-Rx} < \text{LLN}$, use $<0.85 \times \text{Pre-Rx}$).

Leukocytes ($\times 10^3$ cells per microliter: c/uL): $<0.9 \times \text{LLN}$, $>1.2 \times \text{ULN}$ (if $\text{Pre-Rx} < \text{LLN}$, use $<0.85 \times \text{Pre-Rx}$ or $>1.15 \times \text{Pre-Rx}$ or $< \text{LLN}$).

Neutrophils (Absolute) ($\times 10^3$ c/uL): ≤ 1.5 .

Lymphocytes (Absolute) ($\times 10^3$ c/uL): <0.75 or >7.5 .

Monocytes (Absolute) ($\times 10^3$ c/uL): >2.000 .

Basophils ($\times 10^3$ c/uL): >0.4 .

Eosinophils (Absolute) ($\times 10^3$ c/uL): >0.75 .

Blasts (Absolute) ($\times 10^9$ c/L) > 0 .

End point type	Secondary
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End point timeframe:

Day 1 (Pre-dose) to Day 3

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	8	
Units: participants				
Hemoglobin, low (n=8, 8, 8)	0	0	0	
Hematocrit, low (n=8, 7, 8)	0	0	0	
Platelet count, low (n=8, 8, 7)	0	0	0	
Platelet count, high (n=8, 8, 7)	0	0	0	
Leukocytes, low (n=8, 8, 8)	1	0	1	
Leukocytes, high (n=8, 8, 8)	0	0	0	
Basophils, high (n=8, 8, 8)	0	0	0	
Blasts, high (n=0, 0, 0)	0	0	0	
Eosinophils, high (n=8, 8, 8)	0	0	0	
Lymphocytes, low (n=8, 8, 8)	0	0	0	
Monocytes, high (n=8, 8, 8)	0	0	0	
Neutrophils, low (n=8, 8, 8)	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Marked Serum Chemistry Abnormalities

End point title	Number of Participants With Marked Serum Chemistry Abnormalities
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End point description:

All treated participants were analyzed. Lab values that met the following criteria were marked as abnormalities:

Alkaline Phosphatase (units per liter: U/L), Aspartate Aminotransferase (U/L), Alanine Aminotransferase (U/L): $>1.25 \times \text{ULN}$ (if Pre-Rx $> \text{ULN}$, use $>1.25 \times \text{Pre-Rx}$). Bilirubin (milligrams per deciliter: mg/dL): $>1.1 \times \text{ULN}$ (if Pre-Rx $> \text{ULN}$, use $>1.25 \times \text{Pre-Rx}$).

Blood Urea Nitrogen (mg/dL): $>1.1 \times \text{ULN}$ (if Pre-Rx $> \text{ULN}$, use $>1.2 \times \text{Pre-Rx}$).

Creatinine (micromoles per Liter (umol/ L)): $>1.5 \times \text{ULN}$ if Pre-Rx missing or $\leq \text{ULN}$, $>1.33 \times \text{Pre-Rx}$ if Pre-Rx $> \text{ULN}$.

Sodium (mmol/L): $>1.05 \times \text{ULN}$, $1.05 \times \text{Pre-Rx}$ if Pre-Rx $> \text{ULN}$: $<0.95 \times \text{Pre-Rx}$, $> \text{ULN}$. If Pre-Rx $> \text{ULN}$: $>1.05 \times \text{Pre-Rx}$, $< \text{LLN}$).

Potassium (mmol/L), Chloride (mmol/L), Calcium (mmol/L): $<0.9 \times \text{LLN}$, $>1.1 \times \text{ULN}$ (if Pre-Rx $< \text{LLN}$: $<0.9 \times \text{Pre-Rx}$, $> \text{ULN}$. If Pre-Rx $> \text{ULN}$: $>1.1 \times \text{Pre-Rx}$, $< \text{LLN}$).

Phosphorus (mg/dL): $<0.85 \times \text{LLN}$, $>1.25 \times \text{ULN}$ (if Pre-Rx $< \text{LLN}$, $<0.85 \times \text{Pre-Rx}$, $> \text{ULN}$. if Pre-Rx $> \text{ULN}$: $>1.25 \times \text{Pre-Rx}$, $< \text{LLN}$).

End point type	Secondary
End point timeframe:	
Day 1 (Pre-dose) to Day 3	

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	8	
Units: participants				
ALP, high (n=8, 8, 8)	0	0	0	
ALT, high (8, 8, 8)	1	0	0	
AST, high (n=8, 8, 8)	1	0	0	
Bilirubin, high (n=8, 8, 8)	0	0	0	
Blood Urea Nitrogen, high (n=8, 8, 8)	0	0	0	
Calcium, low (n=8, 8, 8)	0	0	0	
Creatinine, high (n=8, 8, 8)	0	0	0	
Chloride, low (n=8, 8, 8)	0	0	0	
Calcium, high (n=8, 8, 8)	0	0	0	
Potassium, low (n=8, 8, 8)	0	0	0	
Potassium, high (n=8, 8, 8)	0	0	0	
Sodium, low (n=8, 8, 8)	0	0	0	
Sodium, high (n=8, 8, 8)	0	0	0	
Phosphorus, Inorganic, low (n=8, 8, 8)	0	0	0	
Phosphorus, Inorganic, high (n=8, 8, 8)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Marked Abnormalities in Other Chemistry Testing

End point title	Number of Participants With Marked Abnormalities in Other Chemistry Testing
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End point description:

All treated participants were analyzed. Lab values that met the following criteria were marked as

abnormalities:

Glucose, fasting serum (mmol/L): $<0.8 \times \text{LLN}$, $>1.3 \times \text{ULN}$ (if Pre-Rx $< \text{LLN}$: $<0.8 \times \text{Pre-Rx}$, $> \text{ULN}$. If Pre-Rx $> \text{ULN}$: $>2.0 \times \text{Pre-Rx}$, $< \text{LLN}$).

Protein (grams per deciliter: g/L): $<0.9 \times \text{LLN}$, $>1.1 \times \text{ULN}$ (if Pre-Rx $< \text{LLN}$: $<0.9 \times \text{Pre-Rx}$, $> \text{ULN}$. If Pre-Rx $> \text{ULN}$: $>1.1 \times \text{Pre-Rx}$, $< \text{LLN}$).

Albumin (g/L): $<0.9 \times \text{LLN}$ (if Pre-Rx $< \text{LLN}$: $<0.9 \times \text{Pre-Rx}$).

Uric Acid (mmol/L): $>1.2 \times \text{ULN}$ (if Pre-Rx $> \text{ULN}$: $>1.25 \times \text{Pre-Rx}$).

Lactate Dehydrogenase (U/L): $>1.25 \times \text{ULN}$ (if Pre-Rx $> \text{ULN}$: $>1.5 \times \text{Pre-Rx}$)

End point type	Secondary
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End point timeframe:

Day 1 (Pre-dose) to Day 3

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	8	
Units: participants				
Glucose, fasting serum, low (n=7, 7, 7)	0	0	0	
Glucose, fasting serum, high (n=7, 7, 7)	1	1	0	
Albumin (n= 8, 8, 8)	0	0	0	
Protein, total (8, 8, 8)	0	0	0	
Uric acid (n=7, 8, 7)	0	0	0	
Lactate dehydrogenase (n=8, 8, 8)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Marked Urinalysis Abnormalities

End point title	Number of Participants With Marked Urinalysis Abnormalities
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End point description:

All treated participants with evaluable urinalysis profiles were analyzed. Lab values that met the following criteria were marked as abnormalities:

Blood, urine (Qualitative): ≥ 2 (If Pre-Rx ≥ 1 , $\geq 2 \times \text{Pre-Rx}$).

Glucose, urine (Qualitative): ≥ 1 , (If Pre-Rx ≥ 1 , $\geq 2 \times \text{Pre-Rx}$).

Protein, urine (Qualitative): ≥ 2 (If Pre-Rx ≥ 1 , $\geq 2 \times \text{Pre-Rx}$).

Red Blood Cells (RBC), urine (RBC per High Power Field (hpf)): ≥ 2 (If Pre-Rx ≥ 2 , ≥ 4).

White Blood Cells (WBC), urine (hpf): ≥ 2 (If Pre-Rx ≥ 2 , ≥ 4).

End point type	Secondary
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End point timeframe:

Day 1 (Pre-dose) to Day 3

End point values	Dapagliflozin 2.5 mg	Dapagliflozin 5 mg	Dapagliflozin 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	8	
Units: participants				
Blood, urine, high (n= 8, 8, 8)	0	0	2	
Glucose, urine, high (n=8, 8, 8)	2	3	4	
Protein, urine, high (n=8, 8, 8)	0	0	3	
RBC, urine, high (n=1, 1, 4)	0	0	3	
WBC, urine, high (n=4, 2, 3)	1	0	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after the last dose of the study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	Dapagliflozin 2.5 mg
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Reporting group description:

Dapagliflozin: Tablet, Oral, 2.5 mg, Single-dose

Reporting group title	Dapagliflozin 10 mg
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Reporting group description:

Dapagliflozin: Tablet, Oral, 10 mg, Single-dose

Reporting group title	Dapagliflozin 5 mg
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Reporting group description:

Dapagliflozin: Tablet, Oral, 5 mg, Single-dose

Serious adverse events	Dapagliflozin 2.5 mg	Dapagliflozin 10 mg	Dapagliflozin 5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Dapagliflozin 2.5 mg	Dapagliflozin 10 mg	Dapagliflozin 5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)	3 / 8 (37.50%)	1 / 8 (12.50%)
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0

Pyrexia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 2	0 / 8 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 2	0 / 8 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0
Skin irritation subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0
Infections and infestations Influenza subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2012	Removed the following urinary PK parameters: %UR and CLR(0-24h)
11 July 2012	Removed the caffeine consumption restriction from the exclusion criteria and specified that the Day -1 labs will be non-fasting. Also clarified that subjects have the option to report to the clinical facility early in the morning on Day 1 for dosing.
08 August 2012	Clarified several eligibility criteria in the protocol
17 January 2013	Clarified that diagnosis of type 2 diabetes will be based on WHO or ADA criteria. Changed the lower bound of the HbA1c range from 6.5% to 6% and removed the requirement for BMI 85th percentile for inclusion. Revised the sampling schedule and pharmacokinetic parameters for dried blood spot (DBS) samples. Clarifications to endpoint objectives and analyses were made. Administrative updates included.
22 October 2013	Removed insulin treatment as exclusion requirement and provided allowance to decrease insulin and adjust dosage schedule as needed on Day -1. Added EUDRACT number.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27291448>