Clinical trial results:
An open-label, randomised, multicentre, single-dose, parallel group trial to evaluate pharmacokinetics and pharmacodynamics of empagliflozin in children and adolescents from 10 to less than 18 years of age with type 2 diabetes mellitus

Summary

EudraCT number	2013-002304-14
Trial protocol	DE Outside EU/EEA AT FR
Global end of trial date	29 February 2016

Results information

Result version number	v1 (current)
This version publication date	13 August 2016
First version publication date	13 August 2016

Trial information

Trial identification

Sponsor protocol code	1245.87

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02121483
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim (BI), +1 800 2430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim (BI), +1 800 2430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000082-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	30 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 February 2016
Global end of trial reached?	Yes
Global end of trial date	29 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this trial were to assess the pharmacokinetics and the pharmacodynamics of a single dose of empagliflozin in children and
adolescents with type 2 diabetes mellitus.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct.

Background therapy:

Patient could take Metformin or basal or multiple dose injection (MDI) insulin as background in addition to diet and exercise.

Evidence for comparator: -

Actual start date of recruitment	30 June 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	France: 1
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	United States: 22
Country: Number of subjects enrolled	South Africa: 10
Worldwide total number of subjects	39
EEA total number of subjects	1

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)	6
Adolescents (12-17 years)	33
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:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

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

Blinding implementation details:

Blinding is not applicable as this trial was conducted in an open-label manner at the trial sites. Also, the trial is uncontrolled trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Empagliflozin 5mg

Arm description:

Single dose (1 tablet) of 5mg, empagliflozin, film-coated tablet administered orally.

Arm type	Experimental
Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Single dose (1 tablet) of 5mg, empagliflozin, film-coated tablet administered orally.

Arm title	Empagliflozin 10mg

Arm description:

Single dose (1 tablet) of 10mg, empagliflozin, film-coated tablet administered orally.

Arm type	Experimental
Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Single dose (1 tablet) of 10mg, empagliflozin, film-coated tablet administered orally.

Arm title	Empagliflozin 25mg

Arm description:

Single dose (1 tablet) of 25mg, empagliflozin, film-coated tablet administered orally.

Arm type	Experimental

Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Single dose (1 tablet) of 25mg, empagliflozin, film-coated tablet administered orally.

Number of subjects in period 1[1]	Empagliflozin 5mg	Empagliflozin 10mg	Empagliflozin 25mg
Started	9	8	10
Completed	9	8	10

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: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Empagliflozin 5mg
Reporting group description:	
Single dose (1 tablet) of 5mg, empagliflozin, film-coated tablet administered orally.	
Reporting group title	Empagliflozin 10mg
Reporting group description:	
Single dose (1 tablet) of 10mg, empagliflozin, film-coated tablet administered orally.	
Reporting group title	Empagliflozin 25mg
Reporting group description:	
Single dose (1 tablet) of 25mg, empagliflozin, film-coated tablet administered orally.	

Reporting group values	Empagliflozin 5mg	Empagliflozin 10mg	Empagliflozin 25mg
Number of subjects	9	8	10
Age categorical Units: Subjects			

Age Continuous			
Treated Set (TS): The TS included all patients who were allocated trial medication and received trial medication (empagliflozin).			
Units: Years			
arithmetic mean	13.7	14.5	14.2
standard deviation	± 2	± 1.9	± 2.1
Gender, Male/Female Units: Participants			
Female	6	5	7
Male	3	3	3

Reporting group values	Total		
Number of subjects	27		
Age categorical Units: Subjects			

Age Continuous			
Treated Set (TS): The TS included all patients who were allocated trial medication and received trial medication (empagliflozin).			
Units: Years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: Participants			
Female	18		
Male	9		

End points

End points reporting groups

Reporting group title	Empagliflozin 5mg
Reporting group description:	
Single dose (1 tablet) of 5mg, empagliflozin, film-coated tablet administered orally.	
Reporting group title	Empagliflozin 10mg
Reporting group description:	
Single dose (1 tablet) of 10mg, empagliflozin, film-coated tablet administered orally.	
Reporting group title	Empagliflozin 25mg
Reporting group description:	
Single dose (1 tablet) of 25mg, empagliflozin, film-coated tablet administered orally.	

Primary: AUC0-inf

End point title	AUC0-inf
End point description:	
Area under the concentration-time curve of analyte in plasma over the time interval from 0 extrapolated to infinity (AUC0-inf). Pharmacokinetic Set (PKS): The PKS included all treated patients who provided at least 1 primary or secondary pharmacokinetic parameter for statistical assessment.	
End point type	Primary
End point timeframe:	
Before drug administration (-0:30 hours (h)) and 0:30h, 1:00h, 1:30h, 2:00h, 4:00h, 8:00h, 12:00 (Day 1), 24:00 (Day 2), 34:00 (Day 2), 48:00 (Day 3) after drug administration.	

End point values	Empagliflozin 5mg	Empagliflozin 10mg	Empagliflozin 25mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9[1]	8[2]	10[3]	
Units: nmol*h/L				
geometric mean (geometric coefficient of variation)	1150 (± 47.6)	1430 (± 17.2)	5060 (± 29.5)	

Notes:

[1] - PKS

[2] - PKS

[3] - PKS

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Dose proportionality was assessed based on a power model that describes the functional relationship between the dose and AUC0-inf. Based on the estimate for the slope parameter β, a 2-sided 95% CI for the slope was computed.	
Comparison groups	Empagliflozin 5mg v Empagliflozin 10mg v Empagliflozin 25mg

Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Linear
Parameter estimate	Slope
Point estimate	0.949
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7276
upper limit	1.1704
Variability estimate	Standard error of the mean
Dispersion value	0.1075

Primary: AUC0-tz

End point title	AUC0-tz

End point description:

Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the time of the last quantifiable concentration (AUC0-tz).

End point type	Primary

End point timeframe:

Before drug administration (-0:30 hours (h)) and 0:30h, 1:00h, 1:30h, 2:00h, 4:00h, 8:00h, 12:00 (Day 1), 24:00 (Day 2), 34:00 (Day 2), 48:00 (Day 3) after drug administration.

End point values	Empagliflozin 5mg	Empagliflozin 10mg	Empagliflozin 25mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9[4]	8[5]	10[6]	
Units: nmol*h/L				
geometric mean (geometric coefficient of variation)	1110 (± 49.9)	1400 (± 17.1)	4980 (± 29.1)	

Notes:

[4] - PKS

[5] - PKS

[6] - PKS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Dose proportionality was assessed based on a power model that describes the functional relationship between the dose and AUC0-tz.
Based on the estimate for the slope parameter β, a 2-sided 95% CI for the slope was computed.

Comparison groups	Empagliflozin 5mg v Empagliflozin 10mg v Empagliflozin 25mg

Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Linear
Parameter estimate	Slope
Point estimate	0.9597
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7356
upper limit	1.1838
Variability estimate	Standard error of the mean
Dispersion value	0.1088

Primary: Cmax

End point title	Cmax

End point description:

Maximum measured concentration in plasma (Cmax).

End point type	Primary

End point timeframe:

Before drug administration (-0:30 hours (h)) and 0:30h, 1:00h, 1:30h, 2:00h, 4:00h, 8:00h, 12:00 (Day 1), 24:00 (Day 2), 34:00 (Day 2), 48:00 (Day 3) after drug administration.

End point values	Empagliflozin 5mg	Empagliflozin 10mg	Empagliflozin 25mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9[7]	8[8]	10[9]	
Units: nmol/L				
geometric mean (geometric coefficient of variation)	159 (± 44.5)	188 (± 50.2)	602 (± 61.1)	

Notes:

[7] - PKS

[8] - PKS

[9] - PKS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Dose proportionality was assessed based on a power model that describes the functional relationship between the dose and Cmax.
Based on the estimate for the slope parameter β, a 2-sided 95% CI for the slope was computed.

Comparison groups	Empagliflozin 5mg v Empagliflozin 10mg v Empagliflozin 25mg

Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Linear
Parameter estimate	Slope
Point estimate	0.8554
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5504
upper limit	1.1603
Variability estimate	Standard error of the mean
Dispersion value	0.1481

Primary: tmax

End point title	tmax[10]

End point description:

Maximum measured concentration in plasma (tmax)

End point type	Primary

End point timeframe:

Before drug administration (-0:30 hours (h)) and 0:30h, 1:00h, 1:30h, 2:00h, 4:00h, 8:00h, 12:00 (Day 1), 24:00 (Day 2), 34:00 (Day 2), 48:00 (Day 3) after drug administration.

Notes:

[10] - 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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	Empagliflozin 5mg	Empagliflozin 10mg	Empagliflozin 25mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9[11]	8[12]	10[13]	
Units: hours				
median (full range (min-max))	1.5 (0.95 to 7.92)	1.25 (0.967 to 4.17)	1.78 (0.5 to 4)	

Notes:

[11] - PKS

[12] - PKS

[13] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: t1/2

End point title	t1/2[14]

End point description:

Terminal half-life in plasma (t1/2).

End point type	Primary

End point timeframe:

Before drug administration (-0:30 hours (h)) and 0:30h, 1:00h, 1:30h, 2:00h, 4:00h, 8:00h, 12:00 (Day 1), 24:00 (Day 2), 34:00

(Day 2), 48:00 (Day 3) after drug administration.

Notes:

[14] - 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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	Empagliflozin 5mg	Empagliflozin 10mg	Empagliflozin 25mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9[15]	8[16]	10[17]	
Units: hours				
geometric mean (geometric coefficient of variation)	6.92 (± 19.4)	7.35 (± 29.3)	7.8 (± 29.6)	

Notes:

[15] - PKS

[16] - PKS

[17] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Urinary Glucose Excretion (UGE) over 24 h after study drug intake

End point title	Change from baseline in Urinary Glucose Excretion (UGE) over 24 h after study drug intake

End point description:

Change from baseline in Urinary Glucose Excretion (UGE) over 24 h after study drug intake. For the changes from baseline in UGE on Day 1 (0 to 24 h postdose) , adjusted means per treatment group were to be calculated based on an ANCOVA including 'treatment' as a fixed effect and 'UGE at baseline' and 'FPG at baseline' as continuous covariates. Means presented are the adjusted means.
Treated Set (TS) including patients with UGE data on both visits is the population set used for the endpoint.

End point type	Secondary

End point timeframe:

baseline and 24 hours

End point values	Empagliflozin 5mg	Empagliflozin 10mg	Empagliflozin 25mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8[18]	8[19]	10[20]	
Units: g/24h				
arithmetic mean (standard error)	53.1 (± 10.24)	73 (± 10.14)	87.4 (± 9.39)	

Notes:

[18] - TS

[19] - TS

[20] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Fasting Plasma Glucose (FPG) at 24 h after study drug intake

End point title	Change from baseline in Fasting Plasma Glucose (FPG) at 24 h after study drug intake

End point description:

Change from baseline in Fasting Plasma Glucose (FPG) at 24h after study drug intake. For the change from baseline in FPG at 24 h postdose (in the morning of Day 2), adjusted means per treatment group were to be calculated based on an ANCOVA including 'treatment' as a fixed effect and 'FPG at baseline' as continuous covariate. Means presented are the adjusted means.
Treated Set (TS) including patients with FPG data on both visits was the population set used for this endpoint.

End point type	Secondary

End point timeframe:

baseline and 24 hours

End point values	Empagliflozin 5mg	Empagliflozin 10mg	Empagliflozin 25mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7[21]	8[22]	10[23]	
Units: mg/dL				
arithmetic mean (standard error)	-15.5 (± 6.53)	-16.6 (± 6.29)	-20.4 (± 5.68)	

Notes:

[21] - TS

[22] - TS

[23] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in 8-point plasma glucose profile over 24 h after study drug intake

End point title	Change from baseline in 8-point plasma glucose profile over 24 h after study drug intake

End point description:

Change from baseline in 8-point plasma glucose profile over 24h after study drug intake (as defined by change from baseline in Mean Daily Glucose (MDG) calculated at Day 1). For the changes from baseline in MDG on Day 1, adjusted means per treatment group were to be calculated based on an ANCOVA including 'treatment' as fixed effect and 'MDG at baseline' as continuous covariate. Means presented are the adjusted means.
Treated Set (TS) including patients with plasma glucose profile data on both visits is the population set used for this endpoint.

End point type	Secondary

End point timeframe:

baseline and 24 hours

End point values	Empagliflozin 5mg	Empagliflozin 10mg	Empagliflozin 25mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[24]	4[25]	7[26]	
Units: mg/dL				
arithmetic mean (standard error)	-12.9 (± 7.95)	-6.5 (± 9.21)	-13.2 (± 7)	

Notes:

[24] - TS

[25] - TS

[26] - TS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: All adverse events reported within 7 days following trial drug administration were considered on treatment, up to 8 days.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Empagliflozin 5mg
Reporting group description: Single dose (1 tablet) of 5mg, empagliflozin, film-coated tablet administered orally.	
Reporting group title	Empagliflozin 10mg
Reporting group description: Single dose (1 tablet) of 10mg, empagliflozin, film-coated tablet administered orally.	
Reporting group title	Empagliflozin 25mg
Reporting group description: Single dose (1 tablet) of 25mg, empagliflozin, film-coated tablet administered orally.	

Serious adverse events	Empagliflozin 5mg	Empagliflozin 10mg	Empagliflozin 25mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 10 (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	Empagliflozin 5mg	Empagliflozin 10mg	Empagliflozin 25mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 9 (44.44%)	1 / 8 (12.50%)	2 / 10 (20.00%)
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			

subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Anal pruritus			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 10 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2014	In agreement with FDA and EMA/PDCO, patient on a stable dose of basal insulin (given alone or in combination with metformin treatment) could also be included in the trial and the clinical trial protocol was adapted throughout to accommodate for this change in the main criteria for inclusion. Exclusion Criterion No. 2 was modified to 'History of acute metabolic de-compensation, such as diabetic ketoacidosis within 3 months before the screening visit with theexception of acute de-compensation at the time of T2DM diagnosis', as it had been discussed at the Investigator Meeting that acute de-compensation at the time of diagnosis of T2DM was not to be a reason for exclusion and was therefore listed as an exception.
09 February 2015	The main criteria for inclusion as well as Inclusion Criteria No. 3 and 4 were adapted by removal of the lower HbA1c limit as well as by removal of a minimum dose of metformin and addition of stable dosing for metformin (for patients on metformin background therapy). As agreed with the FDA and the EMA/PDCO, these changes were to improve recruitment while accounting for special characteristics of paediatric patients with T2DM.
29 July 2015	As agreed with FDA and EMA/PDCO, patients on MDI insulin (with a maximum total daily dose) were to also be included in the trial. In addition, the weekly insulin dose change allowed prior to randomisation was revised. The clinical trial protocol was adapted throughout to accommodate for this change in the main criteria for inclusion. Metabolic acidosis, ketoacidosis, and diabetic ketoacidosis were added to the list of AESIs upon request by the FDA in order to collect as much information as possible about the potential risk in ongoing trials with SGLT-2 inhibitors. The potential risk of diabetic ketoacidosis during treatment with SGLT-2 inhibitors was added in the benefit-risk assessment. Furthermore, recommendations in case of diabetic ketoacidosis symptoms were given and diabetic ketoacidosis was defined as a reason for withdrawal of individual patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported