Clinical trial results:
A 28-day randomised, placebo-controlled, double-blind parallel group phase IIa trial to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of once daily oral doses of 2.5 mg, 10 mg, and 25 mg empagliflozin as adjunctive to insulin in patients with type 1 diabetes mellitus (EASE-1)

Summary

EudraCT number	2011-004354-25
Trial protocol	DE AT
Global end of trial date	20 April 2014

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	17 April 2015

Trial information

Trial identification

Sponsor protocol code	1245.78

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01969747
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim Pharma GmbH & Co. KG
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim Pharma GmbH & Co. KG, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim Pharma GmbH & Co. KG, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 March 2014
Global end of trial reached?	Yes
Global end of trial date	20 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety, tolerability, PK and PD of once daily oral doses of 2.5 mg, 10 mg, and 25 mg of empagliflozin in patients with T1DM as adjunctive therapy to insulin.

To assess the impact of empagliflozin on 24 h urinary glucose excretion (UGE) after seven days of administration compared to placebo and add-on to a stable insulin background therapy in patients with T1DM

In the second part of the treatment period (Day 8 to 28), when each patient's background insulin was to be adjusted to achieve optimal glycaemic control: To gain experience in the need for such adjustments and to provide adjustment recommendations for subsequent trials

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were 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. Rescue medication was allowed for all patients as required.

Background therapy:

Subjects were on multiple daily injections (MDI) of insulin background medication:
From Day 1 up to the morning of Day 8 all subjects were required to keep their algorithm of background insulin as stable as possible;
from Day 8 until end of treatment (Day 28) each subject's algorithm of background insulin was adjusted freely to achieve optimal glycaemic control.

Evidence for comparator: -

Actual start date of recruitment	25 November 2013
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	Austria: 60
Country: Number of subjects enrolled	Germany: 51
Worldwide total number of subjects	111
EEA total number of subjects	111

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	111
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 subject) met all strictly implemented inclusion/exclusion criteria. Subjects were not randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo tablet;
oral administration once daily for 28 days;
background therapy: MDI insulin

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets matching empagliflozin 2.5, 10 and 25 mg;
administered oral once daily.

Arm title	Empagliflozin 2.5 mg

Arm description:

Empagliflozin 2.5 mg tablet;
oral administration once daily for 28 days;
background therapy: MDI insulin

Arm type	Experimental
Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Empagliflozin 2.5 mg tablet;
administered oral once daily

Arm title	Empagliflozin 10 mg

Arm description:

Empagliflozin 10 mg tablet;
oral administration once daily for 28 days;
background therapy: MDI insulin

Arm type	Experimental

Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Empagliflozin 10 mg tablet;
administered oral once daily

Arm title	Empagliflozin 25 mg

Arm description:

Empagliflozin 25 mg tablet;
oral administration once daily for 28 days;
background therapy: MDI insulin

Arm type	Experimental
Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Empagliflozin 25 mg tablet;
administered oral once daily

Number of subjects in period 1[1]	Placebo	Empagliflozin 2.5 mg	Empagliflozin 10 mg
Started	19	19	19
Completed	19	19	19

Number of subjects in period 1[1]	Empagliflozin 25 mg
Started	18
Completed	18

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 and subject disposition data are based on patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo tablet; oral administration once daily for 28 days; background therapy: MDI insulin	
Reporting group title	Empagliflozin 2.5 mg
Reporting group description:	
Empagliflozin 2.5 mg tablet; oral administration once daily for 28 days; background therapy: MDI insulin	
Reporting group title	Empagliflozin 10 mg
Reporting group description:	
Empagliflozin 10 mg tablet; oral administration once daily for 28 days; background therapy: MDI insulin	
Reporting group title	Empagliflozin 25 mg
Reporting group description:	
Empagliflozin 25 mg tablet; oral administration once daily for 28 days; background therapy: MDI insulin	

Reporting group values	Placebo	Empagliflozin 2.5 mg	Empagliflozin 10 mg
Number of subjects	19	19	19
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	40.5	41.9	39.6
standard deviation	± 10.6	± 12.4	± 11.6
Gender categorical Units: Subjects			
Female	6	4	4
Male	13	15	15

Reporting group values	Empagliflozin 25 mg	Total	
Number of subjects	18	75	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	41.9		
standard deviation	± 9.7	-	
Gender categorical Units: Subjects			
Female	8	22	
Male	10	53	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo tablet; oral administration once daily for 28 days; background therapy: MDI insulin	
Reporting group title	Empagliflozin 2.5 mg
Reporting group description:	
Empagliflozin 2.5 mg tablet; oral administration once daily for 28 days; background therapy: MDI insulin	
Reporting group title	Empagliflozin 10 mg
Reporting group description:	
Empagliflozin 10 mg tablet; oral administration once daily for 28 days; background therapy: MDI insulin	
Reporting group title	Empagliflozin 25 mg
Reporting group description:	
Empagliflozin 25 mg tablet; oral administration once daily for 28 days; background therapy: MDI insulin	

Primary: Change From Baseline in 24 h UGE (g/24 h) at Day 7

End point title	Change From Baseline in 24 h UGE (g/24 h) at Day 7

End point description:

Change from baseline in urinary glucose excretion (UGE) (g/24h) after seven days of treatment. The term 'baseline' refers to the last observation prior to the first intake of any randomised study drug (Day -1).

The treatment effect was estimated on the basis of the least square mean treatment difference at Day 7 extracted from the primary analysis model.

The primary endpoint is an exploratory endpoint.

Full analysis set (FAS): all patients randomised, treated with at least one dose of study drug, had a baseline UGE (g/24 h) and a UGE (g/24 h) on Day 1 or Day 7. The last observation carried forward (LOCF) approach was used as the primary method of imputation for missing data.

End point type	Primary

End point timeframe:

Baseline (Day -1) and 7 days after first drug administration (Day 7)

End point values	Placebo	Empagliflozin 2.5 mg	Empagliflozin 10 mg	Empagliflozin 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[1]	19[2]	19[3]	18[4]
Units: g/24h				
arithmetic mean (standard error)	-3.56 (± 4.27)	72.45 (± 7.01)	103.33 (± 6.68)	101.79 (± 6.51)

Notes:
[1] - FAS
[2] - FAS
[3] - FAS
[4] - FAS

Statistical analyses

Statistical analysis title	Comparison of Empagliflozin 2.5 mg and Placebo

Statistical analysis description:

The model includes baseline urine glucose excretion as linear covariate(s) and treatment as fixed effect(s).

The adjusted mean difference is calculated as the adjusted mean of 'Empagliflozin 2.5 mg' minus the adjusted mean of 'Placebo'.

Comparison groups	Empagliflozin 2.5 mg v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	76.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	58.6
upper limit	93.59
Variability estimate	Standard error of the mean
Dispersion value	8.77

Statistical analysis title	Comparison of Empagliflozin 10 mg and Placebo

Statistical analysis description:

The model includes baseline urine glucose excretion as linear covariate(s) and treatment as fixed effect(s).

The adjusted mean difference is calculated as the adjusted mean of 'Empagliflozin 10 mg' minus the adjusted mean of 'Placebo'.

Comparison groups	Empagliflozin 10 mg v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	106.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	88.73
upper limit	124.05

Variability estimate	Standard error of the mean
Dispersion value	8.85

Statistical analysis title	Comparison of Empagliflozin 25 mg and Placebo

Statistical analysis description:

The model includes baseline urine glucose excretion as linear covariate(s) and treatment as fixed effect(s).

The adjusted mean difference is calculated as the adjusted mean of 'Empagliflozin 25 mg' minus the adjusted mean of 'Placebo'.

Comparison groups	Empagliflozin 25 mg v Placebo
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	104.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	86.88
upper limit	122.74
Variability estimate	Standard error of the mean
Dispersion value	8.99

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first drug administration until 7 days after last drug administration (Day 35)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo tablet; oral administration once daily	
Reporting group title	2.5 mg Empagliflozin
Reporting group description: 2.5 mg Empagliflozin tablet; oral administration once daily	
Reporting group title	10 mg Empagliflozin
Reporting group description: 10 mg Empagliflozin tablet; oral administration once daily	
Reporting group title	25 mg Empagliflozin
Reporting group description: 25 mg Empagliflozin tablet; oral administration once daily	

Serious adverse events	Placebo	2.5 mg Empagliflozin	10 mg Empagliflozin
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 19 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	25 mg Empagliflozin		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Metabolism and nutrition disorders			
Hypoglycaemia			

subjects affected / exposed	0 / 18 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	2.5 mg Empagliflozin	10 mg Empagliflozin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 19 (94.74%)	17 / 19 (89.47%)	15 / 19 (78.95%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Phlebitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Thrombophlebitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	3 / 19 (15.79%)	0 / 19 (0.00%)	2 / 19 (10.53%)
occurrences (all)	3	0	5
Lumbar radiculopathy			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			

Application site erythema			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Diarrhoea			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash erythematous			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Back pain			

subjects affected / exposed	2 / 19 (10.53%)	1 / 19 (5.26%)	1 / 19 (5.26%)
occurrences (all)	2	1	1
Neck pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 19 (26.32%)	2 / 19 (10.53%)	0 / 19 (0.00%)
occurrences (all)	5	2	0
Urinary tract infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	17 / 19 (89.47%)	16 / 19 (84.21%)	13 / 19 (68.42%)
occurrences (all)	64	62	47
Polydipsia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	25 mg Empagliflozin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 18 (100.00%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Phlebitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Thrombophlebitis			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		

Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	6 / 18 (33.33%)		
occurrences (all)	6		
Lumbar radiculopathy			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Application site erythema			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0		
Skin and subcutaneous tissue disorders Rash erythematous subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all)	 0 / 18 (0.00%) 0 0 / 18 (0.00%) 0 0 / 18 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1		
Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all) Polydipsia subjects affected / exposed occurrences (all)	 17 / 18 (94.44%) 66 1 / 18 (5.56%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported