Clinical trial results:
Randomized, double-blind, placebo controlled, crossover clinical study to analyse the effect of empagliflozin on microvascular circulation

Summary

EudraCT number	2014-003053-34
Trial protocol	DE
Global end of trial date	01 March 2016

Results information

Result version number	v1 (current)
This version publication date	09 July 2021
First version publication date	09 July 2021

Trial information

Trial identification

Sponsor protocol code	CRC2014EMPA

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	IPPMED Institut für Pharmakologie und präventive Medizin GmbH
Sponsor organisation address	B, C, Germany, 49661
Public contact	Clinical Research Unit, Medizinische Klinik 4, 0049 91318536245, roland.schmieder@uk-erlangen.de
Scientific contact	Clinical Research Unit, Medizinische Klinik 4, 0049 91318536245, roland.schmieder@uk-erlangen.de

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	Interim
Date of interim/final analysis	01 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 March 2016
Global end of trial reached?	Yes
Global end of trial date	01 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to analyse the effect of empagliflozin on the microcirculation as assessed by the pulse wave reflection in the peripheral arterial tree (indicative of microvascular changes) with the parameters central (aortic) systolic pressure and pulse pressure, augmentation pressure, forward and backward wave amplitude.

Protection of trial subjects:

Physical examinations, vital signs, checking concomitant medication, assessment of adverse events, measurement of safety laboratory markers (including glucose levels, biochemistry, haematology and urinanalsis) were done regularly in the course of the study.
Patients were provided with a glucometer and kept an individual diary for blood glucose measurements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 February 2015
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	Germany: 74
Worldwide total number of subjects	74
EEA total number of subjects	74

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)	46
From 65 to 84 years	28

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patient will be recruited simultaneously at the two locations (Erlangen, Nürnberg) from investigator outpatient clinics, referring physicians, and advertisement in local newspapers.
After a first contact by phone eligible patients will be invited to a screening visit.

Pre-assignment

Screening details:

Male and Female patients at the age of 18 - 75 years with Type 2 diabetes mellitus, defined by fasting glucose ≥ 126 mg/dl or HbA1c ≥ 6.5% or on blood glucose lowering medication.
Patients not pretreated with anti-diabetic medication did not have a 4 week run-in/wash-out Phase.

Period 1

Period 1 title	Treatment Period 1 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Empagliflozin

Arm description:

The study followed randomized cross-over-design, i.e. subjects underwent both treatment arms in randomized order for 6 weeks.

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:

25 mg once daily

Arm title	Placebo

Arm description:

The study followed randomized cross-over-design, i.e. subjects underwent both treatment arms in randomized order for 6 weeks.

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

Dosage and administration details:

once daily

Number of subjects in period 1	Empagliflozin	Placebo
Started	74	74
Completed	71	71
Not completed	3	3
Consent withdrawn by subject	1	1
Adverse event, non-fatal	1	1
Protocol deviation	1	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment Period 1

Reporting group description: -

Reporting group values	Treatment Period 1	Total	
Number of subjects	74	74	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	46	46	
From 65-84 years	28	28	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	30	30	
Male	44	44	

End points

End points reporting groups	
Reporting group title	Empagliflozin
Reporting group description:	
The study followed randomized cross-over-design, i.e. subjects underwent both treatment arms in randomized order for 6 weeks.	
Reporting group title	Placebo
Reporting group description:	
The study followed randomized cross-over-design, i.e. subjects underwent both treatment arms in randomized order for 6 weeks.	

Primary: effect of IMP on change of central SBP	
End point title	effect of IMP on change of central SBP
End point description:	
measured by SphygmoCor	
End point type	Primary
End point timeframe:	
6 weeks	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	71		
Units: mmHg				
arithmetic mean (standard deviation)	-6.1 (± 9.4)	-0.96 (± 11)		

Statistical analyses

Statistical analysis title	effect of IMP on change of central SBP
Comparison groups	Placebo v Empagliflozin
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	2.5

Primary: effect of IMP on change of central pulse pressure	
End point title	effect of IMP on change of central pulse pressure
End point description: measured by SphygmoCor	
End point type	Primary
End point timeframe: 6 weeks	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	71		
Units: mmHg				
arithmetic mean (standard deviation)	-4.01 (± 7.8)	-1.24 (± 0.9)		

Statistical analyses

Statistical analysis title	effect of IMP on change of central pulse pressure
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %

Primary: effect of IMP on change of augmentation pressure	
End point title	effect of IMP on change of augmentation pressure
End point description: measured by SphygmCor	
End point type	Primary
End point timeframe: 6 weeks	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	71		
Units: mmHg				
arithmetic mean (standard deviation)	-1.44 (± 4.3)	-0.53 (± 4.6)		

Statistical analyses

Statistical analysis title	effect of IMP on change of augmentation pressure
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	2.5

Primary: effect of IMP on change of forward wave amplitude	
End point title	effect of IMP on change of forward wave amplitude
End point description: measured by SphygmoCor	
End point type	Primary
End point timeframe: 6 weeks	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: mmHg				
arithmetic mean (standard deviation)	-2.13 (± 4.6)	-0.36 (± 5.6)		

Statistical analyses

Statistical analysis title	effect of IMP on change of forward wave amplitude
Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	2.5

Primary: effect of IMP on change of backward wave amplitude	
End point title	effect of IMP on change of backward wave amplitude
End point description: measured by SphygmoCor	
End point type	Primary
End point timeframe: 6 weeks	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: mmHg				
arithmetic mean (standard deviation)	-2.14 (± 4.2)	-0.74 (± 5.2)		

Statistical analyses

Statistical analysis title	effect of IMP on change of backward wave amplitude
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	2.5

Secondary: effect of IMP on change of retinal capillary flow

End point title	effect of IMP on change of retinal capillary flow

End point description:

End point type	Secondary

End point timeframe:
6 weeks

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63		
Units: AU				
arithmetic mean (standard deviation)	7.9 (± 101)	8.21 (± 84)		

Statistical analyses

No statistical analyses for this end point

Secondary: effect of IMP on change of retinal capillary flow after flickering

End point title	effect of IMP on change of retinal capillary flow after flickering

End point description:

End point type	Secondary

End point timeframe:
6 weeks

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	67		
Units: AU				
arithmetic mean (standard deviation)	-0.14 (± 84)	-1.88 (± 85)		

Statistical analyses

No statistical analyses for this end point

Secondary: effect of IMP on change of pulse wave velocity	
End point title	effect of IMP on change of pulse wave velocity
End point description: measured by SphygmoCor	
End point type	Secondary
End point timeframe: 6 weeks	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	67		
Units: m/s				
arithmetic mean (standard deviation)	-0.01 (± 1.5)	0.01 (± 1.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: effect of IMP on change of 24-h-ambulatory systolic blood pressure	
End point title	effect of IMP on change of 24-h-ambulatory systolic blood pressure
End point description:	
End point type	Secondary
End point timeframe: 6 weeks	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	70		
Units: mmHg				
arithmetic mean (standard deviation)	-2.08 (± 8.1)	-0.07 (± 7.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

In the course of the intire study , each adverse event had to be reported on an Adverse Event Case Report Form as soon as known, in general at the subsequent study visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	all patients treated with IMP

Reporting group description: -

Serious adverse events	all patients treated with IMP		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 74 (1.35%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Skin and subcutaneous tissue disorders			
Basal cell carcinoma			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	all patients treated with IMP		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 74 (50.00%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	8		
Musculoskeletal and connective tissue			

disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	 5 / 74 (6.76%) 5 6 / 74 (8.11%) 6		
Infections and infestations Cystitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 5 / 74 (6.76%) 5 8 / 74 (10.81%) 8		

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