Clinical trial results:
A double-blind randomized study to determine the effect of empagliflozin versus placebo on brain insulin sensitivity in patients with prediabetes

Summary

EudraCT number	2016-003477-18
Trial protocol	DE
Global end of trial date	25 October 2019

Results information

Result version number	v1 (current)
This version publication date	29 March 2022
First version publication date	29 March 2022

Trial information

Trial identification

Sponsor protocol code	Empabrain01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03227484
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Tuebingen
Sponsor organisation address	Geissweg 3, Tuebingen, Germany, 72076
Public contact	PD Dr.med. Martin Heni, University Hospital Tuebingen, +49 70712982711, martin.heni@med.uni-tuebingen.de
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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	18 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 October 2019
Global end of trial reached?	Yes
Global end of trial date	25 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Key objective: to assess the effect of treatment with 25 mg empagliflozin daily versus placebo on regional brain insulin sensitivity.

Effect of 8 weeks treatment with 25 mg empagliflozin or placebo on regional brain insulin sensitivity assessed by functional magnetic resonance imaging as change in regional cerebral blood flow from before to 30 minutes after nasal insulin spray application.

Protection of trial subjects:

The study was conducted in a GCP-compliant manner. The ethics committee and the higher federal authority evaluated the study before start. The subjects were informed in detail prior to consent. The study was conducted in conformance to all relevant regulations regarding the protection of human subjects participating in clinical studies.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 July 2017
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: 42
Worldwide total number of subjects	42
EEA total number of subjects	42

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)	27

From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at one site in Germany. Subjects were recruited from July 2017 to August 2019.

Pre-assignment

Screening details:

82 subjects were screened on fasting blood glucose betweeen 100 and 125 mg/dl and/or 2-hour post load glucose betwween 140 and 199 mg/dl during a 75 g oral glucose tolerance test and on a body mass index between 25 and 40 kg/m². 42 were enrolled and randomized.

Pre-assignment period milestones

Number of subjects started	42
Number of subjects completed	

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Empagliflozin

Arm description:

During the treatment phase of this trial participants will receive 25mg Empagliflozin daily. Human nasal insulin was only used to examine brain insulin resistance.

Arm type	Active comparator
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:

The subjects were treated with 25mg empagliflozin daily for 8 weeks.

Investigational medicinal product name	Human nasal insulin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Nasal use

Dosage and administration details:

160 IU, nasal

Arm title	Placebo

Arm description:

Subjects got Placebo matching empagliflozin 25 mg daily for 8 weeks. Human nasal insulin was only used to examine brain insulin resistance.

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:

The subjects got placebo matching empagliflozin 25 mg.

Investigational medicinal product name	Human nasal insulin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Nasal use

Dosage and administration details:

160 IU, nasal

Number of subjects in period 1[1]	Empagliflozin	Placebo
Started	19	21
Completed	19	21

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: 40 patients were planned, 82 were screened between 2017 - 2019. 42 patients were enrolled and 40 analyzed. 2 patients were drop-outs.

Baseline characteristics

Reporting groups	
Reporting group title	Empagliflozin
Reporting group description:	
During the treatment phase of this trial participants will receive 25mg Empagliflozin daily. Human nasal insulin was only used to examine brain insulin resistance.	
Reporting group title	Placebo
Reporting group description:	
Subjects got Placebo matching empagliflozin 25 mg daily for 8 weeks. Human nasal insulin was only used to examine brain insulin resistance.	

Reporting group values	Empagliflozin	Placebo	Total
Number of subjects	19	21	40
Age categorical 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	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	10	25
From 65-84 years	4	11	15
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	19	21	
standard deviation	± 0	± 0	-
Gender categorical Units: Subjects			
Female	14	10	24
Male	5	11	16

End points

End points reporting groups

Reporting group title	Empagliflozin

Reporting group description:

During the treatment phase of this trial participants will receive 25mg Empagliflozin daily. Human nasal insulin was only used to examine brain insulin resistance.

Reporting group title	Placebo

Reporting group description:

Subjects got Placebo matching empagliflozin 25 mg daily for 8 weeks. Human nasal insulin was only used to examine brain insulin resistance.

Primary: • Effect of 8 weeks treatment with 25 mg empagliflozin or placebo on regional brain insulin sensitivity

End point title	• Effect of 8 weeks treatment with 25 mg empagliflozin or placebo on regional brain insulin sensitivity[1]

End point description:

End point type	Primary

End point timeframe:

Effect of 8 weeks treatment with 25 mg empagliflozin or placebo on regional brain insulin sensitivity assessed by functional magnetic resonance imaging as change in regional cerebral blood flow from before to 30 minutes after nasal insulin spray applica

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: No statistical analyses have ben specified for this primary endpoint. Statistical analysis can be found in the attached documents.

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: hypothalamus insulin sensitivity				
number (not applicable)	19	21		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 09.08.2017 - 25.10.2019	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1
Reporting groups	
Reporting group title	Empagliflozin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Empagliflozin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Empagliflozin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 19 (63.16%)	9 / 21 (42.86%)	
Investigations			
Urine leukocyte esterase positive			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	1	
Blood creatine phosphokinase increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			

Fall			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	2	2	
Vascular disorders			
Presyncope			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Haematoma			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Deafness unilateral			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Eye disorders			
Hordeolum			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	1	
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	1	
Gingival pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	1	

Toothache			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Fibrinous bronchitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	1	
Nasopharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 19 (15.79%)	1 / 21 (4.76%)	
occurrences (all)	4	4	
Skin and subcutaneous tissue disorders			
Pruritus			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	1	
Rash			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Dysuria			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 19 (10.53%)	1 / 21 (4.76%)	
occurrences (all)	2	2	
Urinary tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 19 (5.26%)	2 / 21 (9.52%)	
occurrences (all)	3	3	
Renal cyst			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	

Musculoskeletal and connective tissue disorders			
Arthritis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	1	
Spinal pain			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Pain in extremity			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	1	
Back pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	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