Clinical trial results:
Effects on blood pressure and central sympathetic nerve traffic by SGLT2-inhibition with empagliflozin compared to hydrochlorothiazide in patients with type 2 diabetes mellitus

Summary

EudraCT number	2017-002175-25
Trial protocol	DE
Global end of trial date	20 April 2020

Results information

Result version number	v1 (current)
This version publication date	05 December 2021
First version publication date	05 December 2021

Trial information

Trial identification

Sponsor protocol code	Empa2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03254849
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Profil Institut für Stoffwechselforschung GmbH
Sponsor organisation address	Hellersbergstr. 9, Neuss, Germany, 41460
Public contact	Project Management, Profil Institut für Stoffwechselforschung GmbH, +49 21314018146, empa2@profil.com
Scientific contact	Project Management, Profil Institut für Stoffwechselforschung GmbH, +49 21314018146, empa2@profil.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	12 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 April 2020
Global end of trial reached?	Yes
Global end of trial date	20 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To show that BP reduction with empagliflozin treatment is associated with lesser increase in sympathetic nerve traffic when compared to HCT treatment

Protection of trial subjects:

In this study, many patients were on a combination therapy with RAS inhibitors and HCT at screening. Intermediate pausing and re-initiation of HCT treatment appeared to be a safe procedure in patients having previously taken and tolerated the combination therapy. Patients were advised about the risks of volume loss and hypovolemia in association with diuretic treatment, and should report to the investigator immediately in case of vomiting, diarrhea and comparable situations.
Both IMPs are approved for treatment of patients with type 2 diabetes mellitus or hypertension, respectively, in Germany.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 October 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: 41
Worldwide total number of subjects	41
EEA total number of subjects	41

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)	21
From 65 to 84 years	20

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment from the own database; advertisement on homepage

Pre-assignment

Screening details:

- women and men ≥ 50 and ≤ 80 years of age
- type 2 diabetes mellitus for ≥ 2 years
- only metformin monotherapy is allowed; metformin dose must have been stable for ≥ 12 weeks
- stable or no antihypertensive treatment
- HbA1c ≥ 6.5% and ≤ 10.0%
- body mass index > 25 kg/m2 and < 40 kg/m²

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

Blinding implementation details:

Placebo tablets closely match empagliflozin or HCT tablets.

Arms

Are arms mutually exclusive?	Yes
Arm title	Empagliflozin arm

Arm description:

Empagliflozin 25 mg (1 tablet) + HCT placebo (1 tablet)

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

Dosage and administration details:

25 mg/day for 6 weeks

Investigational medicinal product name	HCT Placebo (P-Tabletten weiß 8 mm Lichtenstein)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo administration for 6 weeks

Arm title	HCT arm

Arm description:

Hydrochlorthiazide 25 (1 tablet) + empagliflozin placebo (1 tablet)

Arm type	Experimental
Investigational medicinal product name	HCT-ratiopharm® 25 mg Tabletten
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details: 25 mg/day for 6 weeks	
Investigational medicinal product name	Empagliflozin placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 placebo tablet/day for 6 weeks

Number of subjects in period 1	Empagliflozin arm	HCT arm
Started	20	21
Completed	18	20
Not completed	2	1
unsuccessful MSNA attempts at Profiling 2	2	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	41	41	
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)	21	21	
From 65-84 years	20	20	
85 years and over	0	0	
Age continuous Units: years			
median	64.0		
standard deviation	± 6.35	-	
Gender categorical Units: Subjects			
Female	16	16	
Male	25	25	
BMI			
Body mass index			
Units: kg/m²			
median	30.80		
standard deviation	± 3.489	-	
Weight Units: kg			
median	87.00		
standard deviation	± 14.729	-	
Height Units: cm			
median	171.0		
standard deviation	± 9.66	-	

End points

End points reporting groups	
Reporting group title	Empagliflozin arm
Reporting group description: Empagliflozin 25 mg (1 tablet) + HCT placebo (1 tablet)	
Reporting group title	HCT arm
Reporting group description: Hydrochlorthiazide 25 (1 tablet) + empagliflozin placebo (1 tablet)	

Primary: Change in MSNA (muscle sympathetic nerve activity) burst frequency	
End point title	Change in MSNA (muscle sympathetic nerve activity) burst frequency
End point description:	
End point type	Primary
End point timeframe: From baseline to the end of therapy	

End point values	Empagliflozin arm	HCT arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: MSNA burst frequency (burst/min)				
arithmetic mean (standard deviation)	-0.821 (± 9.6601)	3.621 (± 12.0446)		

Statistical analyses

Statistical analysis title	Primary Endpoint
Comparison groups	Empagliflozin arm v HCT arm
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5406
Method	Mixed models analysis

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From baseline to end of trial	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0
Reporting groups	
Reporting group title	Empagliflozin arm
Reporting group description: -	
Reporting group title	HCT arm
Reporting group description: -	

Serious adverse events	Empagliflozin arm	HCT arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (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: 0 %

Non-serious adverse events	Empagliflozin arm	HCT arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 20 (55.00%)	11 / 21 (52.38%)	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Allodynia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	

Hypoaesthesia			
subjects affected / exposed	0 / 20 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Neuralgia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Thirst			
subjects affected / exposed	3 / 20 (15.00%)	1 / 21 (4.76%)	
occurrences (all)	4	1	
Chest pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Hunger			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 20 (10.00%)	2 / 21 (9.52%)	
occurrences (all)	2	3	
Abdominal pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Dry mouth			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Vomiting			

subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	5 / 20 (25.00%)	5 / 21 (23.81%)	
occurrences (all)	5	5	
Polyuria			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Pruritus genital			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Arthritis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			

subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 20 (5.00%)	3 / 21 (14.29%)	
occurrences (all)	1	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 September 2017	Changes due to BfArM objections
17 January 2019	Changes in matching criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported