



## Clinical trial results:

### Effects of Linagliptin in Addition to Empagliflozin on Islet Cell Physiology and Metabolic Control in Patients with Type 2 Diabetes Mellitus on Stable Metformin Treatment

#### Summary

EudraCT number	2014-004895-48
Trial protocol	DE
Global end of trial date	09 December 2015

#### Results information

Result version number	v1 (current)
This version publication date	31 January 2020
First version publication date	31 January 2020

#### Trial information

##### Trial identification

Sponsor protocol code	EMLIN-001
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02401880
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	Dr. Christoph Kapitza, Profil Institut für Stoffwechselforschung GmbH, +49 21314018157, regulatory@profil.com
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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	08 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 December 2015
Global end of trial reached?	Yes
Global end of trial date	09 December 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Change in glucagon release during liquid meal test (LMT) from Visit 3 (V3) to Visit 4 (V4) between the two treatment groups (linagliptin vs. Placebo)

Protection of trial subjects:

Empagliflozin and linagliptin were shown to increase the risk of hypoglycaemia when used in combination with sulfonylureas and/or insulin. Use of sulfonylureas and insulin is excluded in this trial. Empagliflozin and linagliptin even in triple combination with metformin were shown to be associated with only a minor risk of hypoglycaemia which was comparable to placebo treatment. Moreover study participants will be educated on possible symptoms of low blood glucose levels, and will be equipped with a glucose meter and test stripes for blood glucose self- measurement.

Treatment with empagliflozin might increase the risk of urogenital infections. Patients will be informed about urogenital hygiene provisions as well as about symptoms of urogenital infections and will be instructed to contact the study site in case of any suspicious symptoms.

Treatment with empagliflozin might increase the risk of hypovolemic blood pressure reactions. Patients with low blood pressure values or orthostatic symptoms will be excluded from the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 May 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: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	18
From 65 to 84 years	26
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment occurred in two trial sites

### Pre-assignment

Screening details:

In total, 83 subjects were screened and 44 subjects were included in the trial. Of the 44 subjects, 43 subjects completed the trial, whereas 1 subject withdrew consent at Visit 4 after the LMT but before the clamp.

### 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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	1st arm - Empa/Lina

Arm description:

Empagliflozin / Linagliptin treatment

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

Dosage and administration details:

34 days, 5 mg milligram(s)/day

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:

68 days, 25 mg milligram(s)/day

<b>Arm title</b>	2nd arm - Empa/Placebo
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Arm description:

Empagliflozin / Placebo treatment

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:

68 days, 25 mg milligram(s)/day

<b>Number of subjects in period 1</b>	1st arm - Empa/Lina	2nd arm - Empa/Placebo
Started	22	22
Completed	22	21
Not completed	0	1
Consent withdrawn by subject	-	1

## Baseline characteristics

### Reporting groups

Reporting group title

Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	44	44	
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)	18	18	
From 65-84 years	26	26	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	63.8		
full range (min-max)	42 to 75	-	
Gender categorical			
Units: Subjects			
Female	4	4	
Male	40	40	

## End points

### End points reporting groups

Reporting group title	1st arm - Empa/Lina
Reporting group description:	
Empagliflozin / Linagliptin treatment	
Reporting group title	2nd arm - Empa/Placebo
Reporting group description:	
Empagliflozin / Placebo treatment	

### Primary: Treatment Comparison for AUCGlucagon,0-180min

End point title	Treatment Comparison for AUCGlucagon,0-180min
End point description:	
End point type	Primary
End point timeframe:	
0-180 min	

End point values	1st arm - Empa/Lina	2nd arm - Empa/Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: pmol*h/L				
least squares mean (confidence interval 95%)	-19.60 (-27.33 to -11.87)	-4.84 (-12.57 to 2.89)		

### Statistical analyses

Statistical analysis title	Treatment Comparison (Linagliptin Versus Placebo)
Comparison groups	1st arm - Empa/Lina v 2nd arm - Empa/Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0103
Method	ANCOVA

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Overall trial

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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### Reporting groups

Reporting group title	Overall trial
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Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 44 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 44 (25.00%)		
Surgical and medical procedures			
Toe operation			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
General disorders and administration site conditions			
Hyperhidrosis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Thirst			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Reproductive system and breast disorders			



Balanoposthitis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Genital candidiasis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Phimosis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Investigations			
Red blood cells urine positive			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Cardiac disorders			
Syncope			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Gastrointestinal disorders			
Bowel movement irregularity			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Diarrhoea			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Faeces hard</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oral candidiasis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Toothache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 44 (9.09%)</p> <p>4</p> <p>1 / 44 (2.27%)</p> <p>1</p> <p>1 / 44 (2.27%)</p> <p>1</p> <p>1 / 44 (2.27%)</p> <p>1</p>		
<p>Skin and subcutaneous tissue disorders</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 44 (2.27%)</p> <p>1</p>		
<p>Renal and urinary disorders</p> <p>Polyuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 44 (9.09%)</p> <p>5</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Muscle spasms</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Osteoarthritis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 44 (2.27%)</p> <p>1</p> <p>1 / 44 (2.27%)</p> <p>1</p>		
<p>Infections and infestations</p> <p>Urinary tract infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 44 (2.27%)</p> <p>1</p>		
<p>Metabolism and nutrition disorders</p> <p>Increased appetite</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 44 (2.27%)</p> <p>1</p>		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported