Clinical trial results:
Effects of Linagliptin on endothelial function and global arginine bioavailability ratio in coronary artery disease patients with early diabetes

Summary

EudraCT number	2013-000330-35
Trial protocol	AT
Global end of trial date	28 April 2018

Results information

Result version number	v1 (current)
This version publication date	01 January 2020
First version publication date	01 January 2020

Trial information

Trial identification

Sponsor protocol code	HS-2012-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02350478
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Graz
Sponsor organisation address	Auenbruggerplatz 2, Graz, Austria, 8010
Public contact	Harald Sourij, Medizinische Universität Graz, 0043 31638581310, ha.sourij@medunigraz.at
Scientific contact	Harald Sourij, Medical University of Graz, 0043 31638581310, ha.sourij@medunigraz.at

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	13 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to investigate the impact of a 12 week linagliptin treatment on endothelial function in patients with early type 2 diabetes.

Protection of trial subjects:

All laboratory results will be reviewed and the reports signed by the study physician who will record whether it is normal, abnormal but not clinically significant, or abnormal and clinically significant. In the latter case, the eligibility of the subject will be reviewed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 May 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 49
Worldwide total number of subjects	49
EEA total number of subjects	49

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)	35
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In total 49 randomizations were performed. After randomization, two subjects were excluded due to screening failures without receiving the study medication. Therefore 47 subjects were enrolled in the study and received the study medication. Of those, 3 subjects were lost to follow up without available follow-up data and 1 subject was excluded.

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	Investigator, Monitor, Subject, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Linagliptin

Arm description:

Linagliptin 5mg /daily oral

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

Dosage and administration details:

5mg oral daily

Arm title	Placebo

Arm description:

Placebo

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:

5mg daily oral

Number of subjects in period 1	Linagliptin	Placebo
Started	25	24
Completed	20	23
Not completed	5	1
Lost to follow-up	3	1
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Linagliptin
Reporting group description: Linagliptin 5mg /daily oral	
Reporting group title	Placebo
Reporting group description: Placebo	

Reporting group values	Linagliptin	Placebo	Total
Number of subjects	25	24	49
Age categorical Units: Subjects			
Adults (18-64 years)	10	12	22
From 65-84 years	15	12	27
Age continuous Units: years			
arithmetic mean	63.3	63.3	
standard deviation	± 7.8	± 8.7	-
Gender categorical Units: Subjects			
Female	9	5	14
Male	16	19	35
Blood pressure systolic Units: mmHg			
arithmetic mean	134	128	
standard deviation	± 17	± 18	-
Blood pressure disatolic Units: mmHg			
arithmetic mean	79	78	
standard deviation	± 14	± 10	-

End points

End points reporting groups	
Reporting group title	Linagliptin
Reporting group description: Linagliptin 5mg /daily oral	
Reporting group title	Placebo
Reporting group description: Placebo	

Primary: Changes in Flow Mediated Dilatation	
End point title	Changes in Flow Mediated Dilatation
End point description: Changes in Flow Mediated Dilatation from baseline to 12 weeks	
End point type	Primary
End point timeframe: 12 weeks	

End point values	Linagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	23		
Units: percent				
arithmetic mean (standard deviation)	0.4 (± 4.8)	-0.5 (± 3.0)		

Statistical analyses

Statistical analysis title	Group comparison
Comparison groups	Placebo v Linagliptin
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Changes in Global Arginine Bioavailability Ratio	
End point title	Changes in Global Arginine Bioavailability Ratio
End point description: Changes in Global Arginine Bioavailability Ratio from Baseline to 12 weeks	
End point type	Secondary

End point timeframe:
12 weeks

End point values	Linagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	23		
Units: percent				
arithmetic mean (standard deviation)	-0.11 (± 0.35)	-0.06 (± 0.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Arginine to Ornithine Ratio

End point title	Changes in Arginine to Ornithine Ratio

End point description:
Changes in Arginine to Ornithine Ratio from Baseline to 12 weeks

End point type	Secondary

End point timeframe:
12 weeks

End point values	Linagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	23		
Units: percent				
arithmetic mean (standard deviation)	-0.13 (± 0.45)	-0.05 (± 0.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Soluble cell adhesion molecules-1

End point title	Changes in Soluble cell adhesion molecules-1

End point description:
Changes in Soluble cell adhesion molecules-1 from Baseline to 12 weeks

End point type	Secondary

End point timeframe:
12 weeks

End point values	Linagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	23		
Units: ng/mL				
median (inter-quartile range (Q1-Q3))	-15 (-272 to 103)	-21 (-134 to 310)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Soluble vascular cell adhesion molecule-1

End point title	Changes in Soluble vascular cell adhesion molecule-1

End point description:

Changes in Soluble vascular cell adhesion molecule-1 from Baseline to 12 weeks

End point type	Secondary

End point timeframe:

12 weeks

End point values	Linagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	23		
Units: ng/mL				
arithmetic mean (standard deviation)	-34 (± 84)	5 (± 130)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Area under curve for glucose

End point title	Changes in Area under curve for glucose

End point description:

Changes in Area under curve for glucose from Baseline to 12 weeks

End point type	Secondary

End point timeframe:

12 weeks

End point values	Linagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	23		
Units: mg/dL				
arithmetic mean (standard deviation)	-1135 (± 2619)	481 (± 3185)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Area under curve for free fatty acids

End point title	Change in Area under curve for free fatty acids
End point description:	
Change in Area under curve for free fatty acids from baseline to 12 weeks	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Linagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	23		
Units: µmol/L				
arithmetic mean (standard deviation)	2 (± 28.4)	-3.1 (± 18.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Area under curve for insulin

End point title	Changes in Area under curve for insulin
End point description:	
changes in Area under curve for insulin from baseline to 12 weeks	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Linagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	23		
Units: mU/L				
arithmetic mean (standard deviation)	249 (± 4766)	40 (± 6357)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Area under curve for c-peptide

End point title	Changes in Area under curve for c-peptide

End point description:

Changes in Area under curve for c-peptide from Baseline to 12 weeks

End point type	Secondary

End point timeframe:

12 weeks

End point values	Linagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	23		
Units: mg/dL				
arithmetic mean (standard deviation)	-3 (± 161)	-34 (± 211)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	Linagliptin
Reporting group description: Verum Group	
Reporting group title	Placebo
Reporting group description: Placebo group	

Serious adverse events	Linagliptin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 20 (15.00%)	1 / 23 (4.35%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Coordination abnormal			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Prolapse			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Borrelia infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Linagliptin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 20 (15.00%)	3 / 23 (13.04%)	
Vascular disorders			
Intermittent claudication			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	0	
Cardiac disorders			
Hypotension			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	0	
Nervous system disorders			
Pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Nausea			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 August 2013	Combination of Screening and Baseline Visits
22 October 2013	Inclusion criterion (max age changed from 75 to 80 years)
30 April 2014	Exclusion criteria: HbA1c <6.0% (42mmol/mol) instead of HbA1c <6.5 (48mmol/mol)
24 October 2014	Storage of blood samples in the Biobank (Medical University of Graz)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29773079

http://www.ncbi.nlm.nih.gov/pubmed/27733180