Clinical trial results:
Effects of Linagliptin on active GLP-1 concentrations in subjects with renal impairment

Summary

EudraCT number	2013-000364-28
Trial protocol	DE
Global end of trial date	22 April 2016

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	00/0594-LINARI

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01903070
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	RA, Profil Institut für Stoffwechselforschung GmbH, +49 21314018145, regulatory@profil.com
Scientific contact	RA, Profil Institut für Stoffwechselforschung GmbH, +49 21314018145, regulatory@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	07 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 April 2016
Global end of trial reached?	Yes
Global end of trial date	22 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To quantify differences in GLP-1 concentrations following glucose challenge between subjects with T2DM with or without renal impairment before and after linagliptin therapy

Protection of trial subjects:

To further decrease the risk for hypoglycemia during the study, subjects will be asked to assess their plasma glucose at least 3x/day during the intensification of the treatment and to immediately report any change in hypoglycemia or hyperglycemia occurrence. The dose of insulin can be adapted during the course of the study as judged by the investigator in order to avoid hypo- or hyperglycemia.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 July 2013
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: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

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)	20
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment occured in three trial centres in Germany

Pre-assignment

Screening details:

In total, 115 subjects were screened and 31 subjects were included in the trial (15 subjects with normal renal function and 16 subjects with impaired renal function) and randomised to one of the two possible test visit sequences. A total of 30 subjects completed the trial.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	1st arm

Arm description:

normal renal function: glomerular filtration rate [GFR] > 90 mL/min

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:

TRAJENTA® (linagliptin) 5 mg tablets; 1 tablet/day for 9 to max 12 days in total.

Arm title	2nd arm

Arm description:

impaired renal function (glomerular filtration rate [GFR] < 60 mL/min)

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:

TRAJENTA® (linagliptin) 5 mg tablets; 1 tablet/day for 9 to max 12 days in total.

Number of subjects in period 1	1st arm	2nd arm
Started	15	16
Completed	15	15
Not completed	0	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	1st arm
Reporting group description: normal renal function: glomerular filtration rate [GFR] > 90 mL/min	
Reporting group title	2nd arm
Reporting group description: impaired renal function (glomerular filtration rate [GFR] < 60 mL/min)	

Reporting group values	1st arm	2nd arm	Total
Number of subjects	15	16	31
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)	12	9	21
From 65-84 years	3	7	10
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	56.0	64.0	
full range (min-max)	46 to 74	54 to 73	-
Gender categorical Units: Subjects			
Female	1	7	8
Male	14	9	23
Ethnic group Units: Subjects			
Caucasian	14	16	30
Tunisian	1	0	1
Weight Units: kg			
arithmetic mean	93.97	98.72	
full range (min-max)	72.9 to 137.8	75.0 to 133.9	-

End points

End points reporting groups

Reporting group title	1st arm
Reporting group description: normal renal function: glomerular filtration rate [GFR] > 90 mL/min	
Reporting group title	2nd arm
Reporting group description: impaired renal function (glomerular filtration rate [GFR] < 60 mL/min)	
Subject analysis set title	Efficacy analysis
Subject analysis set type	Full analysis
Subject analysis set description: The analysis of pharmacodynamic endpoints was based on the Pharmacodynamic Analysis Set including the 31 randomised subjects.	

Primary: Change in active GLP-1 concentrations after oral glucose ingestion after linagliptin treatment compared between groups

End point title	Change in active GLP-1 concentrations after oral glucose ingestion after linagliptin treatment compared between groups
End point description:	
End point type	Primary
End point timeframe: 0-240min	

End point values	1st arm	2nd arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: pmol*h/L				
median (full range (min-max))	6.16 (-1.9 to 13.5)	6.05 (-2.6 to 16.6)		

Statistical analyses

Statistical analysis title	Primary Endpoint
Statistical analysis description: Statistical Analysis of ΔAUCIntact GLP-1,OGTT,0-240min, change in active (intact) GLP-1 concentrations during an OGTT from Day 0/1 to Day 9/10 between the two groups (with vs. without renal impairment)	
Comparison groups	1st arm v 2nd arm
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall trial	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Normal Renal Function
Reporting group description: -	
Reporting group title	Renal Impairment
Reporting group description: -	

Serious adverse events	Normal Renal Function	Renal Impairment	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma	Additional description: This was a non-treatment emergent SAE (hepatocellular carcinoma) reported in Subject 306 (renal impairment) with start date 50 days before first planned linagliptin treatment.		
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
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: 5 %

Non-serious adverse events	Normal Renal Function	Renal Impairment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 15 (26.67%)	6 / 15 (40.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nervous system disorders			

Concussion			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	2 / 15 (13.33%)	3 / 15 (20.00%)	
occurrences (all)	2	3	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Hunger			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Hiccups			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

Rhinitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Psychiatric disorders			
Nervousness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Groin pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2013	The possibility of pancreatitis due to exposure to Linagliptinin very rare cases was added in the benefit-risk assessment. Details for contraceptive measures for female subjects were added to the inclusion criteria.
09 April 2015	Due to recruitment problems some in- and exclusion criteria were slighlty adapted.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported