Clinical trial results:
Glimepiride monotherapy vs. combination of glimepiride and linagliptin therapy in patients with HNF1A-diabetes.

Summary

EudraCT number	2017-000204-15
Trial protocol	DK
Global end of trial date	26 April 2019

Results information

Result version number	v1 (current)
This version publication date	08 October 2020
First version publication date	08 October 2020
Summary attachment (see zip file)	Full article (GLIMLINA_full article.pdf)

Trial information

Trial identification

Sponsor protocol code	060286

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Steno Diabetes Center Copenhagen
Sponsor organisation address	Gentofte Hospitals Vej 7, 3. sal, Hellerup, Denmark, 2900
Public contact	Type 2 Biology, Steno Diabetes Center Copenhagen, Gentofte Hospital, 0045 40940825, tina.vilsboell.lauritsen.01@regionh.dk
Scientific contact	Type 2 Biology, Steno Diabetes Center Copenhagen, Gentofte Hospital, 0045 40940825, tina.vilsboell.lauritsen.01@regionh.dk

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	01 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial is to investigate the effect of glimepiride + linagliptin vs. glimepiride + placebo on glycaemic variability in patients with hepatocyte nuclear factor 1-alpha (HNF1A) diabetes in a double-blind, randomised, cross-over trial. HNF1A-diabetes is also known as maturity onset diabetes of the young type 3 (MODY3).

All data is available in Diabetes Care (https://care.diabetesjournals.org/content/early/2020/07/10/dc20-0408) or follow link (Pubmed-identifier: PMID: 32661107).

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice Guidelines.

Background therapy:

Subject were enrolled on either glimepiride monotherapy (19 subjects) or diet (1 subject). Pre-trial treatment with glimepiride continued throughout the trial. The glimepiride dose was either increased or decreased during treatment with linagliptin/placebo according to fasting plasma glucose levels (target mean of 4.5 to 6.0 mmol/L) and without episodes of hypoglycaemia.

Evidence for comparator: -

Actual start date of recruitment	01 September 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	Denmark: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	18
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Two sites were used for recruitment: 1) Steno Diabetes Center Copenhagen, Gentofte Hospital, Hellerup, Denmark; and 2) Steno Diabetes Center Aarhus, Aarhus, Denmark

Pre-assignment

Screening details:

Twenty patients were screened. One dropped out before randomisation and is thus not part of the analysis.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

This is a randomised, double-blind, placebo controlled cross-over trial.

Arms

Arm title	Baseline

Arm description:

All patients at baseline.

Arm type	Active comparator
Investigational medicinal product name	Glimepiride
Investigational medicinal product code	
Other name	Glimepiride (R)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Flexible dosing according to titration ranging from 0.5 mg to 6.0 mg. The dose was once daily (0.5 mg) or twice daily (dose>0.5 mg)

Number of subjects in period 1	Baseline
Started	19
Completed	19

Period 2

Period 2 title	Experimental period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

Patients exposed for glimepiride + linagliptin
Trial design: Patients were exposed to either:
1) 16 weeks with glimepiride + linagliptin 5 mg, a four-week wash-out and then 16 weeks with glimepiride + placebo, or
2) 1) 16 weeks with glimepiride + placebo, a four-week wash-out and then 16 weeks with glimepiride + linagliptin

Arms

Are arms mutually exclusive?	No
Arm title	Glimepiride + placebo

Arm description:

Patients exposed for glimepiride + placebo.
Trial design: Subjects when through a baseline evaluation (mixed meal test and continuous glucose monitoring for six days). After baseline evaluation subjects were treated with either:
1) 16 weeks with glimepiride + linagliptin 5 mg, a four-week wash-out and then 16 weeks with glimepiride + placebo
2) 1) 16 weeks with glimepiride + placebo, a four-week wash-out and then 16 weeks with glimepiride + linagliptin

Linagliptin/placebo dose was fixed. Glimepiride dose was titrated (up or down 0.5 mg) in the first four week of each treatment period. Treatment target was mean fasting plasma glucose levels of 4.5-6.0 mmol/L without episodes of hypoglycaemia. If a subject had recurrent episodes of hypoglycaemia after the titration period glimepiride dose was reduced 0.5 mg.

Arm type	Placebo
Investigational medicinal product name	Glimepiride
Investigational medicinal product code	
Other name	Glimepiride (R)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Flexible dosing according to titration ranging from 0.5 mg to 6.0 mg. The dose was once daily (0.5 mg) or twice daily (dose>0.5 mg)

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily

Arm title	Glimepiride + linagliptin 5 mg

Arm description:

Patients exposed for glimepiride + linagliptin.
Trial design: Subjects when through a baseline evaluation (mixed meal test and continuous glucose monitoring for six days). After baseline evaluation subjects were treated with either:
1) 16 weeks with glimepiride + linagliptin 5 mg, a four-week wash-out and then 16 weeks with glimepiride + placebo
2) 1) 16 weeks with glimepiride + placebo, a four-week wash-out and then 16 weeks with glimepiride + linagliptin

Linagliptin/placebo dose was fixed. Glimepiride dose was titrated (up or down 0.5 mg) in the first four week of each treatment period. Treatment target was mean fasting plasma glucose levels of 4.5-6.0 mmol/L without episodes of hypoglycaemia. If a subject had recurrent episodes of hypoglycaemia after

the titration period glimepiride dose was reduced 0.5 mg.

Arm type	Active comparator
Investigational medicinal product name	Linagliptin
Investigational medicinal product code	
Other name	Trajenta (R)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg tablet

Investigational medicinal product name	Glimepiride
Investigational medicinal product code	
Other name	Glimepiride (R)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Flexible dosing according to titration ranging from 0.5 mg to 6.0 mg. The dose was once daily (0.5 mg) or twice daily (dose>0.5 mg)

Number of subjects in period 2	Glimepiride + placebo	Glimepiride + linagliptin 5 mg
Started	19	19
Completed	19	19

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description:	
All patients at baseline.	

Reporting group values	Baseline	Total	
Number of subjects	19	19	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age			
Units: years			
arithmetic mean	43		
standard deviation	± 13	-	
Gender categorical			
Units: Subjects			
Female	11	11	
Male	8	8	

Subject analysis sets	
Subject analysis set title	Baseline
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects at baseline	

Reporting group values	Baseline		
Number of subjects	19		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			

Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age			
Units: years arithmetic mean standard deviation	 43 ± 14		
Gender categorical Units: Subjects			
Female Male	11 8		

End points

End points reporting groups

Reporting group title	Baseline

Reporting group description:

All patients at baseline.

Reporting group title	Glimepiride + placebo

Reporting group description:

Patients exposed for glimepiride + placebo.
Trial design: Subjects when through a baseline evaluation (mixed meal test and continuous glucose monitoring for six days). After baseline evaluation subjects were treated with either:
1) 16 weeks with glimepiride + linagliptin 5 mg, a four-week wash-out and then 16 weeks with glimepiride + placebo
2) 1) 16 weeks with glimepiride + placebo, a four-week wash-out and then 16 weeks with glimepiride + linagliptin

Linagliptin/placebo dose was fixed. Glimepiride dose was titrated (up or down 0.5 mg) in the first four week of each treatment period. Treatment target was mean fasting plasma glucose levels of 4.5-6.0 mmol/L without episodes of hypoglycaemia. If a subject had recurrent episodes of hypoglycaemia after the titration period glimepiride dose was reduced 0.5 mg.

Reporting group title	Glimepiride + linagliptin 5 mg

Reporting group description:

Patients exposed for glimepiride + linagliptin.
Trial design: Subjects when through a baseline evaluation (mixed meal test and continuous glucose monitoring for six days). After baseline evaluation subjects were treated with either:
1) 16 weeks with glimepiride + linagliptin 5 mg, a four-week wash-out and then 16 weeks with glimepiride + placebo
2) 1) 16 weeks with glimepiride + placebo, a four-week wash-out and then 16 weeks with glimepiride + linagliptin

Linagliptin/placebo dose was fixed. Glimepiride dose was titrated (up or down 0.5 mg) in the first four week of each treatment period. Treatment target was mean fasting plasma glucose levels of 4.5-6.0 mmol/L without episodes of hypoglycaemia. If a subject had recurrent episodes of hypoglycaemia after the titration period glimepiride dose was reduced 0.5 mg.

Subject analysis set title	Baseline
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects at baseline

Primary: Mean amplitude of glycemic excursions (MAGE)

End point title	Mean amplitude of glycemic excursions (MAGE)

End point description:

End point type	Primary

End point timeframe:

Difference between glimepiride + linagliptin vs. glimepiride + placebo at the end of each treatment period based on continuous glucose measurements

End point values	Glimepiride + placebo	Glimepiride + linagliptin 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: mmol/L				
least squares mean (confidence interval 0.05%)				
Glycaemic variability	5.8 (5.0 to 6.4)	5.1 (4.2 to 6.1)		

Statistical analyses

Statistical analysis title	Glimepiride + linagliptin vs. glimepiride + placeb
Comparison groups	Glimepiride + linagliptin 5 mg v Glimepiride + placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1907
Method	Linear Mixed Model
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	0.4

Primary: Coefficient of variation (CV)

End point title	Coefficient of variation (CV)

End point description:

End point type	Primary

End point timeframe:

Difference between glimepiride + linagliptin vs. glimepiride + placebo at the end of each treatment period based on continuous glucose measurements

End point values	Glimepiride + placebo	Glimepiride + linagliptin 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: percent				
least squares mean (confidence interval 95%)				
Glycaemic variability	31.4 (28.3 to 34.4)	27.7 (24.9 to 30.7)		

Statistical analyses

Statistical analysis title	Coefficient of variation
Comparison groups	Glimepiride + placebo v Glimepiride + linagliptin 5 mg
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0401
Method	Linear Mixed Model
Parameter estimate	Mean difference (final values)
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	0

Primary: Standard deviation (SD)

End point title	Standard deviation (SD)

End point description:

End point type	Primary

End point timeframe:

Difference between glimepiride + linagliptin vs. glimepiride + placebo at the end of each treatment period based on continuous glucose measurements

End point values	Glimepiride + placebo	Glimepiride + linagliptin 5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: mmol/mol				
least squares mean (confidence interval 95%)				
Glycaemic variability	2.8 (2.4 to 3.2)	2.3 (1.9 to 2.7)		

Statistical analyses

Statistical analysis title	Standard deviation
Statistical analysis description:	
Difference between glimepiride + linagliptin vs. glimepiride + placebo at the end of each treatment period based on continuous glucose measurements	
Comparison groups	Glimepiride + placebo v Glimepiride + linagliptin 5 mg
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.021
Method	Linear Mixed Model
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.1

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From randomisation to end of study visit	
Adverse event reporting additional description:	
Information about adverse events were collected both during routinely scheduled visits as well when subjects opportunistically contacted the investigators.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23

Reporting groups	
Reporting group title	Glimepiride + linagliptin
Reporting group description: -	
Reporting group title	Glimepiride + placebo
Reporting group description: -	

Serious adverse events	Glimepiride + linagliptin	Glimepiride + placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (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	Glimepiride + linagliptin	Glimepiride + placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 19 (31.58%)	8 / 19 (42.11%)	
Infections and infestations			
Gastroenteritis			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 19 (10.53%)	4 / 19 (21.05%)	
occurrences (all)	2	4	
Upper Airway Infection			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 19 (10.53%)	3 / 19 (15.79%)	
occurrences (all)	2	3	

Acute Rhinitis subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2	1 / 19 (5.26%) 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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32661107