Clinical trial results:
Effects of metformin on hepatic free fatty acid metabolism in type 2 diabetes asssessed by positron emission tomography

Summary

EudraCT number	2012-000808-16
Trial protocol	DK
Global end of trial date	30 June 2016

Results information

Result version number	v1 (current)
This version publication date	11 December 2020
First version publication date	11 December 2020
Summary attachment (see zip file)	Metformin lipid paper (Summary_paper.pdf)

Trial information

Trial identification

Sponsor protocol code	C11palmitatmetformin

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01729156
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensens Boulevard 165, Aarhus N, Denmark, 8200
Public contact	Department of Nuclear Medicine & PET Centre, Aarhus University Hospital, lars.christian.gormsen@ki.au.dk
Scientific contact	Department of Nuclear Medicine & PET Centre, Aarhus University Hospital, 45 78456260, lars.christian.gormsen@ki.au.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 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 June 2016
Global end of trial reached?	Yes
Global end of trial date	30 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

It is the general purpose of the trial to investigate whether the positive effects of metformin on blood lipids are caused by improved glycemic control and changes in body composition or if they are caused by direct effects on lipid metabolism. We specifically plan to:
- investigate hepatic fatty acid uptake, reesterification and oxidation assessed by positron emission tomography (PET)
- investigate the effect of metformin on whole body VLDL-TG oxidation and redeposition in adipose tissue.

Protection of trial subjects:

All trial subjects were investigated using as low a dose of radio-tracer as technically possible, all biopsies were taken during local anesthesia.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 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	Denmark: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	26
From 65 to 84 years	10

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients and healthy subjects were recruited through newspaper adds and from the outpatient clinic on Aarhus University Hospital

Pre-assignment

Screening details:

T2D: age > 50 years, body mass index (BMI) <40 kg/m2 and T2D as defined by American Diabetes Association criteria
Healthy: age > 50 years, body mass index (BMI) <40 kg/m2 and normal glucose tolerance

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:

Randomization to the placebo group or metformin group was performed using random permuted blocks of 4 participants with 1:1 allocation ratio, resulting in 12 participants in the placebo and 12 in the metformin group. Both study participants and investigator were blinded to the allocation until the end of the study

Arms

Are arms mutually exclusive?	Yes
Arm title	PLA_

Arm description:

Individuals with type 2 diabetes randomized to 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:

2 tablets bi-daily

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

Dosage and administration details:

1000 mg bi-daily

Arm title	MET_

Arm description:

Individuals with type 2 diabetes randomized to 1000 mg metformin bi-daily

Arm type	Experimental

Investigational medicinal product name	Metformin "Teva"
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
500 mg x 2 taken orally bi-daily

Arm title	CONT

Arm description:
Non-diabetic individuals

Arm type	Active comparator
Investigational medicinal product name	Metformin "Teva"
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
500 mg x 2 taken orally bi-daily

Number of subjects in period 1	PLA_	MET_	CONT
Started	12	12	12
Completed	12	12	12

Baseline characteristics

Reporting groups	
Reporting group title	PLA_
Reporting group description:	
Individuals with type 2 diabetes randomized to PLACEBO	
Reporting group title	MET_
Reporting group description:	
Individuals with type 2 diabetes randomized to 1000 mg metformin bi-daily	
Reporting group title	CONT
Reporting group description:	
Non-diabetic individuals	

Reporting group values	PLA_	MET_	CONT
Number of subjects	12	12	12
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)	10	7	8
From 65-84 years	2	5	4
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	60	64	62
standard deviation	± 5	± 5	± 6
Gender categorical Units: Subjects			
Female	3	6	6
Male	9	6	6

Reporting group values	Total		
Number of subjects	36		
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)	25		

From 65-84 years	11		
85 years and over	0		

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	15		
Male	21		

End points

End points reporting groups

Reporting group title	PLA_
Reporting group description: Individuals with type 2 diabetes randomized to PLACEBO	
Reporting group title	MET_
Reporting group description: Individuals with type 2 diabetes randomized to 1000 mg metformin bi-daily	
Reporting group title	CONT
Reporting group description: Non-diabetic individuals	

Primary: Hepatic fatty acid oxidation

End point title	Hepatic fatty acid oxidation
End point description: Delta hepatic fatty acid oxidation after three months treatment measured by 11C-palmitate PET	
End point type	Primary
End point timeframe: 3 months	

End point values	PLA_	MET_	CONT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	8	10	
Units: micromol/g/minute				
arithmetic mean (standard deviation)	-0.005 (± 0.032)	0.010 (± 0.018)	0.005 (± 0.022)	

Statistical analyses

Statistical analysis title	ANOVA delta hepatic fatty acid oxidation
Comparison groups	PLA_ v MET_ v CONT
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA
Parameter estimate	F-value

Primary: Hepatic fatty acid uptake

End point title	Hepatic fatty acid uptake
End point description: delta hepatic fatty acid uptake after three months treatment	
End point type	Primary
End point timeframe: 3 months	

End point values	PLA_	MET_	CONT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	8	10	
Units: micromol/g/min				
arithmetic mean (standard deviation)	-0.023 (± 0.047)	0.020 (± 0.023)	0.021 (± 0.053)	

Attachments (see zip file)	Figure2.jpg

Statistical analyses

Statistical analysis title	Lipid statistics
Comparison groups	PLA_ v MET_ v CONT
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Confidence interval	
sides	2-sided

Primary: Hepatic fatty acid esterification

End point title	Hepatic fatty acid esterification
End point description: Delta hepatic fatty acid esterification after three months treatment	
End point type	Primary
End point timeframe: 3 months	

End point values	PLA_	MET_	CONT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	8	10	
Units: micromol/g/min				
arithmetic mean (standard deviation)	-0.020 (± 0.029)	0.010 (± 0.015)	0.015 (± 0.045)	

Statistical analyses

Statistical analysis title	ANOVA delta hepatic fatty metabolism
Comparison groups	PLA_ v MET_ v CONT
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA
Parameter estimate	F-value

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
3 months	
Adverse event reporting additional description:	
Adverse events reported during the trial	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	GCP unit Aarhus
Dictionary version	1

Reporting groups	
Reporting group title	PLA_
Reporting group description:	
Individuals with type 2 diabetes randomized to PLACEBO	
Reporting group title	MET_
Reporting group description:	
Individuals with type 2 diabetes randomized to 1000 mg metformin bi-daily	
Reporting group title	CONT
Reporting group description:	
Non-diabetic individuals	

Serious adverse events	PLA_	MET_	CONT
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	PLA_	MET_	CONT
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No trial related non-serious adverse events were recorded

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Only results from primary endpoint are reported - for secondary endpoints please see publications

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30976851

http://www.ncbi.nlm.nih.gov/pubmed/29405635