Clinical trial results:
The effect of sitagliptin on brown adipose tissue and whole-body metabolism in overweight pre-diabetic men

Summary

EudraCT number	2014-003532-39
Trial protocol	NL
Global end of trial date	01 January 2017

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021
Summary attachment (see zip file)	Nahon et al, Diabetologia 2018 (Nahon et al_Diabetologia 2018.pdf)

Trial information

Trial identification

Sponsor protocol code	SitaBAT01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02294084
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Leiden University Medical Center
Sponsor organisation address	Albinusdreef 2, Leiden, Netherlands, 2333 ZA
Public contact	dr MR Boon (m.r.boon@lumc.nl), Leiden University Medical Center, 0031 648126425, m.r.boon@lumc.nl
Scientific contact	dr MR Boon (m.r.boon@lumc.nl), Leiden University Medical Center, 0031 648126425, m.r.boon@lumc.nl

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	02 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 December 2016
Global end of trial reached?	Yes
Global end of trial date	01 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main object of the trial is to evaluate the effect of sitagliptin treatment on BAT activity in overweight, pre-diabetic subjects.

Protection of trial subjects:

Subjects were placed in a comfortable room and at any time, a medical doctor was present during the study days to make subjects feel safe and comfortable.

Background therapy:

Half of the subjects received the approved medicine Sitagliptin (100 mg/day) for 12 weeks and half of the subjects a placebo. Sitagliptin is a DPP4 inhibitor that increases the action of the intestinal hormone GLP-1. This medicine is currently used in the treatment of type 2 diabetes mellitus.

Evidence for comparator:

The dipeptidyl peptidase-4 (DPP4) inhibitor sitagliptin, which enhances the bioavailability of incretin hormones, improves both glucose tolerance and lipid metabolism in individuals with type 2 diabetes, thereby targeting both microvascular and macrovascular complications. The precise mechanism by which sitagliptin exerts these positive metabolic effects remains largely unknown and in the current study, we aimed to study whether it worked by enhancing activity of metabolically active brown adipose tissue.

Actual start date of recruitment	01 January 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	Netherlands: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from approximately June 2015 until October 2016. Recruitment was done via advertisements.

Pre-assignment

Screening details:

We performed a thorough medical history and physical examination. Furthermore, we performed anthropometric measurements and assessed a venous blood sample to exclude the presence of type 2 diabetes, liver and kidney disease. In addition, we performed an OGTT.

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, Monitor, Data analyst

Blinding implementation details:

On forehand, an unblinded pharmacist set up a list in which each study subject number was coupled to a box number. All boxes (sitagliptin and placebo) were labeled together with a component ID list (this contained the information which box holded the placebo or sitagliptin). The pharmacy then gave out the boxes according to the randomisation list. Therefore, the study was conducted double blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sitagliptin

Arm description:

Sitagliptin (100 mg/day) treatment

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

Dosage and administration details:

100 mg/day per os, for 12 weeks in total

Arm title	Placebo

Arm description:

Placebo treatment

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:

Placebo tablet 100 mg, in total 12 weeks treatment

Number of subjects in period 1	Sitagliptin	Placebo
Started	15	15
Start with study	15	15
Completed	15	15

Baseline characteristics

Reporting groups	
Reporting group title	Sitagliptin
Reporting group description: Sitagliptin (100 mg/day) treatment	
Reporting group title	Placebo
Reporting group description: Placebo treatment	

Reporting group values	Sitagliptin	Placebo	Total
Number of subjects	15	15	30
Age categorical			
Subjects were between 35 and 50 years old.			
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)	15	15	30
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Subjects were between 35 and 50 years.			
Units: years			
geometric mean	45	47	
standard deviation	± 5	± 4	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	15	15	30

End points

End points reporting groups	
Reporting group title	Sitagliptin
Reporting group description: Sitagliptin (100 mg/day) treatment	
Reporting group title	Placebo
Reporting group description: Placebo treatment	

Primary: Change in brown adipose tissue activity	
End point title	Change in brown adipose tissue activity
End point description: Before and after 12 weeks of sitagliptin or placebo treatment brown adipose tissue volume and activity were measured using PET-CT scan.	
End point type	Primary
End point timeframe: 12 weeks	

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: 0-100				
arithmetic mean (standard error)	2.3 (± 0.3)	2.2 (± 0.2)		

Attachments (see zip file)	Overview effects brown fat/Supplementary Table 6.docx

Statistical analyses

Statistical analysis title	Statistical analysis
Statistical analysis description: Mixed model analyses with treatment and occasion as fixed effects and subject specific deviances from the mean as random effects were used to assess the effect of the treatment.	
Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	2.1
Variability estimate	Standard deviation
Dispersion value	0.1

Notes:

[1] - we compared whether sitagliptin was superior to placebo treatment in inducing brown adipose tissue activation
[2] - We considered a P-vlaue < 0.05 as statistically significant

Primary: Change in brown adipose tissue volume

End point title	Change in brown adipose tissue volume

End point description:

Brown adipose tissue volume was measured in mL and was assessed via 18F-FDG PET-CT scan

End point type	Primary

End point timeframe:

Before and after 12 weeks of treatment with sitagliptin and placebo effects on brown adipose tissue volume were measured.

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: mL				
geometric mean (standard error)	32 (± 13)	14 (± 12)		

Attachments (see zip file)	Overview effects brown fat/Supplementary Table 6.docx

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

Mixed model analyses with treatment and occasion as fixed effects and subject specific deviances from the mean as random effects were used to assess the effect of the treatment

Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.05 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	20

Confidence interval	
level	95 %
sides	2-sided
lower limit	12
upper limit	33
Variability estimate	Standard deviation
Dispersion value	12

Notes:

[3] - We assessed whether sitagliptin was superior to enhance brown adipose tissue volume compared with placebo
[4] - We considered a P-value < 0.05 as statistically significant.

Secondary: Change in incremental glucose during OGTT

End point title	Change in incremental glucose during OGTT

End point description:

see above

End point type	Secondary

End point timeframe:

An OGTT was performed before and 12 weeks after sitagliptin treatment. From this OGTT, amongst others, an incremental glucose was assessed.

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	15		
Units: mmol/L				
arithmetic mean (standard error)	166 (± 33)	371 (± 38)		

Statistical analyses

Statistical analysis title	AUC of the incremental glucose (OGTT)

Statistical analysis description:

Mixed model analysis was used to assess differences in the AUC of the incremental glucose during OGTT

Comparison groups	Placebo v Sitagliptin
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	equivalence[5]
P-value	< 0.003 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	4.1

Notes:

[5] - Mixed model analysis was used

[6] - We also assessed the P-value for the difference between t=0 and t=12 weeks, this was also P<0.003

Adverse events

Adverse events information	
Timeframe for reporting adverse events: during the 12 week treatment period we assess adverse events.	
Adverse event reporting additional description: We assessed this by weekly calling the study subjects.	
Assessment type	Systematic

Dictionary used	
Dictionary name	via sponsor
Dictionary version	1

Reporting groups	
Reporting group title	sitagliptin
Reporting group description: subjects who received sitagliptin treatment (100 mg/day)	
Reporting group title	placebo
Reporting group description: subjects that received placebo treatment for 12 weeks	

Serious adverse events	sitagliptin	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (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	sitagliptin	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	14	14	

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.

In this overview, we only report on the effects on brown adipose tissue. The very interesting effects on secondary parameters (glucose and lipid metabolism) can be read in the manuscript that is attached.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30145664