Clinical trial results:
The influence of metformin and a hypocaloric diet on thyroid radioactive iodide uptake in healthy volunteers: a pilot study

Summary

EudraCT number	2016-001455-42
Trial protocol	NL
Global end of trial date	02 June 2017

Results information

Result version number	v1 (current)
This version publication date	11 February 2020
First version publication date	11 February 2020
Summary attachment (see zip file)	Article Scientific Reports on Pilot study (41598_2019_Article_41997.pdf)

Trial information

Trial identification

Sponsor protocol code	NL56309.091.16

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Nederlands Trial Register: NTR5853

Notes:

Sponsors

Sponsor organisation name	Radboud Universitair Medisch Centrum
Sponsor organisation address	Geert Grooteplein Zuid 8, Nijmegen , Netherlands,
Public contact	Internal Medicine-Endocrine Disease, Radboud Universitair Medisch Centrum, 0031 0243614599,
Scientific contact	Internal Medicine-Endocrine Disease, Radboud Universitair Medisch Centrum, 0031 0243614599,

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	31 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 June 2017
Global end of trial reached?	Yes
Global end of trial date	02 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the physiological effects of metformin and hypocaloric dieting on thyroid iodide uptake and thyroid function in healthy volunteers.

Protection of trial subjects:

A complete health screening before enrollment was performed.
Participants were sent home with contact information and clear instructions when to contact the emergency number
During the intervention period, participants were contacted one week after starting intervention to check whether there are any complaints or complications or questions
Because of the low risk of either intervention, no additional specific measurements are taken.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 2016
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: 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)	19
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were invited to participate through advertisements on the Radboud University Medical Centre website and local university websites and placement of advertisements in the medical faculty, other locations on campus and in the city centre between October
and April 2017

Pre-assignment

Screening details:

Complete medical history and physical examination, including height, weight, BMI, and hip- and waist circumferences, and skinfold measurements.. A laboratory test was performed for screen for kidney disorder and thyroid disorders.

Pre-assignment period milestones

Number of subjects started	29[1]
Number of subjects completed	19

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 9
Reason: Number of subjects	Protocol deviation: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: More possible participants were screened; 9 of them dropped out before start of the trial; therefore, according to the protocol, we recruited more participants and screened them to reach our desired number for each subgroup.

Period 1

Period 1 title	baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Baseline - controle
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	baseline diet
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	baseline metformin
Arm description: -	
Arm type	baseline
Investigational medicinal product name	Metformin
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
during baseline: no metformin intake

Number of subjects in period 1	Baseline - controle	baseline diet	baseline metformin
Started	4	7	8
baseline measurement	4	7	8
Completed	4	7	8

Period 2

Period 2 title	Intervention period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:
Iodide depleted diet

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Hypocaloric diet

Arm description:
Hypocaloric diet; 40% caloric restriction (maximum of 1500 kcal/day) with high fat/low carbohydrate content (50% fat, 30% carbohydrate, 20% protein) for two weeks.

Arm type	intervention

No investigational medicinal product assigned in this arm

Arm title	Metformin

Arm description:
2-week course of metformin according to a dosing schedule

Arm type	Experimental
Investigational medicinal product name	Metformin
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
Dosing of Metformin:

- Day 1: 1 x 500 mg (dinner)
- Day 2: 1 x 500 mg (breakfast) & 1 x 500 mg (dinner)
- Day 3: 1 x 500 mg (breakfast) & 1 x 500 mg (dinner)
- Day 4: 1 x 500 mg (breakfast) & 2 x 500 mg (dinner)
- Day 5: 2 x 500 mg (breakfast) & 2 x 500 mg (dinner)
- Day 6 –End of study: 2 x 500 mg (breakfast) & 2 x 500 mg (dinner)

Investigational medicinal product name	Metformin
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosing of Metformin:
- Day 1: 1 x 500 mg (dinner)
- Day 2: 1 x 500 mg (breakfast) & 1 x 500 mg (dinner)
- Day 3: 1 x 500 mg (breakfast) & 1 x 500 mg (dinner)
- Day 4: 1 x 500 mg (breakfast) & 2 x 500 mg (dinner)
- Day 5: 2 x 500 mg (breakfast) & 2 x 500 mg (dinner)
- Day 6 –End of study: 2 x 500 mg (breakfast) & 2 x 500 mg (dinner)

Number of subjects in period 2	Control	Hypocaloric diet	Metformin
Started	4	7	8
Completed	4	7	8

Baseline characteristics

Reporting groups	
Reporting group title	baseline

Reporting group description: -

Reporting group values	baseline	Total	
Number of subjects	19	19	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	19	19	
From 65-84 years	0	0	
85 years and over	0	0	
not recorded	0	0	
Age continuous Units: years			
geometric mean	24.7		
standard deviation	± 5.5	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	19	19	

End points

End points reporting groups

Reporting group title	Baseline - controle
Reporting group description: -	
Reporting group title	baseline diet
Reporting group description: -	
Reporting group title	baseline metformin
Reporting group description: -	
Reporting group title	Control
Reporting group description:	
Iodide depleted diet	
Reporting group title	Hypocaloric diet
Reporting group description:	
Hypocaloric diet; 40% caloric restriction (maximum of 1500 kcal/day) with high fat/low carbohydrate content (50% fat, 30% carbohydrate, 20% protein) for two weeks.	
Reporting group title	Metformin
Reporting group description:	
2-week course of metformin according to a dosing schedule	

Primary: Thyroid iodide uptake

End point title	Thyroid iodide uptake[1]
End point description:	
Primary endpoint of this study is to assess the effect of metformin and hypocaloric diet on thyroid iodide uptake. 123I thyroid uptake is measured by RAIU testing using a gamma probe. Uptake is presented as percentage of total administrated 123I after 4, 24 and 48 hours after ingestion I-123.	
End point type	Primary
End point timeframe:	
thyroid uptake is measured by RAIU testing using a gamma probe. Uptake is presented as percentage of total administrated 123I after 4, 24 and 48 hours after ingestion I-123.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: See summary document for full discription on statiscal analysis and final results

End point values	Control	Hypocaloric diet	Metformin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	7	8	
Units: gamma counts	32	35	29	

Attachments (see zip file)	fig 2/41598_2019_Article_41997.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: TSH

End point title	TSH

End point description:

End point type	Secondary

End point timeframe:
baseline and post-intervention

End point values	Control	Hypocaloric diet	Metformin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	7	8	
Units: mE/L				
log mean (standard deviation)	0.23 (± 0.18)	0.23 (± 0.23)	0.34 (± 0.18)	

Attachments (see zip file)	figure 1/41598_2019_Article_41997.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: fT4

End point title	fT4

End point description:

End point type	Secondary

End point timeframe:
baseline and post-intervention

End point values	Control	Hypocaloric diet	Metformin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	7	8	
Units: pmol/L				
geometric mean (standard deviation)	16.65 (± 4.27)	16.8 (± 1.35)	17.36 (± 1.61)	

Attachments (see zip file)	figure 1/41598_2019_Article_41997.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: T3

End point title	T3

End point description:

End point type	Secondary

End point timeframe:
baseline and post-intervention

End point values	Control	Hypocaloric diet	Metformin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	7	8	
Units: nmol/l				
geometric mean (standard deviation)	2.07 (± 0.5)	2.01 (± 0.38)	1.95 (± 0.19)	

Attachments (see zip file)	figure 1/41598_2019_Article_41997.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening - baseline measurement - check up 1 week after intervention - post - intervention measurements.
Participants received information and contact information for when adverse events occured.

Adverse event reporting additional description:

All AEs will be followed until they have abated, or until a stable situation has been reached.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	Control
Reporting group description: -	
Reporting group title	Hypocaloric dieting
Reporting group description: -	
Reporting group title	Metformin

Reporting group description:

non serious side effects: minor gastro-intenstinal compaints after starting metfromin treatment.

Serious adverse events	Control	Hypocaloric dieting	Metformin
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	0 / 8 (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	Control	Hypocaloric dieting	Metformin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	5 / 8 (62.50%)
Gastrointestinal disorders			
diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	5 / 8 (62.50%)
occurrences (all)	0	0	5

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/30932012