Clinical trial results:
The effect of Mirabegron on brown adipose tissue in healthy young white Caucasian and South Asian men

Summary

EudraCT number	2016-000237-48
Trial protocol	NL
Global end of trial date	10 August 2017

Results information

Result version number	v1 (current)
This version publication date	01 December 2021
First version publication date	01 December 2021
Summary attachment (see zip file)	Published article (2020 Mirabegron study DOM.pdf)

Trial information

Trial identification

Sponsor protocol code	MiraBAT01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03012113
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	Clinical trial information, Leiden University Medical Center, 0031 648126425, m.r.boon@lumc.nl
Scientific contact	Clinical trial information, Leiden University Medical Center, 0031 648126425, m.r.boon@lumc.nl
Sponsor organisation name	Leiden University Medical Center
Sponsor organisation address	Albinusdreef 2, Leiden, Netherlands, 2333 ZA
Public contact	Mariëtte Boon, Leiden University Medical Center, 0031 648126425, m.r.boon@lumc.nl
Scientific contact	Mariëtte Boon, 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 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 July 2017
Global end of trial reached?	Yes
Global end of trial date	10 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of Mirabegron treatment on brown fat activity measured by MRI in South Asians compared with white Caucasians.

Protection of trial subjects:

Subjects were made as comfortable as possible during the study days.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 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: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

20 Participants, of which 10 South Asian and 10 white Caucasian, were enrolled in a randomized, double-blinded, placebo-controlled cross-over study. Participants were recruited through advertisements and by approaching subjects that participated in previous studies.

Pre-assignment

Screening details:

At screening a thorough medical history and physical examination were performed. Subjects were examined while in the fasting state. Anthropometric measurements were performed as well as a BIA measurement for determination of body fat percentage and basal blood sample was taken to assess kidney, liver, thyroid, Hb and electrolites.

Period 1

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

Blinding implementation details:

Beforehand an unblinded pharmacist set up a list in which each study subject number was coupled to a box number. The pharmacy then gave the medication according to the randomisation list. Therefore, the study was conducted double blind. Furthermore, the staff performing the MRI analyses and the laboratory measures only got samples (or the scans) with a subject and occasion number on it.

Arms

Arm title	Baseline period

Arm description:

Baseline period

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

Dosage and administration details:

200 mg, divided in 4 tablets of 50 mg

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

Dosage and administration details:

200 mg, divided in 4 tablets of 50 mg

Number of subjects in period 1	Baseline period
Started	20
Completed	20

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description:	
Baseline characteristics for South Asian (n=10) and white Caucasian (n=10) subjects	

Reporting group values	Baseline	Total	
Number of subjects	20	20	
Age categorical			
Adults			
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)	20	20	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	20	20	

Subject analysis sets	
Subject analysis set title	Cold exposure
Subject analysis set type	Full analysis
Subject analysis set description:	
Effects of cold exposure	
Subject analysis set title	Mirabegron
Subject analysis set type	Full analysis
Subject analysis set description:	
Effects of mirabegron treatment	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Placebo treatment	

Reporting group values	Cold exposure	Mirabegron	Placebo
Number of subjects	20	20	20
Age categorical			
Adults			
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			
Gender categorical Units: Subjects			
Female	0	0	0
Male	20	20	20

End points

End points reporting groups

Reporting group title	Baseline period
Reporting group description: Baseline period	
Subject analysis set title	Cold exposure
Subject analysis set type	Full analysis
Subject analysis set description: Effects of cold exposure	
Subject analysis set title	Mirabegron
Subject analysis set type	Full analysis
Subject analysis set description: Effects of mirabegron treatment	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description: Placebo treatment	

Primary: Brown adipose tissue activity

End point title	Brown adipose tissue activity
End point description: Brown adipose tissue (BAT) activity was measured using MRI. To this end, we assessed the fat fraction percentage in the left supraclavicular BAT depot. The average fat fraction was computed for pre- and post- cooling and post-mirabegron treatment. Only voxels with a fat fraction between 50-100% were included for data analysis. One participant was excluded from all MRI analyses because of failure to reconstruct the scan due to excessive movement.	
End point type	Primary
End point timeframe: 2 hours after cold exposure, mirabegron or placebo treatment	

End point values	Cold exposure	Mirabegron	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	20	20	
Units: percentage				
arithmetic mean (standard deviation)	69 (± 4)	71 (± 4)	73 (± 4)	

Attachments (see zip file)	BAT FF figure.docx

Statistical analyses

Statistical analysis title	Fat fraction analysis
Statistical analysis description: One-way ANOVA was performed to study differences in BAT parameters between treatments	
Comparison groups	Mirabegron v Cold exposure v Placebo

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	< 0.01 [2]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.5
upper limit	4.1
Variability estimate	Standard deviation

Notes:

[1] - Data were analysed using IBM SPSS Statistics for Windows version 22.0 (SPSS Inc, Chicago, IL, USA). All main analyses were also presented per ethnicity (Europids vs. South Asians). However, as we did not observe interaction between ethnicity, treatment and metabolic outcome parameters in any statistical test (all p>0.05), we here show all analyses combined for both ethnicities to increase the statistical power.
Of note, in total 20 subjects were in the analysis since it was a crossover design!
[2] - When both ethnicities were combined in a single analysis, cold exposure lowered BAT fat fraction compared with placebo (−2.3%, P < 0.001). The average BAT fat fraction was lower after mirabegron versus placebo treatment (−1.4%, P <0.01).

Primary: BAT T2*

End point title	BAT T2*

End point description:

Transverse relaxation time (T2*) was assessed using a three-dimensional six-point chemical-shift encoded gradient echo sequence.

End point type	Primary

End point timeframe:

2 hours after treatment with cold, placebo or mirabegron

End point values	Cold exposure	Mirabegron	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	20	20	
Units: ms				
arithmetic mean (standard deviation)	16 (± 3)	17 (± 5)	16 (± 3)	

Attachments (see zip file)	BAT T2 figure.docx

Statistical analyses

Statistical analysis title	T2*

Statistical analysis description:

Data were analysed using IBM SPSS Statistics for Windows version 22.0 (SPSS Inc, Chicago, IL, USA). All main analyses were also presented per ethnicity (Europids vs. South Asians). However, as we did not observe interaction between ethnicity, treatment and metabolic outcome parameters in any statistical test (all p>0.05), we here show all analyses combined for both ethnicities to increase the statistical

power.
Of note, in total 20 subjects were in the analysis since it was a crossover design!

Comparison groups	Cold exposure v Mirabegron v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	> 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.5
upper limit	10.8
Variability estimate	Standard deviation

Notes:
[3] - See description FF

Primary: BAT volume

End point title	BAT volume

End point description:
BAT volume was calculated through MRI, as mentioned in the Methods section of the manuscript

End point type	Primary

End point timeframe:
2 hours after treatment with cold, placebo or mirabegron

End point values	Cold exposure	Mirabegron	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	20	20	
Units: mL				
arithmetic mean (standard deviation)	23 (± 9)	23 (± 10)	24 (± 9)	

Attachments (see zip file)	BAT volume figure.docx

Statistical analyses

Statistical analysis title	BAT volume

Statistical analysis description:
see description under BAT FF

Comparison groups	Cold exposure v Mirabegron v Placebo

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence[4]
P-value	> 0.05 [5]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.4

Notes:

[4] - see description under BAT FF

[5] - For all comparisons, P-value was > 0.05

Secondary: Resting energy expenditure

End point title	Resting energy expenditure

End point description:

Resting energy expenditure was measured using indirect calorimetry and expressed as kcal/day.

End point type	Secondary

End point timeframe:

Resting energy expenditure was measured before and at the end of two hours of cold exposure. Furthermore, energy expenditure was measured at baseline and every hour up to 3 hours after treatment with placebo or mirabegron.

End point values	Cold exposure	Mirabegron	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	20	20	
Units: kcal/day				
arithmetic mean (standard deviation)	1808 (± 384)	1584 (± 264)	1409 (± 291)	

Attachments (see zip file)	Energy expenditure/EE Figure.docx

Statistical analyses

Statistical analysis title	Energy expenditure

Statistical analysis description:

Paired T tests were performed to study the effect of cold exposure on energy expenditure (pre- vs post-cold exposure).
The effect of mirabegron or placebo on energy expenditure was studied by a repated measures two-way ANOVA with 'time' (0,1,2 and 3 hours) and 'treatment (mirabegron or placebo) as within-subjects factors.

Comparison groups	Mirabegron v Placebo v Cold exposure

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence[6]
P-value	< 0.05 [7]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.17
Variability estimate	Standard deviation
Dispersion value	0.09

Notes:

[6] - see above

[7] - Cold exposure significantly increased energy expenditure (P<0.05)
Using a two-way ANOVA, we found that mirabegron significantly increased REE compared with placebo, specifically in the second hour of treatment. Below, I show the cold mean difference

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
7 hours (during the whole study day)	
Adverse event reporting additional description:	
We studied the occurence of adverse events following either cold treatment or the other treatments (placebo and mirabegron)	
Assessment type	Systematic

Dictionary used	
Dictionary name	CPMP
Dictionary version	1

Reporting groups	
Reporting group title	Cold exposure
Reporting group description:	
Subjects that were exposed to 2 hours of cold exposure	
Reporting group title	Mirabegron
Reporting group description:	
Subjects that received mirabegron treatment	
Reporting group title	Placebo
Reporting group description:	
Subjects that received a placebo capsule	

Serious adverse events	Cold exposure	Mirabegron	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 20 (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	Cold exposure	Mirabegron	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	1 / 20 (5.00%)
Nervous system disorders			
headache	Additional description: Cold exposure group		
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Psychiatric disorders			

Feeling of fear subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0

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 summary of results, we have only reported on the primary outcome, namely the effects on BAT activity measured by fat fraction. For an extensive overview of results, please see our publication.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32558052