Clinical trial results:
TAILoR – (TelmisArtan and InsuLin Resistance in HIV): A Dose-Ranging Phase II Randomised Open-Labelled Trial of Telmisartan as a strategy for the Reduction of Insulin Resistance in HIV-Positive Individuals on Combination Antiretroviral Therapy (cART)

Summary

EudraCT number	2012-000935-18
Trial protocol	GB
Global end of trial date	20 June 2016

Results information

Result version number	v1 (current)
This version publication date	05 August 2018
First version publication date	05 August 2018
Summary attachment (see zip file)	TAILOR additional data received after database lock (TAILOR extra data.pdf)

Trial information

Trial identification

Sponsor protocol code	UoL000841

Additional study identifiers

ISRCTN number	ISRCTN51069819
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Funder's Reference Number: 10/60/37, Co-sponsor's Reference Number: 4209, REC reference: 12/NW/0214

Notes:

Sponsors

Sponsor organisation name	University of Liverpool
Sponsor organisation address	Brownlow Hill, Liverpool, United Kingdom, L69 3BX
Public contact	Clinical Research Governance Manager, University of Liverpool, +44 0151 794 8722, lindsay.carter@liverpool.ac.uk
Scientific contact	Clinical Research Governance Manager, University of Liverpool, +44 0151 794 8722, lindsay.carter@liverpool.ac.uk
Sponsor organisation name	Royal Liverpool and Broadgreen Hospitals NHS Trust
Sponsor organisation address	Prescot street, Liverpool, United Kingdom, L7 8XP
Public contact	Research Governance Manager, Royal Liverpool and Broadgreen Hospitals NHS Trust, +44 0151 706 3702, Heather.Rogers@rlbuht.nhs.uk
Scientific contact	Research Governance Manager, Royal Liverpool and Broadgreen Hospitals NHS Trust, +44 0151 706 3702, Heather.Rogers@rlbuht.nhs.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric	No

investigation plan (PIP)	
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	08 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 January 2016
Global end of trial reached?	Yes
Global end of trial date	20 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The trial will assess whether telmisartan can reduce insulin resistance (reduced response to insulin) in HIV-positive individuals being treated with combination antiretroviral therapy (cART).

Primary objective: To determine the effect of telmisartan on insulin resistance in HIV-positive individuals on combination antiretroviral therapy using HOMA-IR (Homeostatic Model Assessment - Insulin Resistance) as a measurable, validated surrogate marker of insulin resistance.

Protection of trial subjects:

TAILOR trial recruited competent adults in their usual clinical care setting. Where the protocol treatment regimen allowed, the trial visits and assessments were scheduled in line with usual clinical practice, with visit windows allowing as much flexibility as possible to fit with participant commitments. Travel expenses were paid for (up to) two dose titration visits and one other visit (generally the baseline visit) that took place outside of routine clinical appointments. TAILOR treatment was administered as a single daily dose as an oral tablet formulation, minimising the pill burden on the population as much as possible.

Background therapy:

No additional interventions were provided.

Evidence for comparator:

In Stage I of the trial, a quarter of the patients will be allocated to the non-intervention control arm. These patients will not receive any investigational drug and therefore do not get any direct benefit of the intervention, if any; however such a non-intervention comparator arm is necessary for the identification of a positive drug effect in the treatment arm(s). However, this does not have any impact on the control of HIV infection since the intended use of telmisartan in this patient population is only as an adjuvant drug and not as the primary drug.

A percentage of the participants could also be on a treatment arm found to be less effective than control or other treatment arms during the interim analysis and hence, be dropped. Again, this does not have any impact on the control of HIV infection since the intended use of telmisartan in this patient population is only as an adjuvant drug and not as the primary drug.

Actual start date of recruitment	21 February 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 377
Worldwide total number of subjects	377
EEA total number of subjects	377

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)	362
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted in 19 UK Sexual Health Clinics and/or HIV treatment centres from February 2013 until July 2015. The target recruitment rate for the study was two to five patients per month per site, based on the original 8 sites recruiting and a target recruitment figure of 370.

Pre-assignment

Screening details:

In total, 1953 patients were screened at the participating centres over the duration of the trial. Of the 1121 patients meeting the eligibility criteria, 698 declined to participate, 44 consented but were not randomised and 379 were randomised initially but there were 2 post randomisation exclusions. Final total randomised was 377.

Pre-assignment period milestones

Number of subjects started	1953[1]
Intermediate milestone: Number of subjects	Eligible: 1121
Intermediate milestone: Number of subjects	Consent obtained: 423
Intermediate milestone: Number of subjects	Randomised: 379
Number of subjects completed	377

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Randomised the same patient in error: 1
Reason: Number of subjects	Patient was not present at randomisation: 1
Reason: Number of subjects	Not eligible: 832
Reason: Number of subjects	Consent not provided: 698
Reason: Number of subjects	Consented but not randomised: 44

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: The number of patients who started the pre-assignment period (screened - 1953) is larger than the number who enrolled in the trial (randomised - 377).

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A (Baseline)

Arm description:

Arm A: Non-intervention (control)

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Arm B (Baseline)

Arm description:	
Arm B: Telmisartan 20mg	
Arm type	Experimental
Investigational medicinal product name	Telmisartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
24 weeks oral telmisartan 20 milligram (mg) dose, once daily	
Arm title	Arm C (Baseline)
Arm description:	
Arm C: Telmisartan 40mg	
Arm type	Experimental
Investigational medicinal product name	Telmisartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
24 weeks oral telmisartan 40 mg dose, once daily. The starting dose for patients in this arm will be 20 mg and dose titration to 40mg will be undertaken over a period of 2 weeks.	
Arm title	Arm D (Baseline)
Arm description:	
Arm D: Telmisartan 80mg	
Arm type	Experimental
Investigational medicinal product name	Telmisartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
24 weeks oral telmisartan 80 mg dose, once daily. The starting dose for patients in this arm will be 20 mg and dose titration to 80mg will be undertaken over a period of 4 weeks.	

Number of subjects in period 1	Arm A (Baseline)	Arm B (Baseline)	Arm C (Baseline)
Started	105	84	82
Completed	105	84	82

Number of subjects in period 1	Arm D (Baseline)
Started	106
Completed	106

Period 2

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

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A (Final)

Arm description:

Arm A: Non-intervention (control)

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Arm D (Final)

Arm description:

Arm D: Telmisartan 80mg

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

Dosage and administration details:

24 weeks oral telmisartan 80 mg dose, once daily. The starting dose for patients in this arm will be 20 mg and dose titration to 80mg will be undertaken over a period of 4 weeks.

Number of subjects in period 2[2]	Arm A (Final)	Arm D (Final)
Started	105	106
Basline	100	100
Week 24	89	82
Included in Final analysis	85	78
Completed	85	78
Not completed	20	28
Withdrew before 24 weeks	11	16
Did not attend week 24	4	3
Haemolysed samples collected 24 weeks	-	2
Samples not collected/un-fasted baseline	1	2
Haemolysed samples collected baseline	3	3

Samples not collected/un-fasted 24 weeks	1	2

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Arms B and C were dropped following interim analysis.

Baseline characteristics

Reporting groups	
Reporting group title	Arm A (Baseline)
Reporting group description: Arm A: Non-intervention (control)	
Reporting group title	Arm B (Baseline)
Reporting group description: Arm B: Telmisartan 20mg	
Reporting group title	Arm C (Baseline)
Reporting group description: Arm C: Telmisartan 40mg	
Reporting group title	Arm D (Baseline)
Reporting group description: Arm D: Telmisartan 80mg	

Reporting group values	Arm A (Baseline)	Arm B (Baseline)	Arm C (Baseline)
Number of subjects	105	84	82
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)	99	79	80
From 65-84 years	6	5	2
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	47.2	47.1	47.9
standard deviation	± 10.5	± 10.1	± 7.5
Gender categorical Units: Subjects			
Female	20	15	13
Male	85	69	69
Ethnicity Units: Subjects			
British	71	52	56
Irish	3	1	0
Any other white	9	8	8
White and black african	1	1	0
Any other mixed	0	2	0
Indian	0	1	0
Any other Asian	0	1	2
Caribbean	8	8	9

African	10	7	4
Any other black	3	2	3
Chinese	0	1	0
Any other ethnic group	0	0	0
Physical exam			
Was a physical exam carried out at this visit (yes/no)?			
Units: Subjects			
No	15	16	12
Yes	90	68	69
Missing	0	0	1
Hepatits C			
Has participant been tested for Hepatitis C within the last 6 months (yes/no)?			
Units: Subjects			
No	23	22	25
Yes	82	62	57
BMI			
Number of participants missing data for baseline characteristic: Arm A: 2, Arm B: 0, Arm C: 1, Arm D: 0			
Units: KG/m^2			
arithmetic mean	26.6	27.1	27.1
standard deviation	± 5.2	± 5.8	± 4.8
Blood pressure Systolic			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 0, Arm C: 1, Arm D: 0			
Units: mmHg			
arithmetic mean	126.8	124.4	126.9
standard deviation	± 13.9	± 14.2	± 14.3
Blood pressure diastolic			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 0, Arm C: 1, Arm D: 0			
Units: mmHg			
arithmetic mean	80.0	78.2	79.7
standard deviation	± 10.7	± 11.2	± 9.9
Heat rate			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 2, Arm C: 2, Arm D: 0			
Units: Beats/min			
arithmetic mean	73.0	72.5	71.6
standard deviation	± 11.5	± 11.7	± 13.1
Temperature			
Number of participants missing data for baseline characteristic: Arm A: 6, Arm B: 6, Arm C: 4, Arm D: 4			
Units: celsius temperature			
arithmetic mean	36.3	36.3	36.4
standard deviation	± 0.5	± 0.4	± 0.3
Respiratory rate			
Number of participants missing data for baseline characteristic: Arm A: 3, Arm B: 1, Arm C: 6, Arm D: 3			
Units: breaths/min			
arithmetic mean	15.6	15.9	16.0
standard deviation	± 2.9	± 4.0	± 4.2
Waist circumference			
Number of participants missing data for baseline characteristic: Arm A: 4, Arm B: 1, Arm C: 3, Arm D: 4			

Units: cm			
arithmetic mean	93.5	94.6	97.1
standard deviation	± 11.8	± 14.7	± 12.2
Thigh circumference			
Number of participants missing data for baseline characteristic: Arm A: 4, Arm B: 2, Arm C: 5, Arm D: 4			
Units: cm			
arithmetic mean	50.8	52.3	51.8
standard deviation	± 7.5	± 7.7	± 6.0
CD4 Cell count			
Number of participants missing data for baseline characteristic: Arm A: 3, Arm B: 1, Arm C: 4, Arm D: 5			
Units: cells/mm^3			
arithmetic mean	640.0	619.2	613.8
standard deviation	± 231.1	± 272.5	± 248.4
CD4 Cell count & HIV viral load			
Number of participants missing data for baseline characteristic: Arm A: 3, Arm B: 0, Arm C: 1, Arm D: 0			
Units: percent			
arithmetic mean	32.1	29.2	30.1
standard deviation	± 7.7	± 8.6	± 9.3
HIV Viral Load (continuous)			
Number of participants missing data for this continuous baseline characteristic: Arm A: 70, Arm B: 67, Arm C: 51, Arm D: 72 The missing data are presented in categorical form due to there being upper and lower limits of measurement: < 10 : Arm A: 2, Arm B: 1, Arm C: 2, Arm D: 1 < 20 : Arm A: 13, Arm B: 20, Arm C: 11, Arm D: 23 < 40 : Arm A: 50, Arm B: 38, Arm C: 35, Arm D: 43 < 45 : Arm A: 2, Arm B: 6, Arm C: 3, Arm D: 3 < 100 : Arm A: 0, Arm B: 1, Arm C: 0, Arm D: 0 Missing: Arm A: 3, Arm B: 1, Arm C: 0, Arm D: 2			
Units: copies/ml			
arithmetic mean	43.0	21.6	58.0
standard deviation	± 96.4	± 31.1	± 119.4
Sodium			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 1, Arm C: 0, Arm D: 1			
Units: mmol/l			
arithmetic mean	139.7	140.1	140.5
standard deviation	± 2.2	± 2.0	± 2.3
Potassium			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 1, Arm C: 0, Arm D: 1			
Units: mmol/l			
arithmetic mean	4.3	4.3	4.3
standard deviation	± 0.3	± 0.3	± 0.4
Urea			
Number of participants missing data for baseline characteristic: Arm A: 15, Arm B: 12, Arm C: 5, Arm D: 16			
Units: mmol/l			
arithmetic mean	5.0	5.1	5.2
standard deviation	± 1.4	± 1.4	± 1.2
Bicarbonate			
Number of participants missing data for baseline characteristic: Arm A: 89, Arm B: 66, Arm C: 60, Arm D: 80			

Units: mmol/l			
arithmetic mean	26.2	26.8	25.8
standard deviation	± 3.5	± 3.0	± 3.1
Creatinine			
Number of participants missing data for baseline characteristic: Arm A: 2, Arm B: 0, Arm C: 0, Arm D: 2			
Units: mmol/l			
arithmetic mean	78.7	80.2	82.6
standard deviation	± 15.6	± 14.9	± 15.1
eGFR (continuous)			
Number of participants missing data for baseline characteristic: Arm A: 55, Arm B: 43, Arm C: 44, Arm D: 52 The missing data are presented in categorical form due to there being upper and lower limits of measurement: < 60 : Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 1 < 90 : Arm A: 1, Arm B: 0, Arm C: 0, Arm D: 0 > 60 : Arm A: 24, Arm B: 23, Arm C: 25, Arm D: 22 > 90 : Arm A: 28, Arm B: 19, Arm C: 19, Arm D: 28 Missing: Arm A: 2, Arm B: 1, Arm C: 0, Arm D: 1			
Units: eGFR score			
arithmetic mean	79.8	79.9	77.9
standard deviation	± 13.6	± 10.8	± 10.5
ALT			
Number of participants missing data for baseline characteristic: Arm A: 13, Arm B: 9, Arm C: 5, Arm D: 10			
Units: iu/l			
arithmetic mean	26.8	29.4	29.1
standard deviation	± 13.5	± 20.3	± 12.8
AST			
Number of participants missing data for baseline characteristic: Arm A: 78, Arm B: 67, Arm C: 64, Arm D: 79			
Units: iu/l			
arithmetic mean	34.7	27.3	28.6
standard deviation	± 50.7	± 6.7	± 8.3
ALP			
Number of participants missing data for baseline characteristic: Arm A: 4, Arm B: 4, Arm C: 10, Arm D: 9			
Units: iu/l			
arithmetic mean	96.5	96.1	83.7
standard deviation	± 45.2	± 46.9	± 29.6
Albumin			
Number of participants missing data for baseline characteristic: Arm A: 3, Arm B: 1, Arm C: 1, Arm D: 3			
Units: g/l			
arithmetic mean	43.7	44.3	44.2
standard deviation	± 4.1	± 3.5	± 3.2
Total protein			
Number of participants missing data for baseline characteristic: Arm A: 33, Arm B: 25, Arm C: 23, Arm D: 37			
Units: g/l			
arithmetic mean	74.5	73.7	74.2
standard deviation	± 5.3	± 4.0	± 4.6
Bilirubin			
Number of participants missing data for baseline characteristic: Arm A: 5, Arm B: 6, Arm C: 6, Arm D: 8 Some data are presented in both continuous and categorical form due to there being upper and lower			

limits of measurement: < 2 : Arm A: 0, Arm B: 1, Arm C: 0, Arm D: 0 < 3 : Arm A: 3, Arm B: 2, Arm C: 2, Arm D: 2 < 15 : Arm A: 1, Arm B: 2, Arm C: 1, Arm D: 4			
Units: µmol/l			
arithmetic mean	11.1	10.9	14.6
standard deviation	± 13.3	± 14.1	± 17.6
Haemoglobin			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 1, Arm C: 0, Arm D: 0			
Units: g/dl			
arithmetic mean	143.77	144.16	146.73
standard deviation	± 12.28	± 13.32	± 12.15
Red blood cell count			
Number of participants missing data for baseline characteristic: Arm A: 7, Arm B: 5, Arm C: 5, Arm D: 9			
Units: 10^12/l			
arithmetic mean	4.55	4.62	4.69
standard deviation	± 0.44	± 0.44	± 0.41
White blood cell count			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 1			
Units: 10^9/l			
arithmetic mean	6.43	6.12	5.92
standard deviation	± 2.3	± 1.99	± 1.74
Platelets			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 0, Arm C: 0, Arm D: 0			
Units: 10^9/l			
arithmetic mean	243.07	226.61	226.16
standard deviation	± 74.67	± 55.48	± 62.24
Mean cell volume			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 0, Arm C: 0, Arm D: 0			
Units: fl			
arithmetic mean	93.40	92.87	92.47
standard deviation	± 5.65	± 5.48	± 5.48
Mean cell Haemoglobin			
Number of participants missing data for baseline characteristic: Arm A: 25, Arm B: 17, Arm C: 21, Arm D: 21			
Units: pg			
arithmetic mean	31.49	31.35	36.17
standard deviation	± 3.92	± 2.06	± 37.78
Mean cell Haemoglobin			
Number of participants missing data for baseline characteristic: Arm A: 37, Arm B: 31, Arm C: 29, Arm D: 41			
Units: g/dl			
arithmetic mean	340.71	335.28	340.57
standard deviation	± 11.83	± 12.97	± 13.03
Red cell distribution width			
Number of participants missing data for baseline characteristic: Arm A: 76, Arm B: 62, Arm C: 56, Arm D: 78			
Units: percent			
arithmetic mean	13.31	13.36	13.18
standard deviation	± 0.98	± 0.7	± 0.65

Neutrophils			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 0			
Units: 10^9/l			
arithmetic mean	3.62	3.27	3.21
standard deviation	± 1.95	± 1.51	± 1.43
Lymphocytes			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 0			
Units: 10^9/l			
arithmetic mean	2.10	2.17	2.05
standard deviation	± 0.69	± 0.72	± 0.66
Eosinophils			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 2, Arm C: 0, Arm D: 0			
Units: 10^9/l			
arithmetic mean	0.17	0.15	0.15
standard deviation	± 0.15	± 0.12	± 0.08
Basophils			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 0			
Units: 10^9/l			
arithmetic mean	0.03	0.02	0.02
standard deviation	± 0.04	± 0.04	± 0.04
Monocytes			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 0			
Units: 10^9/l			
arithmetic mean	0.49	0.46	0.48
standard deviation	± 0.20	± 0.18	± 0.16
Insulin			
Number of participants missing data for baseline characteristic: Arm A: 3, Arm B: 3, Arm C: 4, Arm D: 6			
Units: pmol/l			
arithmetic mean	72.26	76.56	81.29
standard deviation	± 53.42	± 58	± 78.52
Glucose			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 1, Arm C: 2, Arm D: 2			
Units: mmol/l			
arithmetic mean	5.2	5.2	5.29
standard deviation	± 0.5	± 0.58	± 0.7
QUICKI			
Number of participants missing data for baseline characteristic: Arm A: 5, Arm B: 2, Arm C: 4, Arm D: 4			
Units: QUICKI score			
arithmetic mean	0.117	0.116	0.116
standard deviation	± 0.009	± 0.009	± 0.010
Revised QUICKI			
Number of participants missing data for baseline characteristic: Arm A: 5, Arm B: 2, Arm C: 4, Arm D: 5			
Units: revised QUICKI score			
arithmetic mean	0.132	0.134	0.134
standard deviation	± 0.017	± 0.019	± 0.019
HOMAIR			

Number of participants missing data for baseline characteristic: Arm A: 5, Arm B: 2, Arm C: 4, Arm D: 4			
Units: HOMA-IR Score			
arithmetic mean	2.494	2.568	2.820
standard deviation	± 2.083	± 1.923	± 3.040
HDLc			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 2, Arm C: 3, Arm D: 3			
Units: mmol/l			
arithmetic mean	1.19	1.21	1.14
standard deviation	± 0.4	± 0.39	± 0.4
Cholesterol			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 2, Arm C: 3, Arm D: 3			
Units: mmol/l			
arithmetic mean	5.01	5	4.83
standard deviation	± 0.99	± 1.11	± 1.04
LDLc			
Number of participants missing data for baseline characteristic: Arm A: 2, Arm B: 3, Arm C: 4, Arm D: 4			
Units: mmol/l			
arithmetic mean	3.1	3.14	2.97
standard deviation	± 0.91	± 0.97	± 0.9
Adiponectin			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 2, Arm C: 4, Arm D: 5			
Units: microgram(s)/millilitre			
arithmetic mean	15.62	17.89	16.85
standard deviation	± 7.81	± 10.78	± 10.97
Leptin			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 3, Arm C: 4, Arm D: 3			
Units: pg/ml			
arithmetic mean	12484	14046	11842
standard deviation	± 18996	± 25894	± 20774
IL8			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 2, Arm C: 4, Arm D: 4			
Units: pg/ml			
arithmetic mean	33.46	21.38	22.3
standard deviation	± 89.94	± 25.19	± 23.96
TNFalpha			
Number of participants missing data for baseline characteristic: Arm A: 2, Arm B: 2, Arm C: 4, Arm D: 5			
Units: pg/ml			
arithmetic mean	2.9	2.3	2.56
standard deviation	± 1.99	± 0.91	± 1.29
Resistin			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 2, Arm C: 4, Arm D: 5			
Units: pg/ml			
arithmetic mean	6630.2	5779	5602.4
standard deviation	± 4116.6	± 3196.8	± 2753.1
hsCRP			
Number of participants missing data for baseline characteristic:			

Arm A: 1, Arm B: 2, Arm C: 4, Arm D: 3			
Units: mg/ml			
arithmetic mean	4.94	3.08	4.1
standard deviation	± 12.16	± 3.64	± 11.03
NEFA			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 1, Arm C: 3, Arm D: 2			
Units: mmol/l			
arithmetic mean	0.459	0.416	0.396
standard deviation	± 0.240	± 0.229	± 0.204
Chloride			
Number of participants missing data for baseline characteristic: Arm A: 82, Arm B: 69, Arm C: 59, Arm D: 86			
Units: mmol/l			
arithmetic mean	103.0	103.1	102.7
standard deviation	± 2.6	± 3.0	± 1.9
Haematocrit			
Number of participants missing data for baseline characteristic: Arm A: 35, Arm B: 35, Arm C: 32, Arm D: 41			
Units: percentage			
arithmetic mean	42.23	42.16	42.82
standard deviation	± 3.29	± 6.51	± 3.18
Fasting glucose			
Number of participants missing data for baseline characteristic: Arm A: 75, Arm B: 66, Arm C: 59, Arm D: 81			
Units: mmol/l			
arithmetic mean	5.05	4.99	4.97
standard deviation	± 0.73	± 0.48	± 0.56
HBA1c			
Number of participants missing data for baseline characteristic: Arm A: 102, Arm B: 78, Arm C: 80, Arm D: 100			
Units: mmol/l			
arithmetic mean	34.67	36.00	37.00
standard deviation	± 1.15	± 2.53	± 4.24
HBA1c (%)			
Number of participants missing data for baseline characteristic: Arm A: 104, Arm B: 83, Arm C: 82, Arm D: 106 ***Please note for Arm C and Arm D there were no values to report but system requires that field not left blank so entered 0 in these cells. These are not genuine zeros.***			
Units: percent			
median	5.2	5.7	0
inter-quartile range (Q1-Q3)	5.2 to 5.2	5.7 to 5.7	0 to 0
OGTT			
Number of participants missing data for baseline characteristic: Arm A: 104, Arm B: 84, Arm C: 81, Arm D: 106 ***Please note for Arm B and Arm D there were no values to report but system requires that field not left blank so entered 0 in these cells. These are not genuine zeros.***			
Units: mmol/l			
median	5.8	0	7.3
inter-quartile range (Q1-Q3)	5.8 to 5.8	0 to 0	7.3 to 7.3
Random plasma glucose			
Number of participants missing data for baseline characteristic: Arm A: 27, Arm B: 18, Arm C: 25, Arm D: 25			
Units: mmol/l			
arithmetic mean	5.03	5.07	5.12

standard deviation	± 0.83	± 0.80	± 0.84
Triglycerides			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 2, Arm C: 3, Arm D: 3			
Units: mmol/l			
arithmetic mean	1.61	1.42	1.56
standard deviation	± 0.89	± 0.75	± 0.91

Reporting group values	Arm D (Baseline)	Total	
Number of subjects	106	377	
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)	104	362	
From 65-84 years	2	15	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	44.9		
standard deviation	± 9.2	-	
Gender categorical Units: Subjects			
Female	17	65	
Male	89	312	
Ethnicity Units: Subjects			
British	70	249	
Irish	4	8	
Any other white	7	32	
White and black african	0	2	
Any other mixed	1	3	
Indian	0	1	
Any other Asian	0	3	
Caribbean	7	32	
African	9	30	
Any other black	6	14	
Chinese	1	2	
Any other ethnic group	1	1	
Physical exam			
Was a physical exam carried out at this visit (yes/no)?			
Units: Subjects			
No	22	65	
Yes	84	311	
Missing	0	1	
Hepatits C			

Has participant been tested for Hepatitis C within the last 6 months (yes/no)?			
Units: Subjects			
No	28	98	
Yes	78	279	
BMI			
Number of participants missing data for baseline characteristic: Arm A: 2, Arm B: 0, Arm C: 1, Arm D: 0			
Units: KG/m^2			
arithmetic mean	26.0		
standard deviation	± 4.7	-	
Blood pressure Systolic			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 0, Arm C: 1, Arm D: 0			
Units: mmHg			
arithmetic mean	124.8		
standard deviation	± 15.4	-	
Blood pressure diastolic			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 0, Arm C: 1, Arm D: 0			
Units: mmHg			
arithmetic mean	78.6		
standard deviation	± 11.1	-	
Heat rate			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 2, Arm C: 2, Arm D: 0			
Units: Beats/min			
arithmetic mean	72.8		
standard deviation	± 12.2	-	
Temperature			
Number of participants missing data for baseline characteristic: Arm A: 6, Arm B: 6, Arm C: 4, Arm D: 4			
Units: celsius temperature			
arithmetic mean	36.3		
standard deviation	± 0.5	-	
Respiratory rate			
Number of participants missing data for baseline characteristic: Arm A: 3, Arm B: 1, Arm C: 6, Arm D: 3			
Units: breaths/min			
arithmetic mean	16.5		
standard deviation	± 3.4	-	
Waist circumference			
Number of participants missing data for baseline characteristic: Arm A: 4, Arm B: 1, Arm C: 3, Arm D: 4			
Units: cm			
arithmetic mean	93.0		
standard deviation	± 11.6	-	
Thigh circumference			
Number of participants missing data for baseline characteristic: Arm A: 4, Arm B: 2, Arm C: 5, Arm D: 4			
Units: cm			
arithmetic mean	49.6		
standard deviation	± 8.5	-	
CD4 Cell count			
Number of participants missing data for baseline characteristic: Arm A: 3, Arm B: 1, Arm C: 4, Arm D: 5			

Units: cells/mm^3			
arithmetic mean	617.0		
standard deviation	± 266.1	-	
CD4 Cell count & HIV viral load			
Number of participants missing data for baseline characteristic: Arm A: 3, Arm B: 0, Arm C: 1, Arm D: 0			
Units: percent			
arithmetic mean	30.5		
standard deviation	± 7.9	-	
HIV Viral Load (continuous)			
Number of participants missing data for this continuous baseline characteristic: Arm A: 70, Arm B: 67, Arm C: 51, Arm D: 72 The missing data are presented in categorical form due to there being upper and lower limits of measurement: < 10 : Arm A: 2, Arm B: 1, Arm C: 2, Arm D: 1 < 20 : Arm A: 13, Arm B: 20, Arm C: 11, Arm D: 23 < 40 : Arm A: 50, Arm B: 38, Arm C: 35, Arm D: 43 < 45 : Arm A: 2, Arm B: 6, Arm C: 3, Arm D: 3 < 100 : Arm A: 0, Arm B: 1, Arm C: 0, Arm D: 0 Missing: Arm A: 3, Arm B: 1, Arm C: 0, Arm D: 2			
Units: copies/ml			
arithmetic mean	25.1		
standard deviation	± 33.2	-	
Sodium			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 1, Arm C: 0, Arm D: 1			
Units: mmol/l			
arithmetic mean	140.1		
standard deviation	± 2.3	-	
Potassium			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 1, Arm C: 0, Arm D: 1			
Units: mmol/l			
arithmetic mean	4.3		
standard deviation	± 0.3	-	
Urea			
Number of participants missing data for baseline characteristic: Arm A: 15, Arm B: 12, Arm C: 5, Arm D: 16			
Units: mmol/l			
arithmetic mean	5.0		
standard deviation	± 1.3	-	
Bicarbonate			
Number of participants missing data for baseline characteristic: Arm A: 89, Arm B: 66, Arm C: 60, Arm D: 80			
Units: mmol/l			
arithmetic mean	26.2		
standard deviation	± 3.7	-	
Creatinine			
Number of participants missing data for baseline characteristic: Arm A: 2, Arm B: 0, Arm C: 0, Arm D: 2			
Units: mmol/l			
arithmetic mean	80.1		
standard deviation	± 15.1	-	
eGFR (continuous)			
Number of participants missing data for baseline characteristic: Arm A: 55, Arm B: 43, Arm C: 44, Arm D: 52			

The missing data are presented in categorical form due to there being upper and lower limits of measurement: < 60 : Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 1 < 90 : Arm A: 1, Arm B: 0, Arm C: 0, Arm D: 0 > 60 : Arm A: 24, Arm B: 23, Arm C: 25, Arm D: 22 > 90 : Arm A: 28, Arm B: 19, Arm C: 19, Arm D: 28 Missing: Arm A: 2, Arm B: 1, Arm C: 0, Arm D: 1			
Units: eGFR score			
arithmetic mean	81.4		
standard deviation	± 14.5	-	
ALT			
Number of participants missing data for baseline characteristic: Arm A: 13, Arm B: 9, Arm C: 5, Arm D: 10			
Units: iu/l			
arithmetic mean	32.2		
standard deviation	± 31.9	-	
AST			
Number of participants missing data for baseline characteristic: Arm A: 78, Arm B: 67, Arm C: 64, Arm D: 79			
Units: iu/l			
arithmetic mean	28.8		
standard deviation	± 14.0	-	
ALP			
Number of participants missing data for baseline characteristic: Arm A: 4, Arm B: 4, Arm C: 10, Arm D: 9			
Units: iu/l			
arithmetic mean	89.2		
standard deviation	± 40.4	-	
Albumin			
Number of participants missing data for baseline characteristic: Arm A: 3, Arm B: 1, Arm C: 1, Arm D: 3			
Units: g/l			
arithmetic mean	44.7		
standard deviation	± 3.8	-	
Total protein			
Number of participants missing data for baseline characteristic: Arm A: 33, Arm B: 25, Arm C: 23, Arm D: 37			
Units: g/l			
arithmetic mean	73.4		
standard deviation	± 3.9	-	
Bilirubin			
Number of participants missing data for baseline characteristic: Arm A: 5, Arm B: 6, Arm C: 6, Arm D: 8 Some data are presented in both continuous and categorical form due to there being upper and lower limits of measurement: < 2 : Arm A: 0, Arm B: 1, Arm C: 0, Arm D: 0 < 3 : Arm A: 3, Arm B: 2, Arm C: 2, Arm D: 2 < 15 : Arm A: 1, Arm B: 2, Arm C: 1, Arm D: 4			
Units: µmol/l			
arithmetic mean	16.6		
standard deviation	± 15.1	-	
Haemoglobin			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 1, Arm C: 0, Arm D: 0			
Units: g/dl			
arithmetic mean	145.72		

standard deviation	± 12.92	-	
Red blood cell count			
Number of participants missing data for baseline characteristic: Arm A: 7, Arm B: 5, Arm C: 5, Arm D: 9			
Units: 10^12/l			
arithmetic mean	4.60		
standard deviation	± 0.44	-	
White blood cell count			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 1			
Units: 10^9/l			
arithmetic mean	6.07		
standard deviation	± 2.14	-	
Platelets			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 0, Arm C: 0, Arm D: 0			
Units: 10^9/l			
arithmetic mean	226.24		
standard deviation	± 55.37	-	
Mean cell volume			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 0, Arm C: 0, Arm D: 0			
Units: fl			
arithmetic mean	94.37		
standard deviation	± 5.33	-	
Mean cell Haemoglobin			
Number of participants missing data for baseline characteristic: Arm A: 25, Arm B: 17, Arm C: 21, Arm D: 21			
Units: pg			
arithmetic mean	31.35		
standard deviation	± 3.68	-	
Mean cell Haemoglobin			
Number of participants missing data for baseline characteristic: Arm A: 37, Arm B: 31, Arm C: 29, Arm D: 41			
Units: g/dl			
arithmetic mean	336.55		
standard deviation	± 12.48	-	
Red cell distribution width			
Number of participants missing data for baseline characteristic: Arm A: 76, Arm B: 62, Arm C: 56, Arm D: 78			
Units: percent			
arithmetic mean	13.61		
standard deviation	± 1.57	-	
Neutrophils			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 0			
Units: 10^9/l			
arithmetic mean	3.29		
standard deviation	± 1.64	-	
Lymphocytes			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 0			
Units: 10^9/l			
arithmetic mean	2.08		
standard deviation	± 0.68	-	

Eosinophils			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 2, Arm C: 0, Arm D: 0			
Units: 10^9/l			
arithmetic mean	0.16		
standard deviation	± 0.12	-	
Basophils			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 0			
Units: 10^9/l			
arithmetic mean	0.03		
standard deviation	± 0.04	-	
Monocytes			
Number of participants missing data for baseline characteristic: Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 0			
Units: 10^9/l			
arithmetic mean	0.49		
standard deviation	± 0.22	-	
Insulin			
Number of participants missing data for baseline characteristic: Arm A: 3, Arm B: 3, Arm C: 4, Arm D: 6			
Units: pmol/l			
arithmetic mean	73		
standard deviation	± 72.74	-	
Glucose			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 1, Arm C: 2, Arm D: 2			
Units: mmol/l			
arithmetic mean	5.22		
standard deviation	± 0.54	-	
QUICKI			
Number of participants missing data for baseline characteristic: Arm A: 5, Arm B: 2, Arm C: 4, Arm D: 4			
Units: QUICKI score			
arithmetic mean	0.118		
standard deviation	± 0.009	-	
Revised QUICKI			
Number of participants missing data for baseline characteristic: Arm A: 5, Arm B: 2, Arm C: 4, Arm D: 5			
Units: revised QUICKI score			
arithmetic mean	0.133		
standard deviation	± 0.016	-	
HOMAIR			
Number of participants missing data for baseline characteristic: Arm A: 5, Arm B: 2, Arm C: 4, Arm D: 4			
Units: HOMA-IR Score			
arithmetic mean	2.544		
standard deviation	± 2.794	-	
HDLc			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 2, Arm C: 3, Arm D: 3			
Units: mmol/l			
arithmetic mean	1.18		
standard deviation	± 0.38	-	
Cholesterol			

Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 2, Arm C: 3, Arm D: 3			
Units: mmol/l			
arithmetic mean	4.97		
standard deviation	± 1.04	-	
LDLc			
Number of participants missing data for baseline characteristic: Arm A: 2, Arm B: 3, Arm C: 4, Arm D: 4			
Units: mmol/l			
arithmetic mean	3.12		
standard deviation	± 0.91	-	
Adiponectin			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 2, Arm C: 4, Arm D: 5			
Units: microgram(s)/millilitre			
arithmetic mean	15.9		
standard deviation	± 14.36	-	
Leptin			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 3, Arm C: 4, Arm D: 3			
Units: pg/ml			
arithmetic mean	10995		
standard deviation	± 18246	-	
IL8			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 2, Arm C: 4, Arm D: 4			
Units: pg/ml			
arithmetic mean	31.66		
standard deviation	± 46	-	
TNFalpha			
Number of participants missing data for baseline characteristic: Arm A: 2, Arm B: 2, Arm C: 4, Arm D: 5			
Units: pg/ml			
arithmetic mean	3.35		
standard deviation	± 5.67	-	
Resistin			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 2, Arm C: 4, Arm D: 5			
Units: pg/ml			
arithmetic mean	6510.5		
standard deviation	± 3120.9	-	
hsCRP			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 2, Arm C: 4, Arm D: 3			
Units: mg/ml			
arithmetic mean	3.34		
standard deviation	± 6.02	-	
NEFA			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 1, Arm C: 3, Arm D: 2			
Units: mmol/l			
arithmetic mean	0.460		
standard deviation	± 0.240	-	
Chloride			
Number of participants missing data for baseline characteristic:			

Arm A: 82, Arm B: 69, Arm C: 59, Arm D: 86			
Units: mmol/l			
arithmetic mean	103.2		
standard deviation	± 2.3	-	
Haematocrit			
Number of participants missing data for baseline characteristic: Arm A: 35, Arm B: 35, Arm C: 32, Arm D: 41			
Units: percentage			
arithmetic mean	42.46		
standard deviation	± 5.69	-	
Fasting glucose			
Number of participants missing data for baseline characteristic: Arm A: 75, Arm B: 66, Arm C: 59, Arm D: 81			
Units: mmol/l			
arithmetic mean	5.08		
standard deviation	± 0.64	-	
HBA1c			
Number of participants missing data for baseline characteristic: Arm A: 102, Arm B: 78, Arm C: 80, Arm D: 100			
Units: mmol/l			
arithmetic mean	37.17		
standard deviation	± 2.48	-	
HBA1c (%)			
Number of participants missing data for baseline characteristic: Arm A: 104, Arm B: 83, Arm C: 82, Arm D: 106 ***Please note for Arm C and Arm D there were no values to report but system requires that field not left blank so entered 0 in these cells. These are not genuine zeros.***			
Units: percent			
median	0		
inter-quartile range (Q1-Q3)	0 to 0	-	
OGTT			
Number of participants missing data for baseline characteristic: Arm A: 104, Arm B: 84, Arm C: 81, Arm D: 106 ***Please note for Arm B and Arm D there were no values to report but system requires that field not left blank so entered 0 in these cells. These are not genuine zeros.***			
Units: mmol/l			
median	0		
inter-quartile range (Q1-Q3)	0 to 0	-	
Random plasma glucose			
Number of participants missing data for baseline characteristic: Arm A: 27, Arm B: 18, Arm C: 25, Arm D: 25			
Units: mmol/l			
arithmetic mean	4.97		
standard deviation	± 0.83	-	
Triglycerides			
Number of participants missing data for baseline characteristic: Arm A: 1, Arm B: 2, Arm C: 3, Arm D: 3			
Units: mmol/l			
arithmetic mean	1.46		
standard deviation	± 0.88	-	

End points

End points reporting groups	
Reporting group title	Arm A (Baseline)
Reporting group description: Arm A: Non-intervention (control)	
Reporting group title	Arm B (Baseline)
Reporting group description: Arm B: Telmisartan 20mg	
Reporting group title	Arm C (Baseline)
Reporting group description: Arm C: Telmisartan 40mg	
Reporting group title	Arm D (Baseline)
Reporting group description: Arm D: Telmisartan 80mg	
Reporting group title	Arm A (Final)
Reporting group description: Arm A: Non-intervention (control)	
Reporting group title	Arm D (Final)
Reporting group description: Arm D: Telmisartan 80mg	

Primary: Reduction in insulin resistance measured by HOMA-IR (Final analysis)	
End point title	Reduction in insulin resistance measured by HOMA-IR (Final analysis)
End point description: insulin resistance measured by HOMA-IR. HOMA-IR was calculated by HOMA-IR = (fasting insulin (µU/ml) × fasting glucose (mmol/l))/22.5 The conversion factor for fasting insulin to convert from pmol/L to µU/mL is 0.144.	
End point type	Primary
End point timeframe: Change in 24 week HOMA-IR score compared to baseline	

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85[1]	78[2]		
Units: HOMA-IR				
arithmetic mean (standard deviation)				
Baseline	2.5 (± 2.08)	2.5 (± 2.79)		
Week 24	3.0 (± 3.25)	3.4 (± 6.89)		

Notes:

[1] - 100 baseline, 89 week 24, 85 have both baseline and week 24 measurements so included in analysis

[2] - 100 baseline, 82 week 24, 78 have both baseline and week 24 measurements so included in

Attachments (see zip file)	Primary efficacy data.pdf

Statistical analyses

Statistical analysis title	ANCOVA HOMA-IR(Final)

Statistical analysis description:

An ANCOVA model is used by fitting the regression model HOMAIR_24 = HOMAIR_0 + treatment + stratification factor (Black/Non-Black). where HOMAIR_0 is the HOMAIR value at the baseline prior to randomisation and HOMAIR_24 is the HOMA-IR value at 24 weeks. The treatment variable is categorical with control (arm A) as the reference level. The test statistic is given by the t – values. The test statistic will be compared to the final critical value (-2.086).

Comparison groups	Arm D (Final) v Arm A (Final)
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	> 0.05 [4]
Method	ANCOVA

Notes:

[3] - The test statistic is 0.065 and compared to the critical value of -2.086. As 0.065 is not smaller than the critical value we fail to reject the null hypothesis – i.e. no difference between Arm D and Arm A.
[4] - This was a one sided test with an overall type I error of 5%. The treatment effect (slope) from the ANCOVA model was 0.007 and the standard error of the mean was 0.106.

Statistical analysis title	HOMAIR sensitivity analysis 1 (Final)

Statistical analysis description:

Fit the same ANCOVA model by imputing values for missing HOMA-IR values at baseline and 24 weeks using the MICE algorithm. The MICE algorithm imputed missing HOMA-IR values conditional on available HOMA-IR values at baseline, 12 weeks and 24 weeks, treatment allocation (Arm D/Control) and stratification factor (black/non-black).

Comparison groups	Arm D (Final) v Arm A (Final)
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	> 0.05 [6]
Method	ANCOVA

Notes:

[5] - Sensitivity analysis comparing arm D to arm A. The test statistic is 0.172 and compared to the critical value of -2.086. As 0.172 is not smaller than the critical value we fail to reject the null hypothesis – i.e. no difference between Arm D and Arm A.
[6] - This was a two sided test with an overall type I error of 5%. The treatment effect (slope) from the ANCOVA model was 0.02 and the standard error of the mean was 0.116.

Statistical analysis title	HOMA-IR sensitivity analysis 3 (Final)

Statistical analysis description:

A compliance-adjusted primary outcome analysis is undertaken using instrumental variable (IV) regression, in order to estimate the effect of actual dose on outcome. The model includes patients from arm A (assumed to have received dose of 0mg) and patients from arm D who provided compliance data from both the treatment diary and pill count. Dose is based on average between two measures of compliance (treatment diary and pill count).

Comparison groups	Arm D (Final) v Arm A (Final)

Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2885 [7]
Method	ANCOVA
Parameter estimate	Slope
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.028
upper limit	0.008

Notes:

[7] - p-value 0.2885 > 0.05 implies that there is no effect of telmisartan after adjusting for dose.

Secondary: Change in insulin resistance measured by QUICKI (Final)

End point title	Change in insulin resistance measured by QUICKI (Final)

End point description:

Two alternative measures of insulin resistance, QUICKI and revised QUICKI, to further investigate the effect of telmisartan.

QUICKI= 1/(log G + log I), where G is fasting glucose (mg/dl) anf I is fasting insulin (µU/mL).

Fasting glucose is recorded in mmol/l for the primary analysis, and the conversion factor for fasting glucose to convert from mmol/l to mg/dl is 18 (1 mmol/l = 18 mg/dl)

End point type	Secondary

End point timeframe:

Change in QUICKI in telmisartan treated (arm D) after 24 weeks of treatment in comparison with control (arm A)

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85[8]	78[9]		
Units: QUICKI				
arithmetic mean (standard deviation)				
Baseline	0.117 (± 0.0092)	0.118 (± 0.0091)		
Week 24	0.115 (± 0.0093)	0.116 (± 0.0105)		

Notes:

[8] - 100 baseline, 89 week 24, 85 have both baseline and week 24 measurements so included in analysis

[9] - 100 baseline, 82 week 24, 78 have both baseline and week 24 measurements so included in analysis

Attachments (see zip file)	QUICKI and revised QUICKI.pdf

Statistical analyses

Statistical analysis title	ANCOVA QUICKI (Final)

Statistical analysis description:

The same ANCOVA model as the primary HOMAIR analysis is fitted (with QUICK in place of HOMAIR).

Comparison groups	Arm D (Final) v Arm A (Final)
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	> 0.05 [11]
Method	ANCOVA

Notes:

[10] - Comparing arm A to arm D. The test statistic is 0.0813 and compared to the critical value of 2.086. As 0.0813 is not larger than the critical value we fail to reject the null hypothesis, i.e. no difference between Arm D and Arm A.

[11] - This was a two sided test with an overall type I error of 5%. The treatment effect (slope) from the ANCOVA model was 0.00011 and the standard error of the mean was 0.00133.

Secondary: Change in insulin resistance measured by Revised QUICKI (Final)

End point title	Change in insulin resistance measured by Revised QUICKI (Final)

End point description:

Two alternative measures of insulin resistance, QUICKI and revised QUICKI, to further investigate the effect of telmisartan.

Revised QUICKI = 1/(log G + log I + log NEFA), where G is fasting glucose (mg/dl), I is fasting insulin (µU/mL), and NEFA is plasma non esterified fatty acids concentration (mmol/l).

Fasting glucose is recorded in mmol/l for the primary analysis, and the conversion factor for fasting glucose to convert from mmol/l to mg/dl is 18 (1 mmol/l = 18 mg/dl).

End point type	Secondary

End point timeframe:

Change in Revised-QUICKI in telmisartan arm (arm D) after 24 weeks of treatment in comparison with control (arm A)

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84[12]	78[13]		
Units: Revised QUICKI				
arithmetic mean (standard deviation)				
Baseline	0.132 (± 0.0168)	0.133 (± 0.0156)		
Week 24	0.132 (± 0.0176)	0.133 (± 0.0178)		

Notes:

[12] - 100 baseline, 88 week 24, 84 have both baseline and week 24 measurements so included in analysis

[13] - 99 baseline, 82 week 24, 78 have both baseline and week 24 measurements so included in analysis

Attachments (see zip file)	QUICKI and revised QUICKI.pdf

Statistical analyses

Statistical analysis title	ANCOVA Revised-QUICKI (Final)

Statistical analysis description:

The same ANCOVA model as the primary HOMAIR analysis is fitted (with Revised-QUICK in place of

HOMAIR).

Comparison groups	Arm D (Final) v Arm A (Final)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	> 0.05 [15]
Method	ANCOVA

Notes:

[14] - The test statistic is 0.4418 and compared to the critical value of 2.086. As 0.4418 is not larger than the critical value we fail to reject the null hypothesis, i.e. no difference between Arm D and Arm A.
[15] - This was a two sided test with an overall type I error of 5%. The treatment effect (slope) from the ANCOVA model was 0.0011 and the standard error of the mean was 0.00249.

Secondary: HOMA-IR longitudinal (Final)

End point title	HOMA-IR longitudinal (Final)

End point description:

insulin resistance measured by HOMA-IR. HOMA-IR was calculated by

HOMA-IR = (fasting insulin (μU/ml) × fasting glucose (mmol/l))/22.5

The conversion factor for fasting insulin to convert from pmol/L to μU/mL is 0.144.

End point type	Secondary

End point timeframe:

Change in HOMA-IR at T+12, T+24 and T+48 weeks between telmisartan treated arm (arm D) and the control arm (arm A).

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	87		
Units: Number of patients	91	87		

Attachments (see zip file)	Longitudinal HOMAIR.pdf

Statistical analyses

Statistical analysis title	Longitudinal analysis HOMA-IR (Final)

Statistical analysis description:

To identifying change in the expression of the markers in arm D in comparison to arm A, a joint model of the longitudinal marker will be fitted adjusting for the dropout from the study. Patients who had a missing marker were considered as ‘dropouts’ and the first time point (t = 12, 24, or 48) at which marker is missing is taken as the time of dropout. Those who did not dropout from the study before t = 48(had complete record of biomarker) were censored at 48 weeks.

Comparison groups	Arm D (Final) v Arm A (Final)

Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2753
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.096
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.265
upper limit	0.066

Secondary: QUICKI longitudinal (Final)

End point title	QUICKI longitudinal (Final)

End point description:

Two alternative measures of insulin resistance, QUICKI and revised QUICKI, to further investigate the effect of telmisartan.

QUICKI= 1/(log G + log I), where G is fasting glucose (mg/dl) anf I is fasting insulin (µU/mL).

Fasting glucose is recorded in mmol/l for the primary analysis, and the conversion factor for fasting glucose to convert from mmol/l to mg/dl is 18 (1 mmol/l = 18 mg/dl)

End point type	Secondary

End point timeframe:

Change in QUICKI at T+12, T+24 and T+48 weeks between telmisartan treated arm (arm D) and the control arm (arm A).

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	87		
Units: Number of patients	91	87		

Attachments (see zip file)	Longitudinal QUICKI.pdf

Statistical analyses

Statistical analysis title	Longitudinal analysis QUICKI (Final)

Statistical analysis description:

To identifying change in the expression of the markers in arm D in comparison to arm A, a joint model of the longitudinal marker will be fitted adjusting for the dropout from the study. Patients who had a missing marker were considered as ‘dropouts’ and the first time point (t = 12, 24, or 48) at which marker is missing is taken as the time of dropout. Those who did not dropout from the study before t =48 (had complete record of biomarker) were censored at 48 weeks.

Comparison groups	Arm D (Final) v Arm A (Final)

Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4671
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.008
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.013
upper limit	0.03

Secondary: Revised-QUICKI longitudinal (Final)

End point title	Revised-QUICKI longitudinal (Final)

End point description:

Two alternative measures of insulin resistance, QUICKI and revised QUICKI, to further investigate the effect of telmisartan.

Revised QUICKI = 1/(log G + log I + log NEFA), where G is fasting glucose (mg/dl), I is fasting insulin (µU/mL), and NEFA is plasma non esterified fatty acids concentration (mmol/l).

Fasting glucose is recorded in mmol/l for the primary analysis, and the conversion factor for fasting glucose to convert from mmol/l to mg/dl is 18 (1 mmol/l = 18 mg/dl).

End point type	Secondary

End point timeframe:

Change in revised-QUICKI at T+12, T+24 and T+48 weeks between telmisartan treated arm (arm D) and the control arm (arm A).

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	86		
Units: Number of patients	91	86		

Attachments (see zip file)	Longitudinal Revised QUICKI.pdf

Statistical analyses

Statistical analysis title	Longitudinal analysis revised-QUICKI (Final)

Statistical analysis description:

To identifying change in the expression of the markers in arm D in comparison to arm A, a joint model of the longitudinal marker will be fitted adjusting for the dropout from the study. Patients who had a missing marker were considered as ‘dropouts’ and the first time point (t = 12, 24, or 48) at which marker is missing is taken as the time of dropout. Those who did not dropout from the study before t =48 (had complete record of biomarker) were censored at 48 weeks.

Comparison groups	Arm D (Final) v Arm A (Final)

Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0295
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.068

Secondary: HDL-c longitudinal (Final)

End point title	HDL-c longitudinal (Final)

End point description:

Increase in HDL-c is a marker for a change in lipid profile

End point type	Secondary

End point timeframe:

increase in HDL-c at T+12, T+24 and T+48 weeks between telmisartan treated arm (arm D) and the control arm (arm A).

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	90		
Units: Number of patients	94	90		

Attachments (see zip file)	Longitudinal HDLc.pdf

Statistical analyses

Statistical analysis title	Longitudinal analysis HDL-c (Final)

Statistical analysis description:

To identifying change in the expression of the markers in arm D in comparison to arm A, a joint model of the longitudinal marker will be fitted adjusting for the dropout from the study. Patients who had a missing marker were considered as ‘dropouts’ and the first time point (t = 12, 24, or 48) at which marker is missing is taken as the time of dropout. Those who did not dropout from the study before t =48 (had complete record of biomarker) were censored at 48 weeks.

Comparison groups	Arm D (Final) v Arm A (Final)

Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6004
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.036
upper limit	0.05

Secondary: Cholesterol longitudinal (Final)

End point title	Cholesterol longitudinal (Final)

End point description:

Reduction in total cholesterol is a marker for a change in lipid profile

End point type	Secondary

End point timeframe:

Reduction in total cholesterol at T+12, T+24 and T+48 weeks between telmisartan treated arm (arm D) and the control arm (arm A).

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	90		
Units: Number of patients	94	90		

Attachments (see zip file)	Longitudinal Cholesterol.pdf

Statistical analyses

Statistical analysis title	Longitudinal analysis cholesterol (Final)

Statistical analysis description:

To identifying change in the expression of the markers in arm D in comparison to arm A, a joint model of the longitudinal marker will be fitted adjusting for the dropout from the study. Patients who had a missing marker were considered as ‘dropouts’ and the first time point (t = 12, 24, or 48) at which marker is missing is taken as the time of dropout. Those who did not dropout from the study before t =48 (had complete record of biomarker) were censored at 48 weeks.

Comparison groups	Arm D (Final) v Arm A (Final)

Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8375
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.156

Secondary: Triglycerides longitudinal (Final)

End point title	Triglycerides longitudinal (Final)

End point description:

Reduction in Triglycerides profile is a marker for a change in lipid profile

End point type	Secondary

End point timeframe:

Reduction in Triglycerides profile at T+12, T+24 and T+48 weeks between telmisartan treated arm (arm D) and the control arm (arm A).

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	90		
Units: Number of patients	94	90		

Attachments (see zip file)	Longitudinal Triglycerides.pdf

Statistical analyses

Statistical analysis title	Longitudinal analysis Triglycerides (Final)

Statistical analysis description:

To identifying change in the expression of the markers in arm D in comparison to arm A, a joint model of the longitudinal marker will be fitted adjusting for the dropout from the study. Patients who had a missing marker were considered as ‘dropouts’ and the first time point (t = 12, 24, or 48) at which marker is missing is taken as the time of dropout. Those who did not dropout from the study before t =48 (had complete record of biomarker) were censored at 48 weeks.

Comparison groups	Arm D (Final) v Arm A (Final)

Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4997
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.056
upper limit	0.106

Secondary: LDL-c longitudinal (Final)

End point title	LDL-c longitudinal (Final)

End point description:

Reduction in LDL-c profile is a marker for a change in lipid profile

End point type	Secondary

End point timeframe:

Reduction in LDL-c profile at T+12, T+24 and T+48 weeks between telmisartan treated arm (arm D) and the control arm (arm A).

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	89		
Units: Number of patients	93	89		

Attachments (see zip file)	Longitudinal LDLc.pdf

Statistical analyses

Statistical analysis title	Longitudinal analysis LDL-c (Final)

Statistical analysis description:

To identifying change in the expression of the markers in arm D in comparison to arm A, a joint model of the longitudinal marker will be fitted adjusting for the dropout from the study. Patients who had a missing marker were considered as ‘dropouts’ and the first time point (t = 12, 24, or 48) at which marker is missing is taken as the time of dropout. Those who did not dropout from the study before t =48 (had complete record of biomarker) were censored at 48 weeks.

Comparison groups	Arm D (Final) v Arm A (Final)

Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9643
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.131
upper limit	0.11

Secondary: Adiponectin longitudinal (Final)

End point title	Adiponectin longitudinal (Final)

End point description:

Change in Adiponectin is a biomarker of Change in plasma concentration

End point type	Secondary

End point timeframe:

Change in adiponectin at T+12, T+24 and T+48 weeks between telmisartan treated arm (arm D) and the control arm (arm A).

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	87		
Units: Number of patients	93	87		

Attachments (see zip file)	Longitudinal Adiponectin.pdf

Statistical analyses

Statistical analysis title	Longitudinal analysis Adiponectin (Final)

Statistical analysis description:

To identifying change in the expression of the markers in arm D in comparison to arm A, a joint model of the longitudinal marker will be fitted adjusting for the dropout from the study. Patients who had a missing marker were considered as 'dropouts' and the first time point (t = 12, 24, or 48) at which marker is missing is taken as the time of dropout. Those who did not dropout from the study before t =48 (had complete record of biomarker) were censored at 48 weeks.

Comparison groups	Arm D (Final) v Arm A (Final)

Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4172
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.072
upper limit	0.143

Secondary: Leptin longitudinal (Final)

End point title	Leptin longitudinal (Final)

End point description:

Change in Leptin is a biomarker of Change in plasma concentration

End point type	Secondary

End point timeframe:

Change in Leptin at T+12, T+24 and T+48 weeks between telmisartan treated arm (arm D) and the control arm (arm A).

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	89		
Units: Number of patients	94	89		

Attachments (see zip file)	Longitudinal Leptin.pdf

Statistical analyses

Statistical analysis title	Longitudinal analysis Leptin (Final)

Statistical analysis description:

To identifying change in the expression of the markers in arm D in comparison to arm A, a joint model of the longitudinal marker will be fitted adjusting for the dropout from the study. Patients who had a missing marker were considered as ‘dropouts’ and the first time point (t = 12, 24, or 48) at which marker is missing is taken as the time of dropout. Those who did not dropout from the study before t =48 (had complete record of biomarker) were censored at 48 weeks.

Comparison groups	Arm D (Final) v Arm A (Final)

Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6467
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.097
upper limit	0.192

Secondary: IL8 longitudinal (Final)

End point title	IL8 longitudinal (Final)

End point description:

Change in IL8 is a biomarker of change in plasma concentration

End point type	Secondary

End point timeframe:

Change in IL8 at T+12, T+24 and T+48 weeks between telmisartan treated arm (arm D) and the control arm (arm A).

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	89		
Units: Number of patients	94	89		

Attachments (see zip file)	Longitudinal IL8.pdf

Statistical analyses

Statistical analysis title	Longitudinal analysis IL8 (Final)

Statistical analysis description:

To identifying change in the expression of the markers in arm D in comparison to arm A, a joint model of the longitudinal marker will be fitted adjusting for the dropout from the study. Patients who had a missing marker were considered as ‘dropouts’ and the first time point (t = 12, 24, or 48) at which marker is missing is taken as the time of dropout. Those who did not dropout from the study before t =48 (had complete record of biomarker) were censored at 48 weeks.

Comparison groups	Arm D (Final) v Arm A (Final)

Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4712
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.082
upper limit	0.17

Secondary: TNF-α longitudinal (Final)

End point title	TNF-α longitudinal (Final)

End point description:

Change in TNF-α is a biomarker of change in plasma concentration

End point type	Secondary

End point timeframe:

Change in TNF-α at T+12, T+24 and T+48 weeks between telmisartan treated arm (arm D) and the control arm (arm A).

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	88		
Units: Number of patients	93	88		

Attachments (see zip file)	Longitudinal TNFalpha.pdf

Statistical analyses

Statistical analysis title	Longitudinal analysis TNF-α (Final)

Statistical analysis description:

To identifying change in the expression of the markers in arm D in comparison to arm A, a joint model of the longitudinal marker will be fitted adjusting for the dropout from the study. Patients who had a missing marker were considered as ‘dropouts’ and the first time point (t = 12, 24, or 48) at which marker is missing is taken as the time of dropout. Those who did not dropout from the study before t =48 (had complete record of biomarker) were censored at 48 weeks.

Comparison groups	Arm D (Final) v Arm A (Final)

Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7026
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.021
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.077

Secondary: Resistin longitudinal (Final)

End point title	Resistin longitudinal (Final)

End point description:

Change in Resistin is a biomarker of change in plasma concentration

End point type	Secondary

End point timeframe:

Change in Resistin at T+12, T+24 and T+48 weeks between telmisartan treated arm (arm D) and the control arm (arm A).

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	88		
Units: Number of patients	94	88		

Attachments (see zip file)	Longitudinal Resistin.pdf

Statistical analyses

Statistical analysis title	Longitudinal analysis Resistin (Final)

Statistical analysis description:

To identifying change in the expression of the markers in arm D in comparison to arm A, a joint model of the longitudinal marker will be fitted adjusting for the dropout from the study. Patients who had a missing marker were considered as 'dropouts' and the first time point (t = 12, 24, or 48) at which marker is missing is taken as the time of dropout. Those who did not dropout from the study before t =48 (had complete record of biomarker) were censored at 48 weeks.

Comparison groups	Arm D (Final) v Arm A (Final)

Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1308
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.068
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.153
upper limit	0.024

Secondary: hs-CRP longitudinal (Final)

End point title	hs-CRP longitudinal (Final)

End point description:

Change in hs-CRP is a biomarker of change in plasma concentration

End point type	Secondary

End point timeframe:

Change in hs-CRP at T+12, T+24 and T+48 weeks between telmisartan treated arm (arm D) and the control arm (arm A).

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	90		
Units: Number of patients	94	90		

Attachments (see zip file)	Longitudinal hsCRP.pdf

Statistical analyses

Statistical analysis title	Longitudinal analysis hs-CRP (Final)

Statistical analysis description:

To identifying change in the expression of the markers in arm D in comparison to arm A, a joint model of the longitudinal marker will be fitted adjusting for the dropout from the study. Patients who had a missing marker were considered as ‘dropouts’ and the first time point (t = 12, 24, or 48) at which marker is missing is taken as the time of dropout. Those who did not dropout from the study before t =48 (had complete record of biomarker) were censored at 48 weeks.

Comparison groups	Arm D (Final) v Arm A (Final)

Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0289
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.236
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.475
upper limit	-0.062

Secondary: Internal visceral fat (MRI/ MRS Substudy)

End point title	Internal visceral fat (MRI/ MRS Substudy)

End point description:

Reduction in visceral fat at T+24 weeks between telmisartan treated arms and control arm

End point type	Secondary

End point timeframe:

Change in body fat redistribution as measured by MRI/MRS at T+24 weeks between telmisartan treated arm (arm D) and the control arm (arm A).

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[16]	8[17]		
Units: dm^3				
arithmetic mean (standard deviation)				
Baseline	3.53 (± 1.08)	4.10 (± 2.71)		
Week 24	3.74 (± 1.43)	4.74 (± 2.59)		

Notes:

[16] - 8 baseline, 8 week 24, 8 have both baseline and week 24 measurements so included in analysis

[17] - 8 baseline, 8 week 24, 8 have both baseline and week 24 measurements so included in analysis

Attachments (see zip file)	Sub study data.pdf

Statistical analyses

Statistical analysis title	Internal visceral fat (MRI/MRS sub-study)

Statistical analysis description:

Multiple linear regression models will be fitted to explore the differences in outcomes between treatment arms with control as the reference level while accounting for potential confounders. Model :
Internal visceral fat at 24 weeks will be the outcome variable. A multiple linear regression model will be fitted. The relative change of total external fat (=(value at 24 weeks - value at baseline)/value at baseline) will be added in the model to account for this potential confounder.

Comparison groups	Arm D (Final) v Arm A (Final)

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.879
Method	Regression, Linear
Parameter estimate	Slope
Point estimate	0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.563
upper limit	0.65

Secondary: Expected/unexpected SAEs

End point title	Expected/unexpected SAEs

End point description:

Difference in expected and unexpected SAEs between Telmisartan treated arms(s) and the control arm.

End point type	Secondary

End point timeframe:

Adverse event reporting will occur from the point that the participant provides informed consent and throughout the trial treatment period up until seven days after the patient has taken the final dose of investigational medicinal product.

End point values	Arm A (Baseline)	Arm B (Baseline)	Arm C (Baseline)	Arm D (Baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	105[18]	84[19]	82[20]	106[21]
Units: Number of patients	5	3	4	7

Notes:

[18] - Number of events 6

[19] - Number of events 3

[20] - Number of events 4

[21] - Number of events 8

Statistical analyses

Statistical analysis title	Expected/ Unexpected SAEs

Statistical analysis description:

Difference in expected and unexpected SAEs between telmisartan treated arm(s) and the control arm.

Comparison groups	Arm B (Baseline) v Arm C (Baseline) v Arm D (Baseline) v Arm A (Baseline)
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8152
Method	Fisher exact

Secondary: Intrahepatic fat (MRI/ MRS Substudy)

End point title	Intrahepatic fat (MRI/ MRS Substudy)

End point description:

Change in intrahepatic fat as measured by MRI/MRS at T+24 weeks between telmisartan treated arms and control arm

End point type	Secondary

End point timeframe:

Change in intrahepatic fat as measured by MRI/MRS at T+24 weeks between telmisartan treated arm (arm D) and the control arm (arm A).

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[22]	8[23]		
Units: CH2/H20 (%)				
arithmetic mean (standard deviation)				
Baseline	8.21 (± 18.23)	2.24 (± 4.17)		
Week 24	3.01 (± 4.07)	1.60 (± 2.26)		

Notes:

[22] - 12 baseline, 8 week 24, 8 have both baseline and week 24 measurements so included in analysis

[23] - 10 baseline, 8 week 24, 8 have both baseline and week 24 measurements so included in analysis

Attachments (see zip file)	Primary efficacy data.pdf

Statistical analyses

Statistical analysis title	Intrahepatic fat (MRI/MRS sub-study)

Statistical analysis description:

Multiple linear regression models will be fitted to explore the differences in outcomes between treatment arms with control as the reference level while accounting for potential confounders. Model : Intrahepatic triglyceride content in liver at 24 weeks will be the outcome variable. A multiple linear regression model will be fitted.

Comparison groups	Arm D (Final) v Arm A (Final)
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0688
Method	Regression, Linear
Parameter estimate	Slope
Point estimate	-1.309
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.734
upper limit	0.116

Secondary: Lower leg muscle (MRI/ MRS Substudy)	
End point title	Lower leg muscle (MRI/ MRS Substudy)
End point description:	
Change in lower leg muscle fat at T+24 weeks between telmisartan treated arms and control arm	
End point type	Secondary
End point timeframe:	
Change in lower leg muscle fat at T+24 weeks between telmisartan treated arm (arm D) and the control arm (arm A).	

End point values	Arm A (Final)	Arm D (Final)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[24]	8[25]		
Units: CH2/creatine				
arithmetic mean (standard deviation)				
Soleus Baseline	19.50 (± 10.78)	17.29 (± 11.77)		
Soleus Week 24	19.45 (± 13.25)	16.63 (± 8.97)		
Tibialis Baseline	6.25 (± 3.10)	7.82 (± 2.79)		
Tibialis Week 24	8.10 (± 4.97)	7.41 (± 2.73)		

Notes:

[24] - Soleus: 12 baseline, 8 week 24, 8 analysed. Tibialis: 11 baseline, 8 week 24, 8 analysed.

[25] - Soleus: 10 baseline, 8 week 24, 8 analysed. Tibialis: 9 baseline, 8 week 24, 8 analysed.

Attachments (see zip file)	Sub study data.pdf

Statistical analyses

Statistical analysis title	lower leg muscle: bi-dimensional (substudy)
Statistical analysis description:	
Multiple linear regression models will be fitted to explore the differences in outcomes between treatment arms with control as the reference level while accounting for potential confounders. Model: Intramyocellular triglyceride content in the soleus and tibialis anterior at 24 weeks will be treated as a bi-dimensional outcome. A multivariate multiple regression model will be fitted.	
Comparison groups	Arm D (Final) v Arm A (Final)
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7839
Method	Regression, Linear
Variability estimate	Standard error of the mean

Statistical analysis title	Lower leg muscle: Soleus (MRI/ MRS Substudy)

Statistical analysis description:

Multiple linear regression models will be fitted to explore the differences in outcomes between treatment arms with control as the reference level while accounting for potential confounders. Model: Intramyocellular triglyceride content in the soleus at 24 weeks will be the outcome variable. A multiple linear regression model will be fitted.

Comparison groups	Arm A (Final) v Arm D (Final)
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.245
Method	Regression, Linear
Parameter estimate	Slope
Point estimate	-2.977
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.278
upper limit	2.324

Statistical analysis title	Lower leg muscle: Tibialis (MRI/ MRS Substudy)

Statistical analysis description:

Multiple linear regression models will be fitted to explore the differences in outcomes between treatment arms with control as the reference level while accounting for potential confounders. Model: Intramyocellular triglyceride content in the Tibialis at 24 weeks will be the outcome variable. A multiple linear regression model will be fitted.

Comparison groups	Arm D (Final) v Arm A (Final)
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8539
Method	Regression, Linear
Parameter estimate	Slope
Point estimate	-0.442
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.557
upper limit	4.673

Secondary: Urinary biomarker (sub-study)

End point title	Urinary biomarker (sub-study)

End point description:

Change in urinary biomarker levels (creatine, urea, total protein, novel biomarkers such as KIM-1, NGAL, and RBP) at T+12, T+24 and T+48 weeks between telmisartan treated arm(s) and the control arm.The assessment of renal safety biomarkers was not planned to take place as part of the main study assessments, and will not be included in the final report to the TAILoR funder however this analysis has since been conducted and have been included for completion. See attached pdf for details.

End point type	Secondary

End point timeframe:

Change in urinary biomarker levels (creatine, urea, total protein, novel biomarkers such as KIM-1, NGAL, and RBP) at T+12, T+24 and T+48 weeks between telmisartan treated arm(s) and the control arm.

End point values	Arm A (Baseline)	Arm B (Baseline)	Arm C (Baseline)	Arm D (Baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	105[26]	84[27]	82[28]	106[29]
Units: Number randomised	105	84	82	106

Notes:

[26] - Number analysed not specified in final report. 105 is the number randomised - see pdf for analysis.

[27] - Number analysed not specified in final report. 84 is the number randomised - see pdf for analysis.

[28] - Number analysed not specified in final report. 82 is the number randomised - see pdf for analysis.

[29] - Number analysed not specified in final report. 106 is the number randomised - see pdf for analysis.

Attachments (see zip file)	Urine Sub study data.pdf

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Reduction in insulin resistance measured by HOMA-IR (Interim analysis)

End point title	Reduction in insulin resistance measured by HOMA-IR (Interim analysis)

End point description:

The interim analysis was scheduled to take place once the 24 week change in HOMA-IR score was available for at least 42 patients in each arm. The sample standard deviation pooled across all four arms was used to construct test statistics expressing the advantage of each of the three active treatments over the control arm. There were 48/49/47/45 patients who were randomised to arms A/B/C/D respectively, with a total of 189 patients available for analysis. However, only 154 patients had a complete set of baseline and 24 week HOMA-IR data and were therefore included in the analysis. There were 39 in A, 45 in B, 35 in C and 35 in D included in the analysis. 31 patients were unavailable for analysis due to withdrawal from the study, visit not attended and loss to follow-up. There were 7 in A, 4 in B, 11 in C and 9 in D who were unavailable. There were 4 patients who were missing data at either baseline or week 24 and were excluded from the analysis, 2 in A, 0 in B, 1 in C and 1 in D.

End point type	Other pre-specified

End point timeframe:

24 week change in HOMA-IR from baseline. The database requires a p-value or a confidence interval to be reported, however this information was unavailable - see attached pdf for full analysis results for this outcome.

End point values	Arm A (Baseline)	Arm B (Baseline)	Arm C (Baseline)	Arm D (Baseline)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39[30]	45[31]	35[32]	35[33]
Units: HOMA-IR				
arithmetic mean (standard deviation)				
Baseline	2.4 (± 2)	2.3 (± 1.6)	2.8 (± 3.9)	2.6 (± 2.7)
Week 24	2.5 (± 1.9)	2.7 (± 1.9)	3.4 (± 4.4)	2.5 (± 1.7)

Notes:

[30] - Interim analysis: 48 randomised, 7 Withdrew, did not attend wk24 or loss to followup, 2 missing data

[31] - Interim analysis: 49 randomised, 4 Withdrew, did not attend wk24 or loss to followup, 0 missing data

[32] - Interim analysis: 47 randomised, 11 Withdrew, didn't attend wk24 or loss to followup, 1 missing data

[33] - Interim analysis: 45 randomised, 9 Withdrew, did not attend wk24 or loss to followup, 1 missing data

Attachments (see zip file)	Interim.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event reporting will occur from the point that the participant provides informed consent and throughout the trial treatment period up until seven days after the patient has taken the final of investigational medicinal product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Arm A

Reporting group description:

Control arm, no exposure to treatment but still included for reporting of serious adverse events.

Reporting group title	Arm B

Reporting group description:

Telmisartan (20mg daily)

Reporting group title	Arm C

Reporting group description:

Telmisartan (40mg daily)

Reporting group title	Arm D

Reporting group description:

Telmisartan (80mg daily)

Serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 105 (4.76%)	3 / 84 (3.57%)	4 / 82 (4.88%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasmablastic lymphoma			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin cancer			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Joint dislocation			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	1 / 105 (0.95%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 105 (0.95%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			

subjects affected / exposed	1 / 105 (0.95%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 105 (0.95%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Groin pain			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis C			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected bite			
subjects affected / exposed	1 / 105 (0.95%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastitis			

subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis cryptococcal			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 105 (0.95%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm D		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 106 (6.60%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasmablastic lymphoma			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin cancer			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Laceration			

subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Limb injury			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			

subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Groin pain			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis C			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infected bite			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mastitis			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis cryptococcal			

subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 105 (0.00%)	28 / 84 (33.33%)	28 / 82 (34.15%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	0 / 82 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	1 / 82 (1.22%)
occurrences (all)	0	1	2
Orthostatic hypotension			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	2 / 82 (2.44%)
occurrences (all)	0	0	3
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Fatigue			

subjects affected / exposed	0 / 105 (0.00%)	4 / 84 (4.76%)	4 / 82 (4.88%)
occurrences (all)	0	5	4
Feeling cold			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Feeling hot			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	0 / 82 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Ejaculation failure			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Pulmonary fibrosis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	0 / 82 (0.00%)
occurrences (all)	0	1	0
Sinus congestion			

subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	0 / 82 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	3 / 82 (3.66%)
occurrences (all)	0	0	3
Confusional state			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Depressed mood			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	0 / 82 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	0 / 82 (0.00%)
occurrences (all)	0	1	0
Morbid thoughts			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			
Double ureter			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1

Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	0 / 82 (0.00%)
occurrences (all)	0	1	0
Amnesia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Burning sensation			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Disturbance in attention			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 105 (0.00%)	6 / 84 (7.14%)	6 / 82 (7.32%)
occurrences (all)	0	6	7
Dysgeusia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	0 / 105 (0.00%)	6 / 84 (7.14%)	7 / 82 (8.54%)
occurrences (all)	0	6	7
Loss of consciousness			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Syncope			

subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	0 / 82 (0.00%)
occurrences (all)	0	1	0
Tension headache			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Trigeminal neuralgia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	0 / 82 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Lacrimation increased			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	1 / 82 (1.22%)
occurrences (all)	0	1	1
Visual impairment			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	0 / 82 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	3 / 82 (3.66%)
occurrences (all)	0	0	3
Abdominal pain upper			

subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	2 / 82 (2.44%)
occurrences (all)	0	1	3
Dry mouth			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 105 (0.00%)	2 / 84 (2.38%)	1 / 82 (1.22%)
occurrences (all)	0	2	1
Faeces soft			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Mouth ulceration			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	2 / 82 (2.44%)
occurrences (all)	0	1	3
Tongue coated			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	2 / 82 (2.44%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	0 / 82 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1

Hyperhidrosis			
subjects affected / exposed	0 / 105 (0.00%)	2 / 84 (2.38%)	1 / 82 (1.22%)
occurrences (all)	0	2	1
Photosensitivity reaction			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 105 (0.00%)	4 / 84 (4.76%)	1 / 82 (1.22%)
occurrences (all)	0	4	1
Rash			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	1 / 82 (1.22%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Renal impairment			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	1 / 82 (1.22%)
occurrences (all)	0	1	1
Back pain			
subjects affected / exposed	0 / 105 (0.00%)	2 / 84 (2.38%)	0 / 82 (0.00%)
occurrences (all)	0	2	0
Myalgia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	0 / 82 (0.00%)
occurrences (all)	0	1	0
Osteopenia			

subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Pain in jaw			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 105 (0.00%)	2 / 84 (2.38%)	1 / 82 (1.22%)
occurrences (all)	0	2	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Onychomycosis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	0 / 82 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	0 / 82 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 105 (0.00%)	1 / 84 (1.19%)	0 / 82 (0.00%)
occurrences (all)	0	1	0

Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	0 / 105 (0.00%)	0 / 84 (0.00%)	1 / 82 (1.22%)
occurrences (all)	0	0	1

Non-serious adverse events	Arm D		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 106 (46.23%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Orthostatic hypotension			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	6 / 106 (5.66%)		
occurrences (all)	6		
Feeling cold			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Feeling hot			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		

Influenza like illness			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Ejaculation failure			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	2 / 106 (1.89%)		
occurrences (all)	2		
Oropharyngeal pain			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Pulmonary fibrosis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Sinus congestion			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Confusional state			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		

Depressed mood subjects affected / exposed occurrences (all)	0 / 106 (0.00%) 0		
Depression subjects affected / exposed occurrences (all)	0 / 106 (0.00%) 0		
Insomnia subjects affected / exposed occurrences (all)	3 / 106 (2.83%) 3		
Morbid thoughts subjects affected / exposed occurrences (all)	1 / 106 (0.94%) 1		
Investigations Hepatic enzyme increased subjects affected / exposed occurrences (all)	0 / 106 (0.00%) 0		
Weight increased subjects affected / exposed occurrences (all)	0 / 106 (0.00%) 0		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	1 / 106 (0.94%) 1		
Congenital, familial and genetic disorders Double ureter subjects affected / exposed occurrences (all)	0 / 106 (0.00%) 0		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	3 / 106 (2.83%) 3		
Nervous system disorders Ageusia subjects affected / exposed occurrences (all)	0 / 106 (0.00%) 0		
Amnesia			

subjects affected / exposed	1 / 106 (0.94%)			
occurrences (all)	1			
Burning sensation				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences (all)	0			
Disturbance in attention				
subjects affected / exposed	1 / 106 (0.94%)			
occurrences (all)	1			
Dizziness				
subjects affected / exposed	16 / 106 (15.09%)			
occurrences (all)	17			
Dysgeusia				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences (all)	0			
Headache				
subjects affected / exposed	9 / 106 (8.49%)			
occurrences (all)	11			
Loss of consciousness				
subjects affected / exposed	1 / 106 (0.94%)			
occurrences (all)	1			
Paraesthesia				
subjects affected / exposed	2 / 106 (1.89%)			
occurrences (all)	2			
Somnolence				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences (all)	0			
Syncope				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences (all)	0			
Tension headache				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences (all)	0			
Tremor				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences (all)	0			
Trigeminal neuralgia				

subjects affected / exposed occurrences (all)	0 / 106 (0.00%) 0		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	 1 / 106 (0.94%) 1		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	 0 / 106 (0.00%) 0		
Eye disorders Dry eye subjects affected / exposed occurrences (all) Lacrimation increased subjects affected / exposed occurrences (all) Vision blurred subjects affected / exposed occurrences (all) Visual impairment subjects affected / exposed occurrences (all)	 1 / 106 (0.94%) 2 1 / 106 (0.94%) 1 2 / 106 (1.89%) 2 0 / 106 (0.00%) 0		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth	 1 / 106 (0.94%) 1 1 / 106 (0.94%) 1 0 / 106 (0.00%) 0 6 / 106 (5.66%) 6		

subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Faeces soft			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Mouth ulceration			
subjects affected / exposed	2 / 106 (1.89%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	2		
Tongue coated			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Hyperhidrosis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Photosensitivity reaction			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	3 / 106 (2.83%)		
occurrences (all)	3		

Rash			
subjects affected / exposed	4 / 106 (3.77%)		
occurrences (all)	4		
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Renal impairment			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	2 / 106 (1.89%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Osteopenia			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Pain in jaw			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		

Campylobacter gastroenteritis subjects affected / exposed occurrences (all)	1 / 106 (0.94%) 1		
Influenza subjects affected / exposed occurrences (all)	4 / 106 (3.77%) 4		
Lower respiratory tract infection subjects affected / exposed occurrences (all)	1 / 106 (0.94%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 106 (1.89%) 2		
Onychomycosis subjects affected / exposed occurrences (all)	0 / 106 (0.00%) 0		
Rhinitis subjects affected / exposed occurrences (all)	1 / 106 (0.94%) 1		
Sinusitis subjects affected / exposed occurrences (all)	0 / 106 (0.00%) 0		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 106 (0.00%) 0		
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 106 (0.00%) 0		
Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all)	0 / 106 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 June 2012	Exclusion criteria amended in Page 18. An additional criterion was added: 'Patients with cholestasis, biliary obstructive disorders or severe hepatic impairment'
28 September 2012	Section 14 - Indemnity statement amended to show that UoL holds Clinical Trial insurance Section 8.5 – Body fat redistribution amended to reflect that participants are free to withdraw from the sub study and remain in the main study, if they so wish Cover Page – the ISRCTN reference number has been added and the UoL sponsorreference number has been corrected Contact details – Clinical laboratory changed from RLH to UHA, CTRC Sherrington addressadded Section 1 – exclusion criteria number 12 'non hormonal contraception' replaced with 'reliable contraception' Section 1 – point 7 added to 'secondary objectives' Section 1 – mention of 'serum' removed Section 2.1 – paragraph on possible renoprotective effects of Telmisartan added Section 2.3 point 7 added to secondary objectives Section 2.4.1 – paragraph on renal artery stenosis has been added Section 4.2 – point 6 added to secondary outcomes Section 5.2 – exclusion criteria number 12 'non hormonal contraception' replaced with 'reliable contraception' Section 5.3.2 – point b – spelling mistake corrected Section 5.3.2 – Inserted j – it is discovered that the patient is pregnant Section 6.3 – point 7 – changed number of blood samples from 2 to 3 Section 6.3 – point 8 collection of urine sample added Section 7.2.2 – changed packaging description Section 7.3 – replaced phrase 'treatment pack' with 'trial treatment' Section 7.7.3 – amended to state the female patients discovering they are pregnant should let the research team know immediately Section 8.1 – table 1 – removed 'collection of blood sample 1' and collection of blood sample 2' replaced with 'collection of 3 blood samples for bioanalysis' Section 8.1 – table 1 – inserted collection of urine sample Section 8.2.1 – replaced mention of Department of Clinical Biochemistry, Royal Liverpool Hospital, with ClinicalClinical Laboratories, University Hospital Aintree Section 8.2.1 – replaced 'radioimmunoassay' with enzymatic immunoassay'
28 September 2012	Section 8.4.1– replaced mention of Department of Clinical Biochemistry, Royal Liverpool Hospital, with Clinical Laboratories, University Hospital Aintree Section 8.4.2 – replaced mention of Department of Clinical Biochemistry, Royal Liverpool Hospital, with Clinical Laboratories, University Hospital Aintree Section 8.4.4 – section inserted to describe assessment of renal biomarkers Section 9.2 – Changed stratification details and added a sentence on ethnicity Contact details: Institutions– Clinical Laboratory changed from Department of Clinical Biochemistry, Royal Liverpool Hospital, to Clinical Laboratories, University Hospital Aintree Section 10.8– altered to reflect that adverse reactions and all serious events are to be recorded Section 10.8.1– Altered to reflect Telmisartan related ARs only Section 10.9 (– amended to read 'all ARs that are observed or reported.....The investigator is also responsible for reporting all SAEs' Section 10.9 i)– inserted 'if a control (Arm A) patient has experienced an SAE the event does not need to be assessed for expectedness or relationship to study treatment, although the event should still be reported' Section 10.9 ii)– amended phone number Section 10.9 iii)– amended fax number

03 September 2013	Contact details – these have been removed Section 1 – point 2 clarified Section 1 – point 6 clarified Section 1 – point 9 addition of extra drug group due to changes in Summary of Product Characteristics Section 4.2 – point 6 clarified Section 5.2 – point 2 clarified Section 5.2 – point 6 clarified Section 5.2 – point 9 further drug group/class added due to change in Summary of Product Characteristics Section 6.3 – point 3 further clarification of medical history Section 6.4 – added trial coordinator to contacts if a problem with the randomisation system arises and removed helpdesk Section 7.1 – statement inserted to clarify that treatment is not stopped between stage I and II Section 7.3.1 – added statement of time windows for visits Section 7.3.1.2 – clarification on time windows Section 7.3.1.2 – change to dispensing guidelines to minimise drug wastage Section 7.3.1.3 – clarification on time windows Section 7.3.1.3 – change to dispensing guidelines to minimise drug wastage Section 7.3.1.4 – clarification on time windows Section 7.3.1.4 – change to dispensing guidelines to minimise drug wastage Section 7.2 – clarification of 'acceptable period of time Section 8.1 – clarification on time windows Section 8.1, table 1 – clarification on Medical History Section 10.4 – removal of fax number Section 10.9 – removal of fax number Section 10.10 – insertion of table 3 @SAE Evaluator Contacts Section 11.1.5 – insertion of statement on patient travel expenses Section 15.1 – insertion of statement on travel expenses
24 January 2014	Section 1 and section 5.2 – The units for the HbA1C value in exclusion criterion 1 have been Corrected Section 7 – removal of all mentions of 'Micardis' – a brand name of telmisartan Section 7.2.1 – insertion of a statement on dispensing of telmisartan if a high dose is unavailable Section 7.2.1 – insertion of statements on reference safety information and bioequivalence Section 7.2.3 – insertion of word manufacturers
16 June 2014	Section 1 and section 5.2 – the included and excluded drugs have been clarified Section 6.3 – insertion of the phrase 'by a medically qualified person' to the verification of eligibility criteria Section 7.3.3 – removal of the phrase 'in the morning' from the administration instructions Table 1 – Insertion of 'by a medically qualified person' to assessment of eligibility criteria Section 10.8.2 – Insertion of 'All events that meet the serious criteria need to be reported (regardless of causality)'
13 May 2015	Glossary – Addition of abbreviation for Liverpool Clinical Laboratories Glossary – Deletion of University Hospitals Aintree Section 1 – change to the number of participants to be enrolled Section 8.2.1, 8.4.1, and 8.4.2 – replaced Clinical laboratories, University Hospitals Aintree with Liverpool Clinical Laboratories Section 8.4.5 and 8.5.4 – insertion of statement(s) on the reporting of any clinically significant results Section 9.4 – insertion of statement on what happens 'post interim analysis' Section 9.5 – insertion of statement that after interim analysis randomisation will continue in an equal ratio

20 June 2016	***This protocol amendment occurred on 28/07/2016 which was after the global end of trial date 20/06/2016 (defined as last patient last visit). However the EudraCT database gives an error as it does not allow the date of amendment to be input later than the global end of trial date. To get round this error the date was entered was entered as the global end of trial date (20/06/2016) rather than the actual amendment date (28/07/2016).*** Cover page – insertion of trial statistician signature Protocol Summary – insertion of a further secondary objective Section 2.2 – insertion of a statement on alternative surrogate indices of insulin sensitivity Section 2.3 – insertion of a further secondary objective Section 4.2 – insertion of a further secondary outcome Section 8.4.3 – change to novel biomarkers Section 8.4.3 – removal of assessment of renal biomarkers Section 8.4.4 – addition of section on alternate measures of insulin resistance Section 8.5 – changed to sub-study 1 Section 8.6 – Insertion of sub-study 2 (assessment of renal biomarkers) Section 9.4.1 – changed to sub study 1 Section 9.4.2 – insertion of statement on sample size for sub study 2 (renal biomarkers) Section 9.6.2.1 – removal of assessment by structural equation models Section 9.6.2.3- insertion of statement on evaluation of alternate measures of insulin resistance Section 9.6.2.4 – insertion of statement on renal biomarkers References – addition of reference 57

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
10 April 2015	The decision was made as follows: • If the largest of these statistics exceeds a critical value (equal to 2.782), this would mean that one active dose group shows a substantially higher mean reduction of 24 week HOMA-IR score than the control group, and therefore the study will be stopped and the corresponding dose will be recommended for further testing. • If any active dose shows no improvement over control (i.e. has a negative measure of advantage) that active dose will be dropped from the second stage. • If all three active doses satisfy this criterion, then the study will be stopped and no significant improvement over control will be claimed for any of the active doses. • If some improvement over control is detected for at least one of the doses (i.e. if at least one test statistic is between 0 and 2.782), the study will progress to the second stage and the patients will be randomised between these dose(s) and control. Interim decision: • Drop arms B (20mg) and C (40mg). • Progress to the second stage of the study. Randomise patients between dose arm D (80mg) and control.	10 April 2015

Notes:

Limitations and caveats

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

N/A

Notes: