



## 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:

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## Population of trial subjects

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### Subjects enrolled per country

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

Notes:

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### Subjects enrolled per age group

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|   |     |
|---|-----|
| 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 <sup>[1]</sup>   |
| 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              |
| <b>Arm title</b>  | Arm A (Baseline) |
| Arm description:  |                  |
| Arm A: Non-intervention (control)                         |                  |
| Arm type  | No intervention  |
| No investigational medicinal product assigned in this arm |                  |
| <b>Arm title</b>  | 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

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | 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.

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | Arm A (Baseline) | Arm B (Baseline) | Arm C (Baseline) |
|---------------------------------------|------------------|------------------|------------------|
| Started                               | 105              | 84               | 82               |
| Completed                             | 105              | 84               | 82               |

| <b>Number of subjects in period 1</b> | 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           |
| <b>Arm title</b>             | Arm A (Final) |

Arm description:

Arm A: Non-intervention (control)

|          |                 |
|----------|-----------------|
| Arm type | No intervention |
|----------|-----------------|

No investigational medicinal product assigned in this arm

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 2<sup>[2]</sup></b> | Arm A (Final) | Arm D (Final) |
|---|---------------|---------------|
| Started   | 105           | 106           |
| Baseline  | 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 |
|--|---|---|

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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      |
| Hepatitis 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:<br>Arm A: 2, Arm B: 0, Arm C: 1, Arm D: 0 |        |        |        |
| Units: KG/m <sup>2</sup>   |        |        |        |
| 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:<br>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:<br>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  |
| Heart rate   |        |        |        |
| Number of participants missing data for baseline characteristic:<br>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:<br>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:<br>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:<br>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:<br>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:<br>Arm A: 3, Arm B: 1, Arm C: 4, Arm D: 5  |         |         |         |
| Units: cells/mm <sup>3</sup>  |         |         |         |
| 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:<br>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:<br>Arm A: 70, Arm B: 67, Arm C: 51, Arm D: 72<br>The missing data are presented in categorical form due to there being upper and lower limits of measurement:<br>< 10 : Arm A: 2, Arm B: 1, Arm C: 2, Arm D: 1<br>< 20 : Arm A: 13, Arm B: 20, Arm C: 11, Arm D: 23<br>< 40 : Arm A: 50, Arm B: 38, Arm C: 35, Arm D: 43<br>< 45 : Arm A: 2, Arm B: 6, Arm C: 3, Arm D: 3<br>< 100 : Arm A: 0, Arm B: 1, Arm C: 0, Arm D: 0<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>Arm A: 55, Arm B: 43, Arm C: 44, Arm D: 52<br>The missing data are presented in categorical form due to there being upper and lower limits of measurement:<br>< 60 : Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 1<br>< 90 : Arm A: 1, Arm B: 0, Arm C: 0, Arm D: 0<br>> 60 : Arm A: 24, Arm B: 23, Arm C: 25, Arm D: 22<br>> 90 : Arm A: 28, Arm B: 19, Arm C: 19, Arm D: 28<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>Arm A: 5, Arm B: 6, Arm C: 6, Arm D: 8<br>Some data are presented in both continuous and categorical form due to there being upper and lower  |        |        |        |

|   |         |         |         |
|---|---------|---------|---------|
| limits of measurement:<br>< 2 : Arm A: 0, Arm B: 1, Arm C: 0, Arm D: 0<br>< 3 : Arm A: 3, Arm B: 2, Arm C: 2, Arm D: 2<br>< 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:<br>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:<br>Arm A: 7, Arm B: 5, Arm C: 5, Arm D: 9  |         |         |         |
| Units: 10 <sup>12</sup> /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:<br>Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 1  |         |         |         |
| Units: 10 <sup>9</sup> /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:<br>Arm A: 1, Arm B: 0, Arm C: 0, Arm D: 0  |         |         |         |
| Units: 10 <sup>9</sup> /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:<br>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:<br>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:<br>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:<br>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:<br>Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 0 |         |         |         |
| Units: 10 <sup>9</sup> /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:<br>Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 0 |         |         |         |
| Units: 10 <sup>9</sup> /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:<br>Arm A: 1, Arm B: 2, Arm C: 0, Arm D: 0 |         |         |         |
| Units: 10 <sup>9</sup> /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:<br>Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 0 |         |         |         |
| Units: 10 <sup>9</sup> /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:<br>Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 0 |         |         |         |
| Units: 10 <sup>9</sup> /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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>Arm A: 104, Arm B: 83, Arm C: 82, Arm D: 106<br>***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:<br>Arm A: 104, Arm B: 84, Arm C: 81, Arm D: 106<br>***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:<br>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:<br>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 |

| <b>Reporting group values</b>                           | Arm D (Baseline) | Total |  |
|---|------------------|-------|--|
| Number of subjects                                      | 106              | 377   |  |
| Age categorical   |                  |       |  |
| Units: Subjects   |                  |       |  |
| In utero  | 0                | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks)   | 0                | 0     |  |
| Newborns (0-27 days)                                    | 0                | 0     |  |
| Infants and toddlers (28 days-23<br>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     |  |
| Hepatitis 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:<br>Arm A: 2, Arm B: 0, Arm C: 1, Arm D: 0 |        |     |  |
| Units: KG/m <sup>2</sup>   |        |     |  |
| arithmetic mean  | 26.0   |     |  |
| standard deviation   | ± 4.7  | -   |  |
| Blood pressure Systolic  |        |     |  |
| Number of participants missing data for baseline characteristic:<br>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:<br>Arm A: 0, Arm B: 0, Arm C: 1, Arm D: 0 |        |     |  |
| Units: mmHg  |        |     |  |
| arithmetic mean  | 78.6   |     |  |
| standard deviation   | ± 11.1 | -   |  |
| Heart rate   |        |     |  |
| Number of participants missing data for baseline characteristic:<br>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:<br>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:<br>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:<br>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:<br>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:<br>Arm A: 3, Arm B: 1, Arm C: 4, Arm D: 5 |        |     |  |

|   |         |   |  |
|---|---------|---|--|
| Units: cells/mm <sup>3</sup>  |         |   |  |
| arithmetic mean   | 617.0   |   |  |
| standard deviation  | ± 266.1 | - |  |
| CD4 Cell count & HIV viral load   |         |   |  |
| Number of participants missing data for baseline characteristic:<br>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:<br>Arm A: 70, Arm B: 67, Arm C: 51, Arm D: 72<br>The missing data are presented in categorical form due to there being upper and lower limits of measurement:<br>< 10 : Arm A: 2, Arm B: 1, Arm C: 2, Arm D: 1<br>< 20 : Arm A: 13, Arm B: 20, Arm C: 11, Arm D: 23<br>< 40 : Arm A: 50, Arm B: 38, Arm C: 35, Arm D: 43<br>< 45 : Arm A: 2, Arm B: 6, Arm C: 3, Arm D: 3<br>< 100 : Arm A: 0, Arm B: 1, Arm C: 0, Arm D: 0<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>< 60 : Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 1<br>< 90 : Arm A: 1, Arm B: 0, Arm C: 0, Arm D: 0<br>> 60 : Arm A: 24, Arm B: 23, Arm C: 25, Arm D: 22<br>> 90 : Arm A: 28, Arm B: 19, Arm C: 19, Arm D: 28<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>Arm A: 5, Arm B: 6, Arm C: 6, Arm D: 8<br>Some data are presented in both continuous and categorical form due to there being upper and lower limits of measurement:<br>< 2 : Arm A: 0, Arm B: 1, Arm C: 0, Arm D: 0<br>< 3 : Arm A: 3, Arm B: 2, Arm C: 2, Arm D: 2<br>< 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:<br>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:<br>Arm A: 7, Arm B: 5, Arm C: 5, Arm D: 9     |         |   |  |
| Units: 10 <sup>12</sup> /l   |         |   |  |
| arithmetic mean  | 4.60    |   |  |
| standard deviation   | ± 0.44  | - |  |
| White blood cell count   |         |   |  |
| Number of participants missing data for baseline characteristic:<br>Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 1     |         |   |  |
| Units: 10 <sup>9</sup> /l  |         |   |  |
| arithmetic mean  | 6.07    |   |  |
| standard deviation   | ± 2.14  | - |  |
| Platelets  |         |   |  |
| Number of participants missing data for baseline characteristic:<br>Arm A: 1, Arm B: 0, Arm C: 0, Arm D: 0     |         |   |  |
| Units: 10 <sup>9</sup> /l  |         |   |  |
| arithmetic mean  | 226.24  |   |  |
| standard deviation   | ± 55.37 | - |  |
| Mean cell volume   |         |   |  |
| Number of participants missing data for baseline characteristic:<br>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:<br>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:<br>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:<br>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:<br>Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 0     |         |   |  |
| Units: 10 <sup>9</sup> /l  |         |   |  |
| arithmetic mean  | 3.29    |   |  |
| standard deviation   | ± 1.64  | - |  |
| Lymphocytes  |         |   |  |
| Number of participants missing data for baseline characteristic:<br>Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 0     |         |   |  |
| Units: 10 <sup>9</sup> /l  |         |   |  |
| arithmetic mean  | 2.08    |   |  |
| standard deviation   | ± 0.68  | - |  |

|  |         |   |  |
|--|---------|---|--|
| Eosinophils  |         |   |  |
| Number of participants missing data for baseline characteristic:<br>Arm A: 1, Arm B: 2, Arm C: 0, Arm D: 0 |         |   |  |
| Units: 10 <sup>9</sup> /l  |         |   |  |
| arithmetic mean  | 0.16    |   |  |
| standard deviation   | ± 0.12  | - |  |
| Basophils  |         |   |  |
| Number of participants missing data for baseline characteristic:<br>Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 0 |         |   |  |
| Units: 10 <sup>9</sup> /l  |         |   |  |
| arithmetic mean  | 0.03    |   |  |
| standard deviation   | ± 0.04  | - |  |
| Monocytes  |         |   |  |
| Number of participants missing data for baseline characteristic:<br>Arm A: 0, Arm B: 0, Arm C: 0, Arm D: 0 |         |   |  |
| Units: 10 <sup>9</sup> /l  |         |   |  |
| arithmetic mean  | 0.49    |   |  |
| standard deviation   | ± 0.22  | - |  |
| Insulin  |         |   |  |
| Number of participants missing data for baseline characteristic:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>Arm A: 104, Arm B: 83, Arm C: 82, Arm D: 106<br>***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:<br>Arm A: 104, Arm B: 84, Arm C: 81, Arm D: 106<br>***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:<br>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:<br>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:<br>Arm A: Non-intervention (control) |                  |
| Reporting group title   | Arm B (Baseline) |
| Reporting group description:<br>Arm B: Telmisartan 20mg           |                  |
| Reporting group title   | Arm C (Baseline) |
| Reporting group description:<br>Arm C: Telmisartan 40mg           |                  |
| Reporting group title   | Arm D (Baseline) |
| Reporting group description:<br>Arm D: Telmisartan 80mg           |                  |
| Reporting group title   | Arm A (Final)    |
| Reporting group description:<br>Arm A: Non-intervention (control) |                  |
| Reporting group title   | Arm D (Final)    |
| Reporting group description:<br>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:<br>insulin resistance measured by HOMA-IR. HOMA-IR was calculated by<br><br>$\text{HOMA-IR} = (\text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose (mmol/l)}) / 22.5$<br>The conversion factor for fasting insulin to convert from pmol/L to $\mu\text{U/mL}$ is 0.144. |  |
| End point type   | Primary  |
| End point timeframe:<br>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 <sup>[1]</sup> | 78 <sup>[2]</sup> |  |  |
| 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



|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Attachments (see zip file)</b> | Primary efficacy data.pdf |
|-----------------------------------|---------------------------|

## Statistical analyses

|                                   |                       |
|-----------------------------------|-----------------------|
| <b>Statistical analysis title</b> | ANCOVA HOMA-IR(Final) |
|-----------------------------------|-----------------------|

Statistical analysis description:

An ANCOVA model is used by fitting the regression model  $HOMAIR\_24 = HOMAIR\_0 + \text{treatment} + \text{stratification factor (Black/Non-Black)}$ , 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 <sup>[3]</sup>    |
| P-value                                 | > 0.05 <sup>[4]</sup>         |
| 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.

|                                   |                                       |
|-----------------------------------|---------------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[5]</sup>    |
| P-value                                 | > 0.05 <sup>[6]</sup>         |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[7]</sup> |
| 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) and I is fasting insulin ( $\mu$ U/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 <sup>[8]</sup>     | 78 <sup>[9]</sup>     |  |  |
| Units: QUICKI                        |                       |                       |  |  |
| arithmetic mean (standard deviation) |                       |                       |  |  |
| Baseline                             | 0.117 ( $\pm$ 0.0092) | 0.118 ( $\pm$ 0.0091) |  |  |
| Week 24                              | 0.115 ( $\pm$ 0.0093) | 0.116 ( $\pm$ 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 <sup>[10]</sup>   |
| P-value                                 | > 0.05 <sup>[11]</sup>        |
| 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 ( $\mu\text{U/mL}$ ), 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 <sup>[12]</sup>    | 78 <sup>[13]</sup>    |  |  |
| Units: Revised QUICKI                |                       |                       |  |  |
| arithmetic mean (standard deviation) |                       |                       |  |  |
| Baseline                             | 0.132 ( $\pm$ 0.0168) | 0.133 ( $\pm$ 0.0156) |  |  |
| Week 24                              | 0.132 ( $\pm$ 0.0176) | 0.133 ( $\pm$ 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 <sup>[14]</sup>   |
| P-value                                 | > 0.05 <sup>[15]</sup>        |
| 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

$$\text{HOMA-IR} = (\text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose (mmol/l)}) / 22.5$$

The conversion factor for fasting insulin to convert from pmol/L to  $\mu\text{U/mL}$  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 ( $t = 12, 24, \text{ or } 48$ ) 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) and I is fasting insulin ( $\mu$ U/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              |  |  |

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Attachments (see zip file)</b> | Longitudinal QUICKI.pdf |
|-----------------------------------|-------------------------|

## Statistical analyses

|                                   |                                      |
|-----------------------------------|--------------------------------------|
| <b>Statistical analysis title</b> | 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 ( $t = 12, 24, \text{ or } 48$ ) 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 ( $\mu\text{U/mL}$ ), 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              |  |  |

|                                   |                                 |
|-----------------------------------|---------------------------------|
| <b>Attachments (see zip file)</b> | Longitudinal Revised QUICKI.pdf |
|-----------------------------------|---------------------------------|

## Statistical analyses

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 ( $t = 12, 24, \text{ or } 48$ ) 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              |  |  |

|                                   |                       |
|-----------------------------------|-----------------------|
| <b>Attachments (see zip file)</b> | Longitudinal HDLc.pdf |
|-----------------------------------|-----------------------|

## Statistical analyses

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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              |  |  |

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Attachments (see zip file)</b> | Longitudinal Cholesterol.pdf |
|-----------------------------------|------------------------------|

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | 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              |  |  |

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Attachments (see zip file)</b> | Longitudinal Triglycerides.pdf |
|-----------------------------------|--------------------------------|

### Statistical analyses

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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              |  |  |

|                                   |                       |
|-----------------------------------|-----------------------|
| <b>Attachments (see zip file)</b> | Longitudinal LDLc.pdf |
|-----------------------------------|-----------------------|

### Statistical analyses

|  |                                     |
|--|-------------------------------------|
| <b>Statistical analysis title</b>  | 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              |  |  |

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Attachments (see zip file)</b> | Longitudinal Adiponectin.pdf |
|-----------------------------------|------------------------------|

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | 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              |  |  |

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Attachments (see zip file)</b> | Longitudinal Leptin.pdf |
|-----------------------------------|-------------------------|

## Statistical analyses

|  |                                      |
|--|--------------------------------------|
| <b>Statistical analysis title</b>  | 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              |  |  |

|                                   |                      |
|-----------------------------------|----------------------|
| <b>Attachments (see zip file)</b> | Longitudinal IL8.pdf |
|-----------------------------------|----------------------|

### Statistical analyses

|  |                                   |
|--|-----------------------------------|
| <b>Statistical analysis title</b>  | 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              |  |  |

|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Attachments (see zip file)</b> | Longitudinal TNFalpha.pdf |
|-----------------------------------|---------------------------|

### Statistical analyses

|  |                                     |
|--|-------------------------------------|
| <b>Statistical analysis title</b>  | 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              |  |  |

|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Attachments (see zip file)</b> | Longitudinal Resistin.pdf |
|-----------------------------------|---------------------------|

## Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | 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              |  |  |

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Attachments (see zip file)</b> | Longitudinal hsCRP.pdf |
|-----------------------------------|------------------------|

### Statistical analyses

|  |                                      |
|--|--------------------------------------|
| <b>Statistical analysis title</b>  | 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 <sup>[16]</sup> | 8 <sup>[17]</sup> |  |  |
| Units: dm <sup>3</sup>               |                   |                   |  |  |
| 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

|                                   |                    |
|-----------------------------------|--------------------|
| <b>Attachments (see zip file)</b> | Sub study data.pdf |
|-----------------------------------|--------------------|

### Statistical analyses

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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<br>(Baseline) | Arm B<br>(Baseline) | Arm C<br>(Baseline) | Arm D<br>(Baseline) |
|-----------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type          | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed | 105 <sup>[18]</sup> | 84 <sup>[19]</sup>  | 82 <sup>[20]</sup>  | 106 <sup>[21]</sup> |
| 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 <sup>[22]</sup> | 8 <sup>[23]</sup> |  |  |
| Units: CH2/H2O (%)                   |                   |                   |  |  |
| 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

|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Attachments (see zip file)</b> | Primary efficacy data.pdf |
|-----------------------------------|---------------------------|

**Statistical analyses**

|                                   |                                      |
|-----------------------------------|--------------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[24]</sup> | 8 <sup>[25]</sup> |  |  |
| 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.

|                                   |                    |
|-----------------------------------|--------------------|
| <b>Attachments (see zip file)</b> | Sub study data.pdf |
|-----------------------------------|--------------------|

**Statistical analyses**

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | 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                  |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 (creatinine, 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 (creatinine, 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<br>(Baseline) | Arm B<br>(Baseline) | Arm C<br>(Baseline) | Arm D<br>(Baseline) |
|-----------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type          | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed | 105 <sup>[26]</sup> | 84 <sup>[27]</sup>  | 82 <sup>[28]</sup>  | 106 <sup>[29]</sup> |
| 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.

|                                   |                          |
|-----------------------------------|--------------------------|
| <b>Attachments (see zip file)</b> | 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.

| <b>End point values</b>              | Arm A<br>(Baseline) | Arm B<br>(Baseline) | Arm C<br>(Baseline) | Arm D<br>(Baseline) |
|--------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type                   | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed          | 39 <sup>[30]</sup>  | 45 <sup>[31]</sup>  | 35 <sup>[32]</sup>  | 35 <sup>[33]</sup>  |
| 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

|                                   |             |
|-----------------------------------|-------------|
| <b>Attachments (see zip file)</b> | 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 %

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

| <b>Non-serious adverse events</b>                     | 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<br>subjects affected / exposed<br>occurrences (all)  | 0 / 106 (0.00%)<br>0 |  |  |
| Malaise<br>subjects affected / exposed<br>occurrences (all)   | 0 / 106 (0.00%)<br>0 |  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 106 (0.94%)<br>1 |  |  |
| Reproductive system and breast disorders<br>Ejaculation failure<br>subjects affected / exposed<br>occurrences (all) | 1 / 106 (0.94%)<br>1 |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)        | 0 / 106 (0.00%)<br>0 |  |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)   | 2 / 106 (1.89%)<br>2 |  |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 106 (0.94%)<br>1 |  |  |
| Pulmonary fibrosis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 106 (0.00%)<br>0 |  |  |
| Sinus congestion<br>subjects affected / exposed<br>occurrences (all)  | 0 / 106 (0.00%)<br>0 |  |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 106 (0.94%)<br>1 |  |  |
| Confusional state<br>subjects affected / exposed<br>occurrences (all)   | 1 / 106 (0.94%)<br>1 |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| Depressed mood<br>subjects affected / exposed<br>occurrences (all)  | 0 / 106 (0.00%)<br>0 |  |  |
| Depression<br>subjects affected / exposed<br>occurrences (all)  | 0 / 106 (0.00%)<br>0 |  |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 3 / 106 (2.83%)<br>3 |  |  |
| Morbid thoughts<br>subjects affected / exposed<br>occurrences (all)   | 1 / 106 (0.94%)<br>1 |  |  |
| Investigations<br>Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 106 (0.00%)<br>0 |  |  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)  | 0 / 106 (0.00%)<br>0 |  |  |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all)      | 1 / 106 (0.94%)<br>1 |  |  |
| Congenital, familial and genetic disorders<br>Double ureter<br>subjects affected / exposed<br>occurrences (all) | 0 / 106 (0.00%)<br>0 |  |  |
| Cardiac disorders<br>Palpitations<br>subjects affected / exposed<br>occurrences (all)                           | 3 / 106 (2.83%)<br>3 |  |  |
| Nervous system disorders<br>Ageusia<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 106 (0.00%)<br>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<br>occurrences (all)   | 0 / 106 (0.00%)<br>0   |  |  |
| Blood and lymphatic system disorders<br>Neutropenia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 106 (0.94%)<br>1   |  |  |
| Ear and labyrinth disorders<br>Ear pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 106 (0.00%)<br>0   |  |  |
| Eye disorders<br>Dry eye<br>subjects affected / exposed<br>occurrences (all)<br><br>Lacrimation increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Vision blurred<br>subjects affected / exposed<br>occurrences (all)<br><br>Visual impairment<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 106 (0.94%)<br>2<br><br>1 / 106 (0.94%)<br>1<br><br>2 / 106 (1.89%)<br>2<br><br>0 / 106 (0.00%)<br>0 |  |  |
| Gastrointestinal disorders<br>Abdominal distension<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)<br><br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Dry mouth | 1 / 106 (0.94%)<br>1<br><br>1 / 106 (0.94%)<br>1<br><br>0 / 106 (0.00%)<br>0<br><br>6 / 106 (5.66%)<br>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<br>subjects affected / exposed<br>occurrences (all)  | 4 / 106 (3.77%)<br>4   |  |  |
| Renal and urinary disorders<br>Chromaturia<br>subjects affected / exposed<br>occurrences (all)<br><br>Haematuria<br>subjects affected / exposed<br>occurrences (all)<br><br>Renal impairment<br>subjects affected / exposed<br>occurrences (all)  | 1 / 106 (0.94%)<br>1<br><br>0 / 106 (0.00%)<br>0<br><br>1 / 106 (0.94%)<br>1   |  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Back pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Myalgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Neck pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Osteopenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Pain in jaw<br>subjects affected / exposed<br>occurrences (all) | 0 / 106 (0.00%)<br>0<br><br>1 / 106 (0.94%)<br>1<br><br>2 / 106 (1.89%)<br>2<br><br>0 / 106 (0.00%)<br>0<br><br>1 / 106 (0.94%)<br>1<br><br>1 / 106 (0.94%)<br>1 |  |  |
| Infections and infestations<br>Acute sinusitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 106 (0.00%)<br>0   |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| Campylobacter gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 106 (0.94%)<br>1 |  |  |
| Influenza<br>subjects affected / exposed<br>occurrences (all)  | 4 / 106 (3.77%)<br>4 |  |  |
| Lower respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 106 (0.94%)<br>1 |  |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)  | 2 / 106 (1.89%)<br>2 |  |  |
| Onychomycosis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 106 (0.00%)<br>0 |  |  |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 106 (0.94%)<br>1 |  |  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 106 (0.00%)<br>0 |  |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 106 (0.00%)<br>0 |  |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 106 (0.00%)<br>0 |  |  |
| Metabolism and nutrition disorders<br>Increased appetite<br>subjects affected / exposed<br>occurrences (all) | 0 / 106 (0.00%)<br>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 | <p>Section 14 - Indemnity statement amended to show that UoL holds Clinical Trial insurance</p> <p>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</p> <p>Cover Page - the ISRCTN reference number has been added and the UoL sponsorreference number has been corrected</p> <p>Contact details - Clinical laboratory changed from RLH to UHA, CTCRC Sherrington addressadded</p> <p>Section 1 - exclusion criteria number 12 'non hormonal contraception' replaced with 'reliable contraception'</p> <p>Section 1 - point 7 added to 'secondary objectives'</p> <p>Section 1 - mention of 'serum' removed</p> <p>Section 2.1 - paragraph on possible renoprotective effects of Telmisartan added</p> <p>Section 2.3 point 7 added to secondary objectives</p> <p>Section 2.4.1 - paragraph on renal artery stenosis has been added</p> <p>Section 4.2 - point 6 added to secondary outcomes</p> <p>Section 5.2 - exclusion criteria number 12 'non hormonal contraception' replaced with 'reliable contraception'</p> <p>Section 5.3.2 - point b - spelling mistake corrected</p> <p>Section 5.3.2 - Inserted j - it is discovered that the patient is pregnant</p> <p>Section 6.3 - point 7 - changed number of blood samples from 2 to 3</p> <p>Section 6.3 - point 8 collection of urine sample added</p> <p>Section 7.2.2 - changed packaging description</p> <p>Section 7.3 - replaced phrase 'treatment pack' with 'trial treatment'</p> <p>Section 7.7.3 - amended to state the female patients discovering they are pregnant should let the research team know immediately</p> <p>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'</p> <p>Section 8.1 - table 1 - inserted collection of urine sample</p> <p>Section 8.2.1 - replaced mention of Department of Clinical Biochemistry, Royal Liverpool Hospital, with ClinicalClinical Laboratories, University Hospital Aintree</p> <p>Section 8.2.1 - replaced 'radioimmunoassay' with enzymatic immunoassay'</p> |
| 28 September 2012 | <p>Section 8.4.1- replaced mention of Department of Clinical Biochemistry, Royal Liverpool Hospital, with Clinical Laboratories, University Hospital Aintree</p> <p>Section 8.4.2 - replaced mention of Department of Clinical Biochemistry, Royal Liverpool Hospital, with Clinical Laboratories, University Hospital Aintree</p> <p>Section 8.4.4 - section inserted to describe assessment of renal biomarkers</p> <p>Section 9.2 - Changed stratification details and added a sentence on ethnicity</p> <p>Contact details: Institutions- Clinical Laboratory changed from Department of Clinical Biochemistry, Royal Liverpool Hospital, to Clinical Laboratories, University Hospital Aintree</p> <p>Section 10.8- altered to reflect that adverse reactions and all serious events are to be recorded</p> <p>Section 10.8.1- Altered to reflect Telmisartan related ARs only</p> <p>Section 10.9 (- amended to read 'all ARs that are observed or reported.....The investigator is also responsible for reporting all SAEs'</p> <p>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'</p> <p>Section 10.9 ii)- amended phone number</p> <p>Section 10.9 iii)- amended fax number</p>   |

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

|              |  |
|--------------|--|
| 20 June 2016 | <p>***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 as the global end of trial date (20/06/2016) rather than the actual amendment date (28/07/2016).***</p> <p>Cover page – insertion of trial statistician signature<br/> Protocol Summary – insertion of a further secondary objective<br/> Section 2.2 – insertion of a statement on alternative surrogate indices of insulin sensitivity<br/> Section 2.3 – insertion of a further secondary objective<br/> Section 4.2 – insertion of a further secondary outcome<br/> Section 8.4.3 – change to novel biomarkers<br/> Section 8.4.3 – removal of assessment of renal biomarkers<br/> Section 8.4.4 – addition of section on alternate measures of insulin resistance<br/> Section 8.5 – changed to sub-study 1<br/> Section 8.6 – Insertion of sub-study 2 (assessment of renal biomarkers)<br/> Section 9.4.1 – changed to sub study 1<br/> Section 9.4.2 – insertion of statement on sample size for sub study 2 (renal biomarkers)<br/> Section 9.6.2.1 – removal of assessment by structural equation models<br/> Section 9.6.2.3- insertion of statement on evaluation of alternate measures of insulin resistance<br/> Section 9.6.2.4 – insertion of statement on renal biomarkers<br/> References – addition of reference 57</p> |
|--------------|--|

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date          | Interruption  | Restart date  |
|---------------|---|---------------|
| 10 April 2015 | <p>The decision was made as follows:</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> <li>• 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.</li> <li>• 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.</li> </ul> <p>Interim decision:</p> <ul style="list-style-type: none"> <li>• Drop arms B (20mg) and C (40mg).</li> <li>• Progress to the second stage of the study. Randomise patients between dose arm D (80mg) and control.</li> </ul> | 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.

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|-----|
| N/A |
|-----|

Notes: