Telmisartan to reduce insulin resistance in HIV-positive individuals on combination antiretroviral therapy: the TAILoR dose-ranging Phase II RCT

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This report

Abstract

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Background: Combination antiretroviral therapy (cART) is the standard for human immunodeficiency virus (HIV) infection treatment but can result in metabolic abnormalities, such as insulin resistance, dyslipidaemia and lipodystrophy, which can increase the risk of cardiovascular disease.

Objective: The objective of the trial was to evaluate whether or not telmisartan, an angiotensin II receptor antagonist and a peroxisome proliferator-activated receptor-γ partial agonist, could reduce insulin resistance in HIV-positive individuals on cART, and affect blood and imaging biomarkers of cardiometabolic disease.

Design: A Phase II, multicentre, randomised, open-labelled, dose-ranging trial of telmisartan over a period of 48 weeks with an adaptive design comprising two stages was used to identify the optimal dose of telmisartan. Participants were randomised to receive one of the three doses of telmisartan (20, 40 and 80 mg) or no intervention (control).

Setting: Recruitment was from 19 HIV specialist centres in the UK.

Participants: A total of 377 patients infected with HIV who met the prespecified inclusion/exclusion criteria.

Interventions: 20-, 40- and 80-mg tablets of telmisartan.

Main outcome measures: The primary outcome measure was reduction in the homeostatic model assessment of insulin resistance (HOMA-IR), a marker of insulin resistance, at 24 weeks. Secondary outcome measures were changes in plasma lipid profile; Quantitative Insulin Sensitivity Check Index (QUICKI) and revised QUICKI, alternative markers of insulin resistance, plasma adipokines (adiponectin, leptin, interleukin 8, tumour necrosis factor alpha, resistin); high-sensitivity C-reactive protein (hs-CRP); body fat redistribution, as measured by magnetic resonance imaging/proton magnetic resonance spectroscopy; changes in renal markers (albumin-to-creatinine ratio, neutrophil gelatinase-associated lipocalin); and tolerability to telmisartan.

ABSTRACT

Results: At the interim analysis, 80 mg of telmisartan was taken forward into the second stage of the study. Baseline characteristics were balanced across treatment arms. There were no differences in HOMA-IR [0.007, standard error (SE) 0.106], QUICKI (0.001, SE 0.001) and revised QUICKI (0.002, SE 0.002) at 24 weeks between the telmisartan (80 mg; $n = 106$) and non-intervention ($n = 105$) arms. Longitudinal analysis over 48 weeks showed that there was no change in HOMA-IR, lipid or adipokine levels; however, but there were significant, but marginal, improvements in revised QUICKI [0.004, 95% confidence interval (CI) 0.000 to 0.008] and plasma hs-CRP (–0.222, 95% CI –0.433 to –0.011) over 48 weeks. Substudies also showed a significant reduction in the liver fat content at 24 weeks (1.714, 95% CI –2.787 to –0.642; $p = 0.005$) and urinary albumin excretion at 48 weeks (–0.665, 95% CI –1.31 to –0.019; $p = 0.04$). There were no differences in serious adverse events between the telmisartan and control arms.

Limitations: The patients had modest elevations of HOMA-IR at baseline, and our trial could have been under-powered to detect smaller improvements in insulin resistance over time.

Conclusions: Using a novel adaptive design, we demonstrated that there was no significant effect of telmisartan (80 mg) on the primary outcome measure of HOMA-IR and some secondary outcomes (plasma lipids and adipokines). Telmisartan did lead to favourable, and biologically plausible, changes of the secondary longitudinal outcome measures: revised QUICKI, hs-CRP, hepatic fat accumulation and urinary albumin excretion. Taken collectively, our findings showed that telmisartan did not reduce insulin resistance in patients infected with HIV on antiretrovirals.

Future work: The mechanistic basis of adipocyte regulation will be studied to allow for development of biomarkers and interventions.

Trial registration: Current Controlled Trials ISRCTN51069819.

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List of abbreviations

ACE	angiotensin-converting enzyme	ICH	International Conference on Harmonisation
ACR	albumin-to-creatinine ratio	IDSMC	Independent Data Safety and Monitoring Committee
AE	adverse event	IL-6	interleukin 6
ANCOVA	analysis of covariance	IL-8	interleukin 8
AR	adverse reaction	IMP	investigational medicinal product
ARB	angiotensin receptor blocker	IQC	internal quality control
ATP	Adult Treatment Panel	IQR	interquartile range
BAF	Bioanalytical Facility	ITT	intention to treat
BMI	body mass index	IV	instrumental variable
cART	combination antiretroviral therapy	K3EDTA	tripotassium ethylenediaminetetraacetic acid
CCRN	Comprehensive Clinical Research Network	LCL	Liverpool Clinical Laboratories
CD4	cluster of differentiation 4	LDL-C	low-density lipoprotein cholesterol
CI	confidence interval	LLOD	lower limit of detection
CRF	case report form	MedDRA	Medical Dictionary for Regulatory Activities
CTRC	Clinical Trials Research Centre	MHRA	Medicines and Healthcare products Regulatory Agency
CVD	cardiovascular disease		
DAD	Data collection on Adverse events of anti-HIV Drugs	MR	magnetic resonance
		MRI	magnetic resonance imaging
eGFR	estimated glomerular filtration rate	MRS	magnetic resonance scanning
ELISA	enzyme-linked immunosorbent assay	MS	metabolic syndrome
		NEFA	non-esterified fatty acid
EQA	External Quality Assessment	NGAL	neutrophil gelatinase-associated lipocalin
ETC	excess treatment cost		
GCP	good clinical practice	NIHR	National Institute for Health Research
^{1}H-MRS	proton magnetic resonance spectroscopy	NRTI	nucleoside reverse transcriptase inhibitor
HDL	high-density lipoprotein	PCR	polymerase chain reaction
HDL-C	high-density lipoprotein cholesterol	PI	principal investigator
HIV	human immunodeficiency virus	PPAR	peroxisome proliferator-activated receptor
HIVLD	HIV-associated lipodystrophy		
HOMA-IR	homeostatic model assessment of insulin resistance		
hs-CRP	high-sensitivity C-reactive protein		

PRESS	point-resolved spectroscopy	SE	standard error
QUICKI	Quantitative Insulin Sensitivity Check Index	SOC	system organ class
		SOP	standard operating procedure
R&D	research and development	SUSAR	suspected unexpected serious adverse reaction
RCT	randomised controlled trial		
REC	Research Ethics Committee	T2DM	type 2 diabetes mellitus
SAE	serious adverse event	TMG	trial management group
SAR	serious adverse reaction	TNF-α	tumour necrosis factor alpha
SD	standard deviation	TSC	Trial Steering Committee

Plain English summary

Human immunodeficiency virus (HIV) infection in humans is now a chronic disease that is treatable by a combination of anti-HIV drugs. This has resulted in a reduction in HIV-related deaths, but it has also led to the emergence of serious side effects, such as HIV-associated lipodystrophy, diabetes mellitus and, importantly, an increase in the risk of ischaemic heart disease. A key abnormality seems to be insulin resistance. There is a need to find new strategies to reduce insulin resistance in individuals infected with HIV, which would ultimately reduce the associated cardiovascular risk.

In the current randomised clinical trial, we have investigated whether or not telmisartan, a drug that is widely used for hypertension, can reduce insulin resistance in individuals infected with HIV on anti-HIV drugs. We used a novel adaptive trial design to compare three different doses of telmisartan with the control group (those individuals who do not take telmisartan) in the initial stage. We then selected the best telmisartan dose for the second stage, in which it was tested against the control to determine the effect on insulin resistance. We also tested the effect of telmisartan on body, liver and limb fat, blood proteins (markers of metabolic disease) and urine proteins.

A 80-mg dose of telmisartan was taken forward into the second stage of the study. Telmisartan did not reduce the primary marker of insulin resistance [homeostatic model assessment of insulin resistance (HOMA-IR)] over 24 weeks. It also did not affect the levels of lipids or hormones produced by fat cells. However, over 48 weeks, it led to marginal improvements in another marker of insulin resistance [revised Quantitative Insulin Sensitivity Check Index (QUICKI)], a marker of inflammation (high-sensitivity C-reactive protein) and reduced protein excretion from kidneys. Magnetic resonance imaging analysis showed a reduction in liver fat content. Overall, we did not show an effect of telmisartan on our primary marker of insulin resistance in individuals infected with HIV who are on antiretroviral drugs.

Scientific summary

Background

Combination antiretroviral therapy (cART) is the mainstay of treatment for human immunodeficiency virus (HIV) and has dramatically improved the morbidity and mortality associated with HIV, turning it into a chronic disease. However, cART, together with the virus itself, can lead to various metabolic complications such as obesity, type 2 diabetes mellitus (T2DM) and an increased risk of cardiovascular disease (CVD). In the HIV DAD (Data collection on Adverse events of anti-HIV Drugs) cohort, patients with metabolic syndrome (MS) had a fourfold increase in the incidence of T2DM and a twofold to threefold increased risk of CVD. Long-term cART exposure also leads to an increased incidence of myocardial infarction, intima–media thickness and carotid lesions.

Insulin resistance, a key feature of MS, is central to cardiometabolic disease and is an important link between features of MS, obesity, dyslipidaemia, T2DM and CVD. The prevalence of insulin resistance in cART-treated patients infected with HIV ranges from 21% to 37%. Clinical interventions that arrest or reverse cART-associated insulin resistance represent a strategy to reduce the incidence of T2DM and CVD in patients infected with HIV. Insulin sensitisers such as thiazolidinediones and metformin have been investigated, but randomised clinical trials in patients infected with HIV have shown mixed results. Therefore, there is a need for novel clinical interventions with proven safety profiles that can reduce cART-induced insulin resistance in individuals infected with HIV.

The angiotensin II receptor blocker telmisartan also has partial agonist properties at the peroxisome proliferator-activated receptor-γ, an important regulator of adipocyte function. Prospective randomised clinical trials in patients with diabetes mellitus, and those with MS, have shown that telmisartan significantly reduces insulin resistance. Telmisartan also has wide-ranging beneficial effects on various components of the MS: it results in reductions in fasting glucose, insulin, glycosylated haemoglobin, homeostatic model assessment of insulin resistance (HOMA-IR); increases adiponectin; improves lipid parameters; and reduces visceral fat. This study, and others, has shown that telmisartan partially reverses the antiadipogenic effects of antiretrovirals in vitro. This in vitro study also showed a non-monotone relationship of telmisartan on adiponectin and lipin 1 secretion. However, whether or not telmisartan would be clinically efficacious in reducing insulin resistance in cART-treated patients infected with HIV has not been assessed. This trial, therefore, was designed to address this important question, coupled with an assessment of the dose–response relationship of telmisartan in vivo.

Objectives

Primary objective

To determine the effect of telmisartan on insulin resistance in individuals infected with HIV on cART using HOMA-IR as a measurable, validated surrogate marker of insulin resistance.

Secondary objectives

- To define the optimal dose of telmisartan that can significantly reduce insulin resistance.
- To measure HOMA-IR values at baseline (T0) and at 12, 24 and 48 weeks to provide data on time to, and sustainability of, any reduction in HOMA-IR.
- To utilise alternative indices of insulin resistance such as Quantitative Insulin Sensitivity Check Index (QUICKI) and revised QUICKI to determine the effect of telmisartan on insulin resistance.

- To mechanistically evaluate whether or not telmisartan modulates the plasma concentrations of both beneficial (adiponectin) and adverse [leptin, resistin, tumour necrosis factor alpha (TNF-α), high-sensitivity C-reactive protein (hs-CRP)] biomarkers, which may help in further stratifying telmisartan therapy in the future.
- To determine whether or not telmisartan improves general lipid homeostasis and reduces visceral fat accumulation in individuals infected with HIV on cART over a 24-week period.
- To determine, in a substudy, whether or not proton magnetic resonance spectroscopy (^{1}H-MRS)-assessed intrahepatic and intramyocellular triglyceride content, markers of hepatic steatosis and insulin resistance, respectively, are reduced by telmisartan therapy.
- To determine whether or not telmisartan has an effect on urinary biomarkers [albumin-to-creatinine ratio (ACR), neutrophil gelatinase-associated lipocalin (NGAL)] of renal injury in individuals infected with HIV on cART.
- To evaluate the tolerability of telmisartan in this patient group.

Methods

Trial design

TAILoR was a multicentre, randomised open-labelled study with an adaptive design. The adaptive design consisted of two stages. In stage 1, eligible patients were randomised on a 1 : 1 : 1 : 1 basis to either no treatment or 20, 40 or 80 mg of telmisartan once daily. The duration of study treatment was a maximum of 48 weeks, with follow-up visits at 12, 24, and 48 weeks. An interim analysis was performed when half of the planned maximum number of patients had been followed up for at least 24 weeks. A subset of patients in the main study took part in the magnetic resonance imaging (MRI) substudy over 24 weeks.

Participants

TAILoR participants were adults (aged ≥ 18 years) with documented HIV infection who had been receiving a stable cART for at least 6 months prior to randomisation. The backbone of therapy was based on nucleotide reverse transcriptase inhibitors, raltegravir or maraviroc, and patients should have been on a boosted protease inhibitor (lopinavir/ritonavir, atazanavir/ritonavir, darunavir/ritonavir, fosamprenavir/ ritonavir, saquinavir/ritonavir) and/or efavirenz, rilpivirine or etravirine for at least 6 months.

Patients were excluded if they were diabetic, had low blood pressure, renal disease, untreated renal artery stenosis, cholestasis, biliary obstructive disorders or severe hepatic impairment, active chronic hepatitis C infection, were on/had been on hormone therapy, anabolics and insulin sensitisers, or any other product likely to influence insulin sensitivity within 6 months preceding randomisation, and/or were on other angiotensin receptor blockers, angiotensin-converting enzyme inhibitors or direct renin inhibitors within 4 weeks preceding randomisation. Patients with suspected poor compliance, pregnant or lactating women, women of childbearing age unless using reliable contraception, and those co-enrolled into other drug trials were also excluded.

Study settings

The trial was conducted in 19 UK sexual health clinics and/or HIV treatment centres from March 2013 to July 2015.

Interventions

All patients were randomised to either no treatment or telmisartan (20-, 40-, or 80-mg doses taken once daily) depending on treatment allocation. The duration of the treatment was 48 weeks. Patients were asked to complete treatment diaries, detailing compliance.

Sample collection

Blood and urine were collected at four time points during the trial (baseline, 12, 24 and 48 weeks/end of trial). The samples were shipped on dry ice and stored in a category 2 laboratory equipped to handle and store infectious samples.

Laboratory measurements

The objective measure of efficacy of trial treatment on insulin resistance was provided by a comparison of HOMA-IR values, a validated marker of insulin resistance, for the baseline and weeks 12, 24 and 48. Two other surrogate measures of insulin sensitivity, QUICKI and revised QUICKI using serum levels of non-esterified fatty acids, were also assessed.

Other assessments carried out were plasma lipid profile (cholesterol, triglycerides, high- and low-density lipoprotein cholesterol), plasma biomarkers of metabolic function (adiponectin, leptin, TNF-α, resistin and interleukin 8) and renal markers (ACR, NGAL).

Magnetic resonance imaging substudy

Magnetic resonance imaging of total body adipose content was carried out using T1-weighted MRI scans in 10 overlapping blocks of 1-cm slices with 1-cm gap, in upper and lower halves of the body separately. A validated semiautomatic program was used to segment and analyse the images into total body subcutaneous, total internal, subcutaneous abdominal and intra-abdominal adipose tissue volumes.

Pharmacovigilance

Adverse events/reactions for the TAILoR trial were monitored from the time of consent until 7 days after the patient had taken the final dose of telmisartan.

Statistical considerations

Sample size

The original maximum total sample size of the study was 336 patients. The primary response from each patient was the difference between the HOMA-IR score at 24 weeks and the baseline HOMA-IR score (so that negative values indicate improvement). The design had been constructed under the assumption that for all patients this response is normally distributed with a common standard deviation, σ. The sample size calculation was based on a one-sided type I error of 5% and a power of 90%. To fix a power requirement, effect sizes were specified in terms of the percentage chance of a patient on active treatment achieving a greater reduction in HOMA-IR score than a patient on the control arm; as such, the specification did not require knowledge of the value of the common standard deviation σ. The critical values for recommending that a treatment was taken to further testing at the interim and final analyses (–2.782 and –2.086) had been chosen to guarantee these properties that pertain to the whole two-stage testing procedure. The study was designed to recruit additional patients to ensure that the target number of 24-week responses was achieved in the presence of an anticipated 10% dropout rate (which increased the sample size to 370 patients).

Sample size for the substudy 1 (magnetic resonance imaging/proton magnetic resonance spectroscopy)

A sample size of 10 patients per group was expected to provide sufficient data for a reliable estimate of the within-group variance (sample size was increased to 12 to account for 10% dropout).

Interim analysis and stopping guidelines

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 ($n = 168$, which was half of the planned maximum of 336 patients). 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.

Statistical methods

Primary outcome analysis

In order to satisfy the primary objective, we evaluated three different doses against control in the first stage of the study and conducted an interim analysis that allowed ineffective doses to be eliminated quickly while a dose showing a reduction in HOMA-IR was taken forward. The smallest of these test statistics was to be compared with the interim critical value (–2.782). Observing a test statistic below this value corresponded to a significant improvement in HOMA-IR score for the corresponding dose over control and would have led to this dose being immediately taken forward for further study, and to the trial being stopped. Any dose corresponding to a positive test statistic would have been dropped, and if all doses were dropped the trial would also have been stopped. If some reduction in HOMA-IR over control was detected for at least one of the active doses (i.e. test statistic between 0 and –2.782), then the study continued after the interim analysis. At the final analysis, if the smallest comparative test statistic was below the final critical value (–2.086) then this dose would be recommended for further study. Adjustments were made to allow for any discrepancies between target and actual sample sizes while still preserving the one-sided type I error rate at 0.05.

Secondary outcome analysis

Biomarker analysis

To explore the secondary objective of identifying longitudinal change in the expression of biomarkers in telmisartan-treated arm(s) in comparison with controls, joint models were used to fully exploit the serial nature of these outcomes accounting for informative loss to follow-up and missingness.

Analysis of changes in body fat redistribution and intrahepatic and intramyocellular lipid content

The change in visceral, liver and limb fat in 24 weeks was compared across the three treatment groups and controls using multiple linear regression.

Trial procedures

The trial was managed by the Clinical Trials Research Centre at the University of Liverpool. It was conducted in accordance with the European Clinical Trials Directive (European Commission. *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001*. Brussels: European Commission; 2001), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)'s Good Clinical Practice Guidelines [ICH. *ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6(R1)*. 1996. URL: www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/ Efficacy/E6/E6_R1_Guideline.pdf (accessed 24 September 2018)], the Declaration of Helsinki (World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;**310**:2191–4), the NHS Research governance framework [NHS Health Research Authority. *UK Policy Framework for Health and Social Care Research. Version 3.3.* 2017. URL: www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/ (accessed 24 September 2018)] and the Medicines for Human Use (Clinical Trials) Regulations 2004 [Great Britain. *The Medicines for Human Use (Clinical Trials) Regulations 2004*. London: The Stationery Office; 2004]. Three committees oversaw the conduct of the trial: the Trial Management Group, the Trial Steering Committee and the Independent Data and Safety Monitoring Committee. Patient representatives were identified early in the trial and were involved in the overseeing of the trial. One representative sat on the Trial Steering Committee and one on the Trial Management Group.

Results

Screening and participant flow

In total, 1950 patients were screened at the participating centres over the duration of the trial.

Baseline data

The baseline characteristics were balanced across treatment arms. The study participants were predominantly male.

Primary outcome results

Interim analysis

The *t*-statistic for arms B (20 mg of telmisartan) and C (40 mg of telmisartan) showed a positive value (i.e. ≥ 0) which implied that there was no reduction in the HOMA-IR over control (arm A) and, therefore, these active dose arms were dropped from the second stage. As some improvement over control was detected for arm D (80 mg of telmisartan) (i.e. the *t*-statistic was between 0 and –2.782), this arm was selected to progress into the second stage of the study and the patients were thereafter randomised between arm D and the control group (arm A).

Final analysis

Given that the test statistic was not smaller than the critical value of –2.086 [estimated effect 0.007, standard error (SE) 0.106], it was concluded that there was no significant difference in HOMA-IR between arms D and A.

Secondary outcome results

Alternative indices of insulin resistance (Quantitative Insulin Sensitivity Check and revised Quantitative Insulin Sensitivity Check)

For QUICKI (0.001, SE 0.001) and revised QUICKI (0.002, SE 0.002), the test statistic was not smaller than the critical value (–2.086), suggesting no difference between arms A and D.

Longitudinal analysis of Homeostatic Model Assessment of Insulin Resistance, Quantitative Insulin Sensitivity Check and revised Quantitative Insulin Sensitivity Check

There was no significant difference in HOMA-IR and QUICKI between the treatment and control arms over a period of 48 weeks. However, the treatment effect of arm D compared with arm A for the longitudinal revised QUICKI was marginally significant [0.004, 95% confidence interval (CI) 0.000 to 0.008; $p = 0.05$], suggesting that telmisartan (80 mg) led to a small reduction in insulin resistance over a period of 48 weeks.

Longitudinal analysis of lipid profiles and plasma biomarkers

There were no significant differences between the treatment arm and the control arm with any of the lipid markers over a period of 48 weeks. None of the plasma biomarkers, apart from hs-CRP, showed a significant change (–0.222, 95% CI –0.433 to –0.011; $p = 0.04$) over time between the control and the telmisartan (80-mg) treatment arm.

Substudy 1: magnetic resonance imaging

No statistically significant differences were observed in internal visceral fat or intramyocellular triglyceride content in the soleus and tibialis anterior at 24 weeks between the treatment group (80 mg) and the control group ($p > 0.05$). However, a statistically significant difference in the intrahepatic triglyceride content was observed at 24 weeks between arm D and the control group (arm A) (1.714, 95% CI –2.787 to –0.642; $p = 0.005$).

Substudy 2: urine/renal biomarkers

The estimated treatment effects [arm D (80 mg) compared with arm A (control)] on NGAL were not significant in any of the tertile subgroups tested. A telmisartan dose of 80 mg significantly reduced ACR for the subgroup with albumin excretion of > 3 mg/mmol (–0.665, 95% CI –1.31 to –0.019; $p = 0.04$).

Safety data analysis

Diarrhoea, fatigue, dizziness and pruritus were the most common adverse reactions, observed in > 2% of patients. There was no evidence of a difference in the percentage of serious adverse events between the telmisartan-treated arms and the control arm ($p = 0.8$).

Conclusions

Using a novel adaptive design, we demonstrated that there was no significant effect of telmisartan (80 mg) on the primary outcome measure (HOMA-IR) and some secondary outcomes (plasma lipids and adipokines). Telmisartan did lead to favourable changes of the secondary longitudinal outcome measures: revised QUICKI, hs-CRP, hepatic fat accumulation and urinary albumin excretion. Although these changes are biologically plausible and consistent with the literature, whether or not this would translate into improvements in clinical outcomes in patients infected with HIV on cART is unclear. Taken collectively, our findings showed that telmisartan did not reduce insulin resistance in patients infected with HIV on antiretrovirals.

Trial registration

This trial is registered as ISRCTN51069819.

Funding

Chapter 1 Introduction

Background

Combination antiretroviral therapy (cART) is the mainstay of treatment for human immunodeficiency virus (HIV) and has dramatically improved the morbidity and mortality associated with HIV, turning it into a chronic disease. However, cART, together with the virus itself, can lead to various metabolic complications such as obesity,[1] type 2 diabetes mellitus (T2DM) and an increased risk of cardiovascular disease (CVD). These metabolic complications associated with cART are particularly prominent in patients with HIV-associated lipodystrophy (HIVLD) (also called fat redistribution syndrome), a clustering of morphological and metabolic abnormalities comprising peripheral fat loss (lipoatrophy), visceral lipid hypertrophy, insulin resistance and dyslipidaemia.[2] HIVLD is a predictor of metabolic syndrome (MS) and associated CVD risk.[3] However, metabolic complications are also seen in patients infected with HIV without HIVLD. A recent meta-analysis of 65 studies ($n = 55,094$ patients infected with HIV) utilised two of the most widely used MS criteria [Adult Treatment Panel (ATP) III-2004 and ATP III-2005] to calculate the prevalence of MS in HIV-infected people, which was found to be between 16.7% and 18%.[4] The HIV DAD (Data collection on Adverse events of anti-HIV Drugs) cohort, one of the largest HIV clinical cohorts ($n = 33,347$),[5] found the prevalence of MS to increase from 19.4% to 41.6% over a 6-year period;[6] importantly, patients with MS had a fourfold increase in the incidence of T2DM and a two to threefold increased risk of developing CVD. These results have been confirmed by other studies such as the Multicenter AIDS Cohort Study ($n = 1278$),[7] a more recent analysis of the DAD cohort,[8] and national representative surveys in the USA that observed a 3.8% higher T2DM prevalence in HIV-infected adults than in the general population.[9]

Individuals infected with HIV show a higher risk of CVD than that observed in the general population;[10] importantly, cumulative exposure to cART is also associated with an increased risk of CVD in HIV-infected patients. The DAD study reported a linear increase in the incidence of myocardial infarction with long-term cART exposure, with both protease inhibitors[11] and nucleoside reverse transcriptase inhibitors (NRTIs).[12] A recent longitudinal cohort study[13] of HIV-infected US veterans selected from the Veterans Health Administration Clinical Case Registry ($n = 24,510$; 164,059 person-years) observed a modestly increased risk of CVD with both individual antiretroviral (ARV) drugs and ARV drug combinations. Long-term use of cART also results in intima–media thickness and an increase in the prevalence of carotid lesions, making it a risk factor for subclinical atherosclerosis.[14] It is therefore clear that cART-treated HIV-infected patients are at increased risk of cardiometabolic problems.

Insulin resistance, a key feature of HIVLD and MS, has been described as central to cardiometabolic disease and is considered to be an important link between features of MS, obesity, dyslipidaemia, T2DM and CVD.[15] In vitro studies[16] and single-drug studies in healthy individuals[17] and HIV-infected patients[18,19] have shown that protease inhibitors and NRTIs cause insulin resistance. The prevalence of insulin resistance in cART-treated HIV-infected patients ranges from 21% to 37%,[20,21] indicating a significant role for cART in its development. In the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study[21] ($n = 926$), a cross-sectional analysis showed the prevalence of insulin resistance to be 37%. Insulin resistance very much remains an important problem even with some of the newer ARVs; HIV patients ($n = 328$) randomised to tenofovir disoproxil fumarate/lamivudine (TDF/3TC) with either boosted atazanavir or boosted darunavir or raltegravir showed a 1.9-fold increase in homeostatic model assessment of insulin resistance (HOMA-IR) within 4 weeks with no change thereafter over a period of 96 weeks.[22] Several mechanisms have been suggested to be responsible for cART-induced insulin resistance, including cART-induced inhibition of adipocyte differentiation,[23] increased secretion of adipokines such as interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α)[24] and impairment of the insulin signalling pathway.[16]

Clinical intervention to arrest or reverse cART-associated insulin resistance has been suggested as a strategy to reduce the incidence of T2DM and CVD in HIV-infected patients. Insulin sensitisers such as thiazolidinediones and metformin have been trialled, but results from randomised clinical trials in HIV-infected patients have been mixed.[25,26] Moreover, the associated adverse effects may limit their use in HIV-infected patients.[27,28] Statins have been suggested as a potential strategy to reduce cardiometabolic events in patients infected with HIV;[29] however, a recently concluded randomised, double-blinded, placebo-controlled trial in HIV-infected individuals [the SATURN-HIV (Stopping Atherosclerosis and Treating Unhealthy bone with Rosuvastatin in HIV) study][30] observed significant worsening of insulin resistance with 10 mg of rosuvastatin. Therefore, there is a need for novel clinical interventions with proven safety profiles that can reduce cART-induced insulin resistance in individuals infected with HIV.

Some angiotensin receptor blockers (ARBs) have a beneficial effect on insulin resistance and T2DM, owing to their partial agonistic activation of peroxisome proliferator-activated receptor (PPAR)-γ, an important regulator of adipocyte function. Telmisartan shows maximal potency on PPAR-γ when compared with other ARBs and has been reported to reduce insulin resistance in several in vitro,[31,32] animal[33,34] and clinical studies.[35–38] Prospective randomised clinical trials in patients with diabetes mellitus and those with MS have shown that telmisartan significantly reduces insulin resistance: (1) in 188 T2DM patients with MS, telmisartan significantly reduced HOMA-IR by 17% after 6 months' treatment and by 29% after 12 months;[35] and (2) in a comparison with other ARBs in non-diabetic patients ($n = 151$), telmisartan reduced HOMA-IR by 29% after 6 months' treatment.[38] A meta-analysis of randomised controlled trials (RCTs) where telmisartan was compared against other antihypertensive drugs (33 RCTs; 2033 patients) found telmisartan to significantly reduce insulin resistance, with statistically significant reductions in insulin levels and HOMA-IR values.[39] Telmisartan also has wide-ranging beneficial effects on various components of MS; a limited meta-analysis of 10 RCTs[40] (546 patients with MS) observed significant reductions in fasting glucose, insulin, glycosylated haemoglobin and homeostasis model assessment index and a significant increase in per cent changes of adiponectin. Telmisartan not only improved adiponectin levels,[41] an important metabolic marker of insulin resistance and atherosclerotic disease, but also improved lipid control in these patients.[42] It also had favourable effects on fasting serum insulin and high-sensitivity C-reactive protein (hs-CRP; a marker of CVD).[35,43] Telmisartan has also been shown to reduce visceral, but not subcutaneous, fat accumulation, in patients with MS.[44,45] Telmisartan reduced cardiovascular events in a broad group of at-risk patients; one of the largest ARB outcome trials [ONTARGET (The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial); 120,000 patient-years of follow-up][46] established telmisartan to confer similar cardiovascular protection as ramipril but was better tolerated. Importantly, the beneficial effects of telmisartan on insulin sensitivity have been observed at doses lower than those used for hypertension; 20 mg/day of telmisartan significantly reduced HOMA-IR after 20 months' treatment in patients with non-alcoholic steatohepatitis.[36] In addition to its cardiometabolic beneficial effects, telmisartan also shows renoprotective effects;[47] it has been shown to significantly reduce microalbuminuria in HIV-infected patients[48] and may therefore have a positive impact on parameters of renal injury observed in cART-treated HIV-infected patients.

Rationale for the study

There is already strong evidence for the beneficial effects of telmisartan on insulin resistance and other markers of glycaemic control and cardiovascular health in non-HIV populations. This study, and others, has shown that antiretroviral drugs inhibit adipocyte differentiation,[23,24] reduce adiponectin secretion,[23,49] increase the secretion of detrimental cytokines, IL-6 and TNF-α,[23,24] and impair GLUT-4 expression,[50] all of which are suggested to contribute to the development of insulin resistance. This study has also shown that telmisartan partially reverses the antiadipogenic effects of antiretrovirals in vitro.[51] Telmisartan partially reversed the antiretroviral drug-induced inhibition of adipocyte lipid accumulation and downregulation of adiponectin and lipin-1. The beneficial effect of telmisartan on adipocyte function in the presence of antiretrovirals has also been shown by Boccara *et al.*[52] However, the clinical efficacy of telmisartan to reduce insulin resistance in cART-treated HIV-infected patients has not been assessed; this study was designed to address this.

This in vitro study observed a non-monotone relationship of telmisartan on adiponectin and lipin 1 secretion. A study in non-alcoholic steatohepatitis patients also observed that telmisartan improves insulin sensitivity at doses lower than those used for hypertension.[36] This indicates the need to carefully assess the dose–response relationship of telmisartan in vivo.

Chapter 2 Research objectives

Primary objective

To determine the effect of telmisartan on insulin resistance in individuals infected with HIV on cART using HOMA-IR as a measurable, validated surrogate marker of insulin resistance.

Secondary objectives

- To define the optimal dose of telmisartan that can significantly reduce insulin resistance; this dose will then be taken forward into Phase III studies in the future.
- To measure HOMA-IR values at the baseline (T0) and at 12, 24 and 48 weeks to provide data on time to, and sustainability of, reduction in HOMA-IR.
- To utilise alternative indices of insulin resistance such as the Quantitative Insulin Sensitivity Check Index (QUICKI) and revised QUICKI to determine the effect of telmisartan on insulin resistance.
- To mechanistically evaluate whether or not telmisartan favourably modulates the plasma concentrations of both beneficial (adiponectin) and adverse (leptin, resistin, TNF-α, hs-CRP) biomarkers, which may help in further stratifying telmisartan therapy in the future.
- To determine whether or not telmisartan improves general lipid homeostasis and reduces visceral fat accumulation in individuals infected with HIV on cART over a 24-week period.
- To determine, in a substudy, whether or not proton magnetic resonance spectroscopy (^{1}H-MRS)-assessed intrahepatic and intramyocellular triglyceride content, markers of hepatic steatosis and insulin resistance, respectively, are reduced by telmisartan therapy. This will provide us with mechanistic insights into the ability of telmisartan to beneficially affect fat redistribution, hepatic steatosis and insulin resistance.
- To determine whether or not telmisartan has an effect on urinary biomarkers [albumin-to-creatinine ratio (ACR), neutrophil gelatinase-associated lipocalin (NGAL)] of renal injury in individuals infected with HIV on cART.
- To evaluate the tolerability of telmisartan in this patient group.

Chapter 3 Methods

Trial design

TAILoR was a multicentre, randomised open-labelled study with an adaptive design (*Figure 1*). We chose an adaptive design for the first stage of the study because our in vitro studies had shown a non-monotone relationship between telmisartan and various metabolic biomarkers. Furthermore, while there is a clear dose–response relationship with telmisartan in the treatment of hypertension, it is important not to assume that a similar relationship would exist in a repurposed indication. The adaptive trial design was thus designed to carefully assess the dose–response relationship of telmisartan on metabolic parameters, which was the main objective of this study.

The adaptive design consisted of two stages. In stage 1, eligible patients were randomised on a 1 : 1 : 1 : 1 basis to either no treatment or a 20-, 40- or 80-mg dose of telmisartan once daily. The duration of study treatment was a maximum of 48 weeks, with titration visits (if applicable) at 2 and/or 4 weeks and follow-up visits at 12, 24 and 48 weeks.

Magnetic resonance imaging: substudy 1
A subset of patients from Royal Liverpool and Broadgreen University Hospitals NHS Trust (RLBUHT) and the Manchester Centre for Sexual Health were asked to participate in the magnetic resonance imaging (MRI) substudy. It was necessary that these patients were also participating in the main study. The duration of the substudy was 24 weeks, and visits took place at both baseline and 24 weeks.
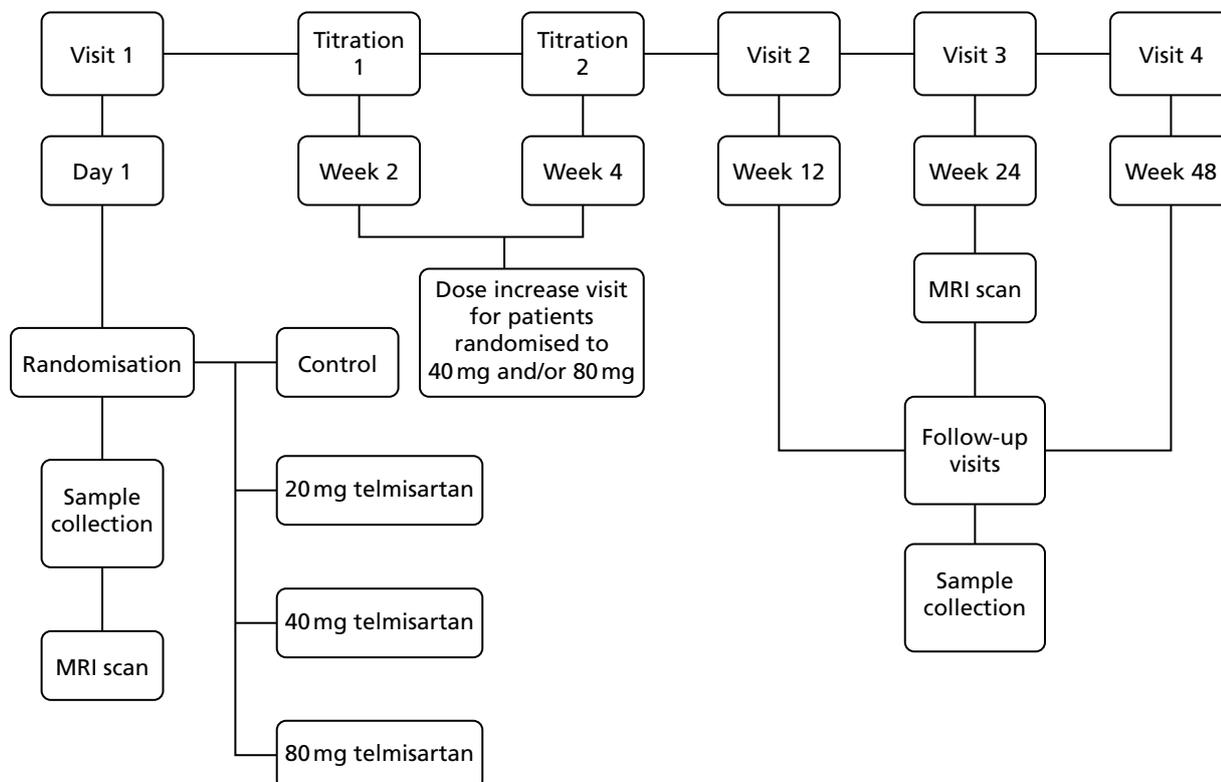
FIGURE 1 Summary of the design for stage 1 of the trial. MRI, magnetic resonance imaging.

Interim analysis

An interim analysis was performed when half of the planned maximum number of patients had been followed up for at least 24 weeks (*Figure 2*). As per the adaptive design, if one active dose group was substantially more effective than control then the study would have been stopped and the corresponding dose would be taken directly into Phase III. Any active dose groups that showed insufficient promise at the interim analysis would be dropped and the study would continue with the remaining doses and control. If no dose showed sufficient promise at the interim analysis, the study would have been stopped. If some improvement over control was detected for at least one of the doses at interim analysis, those dose(s) would be followed up along with the control for a further 24 weeks (total duration of 48 weeks).

Participants

TAILoR participants were adults with documented HIV infection, who had been receiving a stable cART for at least 6 months prior to randomisation.

Inclusion criteria

- Adult (aged ≥ 18 years) HIV-positive individuals receiving antiretroviral therapy containing:

  ○ a boosted protease inhibitor (lopinavir/ritonavir, atazanavir/ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir, saquinavir/ritonavir)
  ○ and/or efavirenz, rilpivirine, or etravirine for at least 6 months.

- Ability to give informed consent.
- Willingness to comply with all study requirements.
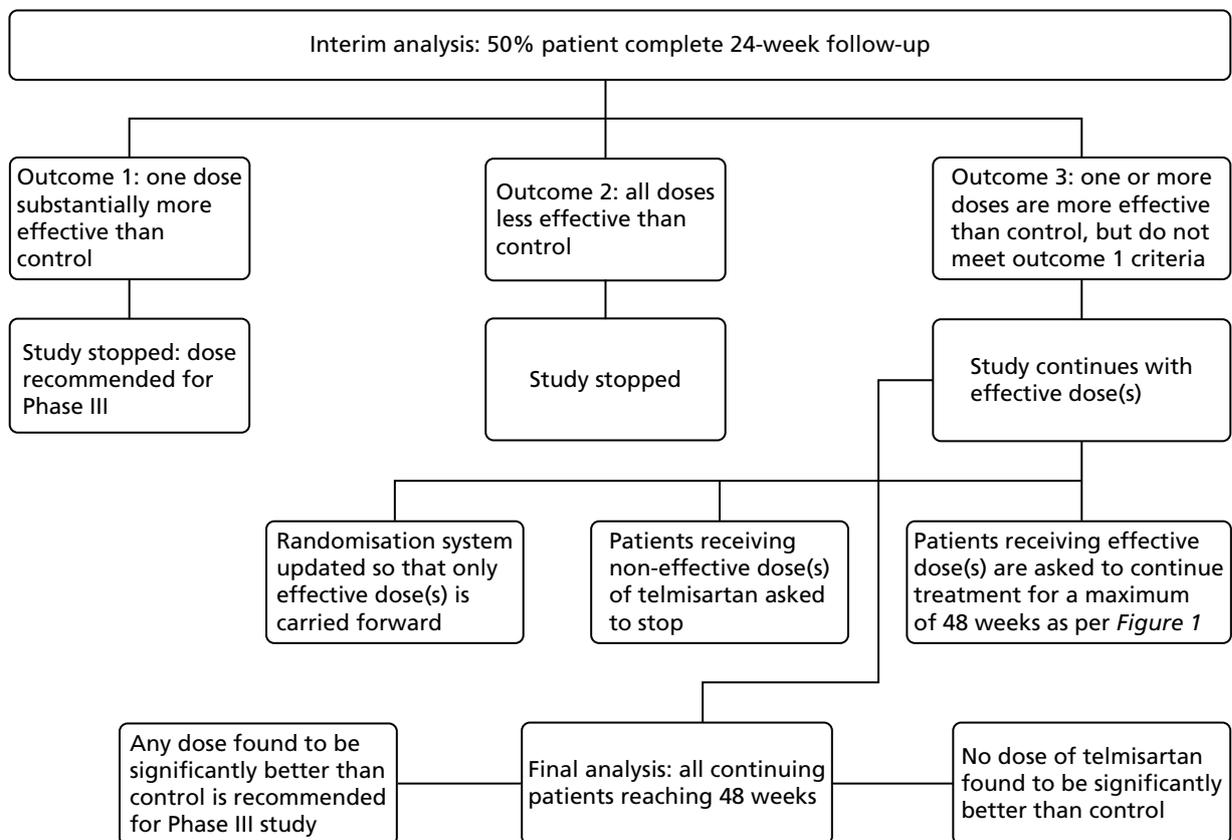
FIGURE 2 Schematic of stage 2 of the adaptive design following interim analysis.

In relation to the antiretroviral therapy, the backbone was based on nucleotide reverse transcriptase inhibitors, raltegravir or maraviroc. Patients on protease inhibitor monotherapy were also included if they met other criteria. However, a decision was made not to include (1) patients on nevirapine or dolutegravir regimens, without concomitant boosted protease inhibitors, (2) patients on elvitegravir which is usually administered in combination with cobicistat [as Stribild® (Gilead Sciences Inc., CA, USA)] and (3) patients on unboosted atazanavir.

Exclusion criteria

The exclusion criteria were as follows:

- Pre-existing diagnosis of type 1 or 2 diabetes mellitus [i.e. fasting glucose level of > 7.2 mmol/l or glycated haemoglobin (HbA_{1c}) level of $\geq 6.5\%$ (48 mmol/mol) or an abnormal oral glucose tolerance test (OGTT) or random plasma glucose concentration of ≥ 11 mmol/l].
- Patients known to have consistently low blood pressure (pre-existing hypotension: a reading below a threshold of 100/60 mmHg on three separate occasions).
- Patients with renal disease [i.e. an estimated glomerular filtration rate (eGFR) of < 60 ml/minute/1.73 m^2 in the 6 months preceding randomisation].
- Patients with known untreated renal artery stenosis.
- Patients with cholestasis, biliary obstructive disorders or severe hepatic impairment.
- Patients with evidence of an active chronic hepatitis C infection (a previously cleared infection is not an exclusion).
- Patients who were on/have been on hormone therapy (e.g. growth hormone), anabolics (e.g. testosterone) or insulin sensitisers (e.g. metformin) within 6 months preceding randomisation. Patients who were on hormonal contraception were eligible.
- Patients who were already on/had been on other ARBs, angiotensin-converting enzyme (ACE) inhibitors or direct renin inhibitors (e.g. aliskiren) within 4 weeks preceding randomisation.
- Those with suspected poor compliance.
- Pregnant or lactating women.
- Women of childbearing age, unless using reliable contraception (e.g. coil, barrier method, hormonal contraceptive that does not interact with their antiretroviral therapy).
- Co-enrolment in other drug trials.
- Patients who had participated in a trial of an investigational medicinal product (IMP) likely to influence insulin sensitivity, plasma insulin, glucose levels or plasma lipid levels within 6 months preceding randomisation.
- For the subcohort of patients undergoing MRI/magnetic resonance scanning (MRS), normal MRI exclusion criteria applied.

Study settings

The trial was conducted in 19 sexual health clinics and/or HIV treatment centres throughout the UK (see *Appendix 1*) and patients were recruited from March 2013 until July 2015.

Centre/clinician inclusion criteria

Each participating centre and principal investigator (PI) was identified on the basis of being a specialist HIV treatment centre; having at least one lead clinician with a specific interest in, and responsibility for supervision and management of, patients with HIV; enthusiasm to participate in the study; sufficient time, staff and adequate facilities available for the trial; identifying that they would be able to recruit the required number of patients; and acknowledging and agreeing to conform to the administrative, ethical and study specific requirements.

Any centre not meeting these criteria was deemed ineligible to participate in the trial.

Interventions

All patients either received no treatment or were treated with telmisartan as per their randomised allocation. Telmisartan was dispensed as either a 20-, 40- or 80-mg dose, depending on treatment allocation. All strengths of telmisartan were to be taken once daily with or without food. The duration of the treatment was a maximum of 48 weeks. The patients were asked to complete treatment diaries, detailing compliance, throughout the duration of treatment.

Investigational medicinal product

The IMP for the TAILoR trial was telmisartan. Telmisartan is an antihypertensive agent used to lower blood pressure and to reduce cardiovascular events in at-risk patients. For this trial, it was used outside the licensed indications of its different manufacturers. Telmisartan is available in doses of 20, 40 and 80 mg. It is produced by a range of manufacturers; the generic formulations were considered to be bioequivalent to the brand leader Micardis® (Boehringer Ingelheim Ltd, Ingelheim am Rhein, Germany). *Appendix 2* details the brands of telmisartan approved for use in the trial.

The IMP was sourced through standard NHS procurement processes at each site and was dispensed to trial participants on receipt of a valid trial specific prescription. Study drug accountability was documented by the pharmacy teams at each site and was monitored by the trial co-ordinator/Clinical Trials Research Centre (CTRC).

Outcomes

Primary outcome

Reduction in insulin resistance (as measured by HOMA-IR) in telmisartan-treated arm(s) after 24 weeks of treatment in comparison with control. This was a pure efficacy outcome.

Secondary outcomes

1. Change in lipid profile at 12, 24 and 48 weeks [increase in high-density lipoprotein cholesterol (HDL-C), reduction in total cholesterol, triglycerides and low-density lipoprotein cholesterol (LDL-C)] between telmisartan-treated arm(s) and the control arm.
2. Change in body fat redistribution as measured by MRI/MRS at 24 weeks between telmisartan-treated arm(s) and control arm (reduction in visceral fat, change in intrahepatic fat, change in lower leg muscle fat).
3. Change in plasma concentrations of biomarkers [adiponectin, leptin, interleukin 8 (IL-8), TNF-α, resistin and hs-CRP] at 12, 24 and 48 weeks between telmisartan-treated arm(s) and the control arm.
4. Change in insulin resistance, measured longitudinally, in telmisartan-treated arm(s) in comparison with the control arm.
5. Difference in expected and unexpected serious adverse events between different telmisartan-treated dose arm(s) and the control arm.

Two additional secondary outcome measures were added on the advice of the Independent Data Safety and Monitoring Committee (IDSMC) and the PIs, which were added after recruitment began:

6. Reduction in insulin resistance (as measured by QUICKI and revised QUICKI) in telmisartan-treated arm(s) after 24 weeks of treatment in comparison with control.
7. Change in urinary biomarker levels (ACR; NGAL) at 12, 24 and 48 weeks between telmisartan-treated arm(s) and the control arm.

Data collection

Paper case report form

A paper case report form (CRF) was used to collect patient data at each study visit. Paper CRFs were designed especially for the study in line with the trial protocol.

Database

On receipt of paper CRFs at the CTRC, data were entered to a good clinical practice- (GCP) compliant database (MACRO 3, Elsevier, Amsterdam, the Netherlands) by trial staff at the CTRC. The configuration of the database was specific for the TAILoR trial, and it had built-in validations on certain aspects of the trial data. A full audit trail was maintained.

Timescale of evaluations

The first visit occurred on the same day as randomisation; subsequent visits took place at 12, 24 and 48 weeks. Patients randomised to higher doses of telmisartan (40 and 80 mg) also attended for dose titration visits (see *Figure 1* and *Table 1*).

Schedule of investigations

A summary of tests and investigations undertaken in each patient is provided in *Table 1*.

Sample collection

Sample collection, processing and storage at participating sites

Biological samples (blood and urine) were collected at four time points during the trial at individual clinical sites participating in the study. For each patient, samples were collected at baseline, 12, 24 and 48 weeks/end of trial visits. At each time point, three fasting blood samples and one urine sample were collected from each participant. The blood samples were collected in:

1. 9-ml tripotassium ethylenediaminetetraacetic acid (K3EDTA) VACUETTE® blood tubes (Grenier Bio-One International Ltd, Gloucestershire, UK) (for DNA extraction)
2. 9-ml Z Serum Clot Activator VACUETTE tubes (for serum separation)
3. 4-ml FX Sodium Fluoride/Potassium Oxalate VACUETTE tubes (for glucose estimation).

The K3EDTA tubes were stored at –20 °C; plasma and serum were extracted locally at each site by the research nurses and aliquoted into two 1.8-ml cryovial tubes (STARLAB, Milton Keynes, UK) and were immediately stored at a minimum temperature of –20 °C. The sample collection, sample processing and storage were all performed in accordance with standardised standard operating procedures (SOPs) supplied by the main study team at Liverpool (all laboratory SOPs can be made available on request).

Sample shipment

Packaging and shipping of all samples collected from the TAILoR study followed the Packaging Provisions for Biological Substances, Category B, UN 3373 and UN1845 (dry ice) guidelines.[53] A SOP was followed by all sites for packaging of samples and shipment of TAILoR samples. The samples were shipped on dry ice in sealed styrofoam™ (The Dow Chemical Company, Midland, MI, USA) boxes by a clinical trial specialist courier with a delivery time of within 24 hours.

Sample collection, processing and storage at the co-ordinating centre (University of Liverpool)

All samples were stored in the Bioanalytical Facility (BAF), Royal Liverpool Hospital, which is a category 2 laboratory equipped to handle and store infectious samples. All samples were stored at a minimum temperature of –20 °C until further processing. Sample transport log sheets were completed, dated and signed by the Wolfson Centre for Personalised Medicine, University of Liverpool, (WCPM) staff and countersigned by the BAF analyst.

TABLE 1 Schedule of trial procedures

Time	Pre T0 — At each recruitment site	T0 — Randomisation/baseline[a]	T + 2 weeks — Dose titration for 40- or 80-mg arms (dose given: 40 mg)	T + 4 weeks — Dose titration for 80-mg arm (dose given: 80 mg)	T + 12 weeks — Follow-up	T + 24 weeks — Follow-up	T + 48 weeks — End of treatment	Premature withdrawal of consent
Database search to identify potential participants or clinic list review	✓							
Information sheet provided to patient	✓							
Signed informed consent		✓						
Assessment of eligibility criteria by a medically qualified person		✓						
Review of medical history (including collection of most recent blood test results for urea and electrolytes, eGFR, liver function, diabetes mellitus screening, etc.		✓[b]					✓	✓
Review of concomitant medications		✓	✓	✓	✓	✓	✓	
Urine pregnancy test		✓			✓	✓		
Randomisation		✓						
Study intervention		✓	✓	✓	✓	✓		
Compliance with study intervention – patient diaries and pill counting			✓	✓	✓	✓	✓	
Physical examination – complete		✓						
Physical examination – symptom directed			✓	✓	✓	✓	✓	✓
Height		✓				✓	✓	✓
Weight		✓			✓	✓	✓	✓

Time	Time point							
	Pre T0	T0	T + 2 weeks	T + 4 weeks	T + 12 weeks	T + 24 weeks	T + 48 weeks	
	At each recruitment site	Randomisation/ baseline[a]	Dose titration for 40- or 80-mg arms (dose given: 40 mg)	Dose titration for 80-mg arm (dose given: 80 mg)	Follow-up	Follow-up	End of treatment	Premature withdrawal of consent
Waist/thigh circumference		✓			✓	✓	✓	✓
Heart rate, blood pressure		✓	✓	✓	✓	✓	✓	✓
Collection of three fasting blood samples for bioanalysis		✓	✓	✓	✓	✓	✓	✓
Collection of urine sample		✓	✓	✓	✓	✓	✓	✓
Assessment of AEs		✓	✓	✓	✓	✓	✓	✓
Consent for substudy		✓	✓	✓	✓	✓	✓	
MRI/MRS scan for substudy		✓	✓	✓	✓	✓	✓	

AE, adverse event.
a   Baseline assessment and randomisation visit should be within 30 days of patient giving consent.
b   Liver function and diabetes mellitus screening result to be collected only at baseline.

The whole-blood samples collected in K3EDTA vacuettes were initially subjected to viral inactivation by incubating the samples at 58 °C in a water bath for 40 minutes. The inactivated samples were transferred to the WCPM for DNA extraction using a magnetic bead-based method on a chemagen chemagic MSM I platform (Perkin Elmer, Waltham, MA, USA). Briefly, a 4.5-ml whole-blood sample was added into 50-ml tubes containing lysis buffer and protease enzyme for cell lysis. Once lysis was completed, binding buffer and magnetic beads were added to elute the extracted DNA. The DNA was dissolved in Tris buffer and its quality and quantity were ascertained using a NanoDrop™ spectrophotometer (ThermoFisher Scientific Ltd, Paisley, UK). The DNA samples were stored at –20 °C for future use. The urine samples were aliquoted into cryovials and stored at –20 °C.

Investigations

A detailed laboratory analysis plan is provided in *Appendix 3*. All laboratory investigations specified below were conducted using SOPs, which can be made available on request.

Assessment of efficacy

Assessment of Homeostatic Model Assessment of Insulin Resistance
The objective measure of efficacy of trial treatment on insulin resistance was provided by a comparison of HOMA-IR values at baseline and at weeks 12, 24 and 48. HOMA-IR is a known surrogate marker for measuring insulin resistance.

For HOMA-IR, serum and plasma aliquots were sent to the Liverpool Clinical Laboratories (LCL), Royal Liverpool Hospital, for the estimation of insulin and glucose levels respectively. LCL is a Clinical Pathology Accredited (CPA) clinical laboratory that participates in the external quality assessment for the analysis of a number of analytes [UK National External Quality Assessment Service (NEQAS)].

Estimation of insulin
Serum insulin was measured using an electrochemiluminescence immunoassay on the Roche Modular e 602 analyzer (Roche Diagnostics Ltd, West Sussex, UK). The assay has a dynamic range of 0.2–1000 mU/l, with a lower detection limit of 3 mU/l. It has an intra-assay precision of between 1.5% and 2.0% for concentrations between 6.36 and 88.3 mU/l. The assay is unaffected by icterus, lipaemia, bilirubinaemia or drugs. However, haemolysis is known to interfere and no results were accepted for samples with a haem index exceeding 50. Internal quality control (IQC) assessments were conducted for the insulin assay and included analysis of three separate IQCs (Technopath Multichem IA Levels 1, 2 and 3, Technopath Clinical Diagnostics, Tipperary, Ireland) at the start of the day once the daily maintenance and any calibrations had been performed. The results for the IQCs had to fall within 2 standard deviations (SD) of the mean to be considered as acceptable performance to allow acceptance of the results. For External Quality Assessment (EQA), LCL received three samples for analysis every 6 weeks and these were processed as per the SOP for the Analysis of External Assessment Samples.

Estimation of glucose
Fluoride EDTA plasma was used for the estimation of glucose using a Roche cobas® c systems assay on a Roche cobas analyzer (Roche Diagnostics Ltd, West Sussex, UK). The assay has a range of 0.11–41.6 mmol/l in serum, with a lower detection limit of 0.11 mmol/l (2 mg/dl). The assay is unaffected by interference from lipaemia, haemolysis or bilirubinaemia. Two IQCs were used and the results for the IQCs had to fall within 2 SD of the mean to be considered as acceptable performance for the results to be included. LCL also takes part in EQA for glucose analysis on a fortnightly basis.

Calculation of Homeostatic Model Assessment of Insulin Resistance

Homeostatic model assessment of insulin resistance was calculated using the equation:

$$\text{Fasting plasma insulin (mU/l)} \times \text{fasting plasma glucose (mmol/l)} \div 22.5. \tag{1}$$

Other assessments

Quantitative insulin sensitivity check index

Fasting glucose and insulin levels were measured as stated in the section above. QUICKI was calculated using the equation:

$$1 \div [\log(\text{fasting insulin in } \mu\text{U/ml}) + \log(\text{fasting glucose in mg/dl})]. \tag{2}$$

Revised quantitative insulin sensitivity check index

Revised QUICKI was calculated using the equation:

$$1 \div [\text{log-fasting insulin } (\mu\text{U/ml}) + \text{log-fasting glucose (mg/dl)}$$
$$+ \text{log-fasting non-esterified fatty acids (mmol/l)}]. \tag{3}$$

Non-esterified fatty acids (NEFAs) were measured in serum samples at time points T0, T + 12, T + 24, and T + 48. Serum NEFA analysis was performed in the GCP Laboratory, University of Liverpool using a colorimetric assay on a RX Daytona analyser (Randox Laboratories Limited, UK). The serum was subjected to viral inactivation by treating with 1% Triton™ X-100 solution (Sigma-Aldrich Company Ltd, Dorset, UK) for 60 minutes at room temperature and then analysed. IQC assessments were conducted for the NEFA assay and included analysis of two separate IQCs (Multisera QC Levels 2 and 3, Randox Laboratories Ltd, County Antrim, UK) at the start of the day once the daily maintenance and any calibrations had been performed. The results for the IQCs had to fall within ± 2 standard deviations of the mean to be considered as acceptable performance to allow the results to be included in the analysis. All samples were analysed in triplicate. Results for any samples with a value outside the detection range or that failed in more than one replicate were not accepted.

Assessment of lipid profile

Fasting serum samples obtained at T0 and at the 12-, 24- and 48-week visits were analysed by the LCL for total cholesterol, triglycerides, LDL-C and HDL-C levels on the Roche modular e 602 analyzer.

The Roche Modular e 602 analyzer utilises an enzymatic colourimetric method for the analysis of total cholesterol. The assay has a measuring range of 0.1–20.7 mmol/l, with a lower detection limit of 0.1 mmol/l. For triglycerides, measuring range of the assay is 0.1–10.0 mmol/l, with a lower limit of detection (LLOD) at 0.1 mmol/l. For the high-density lipoprotein (HDL) assay, the measuring range is 0.08–3.12 mmol/l, with a lower detection limit of 0.08 mmol/l.

Assessment of high-sensitivity C-reactive protein

High-sensitivity C-reactive protein (hs-CRP) in the serum was measured at T0 and at the 12-, 24- and 48-week visits by LCL. The hs-CRP was measured using a particle enhanced immunoturbidimetric assay on a Roche cobas modular analyzer. The assay has a measuring range of 0.15–20.0 mg/l, with a lower detection limit of 0.15 mg/l. The assay is not affected by icterus (up to an I index of 60), haemolysis (up to a H index of 1000) and lipaemia (up to an L index of 600).

Assessment of novel biomarkers of metabolic function

We originally intended to measure the serum concentration of six biomarkers (adiponectin, leptin, IL-6, TNF-α, resistin and IL-8) at T0 and at the 12-, 24- and 48-week visits. However, following validation, the IL-6 assay was found not to meet the desired criteria and, hence, the marker was removed from the protocol (details given in the sample analysis plan in *Appendix 3*). The biomarker analyses were performed in the WCPM utilising human singleplex and/or multiplex kits using electrochemiluminescence-based immunoassays (Meso Scale Discovery, Rockville, MD, USA) as per the manufacturer's protocol on a Meso Scale Discovery Sector Imager 2400A (Meso Scale Discovery, Rockville, MD, USA). Meso Scale Discovery assays use electrochemiluminescent labels called SULFO-TAG that are conjugated to detection antibodies and allow for ultrasensitive detection. The detection antibody for a specific protein target is coated on one electrode (or 'spot') per well. Once the biofluids are added to the detection wells, electricity is applied to the plate electrodes by a Meso Scale Discovery Sector Imager, leading to light emission by SULFO-TAG labels. Light intensity is then measured to quantify analytes in the sample. Investigators performed all analyte measurements blindly and were unaware of the patients' clinical characteristics.

Assay validation

All assays obtained from the manufacturer were initially subjected to one or more validation runs in order to make sure that the assay was working to acceptable standards. Assays for each analyte were tested for a number of parameters such as sensitivity, reproducibility, linearity and analyte recovery. All analytes were quantified using an eight-point logarithmic standard curve that included a zero calibrator and each standard was run in triplicate. The detection range and the LLOD were assessed for each analyte. All validation experiments included 10 healthy control samples and 10 study specific samples (five each from two different time points). All samples were run in duplicate to assess the sensitivity of the assay. Only those values that were within the detection range (above the LLOD) were considered acceptable. For assessing reproducibility, six replicates of a pooled healthy volunteer sample (pooled serum from 10 healthy volunteers) were run on the same detection plate and the values were considered acceptable if the coefficient of variation was < 10%. Linearity was assessed by using at least two serial dilutions of the same sample. Selected samples were spiked with known concentrations of the standard analyte and percentage recovery was assessed; only those with a recovery of > 80% were considered acceptable. A universal plate plan was used for validation of all biomarkers. The dilutions (linearity) and spike concentrations (recovery) used for individual biomarkers are given in *Table 2*.

Adiponectin

Adiponectin was analysed using a single-spot human adiponectin sandwich immunoassay kit (K151-BXC3; Meso Scale Discovery, Rockville, MD, USA) using a seven-point standard curve run with fivefold serial dilution and a zero calibrator. The calibrator for the human adiponectin assay was supplied at 100 µg/ml. Briefly, the serum samples were diluted 1000-fold (1 : 1000) using Diluent 100 (Meso Scale Discovery, Rockville, MD, USA) and were added onto wells coated with the SULFO-TAG-labelled antibody within the detection plates and incubated. The labelled detection antibody bound to adiponectin was then detected using electrochemiluminescence. The LLOD for adiponectin was 0.005 ng/ml.

TABLE 2 Dilutions (linearity) and spike concentrations (recovery) used for individual biomarkers

Biomarker	Dilutions used (linearity)	Spike concentrations (recovery)
Adiponectin	1 : 500, 1 : 1000, 1 : 2000, 1 : 4000	20–50 µg/ml
Leptin	Undiluted sample, 1 : 2, 1 : 4	5.56–50 µg/ml
IL-6	1 : 2, 1 : 4, 1 : 8	1.56–25 pg/ml
TNF-α	1 : 2, 1 : 4, 1 : 8	0.99–15.885 pg/ml
Resistin	1 : 20, 1 : 40, 1 : 80, 1 : 160	7.81–125 pg/ml
IL-8	–	1.56–25 pg/ml

Leptin

Leptin was analysed using a single-spot human leptin sandwich immunoassay kit (K151-BYC3; Meso Scale Discovery, Rockville, MD, USA) using a seven-point standard curve run with threefold serial dilution and a zero calibrator. The calibrator for the human leptin assay was supplied at 10 μg/ml. Briefly, undiluted serum samples were added to wells coated with the SULFO-TAG-labelled antibody within the detection plates and incubated. The labelled detection antibody bound to leptin was then detected using electrochemiluminescence. The LLOD for leptin was 43 pg/ml.

Resistin

Resistin was analysed using a single-spot human resistin sandwich immunoassay kit (K151FND4; Meso Scale Discovery, Rockville, MD, USA) using a seven-point standard curve run with fourfold serial dilution and a zero calibrator. The calibrator for the human resistin assay was supplied at 50,000 pg/ml. Briefly, the serum samples were diluted 100-fold (1 : 100) using Diluent 2 (Meso Scale Discovery, Rockville, MD, USA) and were added onto wells coated with the SULFO-TAG-labelled antibody within the detection plates and incubated. The labelled antibody bound to resistin was then detected using electrochemiluminescence. The LLOD for resistin was 0.2 pg/ml.

Proinflammatory markers (tumour necrosis factor alpha and interleukin 8)

The proinflammatory markers TNF-α and IL-8 were analysed using a multispot V-PLEX human Proinflammatory Panel II (4-Plex) sandwich immunoassay (K15053D-1; Meso Scale Discovery, Rockville, MD, USA). A seven-point standard curve run with threefold serial dilution and a zero calibrator was used for the assay. The calibrator for the V-PLEX Human Proinflammatory Panel II was supplied at 500 pg/ml (IL-8) and 317 pg/ml (TNF-α), respectively. Briefly, the serum samples were diluted twofold (1 : 2) using Diluent 2 and were added onto wells coated with the SULFO-TAG-labelled antibody within the detection plates and incubated. The labelled antibody bound to individual proinflammatory analytes was then detected using electrochemiluminescence. The LLOD range for IL-8 was 0.01–0.11 pg/ml and for TNF-α was 0.01–0.13 pg/ml.

Assessment of renal biomarkers

Urine ACR and urinary NGAL levels were measured at T0 and at the 12-, 24- and 48-week visits. ACR was analysed by LCL, Royal Liverpool Hospital, and NGAL analysis was performed in the WCPM, utilising human singleplex kits (Meso Scale Discovery, Rockville, MD, USA) as specified in *Assessment of novel biomarkers of metabolic function*.

Urine albumin

Urine albumin was estimated using an immunoturbidimetric assay on a Roche cobas c systems analyzer. A six-point calibration curve was run using water and a Roche CFAS PUC calibrator (Roche Diagnostics Ltd, West Sussex, UK). IQC assessments were conducted for urine albumin using two separate IQCs (MAS UriChemTrak Human Level 1 and Level 2, ThermoFisher Scientific Ltd, Paisley, UK) at the start of the day once the daily maintenance and any calibrations had been performed. The results for the IQCs had to fall within 2 SDs of the mean to be considered as acceptable performance to allow the results to be included. LCL also participates in the EQA for urine albumin on a monthly basis. The assay has a range of 3–400 mg/l (for undiluted samples), with a lower detection limit of 3 mg/l. No significant interference is observed with icterus (up to 855 μmol/l of conjugated bilirubin) or haemolysis (haemoglobulin concentration up to 248 μmol/l).

Urine creatinine

Urine creatinine was estimated using a kinetic colorimetric assay based on the Jaffe method[54] on a Roche cobas c analyzer. Calibration was conducted using a two-point calibration curve using deionised water and Roche CFAS reagent (Roche Diagnostics Ltd, West Sussex, UK). Calibration is performed every 4 weeks, if there is reagent lot change or if there is requirement as indicated by the IQCs. IQCs (UrichemTrak 1 and 2) were analysed at the start of the day following any maintenance and daily start up, and approximately every 3 hours throughout the day. The assay has got a range of 375–55,000 μmol/l, with a lower limit of detection of 375 μmol/l. No significant interference is observed with an I index of 10 (bilirubin concentration of 171 μmol/l), H index of 1000 (approximate haemoglobin concentration of 621 μmol/l) or L index of 800.

Urinary neutrophil gelatinase-associated lipocalin

A validation experiment was performed for NGAL to ensure the assay was working to acceptable standards. The assay was tested for several parameters such as sensitivity, reproducibility, linearity and analyte recovery. A seven-point logarithmic standard curve and a zero calibrator was utilised and each standard was run in triplicate. The detection range and the LLOD were assessed for NGAL. The validation experiment included 20 healthy control samples and 10 study-specific samples (five each from two different time points) in the analysis, with all samples being run in duplicate to assess the sensitivity of the assay. Only those values that were within the detection range (above LLOD) were considered to be acceptable. For assessing reproducibility, six replicates of a pooled healthy volunteer sample (pooled urine from 20 healthy volunteers) were run on the same detection plate and the values were considered acceptable if the %CV was < 10%. Linearity was assessed by using at least two serial dilutions of the same sample. Selected samples were spiked with a known concentration of standard analyte and percentage recovery was assessed; only those with a percentage recovery of > 80% were considered acceptable.

Neutrophil gelatinase-associated lipocalin was analysed with a single spot custom human NGAL sandwich immunoassay kit (N45CA-1; Meso Scale Discovery, Rockville, MD, USA) using a seven-point standard curve run and a zero calibrator. The calibrator for the human NGAL assay was supplied at 10,000 pg/ml. Briefly, the urine samples were diluted 250-fold (1 : 250) using Diluent 37 (Meso Scale Discovery, Rockville, MD, USA) and were added onto wells coated with the SULFO-TAG-labelled antibody within the detection plates and incubated. The labelled detection antibody bound to NGAL was then detected using electrochemiluminescence. The LLOD range for NGAL was 0.1–10 pg/ml.

Magnetic resonance imaging substudy

Magnetic resonance scanning was undertaken at the Magnetic Resonance Imaging and Analysis Research Centre, University of Liverpool, on the Siemens 1.5 T Symphony scanner (Siemens, Erlangen, Germany), using well-established methods.[55]

Liver ^{1}H-MRS spectra were acquired with the Siemens body coil (Siemens, Erlangen, Germany), using a point-resolved spectroscopy (PRESS) sequence [repetition time (TR) 1500 milliseconds/echo time (TE) 135 milliseconds] without water saturation, 64 signal averages.[55] Transverse magnetic resonance (MR) images were used to ensure accurate positioning of three $20 \times 20 \times 20$ mm voxels, avoiding blood vessels, the gall bladder and fatty tissue.

Skeletal muscle ^{1}H-MRS spectra were acquired using the Siemens CP extremity coil (Siemens, Erlangen, Germany) using PRESS (TR 1500 milliseconds /TE 135 milliseconds) without water saturation, 64 signal averages.[56] Transverse MR images were used to ensure accurate positioning of a 20- × 20- × 20-mm voxel in each of the soleus and tibialis anterior. Spectra were analysed in the time domain using the AMARES (advanced method for accurate, robust, and efficient spectra) algorithm included in the jMRUI 3.0 software package. Intramyocellular lipid is expressed as methylene relative to creatine signal.[56] Intrahepatic lipid is expressed as methylene relative to unsuppressed water.

Magnetic resonance imaging of total body adipose content was carried out by a method adapted from Thomas *et al.*[55] using T1-weighted MR images (TR 705 milliseconds, TE 12 milliseconds) in 10 overlapping blocks of 1-cm slices with a 1-cm gap, in upper and lower halves of the body separately. A validated semiautomatic program was used to segment and analyse the images into total body subcutaneous, total internal, subcutaneous abdominal and intra-abdominal adipose tissue volumes. This work was outsourced to a commercial analysis service, Vardis Group (London, UK).

The scanner was supported by the manufacturers' top-level service contract, which incorporates specific elements of quality control for MRI.

Pharmacovigilance definitions and procedures

The following were used for the pharmacovigilance procedures in the trial:

Adverse event – any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences that are not necessarily caused by or related to that product.

Adverse reaction (AR) – any untoward and unintended response in a subject to an IMP that is related to any dose administered to that subject.

Unexpected AR – an AR, the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

- the summary of product characteristics for that product (in the case of a product with a marketing authorisation)
- the investigator's brochure relating to the trial in question (in the case of any other IMP product).

A serious adverse event (SAE), serious adverse reaction (SAR) or suspected unexpected serious adverse reaction (SUSAR) is any of the aforementioned that:

- Results in death.
- Is life-threatening (subject at immediate risk of death). Life-threatening in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation. Hospitalisation was defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute a SAE.
- Results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect.
- Other important medical events that may not result in death, be life-threatening or require hospitalisation may be considered a SAE/experience when, based on appropriate medical judgement, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Causality

Unrelated: there is no evidence of any causal relationship, where an alternative cause for the adverse event (AE) is provided.

Unlikely: there is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).

Possibly: there is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).

Probably: there is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Almost certainly: there is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Period of observation

Adverse events/reactions for the TAILoR trial were monitored from the time of consent until 7 days after the patient had taken the final dose of telmisartan (wash-out period of telmisartan) after the patient's participation in the trial was concluded.

Reporting procedures

Adverse reactions and all SAEs (regardless of causality) were reported. The reporting procedures detailed in *Figure 3* and below were followed.

Unrelated, non-serious adverse events

Given the patient group that we were recruiting in this clinical trial, it was assumed that there would be a high number of unrelated, non-serious AEs. It was therefore agreed early in the trial set up by the IDSMC, Trial Management Group (TMG) and Trial Steering Committee (TSC) that these types of AEs would not be reported as part of the trial processes.

Non-serious adverse reactions

All ARs (non-serious events suspected to be related to any dose of telmisartan) were reported.

Serious adverse reactions/adverse events/suspected unexpected serious adverse reactions

All events that met the serious criteria were reported (regardless of causality). SARs, SAEs and SUSARs were reported within 24 hours of the local site becoming aware of the event. The SAE form asked for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator signed the causality form. Additional information was required to be sent within 5 days if the reaction had not resolved at the time of reporting.

The CTRC was responsible for notifying the Medicines and Healthcare products Regulatory Agency (MHRA) and main Research Ethics Committee (REC) of any SUSARs that occurred during the study according to the following timelines: fatal and life-threatening within 7 days of notification and non-life-threatening within 15 days. All investigators were informed of all SUSARs occurring throughout the study. Local investigators were asked to report any SUSARs and/or SAEs as required by their local research and development (R&D) office.

Annual safety reports

Annual safety reports were prepared and provided to the MHRA and main REC on an annual basis. As per the regulatory guidelines, reports were submitted on an annual basis within 60 days of the Clinical Trial Authorisation anniversary. A total of four reports were submitted (in 2013, 2014, 2015 and 2016).

Statistical considerations

Sample size

Original aim

The original maximum total sample size of the study was 336 patients. The primary response from each patient was the difference between the HOMA-IR score at 24 weeks and the baseline HOMA-IR score (so that negative values indicate improvement). The design had been constructed under the assumption that for all patients this response is normally distributed with a common standard deviation, σ. The sample size calculation was based on a one-sided type I error of 5% and a power of 90%.

In a conventional comparison of one active treatment against a control treatment, a criterion was set so that if the measure of advantage of the active over the control exceeded some critical value, the outcome was declared positive. As a negative outcome was indicative of an improvement here, we wanted the measure of advantage to be lower than some critical value. It was required that a positive outcome (i.e. a reduction in
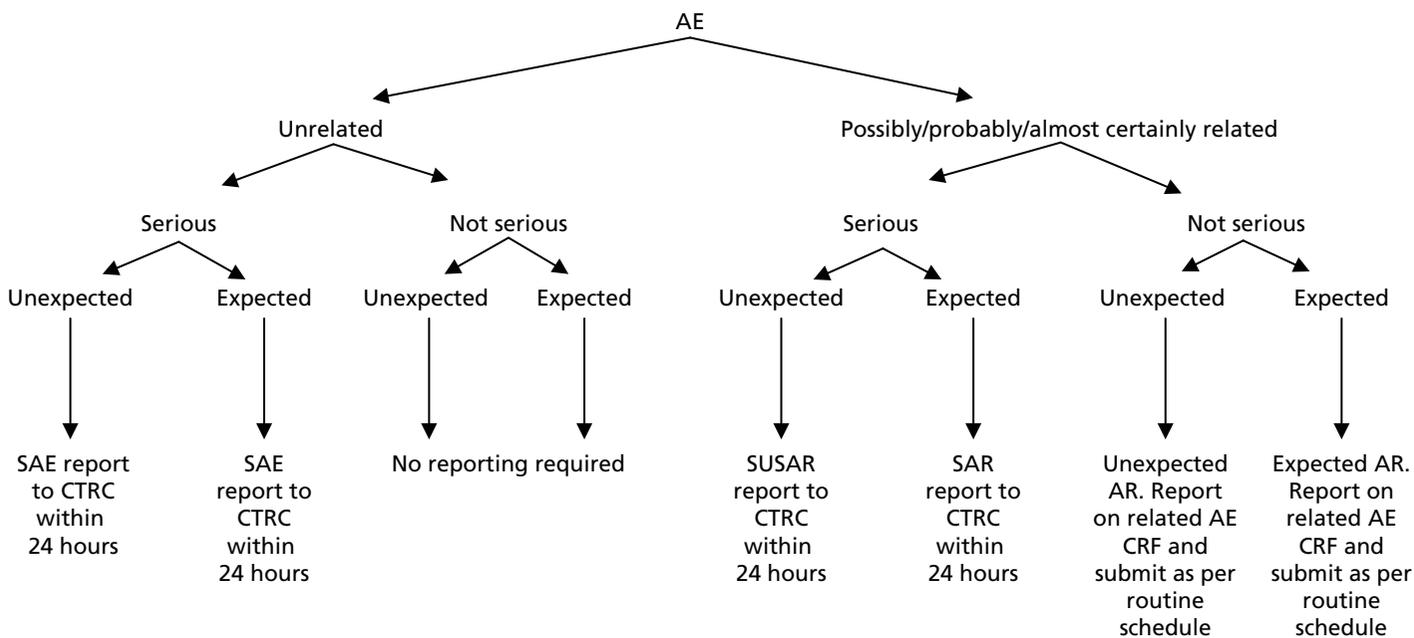
FIGURE 3 Schematic of pharmacovigilance reporting procedures.

HOMA-IR) should occur with probability α if the effects of the treatments were identical (α is the one-sided type I error rate), and with probability 1 – β if the true treatment advantage takes some negative value (1 – β is the power of the study). Here, we adopted a generalisation of this power requirement to multiple active treatments following Dunnett.[57] If there was no difference between the mean response on any treatment and that on control, then a probability of α = 0.05 was set for the risk of erroneously ending the study with a recommendation that any treatment be tested further. To fix a power requirement, effect sizes were specified in terms of the percentage chance of a patient on active treatment achieving a greater reduction in HOMA-IR score than a patient on the control arm; as such, the specification did not require knowledge of the value of the common standard deviation σ. The requirement was that if a patient on the best of the active doses had a 65% chance of showing a better response than a patient on control, whereas patients on either of the other two active treatments had a 55% chance of showing a better response than a patient on control, then the best active dose was to be recommended for further testing with probability 1 – β = 0.90. This condition demanded a high power of making the correct choice if one active dose was substantially better than control, whereas the others showed some advantage, albeit not enough to be recommended for use. The critical values for recommending that a treatment was taken to further testing at the interim and final analyses (–2.782 and –2.086) had been chosen to guarantee these properties using a method described by Magirr and Whitehead,[58] generalising the approach of Whitehead and Jaki.[59] These properties pertain to the whole two-stage testing procedure.

A 55% chance of achieving a better response on active dose relative to control corresponded to a reduction in mean HOMA-IR score of about one-sixth of the standard deviation (0.178 σ), whereas the clinically relevant effect of 65% corresponded to a reduction of about half a standard deviation (0.545 σ). The standard deviation was reported to be around 5.[60,61] Although this value was not felt to be sufficiently reliable to base the design on, were it to be true, and if the changes in HOMA-IR were normally distributed, then the 55% and 65% chances of better outcomes corresponded to mean changes in HOMA-IR of –0.890 and –2.725, respectively.

Although the original maximum sample size of the study was 336 evaluable patients, it was acknowledged that the interim analysis could reduce both the sample size and the study duration, as outlined above. The study was designed to recruit additional patients to ensure that the target number of 24-week responses was achieved in the presence of an anticipated 10% dropout rate (which increased the sample size to 370 patients).

Post-interim analysis

Interim analysis showed that there was a higher than anticipated rate of withdrawals and/or missing primary outcome data. To ensure that we had the required number of patients for the final analysis, the sample size was increased to 377 patients.

Sample size for the substudy 1 (magnetic resonance imaging/proton magnetic resonance spectroscopy)

To explore the secondary objective of using MRI/^{1}H-MRS in a subset of patients to identify the effect of telmisartan on visceral fat distribution and hepatic and muscle fat, we intended to recruit 48 patients locally (12 each in telmisartan dose arms and 12 in the control arm) to undergo whole-body MRI scans and liver and calf MRS at baseline and at 24 weeks. There is limited information[44,45] on the effect of telmisartan on visceral fat distribution for the dose groups considered and no reliable estimates of the within-group variance were available to carry out a formal power calculation. A sample size of 10 patients per group was expected to provide enough data for a reliable estimate of the within-group variance (sample size was increased to 12 to account for 10% dropout). To put this into context, the proposed sample size would allow the detection of a linear reduction in visceral fat of at least 10 cm^2/20 mg with an 80% power at the 5% significance level, assuming a within-group standard deviation of visceral fat reduction, σ = 27 cm^2. Even if deviations from the sample standard deviation (σ = 27 cm^2) occurred (e.g. σ increases to 40 cm^2), the sample size proposed would still have been sufficient to detect a linear reduction in visceral fat distribution ≥ 15 cm^2/20 mg (nQuery calculator, version 6; Statistical Solutions Ltd, Cork, Ireland). The final

sample size achieved was affected by a lower recruitment rate than initially expected and by the decision to stop recruitment for the main study for treatment arms B and C.

Sample size for substudy 2 (renal biomarkers)

To explore the secondary objective of whether or not there was a change in urinary biomarker levels at 12, 24 and 48 weeks between telmisartan-treated arm(s) and the control arm, we used the same sample size as for the main study.

Interim analysis and stopping guidelines

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 ($n = 168$, which was half of the planned maximum of 336 patients). 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. The prespecified analysis was as follows:

1. If the largest of these statistics is below 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.
2. If any active dose shows no improvement over control (i.e. has an increase in HOMA-IR), that active dose will be dropped from the second stage.
3. 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.
4. 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), then the study will progress to the second stage.

Consequently, if arms are dropped after the interim analysis, randomisation will continue to be in an equal ratio (i.e. 1 : 1 or 1 : 1 : 1).

Effect of interim analysis on the sample size and study duration

At the interim analysis, doses may be dropped from the trial, or the trial may be stopped altogether. Consequently, the sample size when the decision is reached could be smaller than the maximum stated number of 336 patients. Given the structure of the design, the values 168 patients (if the study is stopped following interim analysis), 252 patients (if one active dose arm is promoted to the second stage), 294 patients (if two active dose arms are promoted to second stage) and 336 patients (if all three active dose arms are promoted to second stage) are possible. Under the situation in which one treatment has a 65% chance of giving a better outcome than control, while the others achieve 55%, the four sample sizes occur with probabilities of 0.40, 0.08, 0.19 and 0.33, respectively. In this same situation, the probability of dropping the best treatment at the interim analysis is 0.006 and it is even smaller for treatments with larger effects. The reduced sample sizes of 168, 252 and 294 patients mentioned above refer to the numbers of patients with 24-week HOMA-IR scores that are included in the analysis. There will be additional patients who have been recruited and treated during the 24 weeks prior to extracting the data for interim analysis and during the time when the analysis take place, and their number will depend on the recruitment rate achieved. Nevertheless, taking these patients into account, it can be deduced that the impact of the interim analysis will be to shorten the study duration by about 12 months if the conclusion is clear-cut and to reduce the sample size by an expected 40 patients (this figure is calculated by taking into account the number of patients recruited during the conduct of interim analysis from months 24 to 26 and, therefore, does not actually contribute to the analysis).

The IDSMC remit included giving advice on whether or not the accumulated data from the interim analysis justified continuing recruitment of further patients and further follow-up. If a decision was made to continue, the IDSMC were tasked to advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDSMC was to make recommendations to the TSC regarding continuation of the trial.

A decision to discontinue recruitment, in all patients or in selected subgroups, would be made by the IDSMC on the basis of results from the interim analysis.

Blinding
The TAILoR trial was an open trial, with the investigators and patients not blinded to the allocated treatment. However, allocation concealment was possible as participants were randomised using a secure (24-hour) web-based randomisation program controlled centrally by the CTRC.

Method of assignment to treatment
In the first stage of the study, patients were randomised in a 1 : 1 : 1 : 1 ratio to receive 20, 40 or 80 mg of telmisartan or no intervention (control) using a secure (24 hour) web-based randomisation program controlled centrally by the CTRC CTU.

Randomisation lists were generated in a 1 : 1 : 1 : 1 ratio using simple block randomisation with random variable block length. For each recruiting centre, randomisation was stratified by ethnicity (black or non-black). Following the interim analysis, as the trial continued, those eligible that consented to take part in the study were randomised in an equal ratio to receive one of the remaining doses or no intervention (control).

During both stages of the trial, patients were enrolled to the study by clinicians and/or research nurses at each individual site who were delegated to do so by the PI.

Sequence and duration of all study periods
A schematic of the study design can be found in *Data collection*, including descriptions and timings of all assessments and procedures that were needed throughout. In summary, follow-up assessments occurred at 12, 24 and 48 weeks after randomisation.

Statistical analysis plan
Statistical analysis plans were developed for the interim and final analyses of the trial by the trial investigators and trial statistician, and were reviewed and agreed by the TSC and Data Monitoring and Ethics Committee prior to the end of the recruitment period at each stage of the trial. The complete detail of all statistical analysis plans are given in *Appendix 4*.

Statistical methods

Primary outcome analysis
In order to satisfy the primary objective, we evaluated three different doses against control in the first stage of the study and conducted an interim analysis that allowed ineffective doses to be eliminated quickly while a dose showing a reduction in HOMA-IR was taken forward. At the interim analysis, the sample standard deviation pooled across all four arms was determined and used to construct test statistics expressing the advantage of each of the three active treatments over control. These statistics were adjusted for the stratification factor (ethnicity). The smallest of these test statistics was to be compared with the interim critical value (–2.782). Observing a test statistic below this value corresponded to a significant improvement in HOMA-IR score for the corresponding dose over control and would have led to this dose being immediately taken forward for further study, and to the trial being stopped. Any dose corresponding to a positive test statistic would have been dropped and if all doses were dropped, the trial would also have been stopped. If some reduction in HOMA-IR over control was detected for at least one of the active doses (i.e. test statistic of between 0 and -2.782), then the study would continue after the interim analysis. At the final analysis, if the smallest comparative test statistic was below the final critical value (–2.086) then this dose would be recommended for further study. Adjustments were made to allow for any discrepancies between target and actual sample sizes while still preserving the one-sided type I error rate at 0.05.

The design was constructed under the assumption that for all patients the response (HOMA-IR score) is normally distributed with a common standard deviation, σ. If HOMA-IR score was not normally distributed, then a log with base e transformation was used.

Sensitivity analyses

Missing HOMA-IR values at 24 weeks were imputed by the MICE (Multivariate Imputation by Chained Equations)[62] algorithm (MICE package; version 3.3.0) conditional on HOMA-IR values at baseline, HOMA-IR values at 12 weeks and stratification factor (ethnicity). A compliance-adjusted primary outcome analysis was undertaken using instrumental variable (IV) regression, in order to estimate the effect of actual dose on outcome. Further IV regression was carried out but additionally accounting for baseline HIV viral load. More information on sensitivity analyses is provided in the statistical analysis plans (see *Appendix 4*).

Secondary outcome analysis

Biomarker analysis

To explore the secondary objective of identifying longitudinal change in the expression of biomarkers in telmisartan-treated arm(s) in comparison with controls, joint models[63,64] were used to fully exploit the serial nature of these outcomes accounting for informative loss to follow-up and missingness. The models are adjusted for ethnicity, the stratification factor at randomisation. The joint model was constructed under the assumption that longitudinal outcomes were normally distributed. If any biomarker value was not normally distributed, then a log with base e transformation was used.

Analysis of changes in body fat redistribution and intrahepatic and intramyocellular lipid content

The aim of this analysis was to identify the effect of telmisartan on visceral fat distribution and hepatic and muscle fat. The change in visceral fat at 24 weeks was compared across the three treatment groups and the control using multiple linear regression. A multiple linear regression model was considered to explore the differences in visceral fat change between the treatment groups while accounting for potential confounders. The model was adjusted for the relative change of total external fat to account for any confounding effect. The standard error of each estimator of the model coefficients, *p*-values, as well as the 95% confidence intervals (CIs) for the coefficient parameters were provided. A similar strategy was adopted for the analysis of liver and calf MRS data.

Evaluation of alternative methods of insulin resistance (Quantitative Insulin Sensitivity Check Index and Revised Quantitative Insulin Sensitivity Check Index)

The aim of this analysis was to see if telmisartan showed a similar direction of change in insulin resistance measured by QUICKI and revised QUICKI to that observed with HOMA-IR. We used the same analysis as that described in *Primary outcome analysis* for the two alternative measures.

Renal biomarker analysis

Longitudinal measurements of urinary biomarkers were analysed using linear mixed-effect models adjusting for age, weight change and sex, which were included in the final model if found significant. For analysis of NGAL, the sample set was divided into tertiles. For analysis of ACR, the sample set was divided into two subsets based on the KDIGO (Kidney Disease Improving Global Outcomes) 2012 clinical practice guideline for the evaluation and management of chronic kidney disease[65] (i.e. an ACR of < 3 mg/mmol, normal; an ACR of > 3 mg/mmol, microalbuminuria).

Additional analysis

All analyses were undertaken adjusting for weight change. Joint models included data from the dropped arms at the interim analysis and were fitted with longitudinal measurements from all four arms to adjust for informative dropout further and to account for changes in weight over time. Bivariate joint models were fitted using the joineRML package in R (The R Foundation for Statistical Computing, Vienna, Austria).[66,67] Two additional ad hoc exploratory compliance-adjusted analysis were undertaken for HOMA-IR at 24 weeks to address some selection bias.

Trial organisation

Trial management
The trial was managed by the CTRC at the University of Liverpool, which is a UK Clinical Research Collaboration (UKCRC) – Registered Clinical Trial Unit (CTU), a part of the Liverpool Trials Collaborative. The CTRC was responsible for trial management, quality assurance, data management and trial statistics. A dedicated trial manager, data manager and statistician were appointed to the CTRC.

Trial sponsor
The TAILoR trial was co-sponsored by the University of Liverpool and the Royal Liverpool and Broadgreen University Hospitals NHS Trust.

Ethical considerations, regulatory requirements, and research governance framework
The TAILoR trial was conducted in accordance with the European Clinical Trials Directive, ICH GCP Guidelines, the Declaration of Helsinki, NHS Research governance framework, and the Medicines for Human Use (Clinical Trials) Regulations 2004.

The trial was authorised to proceed by the MHRA on 29 June 2012. Its EudraCT number is 2012-000935-18. The trial also received REC (National Research Ethics Service committee – North West – Liverpool Central) approval prior to the start of the study (original approval dated 2 April 2012).

Prior to beginning research at each participating site, REC approval was sought as were local permissions from the R&D departments at each site.

Trial registration

National Institute for Health Research portfolio
The TAILoR trial was adopted onto the National Institute for Health Research (NIHR) portfolio and fulfilled the criteria for UK Clinical Research Network support.

Summary of protocol amendments

During the course of the trial, a number of amendments were made to the TAILoR protocol. Each amendment was assessed by the TMG, Trial Steering Group and the funder. Each amendment was approved by the REC and, if appropriate, by the MHRA. A full list of amendments and summarises can be found in *Appendix 5*.

Trial committees

Trial Management Group
A TMG was set up to be responsible for the day-to-day management of the TAILoR trial. The TMG met on a monthly basis to discuss the conduct and progress of the trial. The TMG membership was as follows:

- Professor Sir Munir Pirmohamed (chief investigator)
- Claire Taylor (trial co-ordinator)
- Catherine Spowart (until June 2016) (supervisory trial manager)
- Dr Ruwanthi Kolamunnage-Dona (study statistician)
- Professor Thomas Jaki (senior study statistician)
- Professor Paula Williamson (senior statistician and co-applicant)
- Dr Sudeep Pushpakom (co-applicant and scientist)

- Professor Saye Khoo (co-applicant and PI at RLBUHT)
- Professor John Whitehead (until retirement in 2014; co-applicant and statistician)
- Helen Reynolds (research nurse at RLBUHT)
- Jenny Harrison (until October 2015; research nurse at RLBUHT)
- Dr Duncan Churchill (PI at the Elton John Centre)
- Dr Gabriel Schembri (PI at the Manchester Centre for Sexual Health)
- Steve Earle (patient representative).

Trial Steering Committee

The TSC was established to provide overall supervision of the trial and to ensure that the trial was conducted to ICH GCP guidelines. The TSC met annually throughout the course of the trial via both teleconference and e-mail. Copies of the minutes were provided to the study funder (NIHR). The TSC were also consulted about any amendments to the trial protocol. The TSC membership was as follows:

- Professor Stephane de Wit (chairperson)
- Professor Lucinda Billingham (independent member)
- Professor Mahesh Parmar (independent member)
- Simon Collins (independent member, patient representative)
- Professor Sir Munir Pirmohamed (chief investigator)
- Professor Paula Williamson (co-applicant).

Meetings were also attended by members of the TMG and sponsor representatives:

- Claire Taylor (trial co-ordinator)
- Catherine Spowart (until June 2016; supervisory trial manager)
- Dr Ruwanthi Kolamunnage-Dona (study statistician)
- Professor Thomas Jaki (senior study statistician)
- Dr Sudeep Pushpakom (co-applicant and scientist)
- Professor Saye Khoo (co-applicant and PI at RLBUHT)
- Professor John Whitehead (until retirement in 2014; co-applicant and statistician)
- Heather Rogers (RLBUHT sponsor representative)
- Lindsay Carter (April 2012–March 2013; University of Liverpool sponsor representative)
- Karen Wilding (University of Liverpool sponsor representative).

Independent Data and Safety Monitoring Committee

An Independent Data and Safety Monitoring Committee (IDSMC) was established at the start of the trial. Its purpose was to review trial data, assess safety issues and/or address any ethics concerns. The IDSMC met annually throughout the course of the trial by both teleconference and e-mail. The IDSMC also received safety reports on a quarterly basis. The IDSMC assessed the interim analysis to decide on the ongoing format of the trial. The IDSMC members were:

- Professor Sir Ian Weller (chairperson)
- Dr Adrian Mander (independent statistician)
- Professor Jacqueline Capeau (independent member).

Risk assessment, monitoring and data management

Risk assessment

A risk assessment was performed by the CTRC team in collaboration with the chief investigator and sponsor at the beginning of the trial. The risk assessment indicated that the TAILoR study was a low-risk study and that monitoring would take place centrally, with site visits taking place if required to resolve issues.

Monitoring and data management

Monitoring was performed centrally. The MACRO database (version 3) contained predefined ranges that flagged queries to the study data manager if data outside the ranges were entered. In addition, the trial statistician performed regular checks on the data to produce IDSMC and trial monitoring reports to look for errors and inconsistencies and to highlight any protocol deviations.

Sites were requested to fax consent forms to the trial co-ordinator within 7 days of completion and these were then checked by the trial co-ordinator to ensure that they were valid.

Site training/initiation visits took place at all participating sites. On site monitoring visits took place if central monitoring indicated a need (e.g. CRFs not being returned/returned late, inconsistencies in CRFs).

Patient and public involvement

Patient representatives were identified early on in the trial and were involved in the oversight of the trial. One representative sat on the TSC and one on the TMG. Both attended regular meetings throughout the course of the trial. The patient representatives reviewed the study website, clinic poster, participant information sheets and consent forms. The design and format of the patient information sheets was altered in response to their feedback. They also gave opinions on how recruitment process could be improved.

Chapter 4 Results

Participant recruitment

Screening and participant flow

In total, 1950 patients were screened at the participating centres over the duration of the trial. Of the 1118 patients meeting the eligibility criteria, 698 declined to participate. *Tables 14–16* in *Appendix 6* summarise the numbers screened and eligible patients recruited to the trial. Further details of screening are given in *Appendix 6*, with *Table 16* summarising the reasons for non-recruitment. The flow of patients is summarised in *Figure 4*, including the numbers of patients screened, randomised, followed up and analysed.

Randomisation checking

Randomisation numbers were sequential by date randomised, and there were no missing randomisation numbers. The last day of randomisation was 20 July 2015. Treatments were balanced across strata (ethnicity) (*Table 3*).

Recruitment and retention

Recruitment took place from March 2013 until July 2015, taking a total of 28 months. This was longer than the originally allocated recruitment period of 1 year. There were a number of delays in starting the trial and in the opening of sites to recruitment. The major issues encountered were:

- lack of funding for excess treatment costs (ETCs)
- slower recruitment
- increased participant dropout and subsequent need to increase from the original sample size
- high staff turnover at some participating sites, which further contributed to delay/interruption in recruitment.

The TAILoR team took a number of measures to counter the above cited impediments:

1. A waiver to underwrite the ETCs was negotiated with the trial sponsor (University of Liverpool) to get the trial started. Over the course of the trial, all participating sites were contacted to cover ETCs and this was eventually agreed by all sites by the time the last patient was recruited.
2. Setting up of additional sites to reach the recruitment target in the same time frame – the number of recruitment sites was increased from the originally planned eight sites to 19 sites.
3. Encouraging patient participation and increasing publicity for the trial among the patient population – the trial team held discussions with the patient and public involvement representatives in the TMG and the TSC on ways to increase recruitment rates. As a result of this, the participant information sheet was altered to make them more reader friendly; we also developed posters for use in participating clinics, and developed a recommended recruitment pitch for researchers. A study website (www.tailortrial.org) was also created to increase visibility and to update the participants of the various developments related to the trial.
4. Ensuring recruiter engagement – to increase recruitment, we continued to engage with research teams at sites holding regular PI and research nurse meetings, and having regular newsletter updates.

Enrolment

Assessed for eligibility
(*n* = 1950)

Excluded
(*n* = 1574)
• Did not meet inclusion criteria, *n* = 832
• Decline to participate, *n* = 698
• Not randomised, *n* = 44

Missing screening logs for those randomised, *n* = 3[a]

Allocation

Randomised
(*n* = 379)

Excluded
(*n* = 2)
• Randomised the same patient in error, *n* = 1
• Patient was not present at the randomisation, *n* = 1[b]

Arm A: non-intervention
(*n* = 105)

Arm B: telmisartan 20 mg
(*n* = 84)

Arm C: telmisartan 40 mg
(*n* = 82)

Arm D: telmisartan 80 mg
(*n* = 106)

Follow-up

Discontinued intervention with no further data collection
(*n* = 47)
• Lost to follow-up, *n* = 2, with AE, *n* = 1
• Patient preference, *n* = 1
• Patient preference, then lost to follow-up, *n* = 1
• Related AE, *n* = 3
• Arm dropped, *n* = 38
• Other, *n* = 1[c]

Discontinued intervention with continued data collection
(*n* = 6)
• Related AE, *n* = 2
• Failure to comply with protocol, *n* = 1
• Other, *n* = 3[e]

Discontinued intervention with no further data collection
(*n* = 51)
• Lost to follow-up, *n* = 5, with AE, *n* = 1
• Withdrew consent for follow-up, *n* = 2, with AE, *n* = 2
• Related AE, *n* = 2
• Serious AE, *n* = 1
• Arm dropped, *n* = 36
• Other, *n* = 2[d]

Discontinued intervention with continued data collection
(*n* = 12)
• Related AE, *n* = 5, serious AE, *n* = 1
• Patient preference, *n* = 2
• Failure to comply with protocol, *n* = 1
• Other, *n* = 3[i]

Discontinued intervention with no further data collection
(*n* = 14)
• Lost to follow-up, *n* = 6
• Death, *n* = 1
• Withdrew consent for follow-up, *n* = 1
• Other, *n* = 6[f]

Discontinued intervention with continued data collection
(*n* = 0)

Discontinued intervention with no further data collection
(*n* = 21)
• Lost to follow-up, *n* = 5, with AE, *n* = 1
• Related AE, *n* = 2
• Patient preference, *n* = 1
• Withdrew consent for follow-up, *n* = 3, with AE, *n* = 1
• Other, *n* = 8[g]

Discontinued intervention with continued data collection
(*n* = 18)
• Related AE, *n* = 4
• Patient preference, *n* = 4
• Serious AE, *n* = 1
• Failure to comply with protocol, *n* = 2
• Other, *n* = 7[h]

Final analysis

Analysed for primary outcome
(*n* = 85)

Excluded from analysis (*n* = 20)
• Did not attend 24 weeks, *n* = 4
• Haemolysed samples collected 24 weeks, *n* = 0
• Haemolysed samples collected baseline, *n* = 3
• Samples not collected/un-fasted 24 weeks, *n* = 1
• Samples not collected/un-fasted baseline, *n* = 1
• Withdrew before 24 weeks , *n* = 11

Analysed for primary outcome
(*n* = 78)

Excluded from analysis (*n* = 28)
• Did not attend 24 weeks, *n* = 4
• Haemolysed samples collected 24 weeks, *n* = 2
• Haemolysed samples collected baseline, *n* = 3
• Samples not collected/un-fasted 24 weeks, *n* = 2
• Samples not collected/un-fasted baseline, *n* = 2
• Withdrew before 24 weeks, *n* = 15

FIGURE 4 Consolidated Standards of Reporting Trials flow diagram. a, Screening data are missing for three patients. b, A patient was randomised in arm B, even before they attended the clinic, because of a communication error. c, Patient concerned about leg swelling (not an AE) and decided to stop study drug. d, Patient has left the country; patient preference. e, Medication ran out 2 days before final visit; appointment was missed, as patient misunderstood the follow-up schedule; patient lost study medication and failed to inform research team until 48-week follow-up visit. f, Patient moved to London with no forwarding address; did not wish to continue the study because of organisational reasons; because of advice from study team following MRI incidental finding; to enter another clinical trial; eGFR < 60 ml/minute/1.73 m^2 at screening; on nevirapine. g, Patient developed a cough and wanted to discontinue study medication; taking Rampiril (general practitioner's orders); switch in ARV; not able to commit to study; eGFR < 60 ml/minute/1.73 m^2 at baseline; did not meet eligibility criteria; did not return for appointment and did not respond to contacts; decided to become pregnant. h, Patient ran out of study medication; eGFR < 60 ml/minute/1.73 m^2; patient ran out of study medication but did not collect extra medication; forgot to take study medication when on holiday abroad; ran out of study medication; ran out of study medication but was unable to come to collect extra medication; did not take study medication as required. i, All three patients had run out of study drug.

TABLE 3 Ethnicity distribution of treatment/non-intervention arms

Ethnicity	Treatment arm, *n* (%)			
	Arm A (control) (*N* = 105)	Arm B (20 mg) (*N* = 84)	Arm C (40 mg) (*N* = 82)	Arm D (80 mg) (*N* = 106)
Black	22 (20.9)	18 (21.4)	16 (19.51)	22 (20.8)
Non-black	83 (79.0)	66 (78.6)	66 (80.49)	84 (79.2)

Recruitment rate

The target recruitment rate for the study was two to five patients per month per site, based on the original eight sites recruiting and a target recruitment figure of 370 patients. Monthly and cumulative monthly accrual of patients was slower than anticipated and is shown in *Figure 5*.

Baseline data

The baseline characteristics of all randomised patients are summarised by treatment arms (see *Tables 4* and *5*). Baseline characteristics were balanced across treatment arms. The median ages were comparable between all arms (*Table 4*). The study participants were predominantly male (ranging between 81.0% and 84.1% across the four arms; see *Table 4*). The body mass index (BMI) and other vital parameters of the participants were comparable between all four arms (see *Table 4*), as was the cluster of differentiation 4 (CD4) cell count (ranging between 580 and 598 cells/mm^3; see *Table 18* in *Appendix 6*). The baseline liver function and full blood count were also comparable between participants in all four arms (see *Tables 19* and *20* in *Appendix 6*). The median HOMA-IR values ranged between 0.408 and 17.495 for the entire cohort (*Table 5*) and were comparable between all four arms. There was also no difference in baseline values for the secondary outcome measures (*Table 5*).

Numbers analysed

In total, 307 (81%) of the patients attended all study assessment visits, and 72% of patients had complete records of longitudinal outcome as planned. *Table 21* (see *Appendix 6*) shows the numbers for missed visits and missing data because of sample issues, and reasons for missingness are given in *Table 22* (see *Appendix 6*).

FIGURE 5 Monthly and cumulative monthly accrual of patients. Post interim analysis: interim analysis has shown that there was a higher than anticipated rate of withdrawals and/or missing primary outcome data. In order to have the required number of patients for final analysis, a total of 377 patients was required.
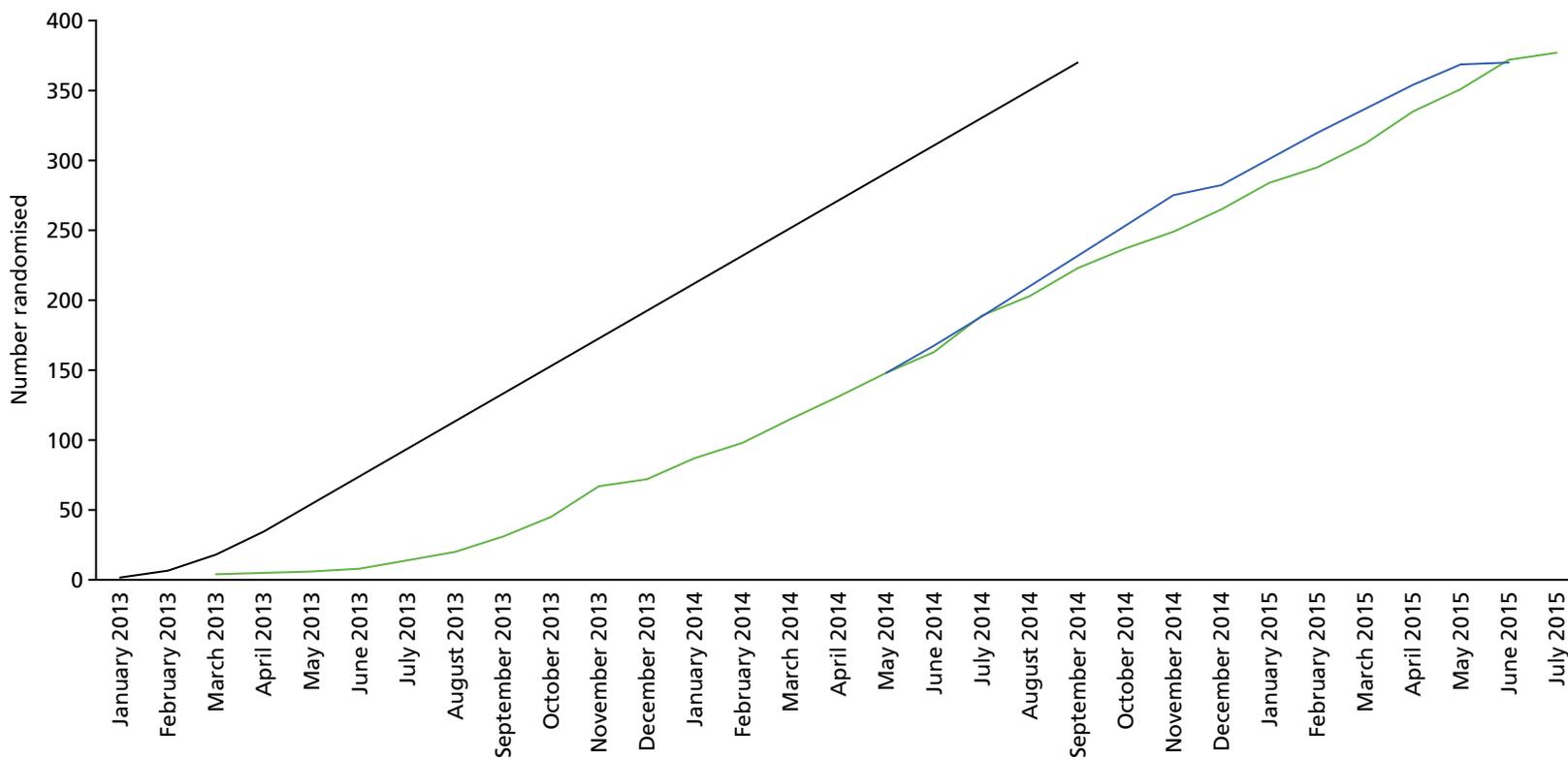
	January 2013	February 2013	March 2013	April 2013	May 2013	June 2013	July 2013	August 2013	September 2013	October 2013	November 2013	December 2013	January 2014	February 2014	March 2014	April 2014	May 2014	June 2014	July 2014	August 2014	September 2014	October 2014	November 2014	December 2014	January 2015	February 2015	March 2015	April 2015	May 2015	June 2015	July 2015
Original target	2	7	18	35	54	74	94	113	133	153	173	192	212	232	252	271	291	311	331	350	370										
Actual			4	5	6	8	14	20	31	45	67	72	87	98	115	131	148	163	189	203	223	237	249	265	284	295	312	335	351	372	377
Extension																	148	168	188	210	232	253	275	282	301	320	337	354	369	370	

TABLE 4 Baseline characteristics of patients by treatment arm

Characteristic	Treatment arm			
	Arm A (*N* = 105)	Arm B (*N* = 84)	Arm C (*N* = 82)	Arm D (*N* = 106)
Age (years)				
Median (IQR); min.–max.	47.2 (39.8–52.4); 20.4–70.5	46.0 (41.0–52.2); 21.6–74.6	47.9 (43.3–51.5); 31.5–70.8	45.8 (38.2–51.7); 22.5–67.3
Sex, *n* (%)				
Female	20 (19.0)	15 (17.9)	13 (15.9)	17 (16.0)
Male	85 (81.0)	69 (82.1)	69 (84.1)	89 (84.0)
BMI (kg/m^2)	(*n* = 103)		(*n* = 81)	
Median (IQR); min.–max.	25.4 (23.1–29.2); 16.7–42.0	25.6 (23.3–29.2); 18.8–52.2	26.3 (24.4–29.6); 16.7–46.3	25.4 (23.0–27.8); 7.9–43.7
Systolic blood pressure (mmHg)			(*n* = 81)	
Mean (SD); min.–max.	126.8 (13.9); 100.0–160.0	124.4 (14.2); 100.0–162.0	126.9 (14.3); 92.0–158.0	124.8 (15.4); 100.0–172.0
Diastolic blood pressure (mmHg)				
Mean (SD); min.–max.	80.0 (10.7); 60.0–122.0	78.2 (11.2); 56.0–107.0	79.7 (9.9); 54.0–102.0	78.6 (11.1); 55.0–107.0
Heart rate (beats per minute)		(*n* = 82)	(*n* = 80)	
Mean (SD); min.–max.	73.0 (11.5); 50.0–101.0	72.5 (11.7); 51.0–105.0	71.6 (13.1); 39.0–113.0	72.8 (12.2); 51.0–115.0
Temperature (°C)	(*n* = 99)	(*n* = 78)	(*n* = 78)	(*n* = 102)
Mean (SD); min.–max.	36.3 (0.5); 35–38	36.3 (0.4); 35.3–37.8	36.4 (0.3); 35.5–37.1	36.3 (0.5); 34.5–37.8
Respiratory rate (breaths per minute)	(*n* = 102)	(*n* = 83)	(*n* = 76)	(*n* = 103)
Mean (SD); min.–max.	15.6 (2.9); 10.0–28.0	15.9 (4.0); 10.0–41.0	16.0 (4.2); 10.0–37.0	16.5 (3.4); 10.0–28.0
Waist circumference (cm)	(*n* = 101)	(*n* = 83)	(*n* = 79)	(*n* = 102)
Mean (SD); min.–max.	93.5 (11.8); 65.0–137.0	94.6 (14.7); 66.0–145.0	97.1 (12.2); 70.0–143.0	93.0 (11.6); 67.5–122.0
Thigh circumference (cm)	(*n* = 101)	(*n* = 82)	(*n* = 77)	(*n* = 102)
Mean (SD); min.–max.	50.8 (7.5); 33.5–80.0	52.3 (7.7); 39.0–90.5	51.8 (6.0); 37.0–69.0	49.6 (8.5); 22.7–84.0
eGFR[a] (ml/minute/1.73 m^2)	(*n* = 50)	(*n* = 41)	(*n* = 38)	(*n* = 54)
Mean (SD); min.–max.	79.8 (13.6); 45.0–129.0	79.9 (10.8); 60.0–105.0	77.9 (10.5); 62.0–107.6	81.4 (14.5); 53.0–122.0
< 60, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
< 90, *n* (%)	0 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
> 60, *n* (%)	24 (22.9)	23 (27.4)	25 (30.5)	22 (20.8)
> 90, *n* (%)	28 (26.7)	19 (22.6)	19 (23.2)	28 (26.4)

IQR, interquartile range; max., maximum; min., minimum.
a Some data are presented in both continuous and categorical form as a result of there being upper and lower limits of measurement.

TABLE 5 Baseline values of primary and secondary outcome data by treatment arm

Characteristic	Treatment arm			
	Arm A (*N* = 105)	Arm B (*N* = 84)	Arm C (*N* = 82)	Arm D (*N* = 106)
Insulin (pmol/l)	(*n* = 102)	(*n* = 81)	(*n* = 78)	(*n* = 100)
Median (IQR); min.–max.	54 (35–90); 11–279	57 (37–87); 21–319	61 (40–85); 21–432	51 (36.5–75.5); 21–454
Glucose (mmol/l)	(*n* = 104)	(*n* = 83)	(*n* = 80)	(*n* = 104)
Mean (SD); min.–max.	5.2 (0.5); 4.2–6.9	5.2 (0.58); 4.0–7.6	5.29 (0.7); 3.2–8.5	5.22 (0.54); 4.1–6.8
NEFAs (mmol/l)	(*n* = 104)	(*n* = 82)	(*n* = 79)	(*n* = 102)
Median (IQR); min.–max.	0.42 (0.27–0.615); 0.08–1.21	0.385 (0.25–0.58); 0.07–1.08	0.35 (0.25–0.55); 0.05–0.84	0.40 (0.30–0.59); 0.08–1.21
HOMA-IR	(*n* = 100)	(*n* = 81)	(*n* = 78)	(*n* = 100)
Median (IQR); min.–max.	1.808 (1.120–2.903); 0.408–10.775	1.860 (1.208–3.508); 0.578–9.800	2.117 (1.223–3.297); 0.618–17.495	1.628 (1.175–2.490); 0.591–16.852
QUICKI	(*n* = 100)	(*n* = 81)	(*n* = 78)	(*n* = 100)
Mean (SD); min.–max.	0.117 (0.009); 0.097–0.142	0.116 (0.009); 0.098–0.135	0.116 (0.010); 0.093–0.134	0.118 (0.009); 0.093–0.135
Revised QUICKI	(*n* = 100)	(*n* = 81)	(*n* = 78)	(*n* = 99)
Mean (SD); min.–max.	0.132 (0.017); 0.101–0.184	0.134 (0.019); 0.100–0.211	0.134 (0.019); 0.100–0.212	0.133 (0.016); 0.096–0.178
HDL-C (mmol/l)	(*n* = 104)	(*n* = 82)	(*n* = 79)	(*n* = 103)
Median (IQR); min.–max.	1.15 (0.9–1.4); 0.5–3.0	1.1 (1.0–1.4); 0.3–2.7	(0.9–1.4); 0.2–2.8	(1.0–1.4); 0.5–2.9
Cholesterol (mmol/l)	(*n* = 104)	(*n* = 82)	(*n* = 79)	(*n* = 103)
Mean (SD); min.–max.	5.01 (0.99); 2.2–8.2	5.0 (1.11); 2.6–8.3	4.83 (1.04); 2.5–7.1	4.97 (1.04); 2.9–7.64
Triglycerides (mmol/l)	(*n* = 104)	(*n* = 82)	(*n* = 79)	(*n* = 103)
Median (IQR); min.–max.	1.4 (1.0–2.0); 0.5–6.5	1.25 (0.9–1.8); 0.4–4.8	1.4 (1.0–1.9); 0.5–6.1	1.2 (0.9–1.8); 0.4–6.7
LDL-C (mmol/l)	(*n* = 103)	(*n* = 81)	(*n* = 78)	(*n* = 102)
Mean (SD); min.–max.	3.1 (0.91); 1.1–6.4	3.14 (0.97); 1.1–6.2	2.97 (0.9); 0.8–5.2	3.12 (0.91); 0.8–5.6
Adiponectin (μg/ml)	(*n* = 104)	(*n* = 82)	(*n* = 78)	(*n* = 101)
Median (IQR); min.–max.	14.62 (10.11–20.50); 3.14–44.34	16.27 (12.05–21.84); 1.73–60.49	13.69 (9.22–20.31); 2.01–66.19	13.47 (8.28–18.51); 2.74–129.01[a]
Leptin (pg/ml)	(*n* = 104)	(*n* = 81)	(*n* = 78)	(*n* = 103)
Median (IQR); min.–max.	4856.7 (1885.9–13,879); 253.64–123,299	4688.7 (2149–15,786); 388.38–192,842	5227.2 (2271.4–9710); 168.11–119,430	4492.2 (2126.5–10,192); 502.59–104,002
IL-8 (pg/ml)	(*n* = 104)	(*n* = 82)	(*n* = 78)	(*n* = 102)
Median (IQR); min.–max.	17 (12.98–22.7); 5.67–744.98[a]	14.38 (11.65–18.67); 5.18–166.7	16.32 (11.83–25.12); 6.04–187.86	18.57 (12.75–29.53); 4.51–368.69

TABLE 5 Baseline values of primary and secondary outcome data by treatment arm (*continued*)

Characteristic	Treatment arm			
	Arm A (*N* = 105)	Arm B (*N* = 84)	Arm C (*N* = 82)	Arm D (*N* = 106)
TNF-α (pg/ml)	(*n* = 103)	(*n* = 82)	(*n* = 78)	(*n* = 101)
Median (IQR); min.–max.	2.31 (1.69–3.49); 0.58–12.61	2.1 (1.74–2.49); 1.04–6.27	2.39 (1.71–2.99); 0.49–8.11	2.35 (1.77–3.09); 0.85–56.89*
Resistin (pg/ml)	(*n* = 104)	(*n* = 82)	(*n* = 78)	(*n* = 101)
Median (IQR); min.–max.	5602.7 (3936.6–7998.5); 1667.2–30,299	4790.2 (3713.7–6966.3); 1288.2–20,357	5114 (3656.4–6861); 1180–13,781	5684.9 (4590.9–8367.2); 1607.7–19,692
hs-CRP (mg/ml)	(*n* = 104)	(*n* = 82)	(*n* = 78)	(*n* = 103)
Median (IQR); min.–max.	2.24 (1.03–4.04); 0.31–98.12[a]	1.4 (0.71–3.93); 0.35–18.97	1.32 (0.59–4.17); 0.25–91.56[a]	1.32 (0.66–3.14); 0.28–41.74
NGAL (pg/ml)	(*n* = 99)	(*n* = 82)	(*n* = 72)	(*n* = 101)
Median (IQR); min.–max.	5.99 (1.98–15.31); 0.46–160.79	5.59 (2.38–15.76); 0.59–325.54	6.30 (1.70–17.59); 0.49–282.04	5.48 (1.85–15.85); 0.61–160.50
ACR (mg/mmol)	(*n* = 40)	(*n* = 34)	(*n* = 31)	(*n* = 40)
Median (IQR); min.–max.	0.8 (0.4–3.6); 0.2–37.0	0.9 (0.6–1.8); 0.2–8.5	0.9 (0.5–2.0); 0.2–7.4	0.5 (0.4–1.65); 0.3–38.8

IQR, interquartile range; max., maximum; min., minimum.
a Confirmed correct.

Primary outcome results

Interim analysis

There were 48, 49, 47 and 45 patients who were randomised to arms A, B, C and D, respectively, with a total of 189 patients available for interim analysis. However, only 154 patients had a complete set of baseline and 24-week HOMA-IR data and were therefore included in the interim analysis. A total of 32 patients did not have a HOMA-IR value at the 24-week time point, and three patients did not have baseline HOMA-IR data. In 31 out of 32 cases, the 24-week HOMA-IR data were unavailable because of withdrawal from the study, visit not attended and loss to follow-up. There were seven patients (14.6%) in arm A, four patients (8.2%) in arm B, 11 patients (23.4%) in arm C and nine patients (20.0%) in arm D who were unavailable for interim analysis. *Figure 6* shows the box plots for HOMA-IR at baseline and 24 weeks by treatment arm and the summary statistics are given in *Table 23* (see *Appendix 6*).

The HOMA-IR data were not normally distributed; hence the analysis was performed in log-scale. The model estimates are presented in *Table 6*; the *t*-statistic for arms B and C showed a positive value (i.e. higher than 0), which implied that there was no reduction in the HOMA-IR over control (arm A) for arms B and C and, therefore, these active dose arms were dropped from the second stage. As some improvement over control was detected for arm D (i.e. the *t*-statistic was between 0 and –2.782), this arm was selected to progress into the second stage of the study and the patients were thereafter randomised between arm D and the control arm (arm A).

Final analysis

At the end of the study, there were 105 patients randomised in arm A and 106 patients in arm D (total *n* = 211). One patient from arm D had an extreme HOMA-IR value at 24 weeks (62.0). This was because of a high insulin value of 1242 (glucose value was 7.8). The summary statistics for HOMA-IR at baseline and
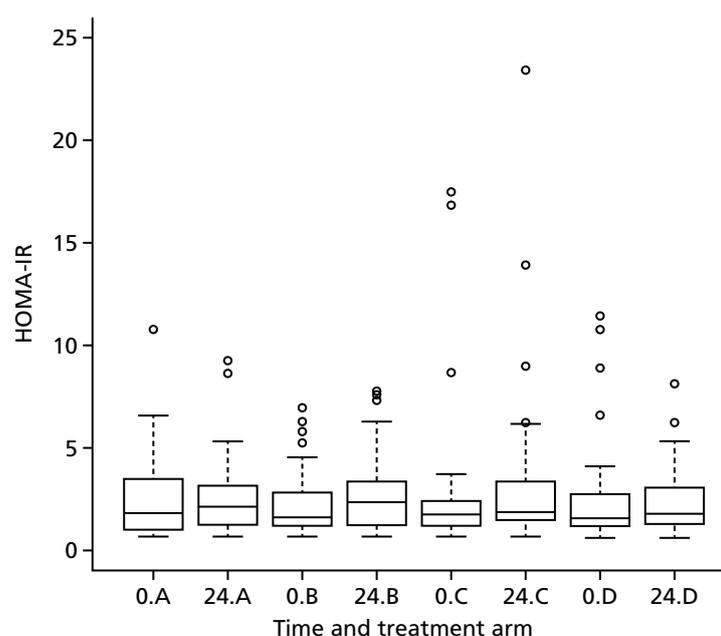
FIGURE 6 Box plots for HOMA-IR at baseline and 24 weeks by treatment arm at the interim analysis. A refers to the control arm; B, C and D refer to arms treated with 20, 40 and 80 mg of telmisartan, respectively. 0, baseline; 24, 24 weeks.

TABLE 6 Model estimates for log-HOMA-IR and decision at the interim analysis

Variable	Parameter estimate	Standard error	*t*-value for treatment	Decision
Intercept	0.3799	0.1414	–	–
Log(HOMA-IR) at baseline	0.5529	0.0681	–	–
Ethnicity	–0.0164	0.1228	–	–
Arm B vs. arm A	0.0486	0.1300	0.3738	Drop arm B
Arm C vs. arm A	0.1009	0.1383	0.7297	Drop arm C
Arm D vs. arm A	–0.0247	0.1386	–0.1778	Keep arm D

24 weeks by treatment arm are given in *Table 7*, and the model estimates are presented in *Table 8*. As the HOMA-IR was not normally distributed, all analyses were performed in log scale. Since the test statistic (*t*-value 0.065) was not smaller than the critical value of –2.086, it was concluded that there was no significant difference in HOMA-IR between arms D and A (*t*-value 0.007, SE 0.106).

We have investigated the effect of inclusion of this extreme value further by plotting the change in HOMA-IR at 24 weeks from baseline against HOMA-IR at baseline; this is presented in *Figure 10* (see *Appendix 6*). This patient was considered to be a statistical outlier and was therefore excluded from the analyses shown below.

A total of 85 patients from arm A and 78 patients from arm D with both baseline and 24-week HOMA-IR measurements were included in the final analysis. *Figure 7* shows the box plots for HOMA-IR at baseline and 24 weeks by treatment arm, and the summary statistics are given in *Table 24* (see *Appendix 6*). The model estimates are presented in *Table 25* (see *Appendix 6*). Since the test statistic (–0.347) was not smaller than the critical value of –2.086, it was concluded that there was no significant difference in HOMA-IR between arms D and A (–0.034, SE 0.099).

TABLE 7 Summary statistics for HOMA-IR at baseline and 24 weeks by treatment arm

| Summary statistic | Time point | | | |
| | HOMA-IR at baseline | | HOMA-IR at 24 weeks | |
	Arm A (control)	Arm D (80 mg)	Arm A (control)	Arm D (80 mg)
Number of patients (%)	100 (95.2)	100 (94.3)	89 (84.8)	82 (77.4)
Mean (SD), min.–max.	2.5 (2.08), 0.4–10.8	2.5 (2.79), 0.6–16.9	3.0 (3.25), 0.6–19.6	3.4 (6.89), 0.6–62.0
Median (IQR)	1.8 (1.1–2.9)	1.6 (1.2–2.5)	2.1 (1.3–3.2)	2.0 (1.1–3.6)
Missing (%)	5 (4.8)	6 (5.7)	16 (15.2)	24 (22.6)
Number of patients randomised	105	106	105	106

IQR, interquartile range; max., maximum; min., minimum.

TABLE 8 Model estimates for log-HOMA-IR and test statistic (including the extreme HOMA-IR value at 24 weeks)

Variable	Parameter estimate	Standard error	*t*-value for treatment
Intercept	0.428	0.135	–
Log-(HOMA-IR) at baseline	0.594	0.079	–
Ethnicity (non-black)	0.010	0.132	–
Arm D vs. arm A	0.007	0.106	0.065
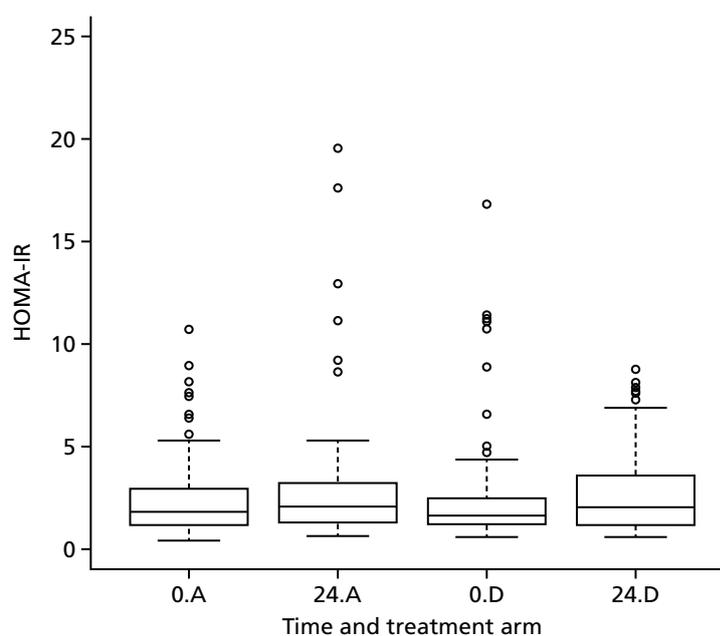
FIGURE 7 Box plots for HOMA-IR at baseline and 24 weeks by treatment arm at the final analysis for continued treatment arms. A refers to the control arm; D refers to arm treated with 80 mg of telmisartan. 0, baseline; 24, 24 weeks.

The model was further adjusted for change in weight between 24 weeks and baseline in a post hoc analysis. A total of 84 patients from arm A and 77 patients from arm D (one patient was excluded because of unavailability of weight at baseline data) were included in this analysis. The test statistic, –0.399, was still not smaller than the critical value (–2.086), and thus there was no significant difference in HOMA-IR between the two arms (–0.039, SE 0.097; see *Appendix 6*, *Table 26*).

Sensitivity analyses were also carried out to adjust for (1) potential missing HOMA-IR values and (2) treatment compliance. The parameter estimates in each of these sensitivity analyses [imputation for missing HOMA-IR, test statistic = –0.393, effect size –0.038, SE 0.096; treatment compliance, –0.010 (95% CI –0.028 to 0.008; $p = 0.3$] showed that there was no significant difference between arms A and D. Details of these analyses are presented in *Appendix 6*, *Tables 27–30*.

Secondary outcome results

Alternative indices of insulin resistance (Quantitative Insulin Sensitivity Check and revised Quantitative Insulin Sensitivity Check)

We used two alternative measures of insulin resistance, QUICKI and revised QUICKI, to further investigate the effect of telmisartan. *Figure 8* shows the box plots for QUICKI and revised QUICKI at baseline and 24 weeks by treatment arm, and the summary statistics are given in *Tables 31* and *32* (see *Appendix 6*).

For QUICKI, the test statistic (0.4471) was not smaller than the critical value (–2.086), suggesting no difference between arms A and D (0.0006, SE 0.0013), a result similar to that observed with HOMA-IR (see *Table 33* in *Appendix 6*). Similarly, for revised QUICKI, the test statistic (0.6882) was not smaller than the critical value (–2.086), again showing no difference between arms A and D (0.0017, SE 0.0025; see *Table 34* in *Appendix 6*).

The model diagnostics related to the above models are shown in *Appendix 6*.
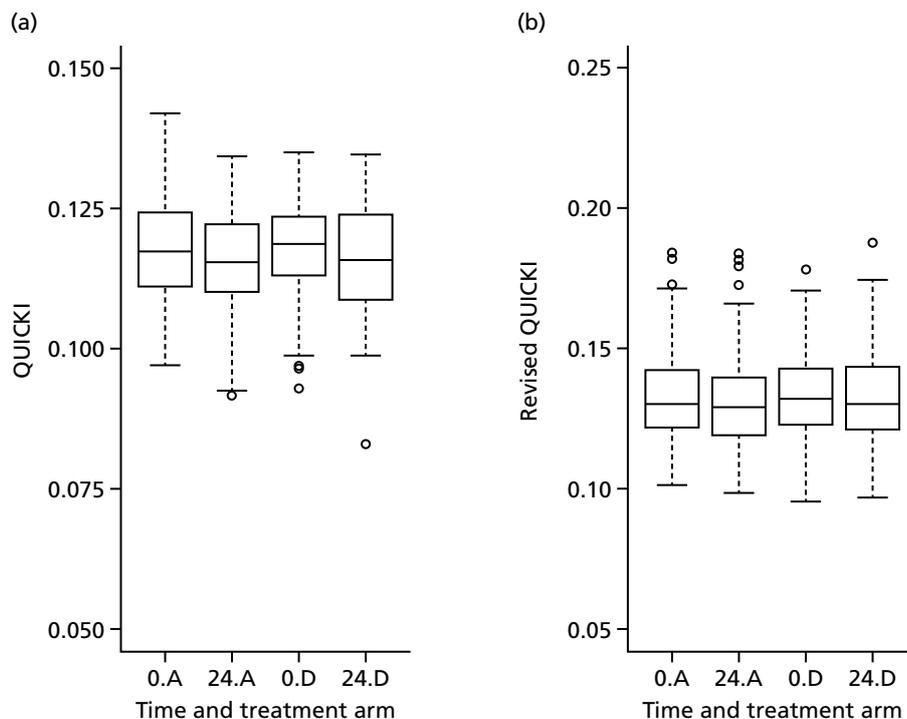
FIGURE 8 Box plots for QUICKI and revised QUICKI at baseline and 24 weeks by treatment arm. A refers to the control arm; D refers to arm treated with 80 mg of telmisartan. 0, baseline; 24, 24 weeks.

Longitudinal outcomes

Longitudinal analysis of Homeostatic Model Assessment of Insulin Resistance, Quantitative Insulin Sensitivity Check and revised Quantitative Insulin Sensitivity Check

The longitudinal profiles of HOMA-IR, QUICKI and revised QUICKI at weeks 12, 24 and 48 for all four arms were analysed using a bivariate joint model, adjusted for weight changes over time. A total of 321 patients and 812 individual measurements (320 patients and 808 individual measurements in the case of revised QUICKI) were included in this analysis.

There was no significant difference in HOMA-IR (treatment effect of arm D compared with arm A for the longitudinal log-HOMA-IR was –0.083, 95% CI –0.247 to 0.082; $p = 0.3$) and QUICKI (0.001, 95% CI –0.001 to 0.003; $p = 0.3426$) between the treatment and control arms over a period of 48 weeks. However, the treatment effect of arm D compared with arm A for the longitudinal revised QUICKI was marginally significant (0.004, 95% CI 0.000 to 0.008; $p = 0.05$), suggesting that telmisartan (80 mg) led to a small reduction in insulin resistance over a period of 48 weeks. The complete set of estimated parameters from the model is given in *Appendix 6*.

Longitudinal analysis of lipid profiles (high-density lipoprotein cholesterol, total cholesterol, triglycerides and low-density lipoprotein cholesterol)

The bivariate joint models included 328 patients and 845 individual measurements on average for the lipid profiles; HDL-C and triglycerides were fitted in log-transformed scale for normality. There was no significant difference between the treatment arm and the control arm with any of the lipid markers over a period of 48 weeks. The treatment effect [arm D (80 mg) compared with arm A (control)] on the longitudinal profiles of HDL-C, total cholesterol, triglycerides and LDL-C was 0.001 (95% CI –0.046 to 0.047: $p = 1.0$), 0.013 (95% CI –0.173 to 0.199; $p = 0.9$), 0.030 (95% CI –0.056 to 0.116; $p = 0.5$) and 0.000 (95% CI –0.145 to 0.144; $p = 1.0$), respectively. The longitudinal profiles and complete set of parameter estimates are given in *Appendix 6*.

Longitudinal analysis of plasma biomarkers

The longitudinal profiles of plasma biomarkers (adiponectin, leptin, IL-8, TNF-α, resistin and hs-CRP) at weeks 12, 24 and 48 were analysed using a bivariate joint model. The joint models included 326 patients and 840 individual measurements on average for each of the above plasma biomarkers and all were fitted in log-transformed scale for normality.

None of the plasma biomarkers apart from hs-CRP showed a significant change over time between the control and the telmisartan (80-mg) treatment arm. The estimated treatment effect on the longitudinal profiles of adiponectin, leptin, IL-8, TNF-α and resistin was 0.035 (95% CI –0.078 to 0.148; $p = 0.5$), 0.004 (95% CI –0.179 to 0.187; $p = 1.0$), 0.041 (95% CI –0.111 to 0.193; $p = 0.6$), –0.025 (95% CI –0.133 to 0.082; $p = 0.6$) and –0.066 (95% CI –0.171 to 0.039; $p = 0.2$), respectively. However, hs-CRP showed a significant change over time (treatment effect of –0.222, 95% CI –0.433 to –0.011; $p = 0.04$), with patients in the treatment arm showing significantly lower plasma hs-CRP levels over 48 weeks than those in the control arm. The longitudinal profiles and complete set of parameter estimates are given in *Appendix 6*.

An interaction between treatment and time was not considered as both treatment and time effects were not found to be significant in any outcome. In cases where only time effect was significant, a trend was revealed (i.e. the longitudinal outcome was changing over time) despite a significant treatment effect.

Substudy 1: magnetic resonance imaging

We assessed the effect of telmisartan (80 mg) on internal visceral fat and intrahepatic and intramyocellular (soleus and tibialis anterior) lipid content over a period of 24 weeks using MRI and ^{1}H-MRS. The summary statistics for these are presented in *Table 48* (see *Appendix 6*) and *Figure 9*. Other related outcome measures such as external abdominal fat, total internal fat, total external fat and total body fat were also assessed and the summary statistics are given in *Table 49* (see *Appendix 6*).
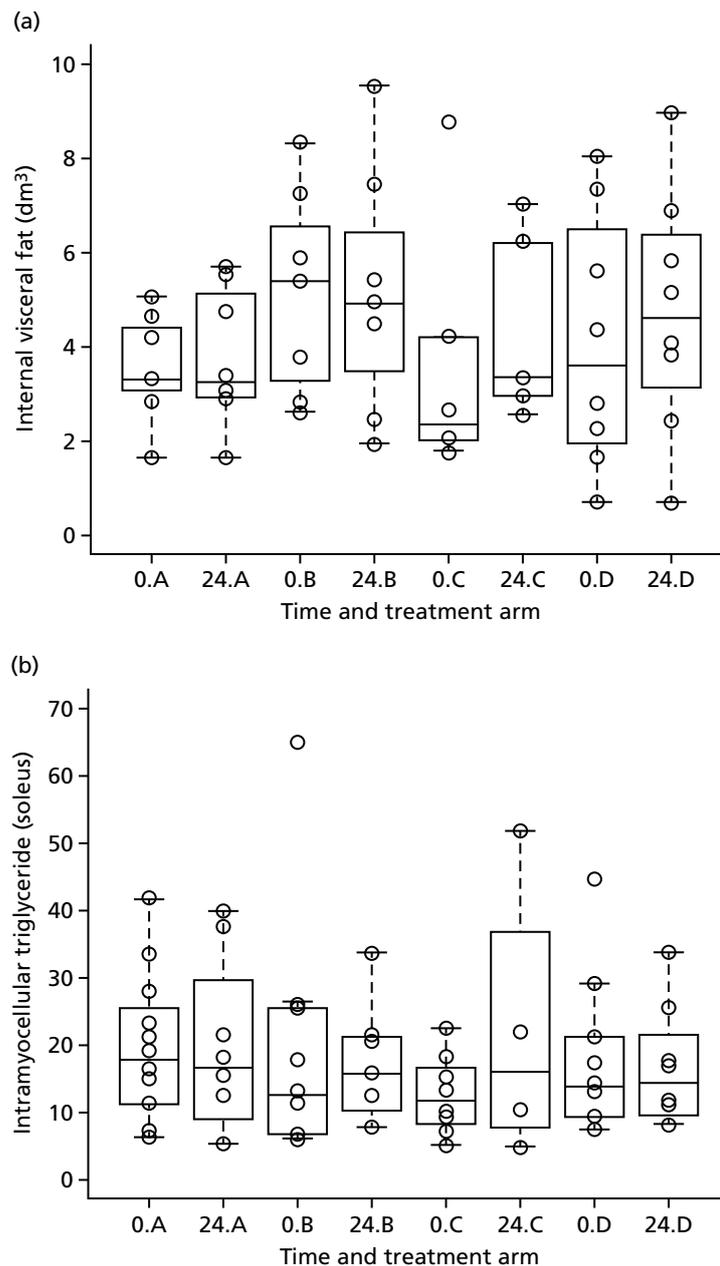
FIGURE 9 Box plots for the MRI and ^{1}H-MRS measurements at baseline and 24 weeks by treatment arm (with individual data points). (a) Internal visceral fat; (b) intramyocellular triglyceride (soleus); (c) intrahepatic triglyceride; and (d) intramyocellular triglyceride (tibialis anterior). In all figures, A refers to the control arm; B, C and D refer to arms treated with 20, 40 and 80 mg of telmisartan, respectively; 0 refers to baseline and 24 refers to 24 weeks. (*continued*)
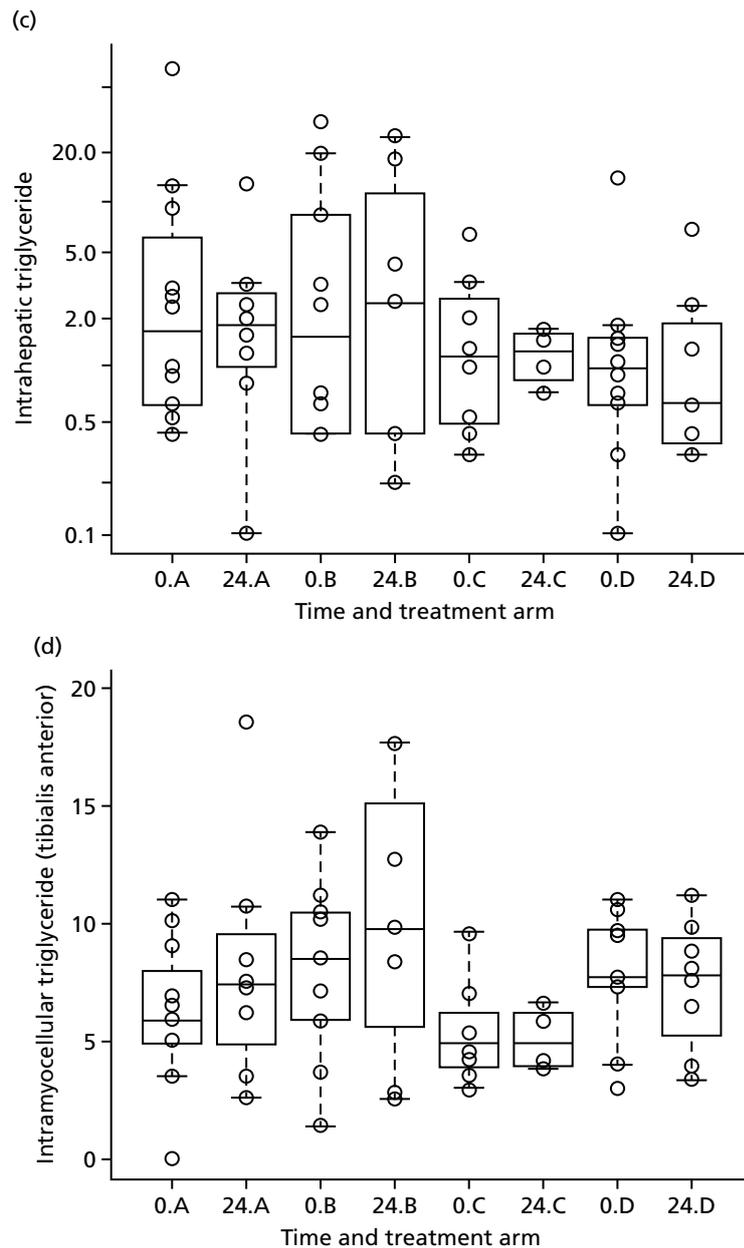
FIGURE 9 Box plots for the MRI and ^{1}H-MRS measurements at baseline and 24 weeks by treatment arm (with individual data points). (a) Internal visceral fat; (b) intramyocellular triglyceride (soleus); (c) intrahepatic triglyceride; and (d) intramyocellular triglyceride (tibialis anterior). In all figures, A refers to the control arm; B, C and D refer to arms treated with 20, 40 and 80 mg of telmisartan, respectively; 0 refers to baseline and 24 refers to 24 weeks.

All models were adjusted for the baseline value of the outcome and for weight change between baseline and 24 weeks. No statistically significant differences were observed in internal visceral fat at 24 weeks between the treatment arm (80 mg) and the control arm ($p = 0.9$).

A statistically significant difference in the intrahepatic triglyceride content was observed at 24 weeks between arm D and arm A (the control group) (mean reduction 1.74, 95% CI –2.787 to –0.642; $p = 0.005$). Although the model was adjusted for differences in baseline, these results should be interpreted with caution given the large within-group variability and low sample size (as reflected by the wide 95% CIs). No statistically significant differences were observed in intramyocellular triglyceride content in the soleus and tibialis anterior at 24 weeks between the treatment (80 mg) and control groups ($p = 0.8$). The complete set of parameter estimates are shown in *Appendix 6*.

Substudy 2: urine/renal biomarkers

The longitudinal profiles of biomarkers NGAL and ACR were considered in subgroups defined by tertiles (for NGAL) and thresholds (for ACR) at baseline. For analysis of ACR, the sample set was divided into three subsets based on KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease[65] (ACR < 3 mg/mmol, normal; ACR 3–30 mg/mmol, microalbuminuria; ACR > 30 mg/mmol, macroalbuminuria). Given the lower number of dropout in each subgroup (< 20), linear mixed-effect models were used rather than joint models to analyse the longitudinal variations. The models were adjusted for ethnicity, age and sex.

The three tertile subgroups for NGAL included 106, 106 and 105 patients, respectively, and NGAL scores were fitted in log-transformed scale for normality. The changes in weight from baseline were not significant and the final models were adjusted for age and sex, and information from dropped arms. The estimated treatment effects [arm D (80 mg) compared with arm A (control)] on NGAL were not significant in any of the tertile subgroups: –0.215 (95% CI –0.627 to 0.196; $p = 0.3$), –0.065 (95% CI –0.512 to 0.382; $p = 0.8$) and –0.347 (95% CI –0.893 to 0.198; $p = 0.3$).

The subgroup of ACR < 3 mg/mmol included 70 patients; 21 were included in the subgroup of ACR 3–30 mg/mmol and just one patient had an ACR of > 30 mg/mmol. Therefore, subgroups of ACR 3–30 mg/mmol and ACR > 30 mg/mmol were combined. ACR scores were fitted in log-transformed scale for normality. The changes in weight from baseline or sex were not significant, and the final models for the subgroups ACR < 3 mg/mmol and ACR > 3 mg/mmol were adjusted for age and information from dropped arms. The treatment effect on the longitudinal ACR for the subgroup with an ACR of > 3 mg/mmol was –0.665 (95% CI –1.310 to –0.019; $p = 0.04$), suggesting a significant but marginal treatment effect in arm D compared with the control arm.

There was no evidence of significant correlations between NGAL and ACR at baseline or at any other follow-up time points ($p < 0.05$). The longitudinal profiles, complete set of parameter estimates and scatterplots of ACR versus NGAL are shown in *Appendix 6*.

Safety data analysis

Each AR was categorised using the Medical Dictionary for Regulatory Activities (MedDRA)'s coding system organ class (SOC) terms (version 19.0) by the chief investigator. The number of ARs and number and percentage of patients affected in each category by treatment arm are presented in *Table 9*. Diarrhoea, fatigue, dizziness and pruritus were the most common ARs, observed in > 2% of patients. The number of occurrences of diarrhoea and dizziness was proportionately higher in the higher-dose arms. The number of ARs and number and percentage of patients affected in each category by treatment arm and by severity are shown in *Table 58* (see *Appendix 6*).

Serious adverse events
From a total of 377 patients, 21 SAEs were reported from 19 (5.0%) patients: five patients (4.8% of the allocated 105 patients; six events) in arm A (control), three patients (3.6%; three events) in arm B (20 mg), four patients (4.9%; four events) in arm C (40 mg) and seven patients (6.6%; eight events) in arm D (80 mg). No SUSARs were reported (see *Table 59* in *Appendix 5* for full details). We compared the percentage of patients who had one or more SAEs between telmisartan-treated arms and the control arm using the Fisher's exact test. There was no evidence of difference in percentage of SAEs between telmisartan-treated arms and the control arms ($p = 0.8$).

TABLE 9 Adverse reactions (by SOC and preferred terms according to the Medical Dictionary for Regulatory Activities)

| Category of events (SOC term) | AR description (PT) | Treatment arm | | | | | | | | | | | |
| | | Arm B (20 mg) (N = 84) | | | Arm C (40 mg) (N = 82) | | | Arm D (80 mg) (N = 106) | | | Total randomised (N = 377) | | |
		Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients
Blood and lymphatic system disorders	Neutropenia	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
Cardiac disorders	Palpitations	0	0	0.0	0	0	0.0	3	3	2.8	3	3	0.8
Congenital, familial and genetic disorders	Double ureter	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
Ear and labyrinth disorders	Ear pain	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
Eye disorders	Dry eye	0	0	0.0	0	0	0.0	2	1	0.9	2	1	0.3
	Lacrimation increased	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Vision blurred	1	1	1.2	1	1	1.2	2	2	1.9	4	4	1.1
	Visual impairment	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
Gastrointestinal disorders	Abdominal distension	0	0	0.0	3	3	3.7	1	1	0.9	4	4	1.1
	Abdominal pain (upper)	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Constipation	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Diarrhoea	1	1	1.2	3	2	2.4	6	6	5.7	10	9	2.4
	Dry mouth	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Dyspepsia	2	2	2.4	1	1	1.2	1	1	0.9	4	4	1.1
	Faeces (soft)	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Mouth ulceration	0	0	0.0	0	0	0.0	2	2	1.9	2	2	0.5
	Nausea	1	1	1.2	3	2	2.4	2	1	0.9	6	4	1.1
	Tongue coated	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Vomiting	0	0	0.0	2	2	2.4	1	1	0.9	3	3	0.8

TABLE 9 Adverse reactions (by SOC and preferred terms according to the Medical Dictionary for Regulatory Activities) (*continued*)

Category of events (SOC term)	AR description (PT)	Treatment arm											
		Arm B (20 mg) (*N* = 84)			Arm C (40 mg) (*N* = 82)			Arm D (80 mg) (*N* = 106)			Total randomised (*N* = 377)		
		Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients
General disorders and administration site conditions	Asthenia	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Chest pain	0	0	0.0	1	1	1.2	1	1	0.9	2	2	0.5
	Fatigue	5	4	4.8	4	4	4.9	6	6	5.7	15	14	3.7
	Feeling cold	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Feeling hot	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Influenza-like illness	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Malaise	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Pyrexia	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
Infections and infestations	Acute sinusitis	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Campylobacter gastroenteritis	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Influenza	2	2	2.4	1	1	1.2	4	4	3.8	7	7	1.9
	Lower respiratory tract infection	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Nasopharyngitis	0	0	0.0	1	1	1.2	2	2	1.9	3	3	0.8
	Onychomycosis	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Rhinitis	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Sinusitis	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Upper respiratory tract infection	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Urinary tract infection	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
Injury, poisoning and procedural complications	Fall	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
Investigations	Hepatic enzyme increased	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Weight increased	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3

Category of events (SOC term)	AR description (PT)	Treatment arm											
		Arm B (20 mg) (*N* = 84)			Arm C (40 mg) (*N* = 82)			Arm D (80 mg) (*N* = 106)			Total randomised (*N* = 377)		
		Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients
Metabolism and nutrition disorders	Increased appetite	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
Musculoskeletal and connective tissue disorders	Arthralgia	1	1	1.2	1	1	1.2	0	0	0.0	2	2	0.5
	Back pain	2	2	2.4	0	0	0.0	1	1	0.9	3	3	0.8
	Myalgia	0	0	0.0	0	0	0.0	2	2	1.9	2	2	0.5
	Neck pain	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Osteopenia	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Pain in jaw	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
Nervous system disorders	Ageusia	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Amnesia	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Burning sensation	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Disturbance in attention	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Dizziness	6	6	7.1	7	6	7.3	17	16	15.1	30	28	7.4
	Dysgeusia	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Headache	6	6	7.1	7	7	8.5	11	9	8.5	24	22	5.8
	Loss of consciousness	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Paraesthesia	0	0	0.0	0	0	0.0	2	2	1.9	2	2	0.5
	Somnolence	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Syncope	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Tension headache	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Tremor	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Trigeminal neuralgia	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3

TABLE 9 Adverse reactions (by SOC and preferred terms according to the Medical Dictionary for Regulatory Activities) (*continued*)

Category of events (SOC term)	AR description (PT)	Arm B (20 mg) (*N* = 84)			Arm C (40 mg) (*N* = 82)			Arm D (80 mg) (*N* = 106)			Total randomised (*N* = 377)		
		Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients
Psychiatric disorders	Anxiety	0	0	0.0	3	3	3.7	1	1	0.9	4	4	1.1
	Confusional state	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Depressed mood	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Depression	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Insomnia	1	1	1.2	0	0	0.0	3	3	2.8	4	4	1.1
	Morbid thoughts	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
Renal and urinary disorders	Chromaturia	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Haematuria	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Renal impairment	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
Reproductive system and breast disorders	Ejaculation failure	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
Respiratory, thoracic and mediastinal disorders	Cough	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Epistaxis	0	0	0.0	0	0	0.0	2	2	1.9	2	2	0.5
	Oropharyngeal pain	0	0	0.0	1	1	1.2	1	1	0.9	2	2	0.5
	Pulmonary fibrosis	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Sinus congestion	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
Skin and subcutaneous tissue disorders	Angioedema	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Dry skin	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Hyperhidrosis	2	2	2.4	1	1	1.2	0	0	0.0	3	3	0.8
	Photosensitivity reaction	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Pruritus	4	4	4.8	1	1	1.2	3	3	2.8	8	8	2.1
	Rash	1	1	1.2	1	1	1.2	4	4	3.8	6	6	1.6

| Category of events (SOC term) | AR description (PT) | Treatment arm | | | | | | | | | | | |
| | | Arm B (20 mg) (N = 84) | | | Arm C (40 mg) (N = 82) | | | Arm D (80 mg) (N = 106) | | | Total randomised (N = 377) | | |
		Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients
Vascular disorders	Haematoma	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Hypertension	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Hypotension	1	1	1.2	2	1	1.2	1	1	0.9	4	3	0.8
	Orthostatic hypotension	0	0	0.0	3	2	2.4	1	1	0.9	4	3	0.8
Total		50	28	33.3	69	28	34.1	104	49	46.2	223	105	27.9

Compliance with study drug schedule

Any unused drug was collected during the follow-up and study medication compliance was assessed by counting the number of pills returned and entries made in the treatment diary. *Table 57* (see *Appendix 6*) presents a descriptive summary of compliance of the total dose consumed according to the treatment diary and according to the number of pills returned at each visit (at weeks 2, 4, 12 and 24) split by treatment arm. The baseline characteristics of those who provided compliance information were compared with the characteristics of patients who did not provide compliance information (see *Table 61* in *Appendix 6*).

There were no clinically important differences observed in the systolic or diastolic blood pressure, CD4 cell count and eGFR between those with compliance data and those without. However, on average, HIV viral load was higher in those who provided compliance data than in those who did not (see *Table 61* in *Appendix 6*). Analysis according to compliance (dose received) was carried out as a sensitivity analysis using IV regression (with randomisation as the instrument). We also carried out two additional exploratory compliance-adjusted analyses for HOMA-IR at 24 weeks to address the selection bias, given the above observation on HIV viral load. The results remained the same as the original sensitivity analysis (see *Appendix 6*, *Tables 28–30*).

Chapter 5 Discussion

A number of small clinical studies in the non-HIV-infected population[31,68–71] and meta-analyses of telmisartan's effect on insulin resistance[39] and other markers of glycaemic control[41] have suggested that telmisartan has a beneficial effect on glucose and lipid homeostasis. This study[51] and others[52] have shown that telmisartan results in partial reversal of metabolic toxicity induced by antiretrovirals in vitro, suggesting a potential beneficial effect of telmisartan in individuals infected with HIV, in whom cART-induced cardiometabolic toxicity is a concern. Based on these observations, in order to determine whether or not telmisartan has clinical utility, a robust, methodologically sound, adequately powered, randomised clinical trial was needed in individuals infected with HIV to investigate the effect of telmisartan on various metabolic parameters. Our in vitro study[51] also suggested a need for defining the dose–response of telmisartan; hence, a clinical trial with a novel adaptive design to investigate the effect of multiple doses of telmisartan was adopted. This was also considered to be necessary because it should not be assumed that the dose–response of telmisartan in hypertension (i.e. telmisartan is already licensed for use in the treatment of hypertension) would be equivalent in a repurposed indication (i.e. reduction of insulin resistance).

To the best of our knowledge, the TAILoR trial is the only RCT to date which has assessed the effect of telmisartan on insulin resistance in individuals infected with HIV. It is also important to note that this trial is also the largest RCT to investigate the effect of telmisartan on insulin resistance and other metabolic parameters in any clinical setting (HIV positive or negative).

Main findings

Primary outcome

The primary objective of the trial was to investigate whether or not telmisartan, at any of the doses tested, resulted in a reduction in HOMA-IR, a validated marker of insulin resistance, in individuals infected with HIV over a period of 24 weeks. Using a novel adaptive design, the trial was divided into two stages; the first was to identify the best dose(s) of telmisartan (20, 40 or 80 mg) when compared with current standard of care, and the second stage was to compare one or more doses of telmisartan for a further 24 weeks. The first stage, conducted in 154 patients, identified one dose (80 mg of telmisartan) that met the prespecified end point and was subsequently tested in the second stage. The final analysis, conducted in 211 individuals, demonstrated that telmisartan (80 mg) did not result in a statistically significant reduction in HOMA-IR when compared with the control arm over 24 weeks.

Secondary outcomes

We used QUICKI and revised QUICKI, two alternative indices of insulin resistance, to confirm the effect of telmisartan on HOMA-IR. Telmisartan did not show a statistically significant increase (QUICKI and revised QUICKI are log measures and, therefore, are expected to increase if there is any reduction in insulin resistance) in these indices at 24 weeks in comparison with the control arm.

A longitudinal analysis of the effect of telmisartan on HOMA-IR, QUICKI and revised QUICKI over a period of 48 weeks, when compared with the control arm, showed that while there was no change in HOMA-IR and QUICKI, there was a significant, but marginal, improvement in revised QUICKI ($p = 0.05$). Telmisartan (80 mg) did not have any effect on serum lipids (cholesterol, triglycerides, HDL-C and LDL-C) and adipokines (markers of homeostasis and inflammation: adiponectin, leptin, resistin, IL-8, TNF-α), but there was a significant decrease in hs-CRP over 48 weeks.

Two different substudies were conducted as part of this trial:

- Substudy 1 was an exploratory evaluation of the effect of telmisartan on total body, liver (intrahepatic) and limb (intramyocellular) fat distribution using MRI and ^{1}H-MRS. Telmisartan did not show any significant reduction in total body fat or limb fat, but significantly reduced liver fat over a period of 24 weeks.
- Substudy 2 investigated the effect of telmisartan on renal parameters. Telmisartan (80 mg) showed a significant decrease in ACR ($p = 0.04$) over a period of 48 weeks in patients with microalbuminuria (ACR > 3 mg/mmol), but did not affect urinary NGAL, a marker of kidney disease.

There were no safety concerns with any of the doses of telmisartan and, although 21 SAEs were reported throughout the study, these were similar between the treatment arms and the non-intervention arm, and there was no dose-dependent increase in AEs. Of course, telmisartan has been used in a significant number of patients with hypertension, and it was not expected that this study would find any new, previously unreported, AEs. However, the finding of no decrease in blood pressure, even in patients without hypertension, was reassuring.

Interpretation and comparison with other studies

Telmisartan does not result in the reduction of Homeostatic Model Assessment of Insulin Resistance

Most of the evidence for telmisartan's beneficial effect on insulin resistance and other glycaemic markers has so far come from non-HIV clinical studies.[35,38] Since the inception of this trial, three studies have reported in patients infected with HIV:

- two observational studies showed a reduction in insulin resistance with telmisartan[48,72] with smaller sample sizes (18 and 13 participants)
- a single-arm open-label trial conducted in 35 individuals infected with HIV (the MATH trial[73]) that failed to find a significant change in HOMA-IR over 24 weeks.

Telmisartan has two main modes of action: it acts as an angiotensin II receptor antagonist and is a partial agonist at the adipocyte nuclear receptor PPAR-γ. Its effects have been attributed to the activation of PPAR-γ,[74] but its anti-angiotensin effects may also play a role.[52]

Human immunodeficiency virus causes disruption in glucose metabolism; in particular, the HIV viral protein inhibits PPAR-γ.[75] Adipose tissue, a major mediator of insulin sensitivity in the body, acts as a reservoir for HIV.[76] HIV infection causes inflammation that can lead to dysregulation of insulin signalling. HIV replication also causes upregulation of fatty acid synthase, an enzyme responsible for fatty acid synthesis;[77] this increases the production of fatty acids, which could result in lipotoxicity and insulin resistance. In addition to the effect of HIV, cART is known to be toxic to adipose tissue, with cART-induced inhibition of PPAR-γ well documented.[52,78,79] Therefore, both HIV and cART, independently, have a direct effect on PPAR-γ. Therefore, our decision to trial telmisartan to reduce insulin resistance had a biological basis. The reason that we did not any reduction in HOMA-IR find may have been either because (1) telmisartan was not potent enough to compete with the adverse effects of HIV and cART on adipocytes and/or (2) the cause of the rise in insulin resistance in HIV is dependent on many other pathways, and blocking one is not adequate enough to lead to an improvement.

In the non-HIV setting, there have only been a handful of RCTs to assess the effect of telmisartan on insulin resistance as a primary outcome measure. Two of the largest RCTs compared telmisartan with other ARBs but in the presence of either rosiglitazone[35] or rosuvastatin,[38] two drugs with independent effects on glucose and lipid homeostasis. Derosa *et al.*'s study[35] in 188 T2DM patients with MS who were on rosiglitazone demonstrated that telmisartan (40 mg) significantly reduced HOMA-IR by 17% at 24 weeks and by 29% at

48 weeks. Rizos *et al.*'s comparison[38] of telmisartan (80 mg) with olmesartan and irbesartan ($n = 151$) in hypertensive individuals with impaired glucose function demonstrated that telmisartan reduced HOMA-IR by 29% (whereas the other ARBs resulted in an increase in HOMA-IR). It is important to note that the patients studied in these trials were highly insulin resistant at baseline (median baseline HOMA-IR was 7.2 in the telmisartan arm in Derosa *et al.*;[35] and 2.6 in the telmisartan arm in Rizos *et al.*[38]). By contrast, in the present trial, the median baseline HOMA-IR was 1.6 in arm D. Therefore, detecting a reduction in HOMA-IR even further with telmisartan would be improbable without a much larger trial. It is also important to note that patients infected with HIV are treated with different cART combinations, each with a differing propensity to cause insulin resistance; this heterogeneity may have masked any positive effect, given the small numbers of patients in each drug combination group. Recruitment restricted to patients with higher HOMA-IRs may have been beneficial, but the feasibility of recruiting to such a trial would have been difficult.

Finally, it is important to highlight that 80 mg of telmisartan did have a positive impact on HOMA-IR. Even though patients in both the treatment and the control arms showed an increase in HOMA-IR between baseline and 24 weeks, the increase was of lesser magnitude in the treatment arm (+0.18; 7% increase) when compared with the control arm (+0.5; 20% increase). This was also observed at 48 weeks: HOMA-IR increased less with telmisartan (+0.74; 29% increase) than in the control arm (+1.2; 49% increase). It is not clear from the literature whether or not the effects of telmisartan increase with duration of treatment; we chose a 24-week time period based on observations in the non-HIV literature. A longer duration of treatment may have been more ideal but previous studies have shown that HOMA-IR changes within 4 weeks of starting antiretrovirals.[22]

Telmisartan showed a marginal beneficial effect on revised QUICKI ($p = 0.05$) in a longitudinal analysis over 48 weeks. Although HOMA-IR has been most commonly used as an index of insulin resistance under fasting conditions, a meta-analysis of surrogate measures of insulin resistance/sensitivity under fasting conditions identified revised QUICKI as the index that has the strongest correlation ($r = 0.68$) with the gold standard, the hyperinsulinaemic–euglycaemic clamp.[80] Revised QUICKI takes into account fasting serum NEFA levels, in addition to plasma glucose and serum insulin, which has been suggested to improve its correlation with the clamp-based index of insulin sensitivity and its discriminatory power, particularly in non-obese individuals who present with mild insulin resistance.[81] Given that the TAILoR cohort had a median baseline BMI of 26.7 kg/m^2 (marginally overweight as per NICE Clinical Guidelines[82]), revised QUICKI may be a more a sensitive indicator of the effect of telmisartan than HOMA-IR.

Telmisartan significantly reduced liver fat, but not total body or limb fat

A limited meta-analysis of three RCTs[83] with telmisartan treatment duration of 16–24 weeks (combined sample size of 62 participants) showed that telmisartan caused a significant reduction in visceral, but not in subcutaneous, fat suggesting a beneficial effect on body fat. However, the current study did not observe any significant reduction in internal visceral fat with any of the telmisartan doses over a period of 24 weeks. This is in line with the findings from the only other study that assessed the effect of telmisartan in patients infected with HIV on cART.[73] It is possible a longer timeframe may be required to reduce visceral fat in patients infected with HIV.

Our trial did find a significant reduction in liver, but not limb, fat in the 80 mg of telmisartan arm over a period of 24 weeks. This is the first time a positive effect on liver fat has been reported with telmisartan in patients infected with HIV, but given the small numbers ($n = 10$ in each of the three treatment arms; $n = 13$ in the non-intervention arm), the findings have to be interpreted with caution. Indeed, intrahepatic fat has been suggested to be a better marker of metabolic disease than visceral fat,[84] and may provide a better estimate of ectopic fatty acid deposition, which is one of the main reasons for the development of insulin resistance. However, our finding contrasts with a previous randomised trial[85] in obese adult individuals using 160 mg of telmisartan that did not find any changes in total, liver or limb fat.

Telmisartan did not change any of the plasma markers except high-sensitivity C-reactive protein

Telmisartan treatment did not improve lipids (total cholesterol, triglycerides, HDL and LDL-C) or plasma adipokines (adiponectin, leptin, resistin, IL-8 and TNFα) over a period of 48 weeks. This is in line with results from the MATH trial,[73] which also did not find any change in lipids or adipokines with the exception of a marginal increase in TNFα. However, meta-analyses of non-HIV clinical studies have shown that telmisartan results in a reduction in lipids[42] and adiponectin.[41] The effect of telmisartan on leptin, resistin, IL-8 and TNFα in patients not infected with HIV, however, has been contradictory and may be primarily because of small scale studies with limited generalisability.[35,86,87] The lack of effect of telmisartan on lipids in our trial may be because of the more complex clinical picture in patients infected with HIV (interaction with HIV and cART, duration of treatment) and because 58 (15.4%) of our patients were already on statins.

Many non-HIV clinical studies,[38,88] and a meta-analysis[43] ($n = 2632$ patients), have shown that telmisartan reduces hs-CRP levels. We observed a similar effect of telmisartan on hs-CRP over a period of 48 weeks in this trial. C-reactive protein promotes the proatherogenic activity of angiotensin, directly and indirectly stimulates structural and functional modification of arterial walls, heart and vascular remodelling and is considered to be an inflammatory marker.[89] In patients infected with HIV, hs-CRP may be an independent predictor of CVD;[90] the anti-inflammatory effect of telmisartan, through its direct blockade of angiotensin action, may be responsible for the reduction in hs-CRP in patients infected with HIV, and may thus have the potential to reduce the associated CVD risk.

Telmisartan and effect on microalbuminuria

There is already some preliminary evidence of the renoprotective effect of telmisartan in patients infected with HIV; Ucciferri et al.[48] showed that telmisartan reduced microalbuminuria in patients infected with HIV. A meta-analysis of 20 RCTs, including > 12,000 patients not infected with HIV on telmisartan, by Takagi et al.[47] also showed that telmisartan results in a significant reduction in urinary ACR. Our study was not designed to investigate renal outcomes, but telmisartan (80 mg) did result in a significant reduction ($p = 0.04$) in ACR over 48 weeks in patients with microalbuminuria (defined by an ACR of > 3 mg/mmol) when compared with the current standard of care. However, it should be noted that this effect was observed in a small sample size of only 22 participants who had microalbuminuria and, therefore, the results should be interpreted with caution. Telmisartan did not have an effect on NGAL, another marker of renal health. It may also be important to note that NGAL did not show any correlation with urinary ACR. ACR is a marker of glomerular injury, whereas NGAL is a marker of tubular damage.

Strength and weaknesses

Design of the study

The study used a novel adaptive design in order to investigate the optimal dose of telmisartan, with the potential to cause a reduction in HOMA-IR. Adaptive designs are allowed to incorporate a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of the interim data.[91] Adaptive trial designs are innovative designs recommended by both the US Food and Drug Administration[92] and the European Medicines Agency[93] for clinical R&D because they offer flexibility in identifying the optimal clinical benefit of the test treatment under study without undermining the validity and integrity of the study. In the current study, the adaptive design allowed for testing three different doses of telmisartan simultaneously and dropping two different 'loser doses' so that a potential 'winner dose' could be taken into the second stage of the study. Such a design also took into account the fact that the dose–response profile of telmisartan, when used, as in our study, to reduce insulin resistance, may differ from its dose–response profile when used for its licensed indication, which is to reduce hypertension. This design also provided an opportunity to stop the study at the interim analysis stage if the required benefit was not identified with any of the doses.

Given that no further data were collected on dose arms dropped at interim analysis, a potential weakness is our incomplete understanding of the effect of these dose arms.

Recruitment and retention

Despite positive results from feasibility assessments, recruitment to the study was slower than expected. Recruitment was also beset by delays in funding for extra treatment costs, which led to delays in the study set-up at various sites. We overcame these limitations, as described, but this nevertheless had an impact on the start of recruitment at different sites. The trial was supported by the Comprehensive Local Research Networks, which helped promote the trial nationally; this had a positive impact on recruitment.

Outcome measures and effect size

We used HOMA-IR as our primary outcome measure, which is the most commonly used measure of insulin resistance. In addition, several other markers of insulin resistance/sensitivity were used as secondary outcome measures. Ideally, an insulin clamp should have been used as the primary outcome measure, but the invasiveness and complexity of undertaking this in a large-scale trial ruled it out. Although there was no significant effect on HOMA-IR longitudinally over 48 weeks, there was a significant increase in revised QUICKI, which is biologically plausible, and perhaps is indicative of its greater sensitivity than HOMA-IR in evaluating changes in insulin action. Using QUICKI as a primary outcome measure may therefore have been preferable. A 24-week time point was selected for the primary outcome and 48 weeks for the total duration of drug treatment based on data on patients not infected with HIV. Whether or not a longer duration of treatment may show an effect is debatable. Furthermore, our patient group had relatively modest elevations in HOMA-IR and, it is possible, on the basis of data from patients not infected with HIV, that its effects may have been greater if the patients had been stratified to higher HOMA-IR elevations. The likely effect of HIV and cART on insulin resistance is likely to be complex and rely on multiple pathways; thus, blocking one pathway to overcome this may have been over simplistic.

Chapter 6 Conclusions and recommendations

In conclusion, this trial used a novel adaptive design to assess the effect of different doses of telmisartan on insulin resistance in patients infected with HIV on cART. There was no significant effect of telmisartan on our primary outcome measure, which was a reduction in HOMA-IR after 24 weeks' treatment, although we found a smaller elevation in HOMA-IR in patients on telmisartan than in the control arm. Interestingly, a longitudinal analysis over 48 weeks showed telmisartan increased revised QUICKI, a sensitive surrogate marker of insulin sensitivity, indicating that it may have potential beneficial metabolic effects in this population. This is also consistent with the positive effects of telmisartan on hs-CRP and hepatic fat accumulation. Consistent with the vast body of literature, telmisartan also reduced ACR, even though we had only a small number of patients who were albuminuric at baseline. It is, however, important to note that many of the positive effects of telmisartan we identified in this trial were marginally significant and thus could be false positives as a result of multiple testing. This has to be balanced against the fact that all the effects are biologically plausible, and the combination of effects taken together, particularly at 48 weeks, suggests that telmisartan's use in patients infected with HIV may have some benefits. However, whether or not improvement in these surrogate markers, which were secondary outcomes in our trial, would have any effect on clinical outcomes, including a reduction in cardiovascular events and mortality, is unclear.

Implications for clinical practice

Despite the use of newer agents and newer combinations, insulin resistance, related metabolic disease manifestations and the increased risk of CVD remain key problems in HIV-infected individuals on cART. Currently, these metabolic manifestations in patients infected with HIV are treated symptomatically using various drug classes such as statins (to reduce lipids), antidiabetic drugs such as metformin or glitazones (to lower glucose) and the growth hormone-releasing factor analogue tesamorelin.[94] Telmisartan is not used in current clinical practice for the prevention or treatment of metabolic disease, despite the accumulating evidence in the non-HIV setting. This trial does show some positive findings, such as telmisartan's effect on revised QUICKI (a surrogate for insulin sensitivity), hs-CRP (a marker of CVD) and intrahepatic fat (a marker of metabolic disease). Based on the results of the trial, telmisartan did not affect our primary outcome measure, reduction in insulin resistance, in HIV-infected individuals.

Recommendations for future research

- All the markers used in this trial, although clinically acceptable, are relatively crude. It is important to undertake detailed analysis in this patient group, for example of the lipidome, to understand in more detail the derangements that occur in adipocyte function with HIV infection and cART, and to understand more about the biology of this adipocyte dysfunction and whether or not drugs may be able to improve this.
- The detrimental effect of HIV infection and cART may be complex and dependent on multiple pathways. Given that less toxic cART is now available, and widely used, any future studies should be adequately powered to evaluate improvements in milder degrees of insulin resistance and should consider the use of multiple drugs, affecting different biological pathways. The duration of the study should be dependent on the drug(s) studied and outcome measures, and should be determined carefully during study design.
- Although the trial did not show any effect in our primary outcome measure over 24 weeks, there were improvements in some secondary outcome measures (revised QUICKI, hs-CRP and urinary albumin excretion over 48 weeks and hepatic fat accumulation over 24 weeks), all of which are biologically plausible and consistent with the literature. Whether or not telmisartan use would therefore lead to improvement in clinical outcomes is unclear. This remains an area of unmet medical need, not only in the HIV population, but also in the general population given the increasing prevalence of obesity and insulin resistance. Any future novel interventions, which may be individual therapies of novel targets or combination therapies (with or without telmisartan), should be powered on clinical outcome measures, with validation of some of the surrogate end points that have been used in this trial as well as novel biomarkers.

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Data-sharing statement

All available data are contained within the report. All queries should be submitted to the corresponding author.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, to develop new treatments, to monitor safety, and to plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Trial sites and principal investigators

TABLE 10 List of participating centres, PIs and initiation dates

Trial site	PI	Date opened
Brighton and Sussex Hospital	Dr Duncan Churchill	23 September 2013
Coventry and Warwickshire	Dr Satyajit Das	20 September 2013
George Eliot Hospital	Dr David Loay	26 January 2015
Guy's and St Thomas'	Dr Barry Peters	14 June 2013
Harrogate District Hospital	Dr Fabiola Martin	10 June 2014
James Cook University Hospital	Dr David Chadwick	29 October 2013
King's College	Dr Frank Post	4 June 2013
Manchester Royal Infirmary	Dr Gabriel Schembri	30 May 2014
New Croft Clinic (Royal Victoria Infirmary)	Dr Mayur Chauhan	15 April 2015
North Middlesex Hospital	Dr Jonathan Ainsworth	24 March 2014
Royal Bournemouth and Christchurch Hospitals	Dr Elbushra Herieka	2 May 2013
Royal Free, London	Professor Margaret Johnson	26 July 2013
Royal Liverpool Hospital	Professor Saye Khoo	21 February 2013
Southmead Hospital	Dr Mark Gompels	14 January 2015
St Helens Hospital	Dr Mas Chapomda	18 November 2014
St James's University Hospital	Dr Jane Minton	19 September 2013
St Stephen's Trust at Chelsea and Westminster	Dr Graeme Moyle	6 June 2014
Western General Hospital	Professor Clifford Leen	19 September 2013
YorClinic	Dr Fabiola Martin	4 December 2013

Appendix 2 List of approved brands of telmisartan

TABLE 11 Approved brands of telmisartan for use in the TAILoR trial

Brand/manufacturer	Date approved by TMG	Date approved for use in trial
Actavis	17 February 2014	4 April 2014 (needed MHRA approval to use generics)
Teva	17 February 2014	4 April 2014 (needed MHRA approval to use generics)
Pritor	20 February 2014	4 April 2014 (needed MHRA approval to use generics)
Tolura	7 May 2014	7 May 2014
Glenmark	22 June 2014	22 June 2014
Mylan	10 November 2014	7 May 2014

Appendix 3 Sample analysis plan

Sample shipment and storage

1. The TAILoR trial will use a specialist clinical trial courier for shipping of samples at a cost of £80 per shipment. A definitive timetable for shipment of samples is not provided here; the aim is to have regular shipments of samples from all sites so that:

    i. The shipment fits in with the analysis timelines presented in the progress reports and all outcome measures are analysed in time for statistical analysis.
    ii. There is always a readily available set of samples for transfer to the LCL for analysis.
    iii. Wherever possible, a full courier load is available so that the shipment is cost-effective.
    iv. All samples are shipped as soon as any site finishes the last follow-up of the last patient.

2. Shipments will also depend on individual site's storage capacity.
3. The Trial Co-ordinator, in liaison with sites and the TAILoR team in the Wolfson Centre, will arrange shipment of samples to Liverpool.
4. All samples will be stored in the –40 °C and –20 °C freezers in the BAF in the Royal Liverpool Hospital.
5. Both BAF and TAILoR SOPs will be followed to verify the samples on receipt at the BAF and appropriate records for sample receipt and transfer will be retained by all parties concerned (BAF, Wolfson Centre and CTRC).

Standard operating procedures and log sheets relevant to shipping and storage:

- SOP1 _ TAILoR Sample Processing and Storage. Version 1.0; dated 12 February 2013.
- SOP2 _ TAILoR Sample Processing and Storage for Samples Processed Offsite. Version 1.0; dated 11 July 2013.
- SOP3 _ TAILoR SOP _ Packaging and Shipment of Samples. Version 4.0; dated 24 March 2014.
- TAILoR SOP _ Sample Reception. Version 3.0; dated 25 March 2014.
- TAILoR Sample Transfer Log Sheet (BAF to Aintree Labs). Version 3.0; dated 10 April 2014.
- TAILoR Sample Transfer Log Sheet (BAF to LCL and back). Version 1.0; dated 15 January 2015.
- TAILoR Sample Transfer Log Sheet (BAF to WCPM). Version 1.0; dated 10 April 2014.

Laboratory analysis: primary outcome measure (Homeostatic Model Assessment of Insulin Resistance)

- The primary outcome measure, HOMA-IR, is calculated using plasma glucose and serum insulin levels; both of these will be analysed in the LCL, Royal Liverpool Hospital.
- Plasma glucose and serum insulin will be measured using standard clinical chemistry kits and analysers.
- All samples will be analysed in duplicates.
- Plasma and serum aliquots will be routinely batched and transferred to LCL. All samples will be analysed for plasma glucose, serum insulin, serum lipid profile and hs-CRP simultaneously.
- Results will be uploaded by LCL in batches directly on to the designated folder in the VOCAL (UoL) for further analyses.

Laboratory analysis: secondary outcome measures

1. Lipid profile (high-density lipoprotein cholesterol, total cholesterol, triglycerides and low-density lipoprotein cholesterol).

- High-density lipoprotein cholesterol, total cholesterol, triglycerides and LDL-C will be analysed by LCL using routine clinical chemistry methods.

2. Blood biomarkers (exploratory biomarkers).

- High-sensitivity C-reactive protein: this will be analysed by LCL using routine clinical chemistry methods.
- Adiponectin: this will be performed in the WCPM utilising electrochemiluminescence immunoassays (Meso Scale Discovery, Rockville, MD, USA) as per the manufacturer's protocol and analysed on a Meso Scale Discovery Sector Imager 2400A (Meso Scale Discovery, Rockville, MD, USA).

  - All samples will be analysed in duplicate.
  - Appropriate validation of the assay will be conducted and parameters such as accuracy, precision, linearity, reproducibility, sample recovery after spiking, inter and intra-assay variability will be measured before undertaking full sample analysis.

- Interleukin 6, TNF-α and resistin: this analysis will be performed in the WCPM, utilising electrochemiluminescence immunoassays as per the manufacturer's protocol and analysed on a Meso Scale Discovery Sector Imager 2400A.

  - All samples will be analysed in duplicate.
  - Appropriate validation of the assay will be conducted and parameters such as accuracy, precision, linearity, reproducibility, sample recovery after spiking, inter and intra-assay variability will be measured before undertaking full sample analysis.

Following validation, the IL-6 mesoscale assay was found not to meet desired criteria and hence the marker has been removed from the protocol. An amendment of the protocol to this effect has been submitted.

- Lipin 1: lipin 1 was originally included in the grant application on the assumption that it is secreted outside the adipose tissue and, therefore, measurable in plasma or serum using an enzyme-linked immunosorbent assay (ELISA). There is only one ELISA kit available in the market for human lipin 1 and this has been tested in-house but does not work. The current knowledge specifies that lipin 1 is integral to the cell and does not get secreted outside the cell. Therefore, the TMG has decided to replace lipin 1 with an alternative marker, leptin. An amendment of the protocol to this effect has been submitted.
- Leptin: this will be performed in the WCPM utilising electrochemiluminescence immunoassays as per the manufacturer's protocol and analysed on a Meso Scale Discovery Sector Imager 2400A.

  - All samples will be analysed in duplicate.
  - Appropriate validation of the assay will be conducted and parameters such as accuracy, precision, linearity, reproducibility, sample recovery after spiking, inter and intra-assay variability will be measured before undertaking full sample analysis.

- Non-esterified fatty acids: NEFAs are a new marker included following discussion with the IDSMC. Serum NEFA levels will be analysed using a colorimetric method on Randox RX daytona (Randox Laboratories Ltd, County Antrim, UK) in the GCLP facility, Royal Liverpool Hospital.

  - All samples will be analysed in triplicate.
  - Appropriate validation of the assay will be conducted and parameters such as accuracy, precision, linearity, reproducibility, sample recovery after spiking, inter- and intra-assay variability will be measured before undertaking full sample analysis.

Standard operating procedures relevant to biomarker analyses

- SOP _ Preparation of TAILoR Samples Master Plate. Version 2.0; dated 25 March 2016.
- SOP _ Adiponectin Assay – TAILoR samples. Version 1.0; dated 25 March 2016.
- SOP _ Resisitn Assay – TAILoR Samples. Version 2.0; dated 27 April 2016.
- SOP _ Leptin Assay – TAILoR Samples. Version 2.0; dated 27 April 2016.
- SOP _ Proinflammatory markers Assay – TAILoR Samples. Version 3.0; dated 25 April 2016.

3. Urinary biomarkers:

- Neutrophil gelatinase-associated lipocalin: this will be performed in the WCPM utilising electrochemiluminescence immunoassays as per the manufacturer's protocol and analysed on a Meso Scale Discovery Sector Imager 2400A.

    ○ All samples will be analysed in duplicate.
    ○ Appropriate validation of the assay will be conducted and parameters such as accuracy, precision, linearity, reproducibility, sample recovery after spiking, inter and intra-assay variability will be measured before undertaking full sample analysis.

- Albumin-to-creatinine ratio: this will be carried out in the LCL, Royal Liverpool Hospital.

Appendix 4 Statistical analysis plans

Interim analysis

Patient groups for analysis

The principle of intention to treat (ITT), as far as is practically possible, will be the main strategy of the analysis adopted for the primary outcome. The analysis will be conducted on all patients randomised to the treatment arms.

Patients who withdrew consent for trial continuation will contribute outcome data up until the point of withdrawal, unless the patient specifically requests that the data not to be used.

The membership of the analysis set will be determined and documented, and reasons for participant exclusion will be given prior to the randomisation lists being requested. Reasons may include missing data, loss to follow-up and treatment withdrawal (not excluded for ITT analysis set).

Analysis of primary outcome

The primary analysis will use the principle of ITT based on all the randomised participants, as far as is practically possible.

Homeostatic model assessment of insulin resistance was calculated by:

$$\text{HOMA-IR} = [\text{fasting insulin (µU/ml)} \times \text{fasting glucose (mmol/l)}] \div 22.5. \tag{1}$$

The conversion factor for fasting insulin is 0.144 to convert from pmol/l to µU/ml.

In order to satisfy the primary objective, we will evaluate three different doses against control in the first stage of the study. We will conduct an interim analysis that will allow ineffective doses to be eliminated quickly, while a dose showing a positive effect can be taken forward.

At the interim analysis, an analysis of covariance (ANCOVA) model is used by fitting the regression model:

$$\text{HOMA-IR}\_24 = \text{HOMA-IR}\_0 + \text{treatment} + \text{stratification factor (black/non-black)}. \tag{2}$$

Analysis of covariance is a more efficient approach when dealing with small group numbers and when there is imbalance in baseline HOMA-IR.

The test statistics are given by the t-values for each active dose treatment.

The largest of these test statistics will be compared with the interim critical value (2.782). The above ANCOVA model means that the coefficient related to treatment is positive for an increase in HOMA-IR. Therefore, we look at the negative of the test statistic and use in the decision below. Exceeding this value would correspond to a significant improvement in HOMA-IR score for the corresponding dose over control and would lead to this dose being immediately taken forward for further study, and to the trial being stopped.

The analysis will be proceeding as follows:

- If the largest of these statistics exceeds a critical value (equal to 2.782), this would mean that one active dose group shows a substantially higher mean reduction of 24-week HOMA-IR score than the control group and, therefore, the study will be stopped and the corresponding dose will be recommended for further testing.

- If any active dose show no improvement over control (i.e. has a negative measure of advantage), then that active dose will be dropped from the second stage*.
- If all three active doses satisfy this criterion, then the study will be stopped and no significant improvement over control will be claimed for any of the active doses.
- If some improvement over control is detected for at least one of the doses (i.e. if at least one test statistic is between 0 and 2.782), the study will progress to the second stage and the patients will be randomised between these dose(s) and control.

The design has been constructed under the assumption that for all patients the response (HOMA-IR score) is normally distributed with a common standard deviation, σ. These assumptions will be checked at the interim analysis stage (Levene's test for checking equal group variances and histogram for checking normality).

If any arm is dropped and the study progresses to the second stage, then the patients in the dropped arm(s) will stop the medication and will not be involved in second stage of the study.

Analysis of secondary efficacy outcomes
This analysis will not be presented in the interim analysis report.

Analyses of missing data/withdrawals
A summary table of the missing data will be presented, detailing the proportion of missing assessments overall and for each visit split by each treatment arm.

No sensitivity analyses will be carried out at this interim analysis stage.

The decision to drop treatments at the interim analysis stage will be based only on observed data at 24 weeks. The non-fasting samples data will be excluded from the analysis as they could interfere with the primary outcome (PI clinical judgement).

Final analysis

Data sets analysed
The principle of ITT, as far as is practically possible, will be the main strategy of the analysis adopted for the primary outcome. The analysis will be conducted on all patients randomised to the treatment arms, and for whom the outcome(s) of interest have been observed/measured. No imputations will be made.

The membership of the analysis set will be determined and documented, and reasons for participant exclusion will be given prior to the randomisation lists being requested. Reasons may include missing data, loss to follow-up and treatment withdrawal (not excluded for ITT analysis set).

Per-protocol analysis will not be considered.

Demographic and other baseline characteristics
Patients in each arm will be described separately with respect to sex, ethnicity, age, BMI, waist circumference (cm), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), CD4 cell count (cells/mm^3), HIV viral load (copies/ml), urea (mmol/l), potassium (mmol/l), creatinine (mmol/l), eGFR (ml/minute/1.73 m^2), ALT (IU/l), albumin (g/l) and sodium (mmol/l).

Categorical data will be presented using counts and percentages, and continuous data will be presented using number of patients, mean, mode, median, SD, minimum, maximum and interquartile range (IQR). Tests of statistical significance will not be undertaken for baseline characteristics; rather, the clinical importance of any imbalance will be noted.

Compliance with treatment

A descriptive summary of compliance will be presented. Total dose consumed according to the treatment diary is summarised by mean, mode, median, SD, minimum, maximum and IQR and split by site and by treatment.

Total dose will also be calculated according to the number of pills returned at each visit (week 2, 4, 12 and 24).

Discrepancies between these two estimates of total dose will be summarised by mean, mode, median, SD, minimum, maximum and IQR and split by site and by treatment.

Analysis of the primary outcome

Derivation
HOMA-IR was calculated by:

$$\text{HOMA-IR} = \frac{\text{fasting insulin } (\mu U / ml) \times \text{fasting glucose } (mmol/l)}{22.5}. \tag{3}$$

The conversion factor for fasting insulin to convert from pmol/l to µU/ml is 0.144.

Analysis
In order to satisfy the primary objective, we will evaluate all doses remaining after the interim analysis against control. An ANCOVA model is used by fitting the regression model:

$$\text{HOMA-IR}\_24 = \text{HOMA-IR}\_0 + \text{treatment} + \text{stratification factor (black/non-black)}, \tag{4}$$

where HOMA-IR _ 0 is the HOMA-IR value at the baseline prior to randomisation and HOMA-IR _ 24 is the HOMA-IR value at 24 weeks. The treatment variable is categorical with control as the reference level.

The test statistics are given by the *t*-values for each active dose treatment. The smallest of these test statistics will be compared with the final critical value (–2.086). A test statistic below the critical value would correspond to a significant improvement in HOMA-IR score for the corresponding dose over control.

If the smallest of these statistics is below a critical value (equal to –2.086), this would mean that (at least) one active dose group shows a substantially higher mean reduction of 24-week HOMA-IR score than the control group.

The design has been constructed under the assumption that for all patients the response (HOMA-IR score) is normally distributed with a common standard deviation, σ. These assumptions will be checked at the final analysis (Levene's test for checking equal group variances and histogram for checking normality). If HOMA-IR score is not normally distributed, then a log with base *e* transformation is used.

The primary decision will be based only on observed data at 24 weeks. The non-fasting sample data will be excluded from the primary analysis as HOMA-IR calculation required the fasting insulin and glucose to be a valid measurement.

Secondary outcome analyses

Longitudinal markers and outcomes
To identify change in the expression of the markers in telmisartan-treated arms remaining after the interim analysis in comparison with the control, 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 the marker is missing will be taken as the time of dropout. Those who

did not drop out from the study before $t = 48$ (i.e. had complete record of biomarker) were censored at 48 weeks.

Adjusting for the dropout, a joint model with random intercept and slope will be fitted to fully exploit the serial nature of the longitudinal marker data. The longitudinal submodel is defined by:

$$Y(t) = \beta_0 + \beta_1 t + \beta_2 X + W_1(t) + \epsilon(t), \tag{5}$$

where $Y(t)$ is the marker measurement at time $t = 0$ (baseline), T + 12 ($t = 12$), T + 24 ($t = 24$) and T + 48 ($t = 48$) weeks, and X includes categorical variables representing the treatment arm and stratification factor (black/non-black). β_0, β_1 and $\beta_2 = \{\beta_{21}, \beta_{22}\}$ are regression coefficients related to intercept, slope and the two covariates. $\epsilon(t)$ denotes the measurement error process and assumes Gaussian distribution with mean zero and variance σ^2_e. The hazard for dropout is modelled by:

$$\lambda(t) = \lambda_0(t) e^{\gamma W_1(t) + \beta_3 X}, \tag{6}$$

where $\lambda_0(t)$ is an unspecified baseline hazard and $\beta_3 = \{\beta_{31}, \beta_{32}\}$ and γ are regression coefficients related to covariates and association between dropout and longitudinal HOMA-IR outcome over time (0 and 48 weeks). We assume $W_1(t) = U_0 + U_1 t$ is an unobserved zero-mean Gaussian random process. β_{21} indicates the average treatment effect for each treatment arm compared with the control, once adjusted for potential informative dropout or missingness in the longitudinal marker outcome.

Difference in expected and unexpected serious adverse events
We compare the percentage of patients who had one or more SAEs using a chi-squared or Fisher's exact test of independence (if numbers are below five).

Change in Quantitative Insulin Sensitivity Check Index and revised Quantitative Insulin Sensitivity Check Index after 24 weeks of treatment in comparison with control
The two alternative measures of insulin resistance are calculated as:

$$\text{QUICKI} = 1/(\log G + \log I), \tag{7}$$

$$\text{Revised QUICKI} = 1/(\log G + \log I + \log NEFA), \tag{8}$$

where G is fasting glucose (mg/dl), I is fasting insulin (μU/ml) and NEFA is plasma NEFAs 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; Blood Sugar Converter, www.diabetes.co.uk/blood-sugar-converter.html; accessed 23 February 2016).

The ANCOVA model (see *Analysis of the primary outcome*) is used to analyse the two alternative measures. If the measures were not normally distributed, then a log with base *e* transformation will be used.

Unlike HOMA-IR, the log-insulin and log-glucose values are in the denominator for QUICKI/revised QUICKI. If there is a reduction in insulin resistance (i.e. increased insulin sensitivity), the above two measures will be increased at 24 weeks as compared with that at the baseline. Therefore, the largest of the test statistics from the ANCOVA of each active treatment arm (against the control arm) will be compared with the final critical value of 2.086. A test statistic above the critical value would correspond to a significant improvement in the score for the corresponding dose over control.

The fasting insulin and glucose are required to be valid measurements.

Substudy 1: magnetic resonance imaging/magnetic resonance scanning

Change in visceral, hepatic and muscle fat will be calculated by subtracting the visceral, hepatic and muscle fat values at baseline visit from those at the 24-week visit.

Summary estimates of location and variability will be reported for all treatment arms. Mean, median, SD, IQR and maximum and minimum values will be reported at each time point (at baseline and at 24 weeks) for the MRI measurements of internal visceral fat (dm^3), external abdominal fat (dm^3), total internal fat (dm^3), total external fat (dm^3) and total body fat (dm^3) and for the following ^{1}H-MRS measurements: intrahepatic and intramyocellular triglyceride content in liver, soleus and tibialis anterior (without dimensions, measured as a percentage).

In addition, three separate 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:

1. Model 1: 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 to the model to account for this potential confounder.
2. Model 2: intrahepatic triglyceride content in liver at 24 weeks will be the outcome variable. A multiple linear regression model will be fitted.
3. Model 3: intramyocellular triglyceride content in the soleus and tibialis anterior at 24 weeks will be treated as a bidimensional outcome. A multivariate multiple regression model will be fitted.

The treatment arm (as a factor) and the corresponding baseline values will be added in all models and sex will be included as covariates. Model assumptions regarding residuals will be assessed and non-parametric models will be considered, if appropriate. Summary statistics for patients with baseline measurements but with missing measurement at 24 weeks will be described.

Substudy 2: longitudinal expressions of urinary biomarkers

Change in urinary biomarker levels [creatine, urea, total protein and novel biomarkers such as kidney injury molecule-1 (KIM-1), NGAL and retinol-binding protein (RBP)] at 12, 24 and 48 weeks between telmisartan-treated arm(s) and the control arm will be determined by a joint longitudinal biomarker. The dropout model with random intercept and slope will be fitted to fully exploit the serial nature of the longitudinal biomarker data.

Sensitivity analyses

A summary table of the missing primary outcome data will be presented detailing the proportion of missing assessments overall and for each visit split by each treatment arm.

Sensitivity analyses 1: imputing values for missing Homeostatic Model Assessment of Insulin Resistance at 24 weeks

Missing HOMA-IR at 24 weeks values will be imputed using the MICE algorithm, conditional on HOMA-IR values at baseline, HOMA-IR values at 12 weeks and stratification factor (black/non-black). This analysis of missing data will be restricted to the primary outcome only; no imputation methods will be used on any of the secondary outcomes.

Sensitivity analyses 2: joint modelling for missing Homeostatic Model Assessment of Insulin Resistance at 24 weeks

The problem of non-ignorable missingness for HOMA-IR at 24 weeks is addressed through joint modelling of the longitudinal HOMA-IR and the time to dropout from the study. In this analysis, time to dropout is defined by patients who withdrew from the study or had missing HOMA-IR for any other reason at times $t = 0$, 12, or 24. Those who did not drop out from the study before $t = 24$ and those who had complete record of HOMA-IR will be censored at 24 weeks.

Sensitivity analyses 3: compliance-adjusted analysis

A compliance-adjusted primary outcome analysis will be undertaken using IV regression, in order to estimate the effect of actual dose on outcome. In the event of a discrepancy between the two measures of total dose for a given patient, the average of these two total doses will be used. When compliance information is missing for a given patient for some (but not the entire) treatment period, doses will be imputed for the missing weeks using simple imputation (i.e. based on patient average compliance over the whole treatment period for which compliance data are available). If compliance data are missing entirely for a given patient, they will be excluded from any further compliance analyses.

The suitability of randomisation as the sole instrument will be assessed using tests of exogeneity, redundancy and under/weak identification. The IV regression analysis will be undertaken using data from only those patients who provided some compliance information. Thus, the baseline characteristics of patients without any compliance information (in particular, in terms of blood pressure, CD4 cell count, HIV viral load, eGFR) will be presented and compared with those who provided any compliance information, in order to aid interpretation (in terms of likely bias and generalisability) of the results of the IV regression.

Safety evaluations

Data sets analysed
The safety analysis dataset will contain all participants that are randomised and commenced treatment.

Presentation of the data
All ARs reported by the clinical investigator will be presented in a table. The number (and percentage) of patients experiencing each AR (in terms of MedDRA coding of PT and SOC) will be presented for each treatment arm categorised by severity (mild, moderate, severe). For each patient, only the maximum severity experienced of each type of AR will be displayed. The number (and percentage) of occurrences of each AR will also be presented for each treatment arm. No formal statistical testing will be undertaken.

Total number of SAEs/SUSARs will be presented for each treatment arm, along with line listings for each case, including the following: randomisation number, SAE number, report type (final/initial), description (PT), description (SOC), SAE number, seriousness, additional description if medically significant, treatment, severity, expectedness, relationship (PI assessment, chief investigator's assessment), outcome and patient status in trial (continuing in trial/withdrawn from treatment).

All safety analyses will have independent quality control checking by an independent statistician.

Deviations from the final statistical analysis plan

Homeostatic Model Assessment of Insulin Resistance, Quantitative Insulin Sensitivity Check Index and revised Quantitative Insulin Sensitivity Check Index between 24 weeks and baseline
Analyses were undertaken adjusting for the weight change.

Change in weight (kg) is computed by: weight change = weight at 24 weeks – weight at baseline. Weight change is fitted as a continuous variable and fitted the ANCOVA model:

$$HOMA\text{-}IR\_24 = HOMA\text{-}IR\_0 + treatment + weight\ change + stratification\ factor\ (black/non\text{-}black) \qquad (9)$$

where HOMA-IR _ 0 is the HOMA-IR value at the baseline prior to randomisation and HOMA-IR _ 24 is the HOMA-IR value at 24 weeks.

Longitudinal outcomes

Analyses were undertaken adjusting for the weight change. Joint models for longitudinal outcomes also included data from the dropped arms.

We have used a bivariate joint model to simultaneously include longitudinal measurements of the marker and longitudinal weight as outcomes adjusting for the dropout. Data from the two dropped arms (B and C) were also included to further adjust for informative dropout and assumed that these patients completed the trial as planned. The fitted model takes the following form:

$$Y_1(t) = \beta_{01} + \beta_{11}t + \beta_{21}X + W_{11}(t) + \varepsilon_1(t) \tag{10}$$

$$Y_2(t) = \beta_{02} + \beta_{12}t + \beta_{22}X + W_{12}(t) + \varepsilon_2(t) \tag{11}$$

$$\lambda(t) = \lambda_0(t)e^{\gamma_1 W_{11}(t) + \gamma_2 W_{12}(t) + \beta_3 X}, \tag{12}$$

where $Y_1(t)$ is the marker measurement and $Y_2(t)$ is the weight at time t, where $t = 12$, 24 or 48 weeks, and X includes categorical variables representing the treatment arm (A, B, C and D), stratification factor (black/non-black) and marker or weight value at the baseline. β_0, β_1 and β_2 are regression coefficients related to intercept, slope and the covariates. $\epsilon(t)$ denotes independent measurement error process. $\lambda(t)$ models the hazard for dropout, $\lambda_0(t)$ is an unspecified baseline hazard and β_3 and $\gamma = \{\gamma_1, \gamma_2\}$ are regression coefficients related to covariates and association parameters. The dependence between the marker and weight was accounted for by correlated random-effects W_{11} and W_{12}. We assumed $W_1(t) = U_{01} + U_{11}t$ and $W_{12}(t) = U_{02} + U_{12}t$ with $\{U_{01}, U_{11}, U_{02}, U_{12}\} \sim N_4(0, \Sigma)$.

The treatment effect coefficient in β_{21} indicates the average treatment effect for each treatment arm compared with the control, once adjusted for potential informative dropout, while accounting for the weight changes over time. Approximate standard errors and 95% CIs were produced. The joineRML package in R was used for this analysis.

Magnetic resonance imaging/magnetic resonance scanning substudy

Models were fitted adjusted for weight change between baseline and 24 weeks. Change in weight is added as a covariate in the current model.

Longitudinal expressions of urinary biomarkers

Data were available for NGAL and ACR only.

The longitudinal profiles of the biomarker NGAL were considered in subgroups defined by tertiles at baseline (tertiles divide an ordered distribution of baseline NGAL into three parts, so each subgroup contains one-third of the sample).

For analysis of ACR, the subgroups were based on an ACR of < 3 mg/mmol, an ACR of 3–30 mg/mmol and an ACR of > 30 mg/mmol at baseline.

Given the lower number of dropouts in each subgroup (< 20), linear mixed-effect models were used to analyse the longitudinal variations rather than joint models. The models were adjusted for age. Weight change and sex were also added and, if found significant, they were included in the final model.

Sensitivity analyses 2: joint modelling for missing Homeostatic Model Assessment of Insulin Resistance at 24 weeks

The proposed joint model of random intercepts and random slopes was failed because the number of random effects and parameters requiring estimation exceeds the total number of observation points.

Although fitting a joint model with random intercepts is possible in principle, the model may not fully initialise the parameter estimates for the baseline hazard function. Hence, the proposed analysis was not carried out.

Sensitivity analyses 3: compliance-adjusted analysis

Two additional ad hoc exploratory compliance-adjusted analyses were carried out for HOMA-IR at 24 weeks to address the selection bias that is evident in original compliance-adjusted analysis (see *Sensitivity analyses*), given that patients who provided some compliance data had higher HIV viral load at baseline than those who did not provide any compliance data.

1. Instrumental variable regression was as for sensitivity analysis 3 (i.e. using complete case population), but additionally accounting for baseline HIV viral load.

Assumption: baseline HIV viral load is missing at random and there are no other factors (i.e. other than HIV viral load) that influence whether or not patients provide compliance data.

2. Multiple imputation was used to impute missing compliance information prior to carrying out IV regression, with HIV viral load at baseline as the key predictor in the imputation model (i.e. imputed compliance information used for all participants who had missing compliance information but who had baseline HIV viral load data). The same conditions as above using multiple imputation (20 imputations per patient using predictive mean matching with baseline HIV viral load as predictor variable) rather than including baseline HIV viral load in model.

Appendix 5 Protocol amendments

TABLE 12 List of amendments to the TAILoR trial

Amendment number	Details of amendment
Original application	Protocol version 1, 29 February 2012
Modified submission	Additional exclusion criteria added to protocol (version 2, 14 June 2012)
Amendment 1 (substantial)	Additional exclusion criteria added to protocol (version 2, 14 June 2012)
	Changes to PISC (version 3, 1 August 2012) to reflect transfer of data to a private company
	Change of PI at Brighton and Sussex Hospital
Amendment 2 (substantial)	Number of changes to protocol (version 3, 2 November 2012) including change in central laboratory, change in exclusion criteria, change in number and type of biological samples to be collected
	Changes to PISC (version 4.0, 2 November 2012)
	Addition of further site
Amendment 3 (substantial)	Addition of Royal Bournemouth and Christchurch Hospitals as a participating site
Amendment 4 (non-substantial)	Minor amendments to treatment diary
Amendment 5 (substantial)	Addition of St James's University Hospital Leeds
	Margaret Johnson replaces Dr Mike Youle as PI at the Royal Free London
Amendment 7 (minor)	Admin changes to protocol (version 4.0, 18 October 2013) including: • Travel expenses • Time windows for visits • Rewording of exclusion criteria • Clarification of what is meant by 'medical history' (test results to be included) • Removal of addresses • Change to contact details • Addition of website • Addition of clinic poster (version 1.0, 24 October 2013) • Change to main and substudy PISC (version 5.0, 29 October 2013) (contact details of trial co-ordinator) • Change to treatment diary (version 3.0, 29 October 2013) • Change to contact card (version 2.0, 24 June 2013)
Amendment 8 (substantial)	Addition of participating sites: • North Middlesex Hospital • Manchester Royal Infirmary • North Bristol NHS Trust • St Helens Hospital • Harrogate District Hospital
Amendment 9 (substantial)	Change to protocol (version 5.0, 24 February 2014) to allow the use of generic IMP
	Change to PISC (main study) (version 6.0, 3 February 2014)
Amendment 10 (substantial)	Addition of participating site: • George Eliot Hospital Nuneaton

TABLE 12 List of amendments to the TAILoR trial (*continued*)

Amendment number	Details of amendment
Amendment 11 (substantial)	Change to protocol (version 6.0, 19 August 2014) to clarify drugs in inclusion criteria, to allow substudy to be performed at other sites
	Change to PISC (version 7.0, 19 August 2014) main study
	Change to substudy PISC (version 6.0, 19 August 2014)
Amendment 12 (substantial)	Addition of Newcastle Upon Tyne Foundation Trust as a participating site
Amendment 13 (substantial)	Change to PISC to reflect potential interim analysis results (version 8a, 8b, 8c, 8d, 8e, 8f, 8g, 16 March 2015)
Amendment 14 (substantial)	Change to PISC (version 9.0, 20/05/2015)
	Production of additional information sheet (version 1.0, 29 May 2015)
	Increase in number of patients to be recruited (protocol version 7.0, 13 May 2016)
Notification of extension	Notification of extension to recruitment period
Amendment 15 (substantial)	Letter to notify sub-study patients of typo in version 4 substudy PISC
Amendment 16 (substantial)	Update to serum biomarker tests to be performed
	Urinary biomarkers to become a substudy
	Protocol version 8.0

Protocol deviations

The number of protocol deviations are summarised by treatment arm and presented in *Table 13*.

TABLE 13 Number of protocol deviations

Protocol deviation	Impact	Treatment arm, *n* (%)				Total number of patients, *n* (%)
		Arm A (*N* = 105)	Arm B (*N* = 84)	Arm C (*N* = 82)	Arm D (*N* = 106)	
Inclusion criteria – patients recruited that are not on an accepted drug treatment	Major	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Exclusion criteria – eGFR of < 60 ml/minute/1.73 m^2	Major	1 (1.0)	0 (0.0)	0 (0.0)	2 (1.9)	3 (0.8)
Exclusion criteria – patients who are already on/have been on other ARBs and/or ACE inhibitors within 4 weeks preceding randomisation	Major	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.9)	2 (0.5)
Treatment regime – premature discontinuation of randomised treatment for safety reasons	Major	1 (1.0)	6 (7.1)	12 (14.6)	9 (8.5)	28 (7.4)
Treatment regime – use of non-protocol dosing regime	Major	0 (0.0)	0 (0.0)	0 (0.0)	11 (10.4)	11 (2.9)
Study assessments at 12 weeks – missing or visits that occur outside the 2-week window	Minor	25 (23.8)	4 (4.8)	16 (19.5)	17 (16.0)	62 (16.4)

TABLE 13 Number of protocol deviations (*continued*)

| Protocol deviation | Impact | Treatment arm, *n* (%) | | | | Total number of patients, *n* (%) |
		Arm A (*N* = 105)	Arm B (*N* = 84)	Arm C (*N* = 82)	Arm D (*N* = 106)	
Study assessment at 48 weeks – missing or visits that occur outside the 2-week window	Minor	30 (28.6)	3 (3.6)	25 (30.5)	36 (34.0)	94 (24.9)
Study assessment at 24 weeks – missing or visits that occur outside the 2-week window	Major	31 (29.5)	5 (6.0)	19 (23.2)	26 (24.5)	81 (21.5)
Titration visit at 2 weeks – missing or visits that occur outside the 4-day window	Major	0 (0.0)	0 (0.0)	13 (15.9)	13 (12.3)	26 (13.8)[a]
Titration visit at 4 weeks – missing or visits that occur outside the 4-day window	Major	0 (0.0)	0 (0.0)	0 (0.0)	23 (21.7)	23 (21.7)[b]
Study assessments – samples not collected/ unfasted at 12 weeks	Minor	1 (1.0)	1 (1.2)	0 (0.0)	4 (3.8)	6 (1.6)
Study assessments – samples not collected/ unfasted at 48 weeks	Minor	3 (2.9)	4 (4.8)	3 (3.7)	2 (1.9)	12 (3.2)
Study assessments – haemolysed samples collected at 12 weeks	Minor	2 (1.9)	0 (0.0)	2 (2.4)	1 (0.9)	5 (1.3)
Study assessments – haemolysed samples collected at 48 weeks	Minor	2 (1.9)	0 (0.0)	3 (3.7)	1 (0.9)	6 (1.6)
Study assessments – samples not collected/ unfasted at 24 weeks	Major	1 (1.0)	1 (1.2)	1 (1.2)	2 (1.9)	5 (1.3)
Study assessments – haemolysed samples collected at 24 weeks	Major	0 (0.0)	1 (1.2)	2 (2.4)	2 (1.9)	5 (1.3)
Study assessments – samples not collected/ unfasted at baseline	Major	1 (1.0)	1 (1.2)	0 (0.0)	2 (1.9)	4 (1.1)
Study assessments – haemolysed samples collected at baseline	Major	3 (2.9)	2 (2.4)	2 (2.4)	3 (2.8)	10 (2.7)
Blood pressure not being checked at baseline and follow-up visits	Major	0 (0.0)	1 (1.2)	1 (1.2)	0 (0.0)	2 (0.5)

a Titration visit at 2 weeks occurred for arm C and arm D only.
b Titration visit at 4 weeks occurred for arm D only.

Appendix 6 Further details of results

Screening and participant flow

TABLE 14 Summary of screening data for all sites

	Date			Number of patients	
Site	Opened	First patient randomised	Last patient randomised	Screened	Recruited
Brighton and Sussex Hospital	23 September 2013	1 November 2013	15 June 2015	43	39
Coventry and Warwickshire	20 September 2013	23 September 2013	14 November 2014	50	22
George Eliot Hospital	26 January 2015	27 January 2015	26 June 2015	60	15
Guy's and St Thomas'	14 June 2013	25 July 2013	26 May 2015	109	47
Harrogate District Hospital	10 June 2014	11 June 2014	13 July 2015	10	6
James Cook University Hospital	29 October 2013	14 November 2013	14 May 2015	68	27
King's College	4 June 2013	25 July 2013	3 July 2015	84	24
Manchester Royal Infirmary	30 May 2014	26 June 2014	17 June 2015	42	20
New Croft Clinic (Royal Victoria Infirmary)	15 April 2015	11 June 2015	9 July 2015	3	2
North Middlesex Hospital	24 March 2014	1 April 2014	18 May 2015	94	11
Royal Bournemouth Hospital	2 May 2013	25 July 2013	29 June 2015	525	14
Royal Free, London	26 July 2013	18 September 2013	28 April 2015	104	24
Royal Liverpool Hospital	21 February 2013	19 March 2013	10 April 2015	143	41
Southmead Hospital	14 January 2015	22 January 2015	20 July 2015	9	8
St Helens Hospital	18 November 2014	30 January 2015	7 July 2015	7	4
St James's University Hospital	19 September 2013	28 November 2013	28 May 2015	134	11
St Stephen's Trust at Chelsea and Westminster	6 June 2014	20 June 2014	16 June 2015	40	40
Western General Hospital	19 September 2013	10 March 2014	14 May 2015	287	12
YorClinic	4 December 2013	23 January 2014	16 April 2015	138	10
Total	–	–	–	1950	377

TABLE 15 Detailed summary of screening data for all sites

Site ID	Site	Number of patients who were assessed for eligibility at the screening visit	Those who met the study inclusion criteria at screening prior to consent being sought, n (%)	Those who did not meet the study inclusion criteria at screening prior to consent being sought, n (%)	Those who were eligible at screening and consent obtained, n (%)	Those who were eligible at screening but consent not obtained, n (%)	Those who provided consent but were not randomised, n (%)	Those who provided consent and were randomised, n (%)
0149	Brighton and Sussex Hospital	43	42 (97.7)	1 (2.3)	40 (95.2)	2 (4.8)	1 (2.5)	39 (97.5)
2575	Coventry and Warwickshire	50	50 (100.0)	0 (0.0)	22 (44.0)	28 (56.0)	0 (0.0)	22 (100.0)
0187	George Eliot Hospital	60	36 (60.0)	24 (40.0)	15 (41.7)	21 (58.3)	0 (0.0)	15 (100.0)
0241	Guy's and St Thomas'	109	101 (92.7)	8 (7.3)	47 (46.5)	54 (53.5)	0 (0.0)	47 (100.0)
0076	Harrogate District Hospital	10	10 (100.0)	0 (0.0)	6 (60.0)	4 (40.0)	0 (0.0)	6 (100.0)
0006	James Cook University Hospital	68	67 (98.5)	1 (1.5)	27 (40.3)	40 (59.7)	0 (0.0)	27 (100.0)
0161	King's College	84	73 (86.9)	11 (13.1)	24 (32.9)	49 (67.1)	0 (0.0)	24 (100.0)
0080	Manchester Royal Infirmary	42	41 (97.6)	1 (2.4)	20 (48.8)	21 (51.2)	0 (0.0)	20 (100.0)
0072	New Croft Clinic (Royal Victoria Infirmary)	3	2 (66.7)	1 (33.3)	2 (100.0)	0 (0.0)	0 (0.0)	2 (100.0)
0145	North Middlesex Hospital	94	87 (92.6)	7 (7.4)	11 (12.6)	76 (87.4)	0 (0.0)	11 (100.0)
0112	Royal Bournemouth Hospital	525	123 (23.4)	402 (76.6)	50 (40.7)	73 (59.3)	36[a] (72.0)	14 (28.0)
0155	Royal Free, London	104	89 (85.6)	15 (14.4)	28 (31.5)	61 (68.5)	5 (17.9)	23 (82.1)
0046	Royal Liverpool Hospital	143	136 (95.1)	7 (4.9)	42 (30.9)	94 (69.1)	2 (4.8)	40 (95.2)
0230	Southmead Hospital	9	8 (88.9)	1 (11.1)	8 (100.0)	0 (0.0)	0 (0.0)	8 (100.0)
7478	St Helens Hospital	7	7 (100.0)	0 (0.0)	5 (71.4)	2 (28.6)	0 (0.0)	5 (100.0)
0050	St James's University Hospital	134	79 (59.0)	55 (41)	11 (13.9)	68 (86.1)	0 (0.0)	11 (100.0)

Site ID	Site	Number of patients who were assessed for eligibility at the screening visit	Those who met the study inclusion criteria at screening prior to consent being sought, *n* (%)	Those who did not meet the study inclusion criteria at screening prior to consent being sought, *n* (%)	Those who were eligible at screening and consent obtained, *n* (%)	Those who were eligible at screening but consent not obtained, *n* (%)	Those who provided consent but were not randomised, *n* (%)	Those who provided consent and were randomised, *n* (%)
0016	St Stephen's Trust at Chelsea and Westminster	40	40 (100.0)	0 (0.0)	40 (100.0)	0 (0.0)	0 (0.0)	40 (100.0)
0361	Western General Hospital	287	72 (25.1)	215 (74.9)	12 (16.7)	60 (83.3)	0 (0.0)	12 (100.0)
9446	YorClinic	138	55 (39.9)	83 (60.1)	10 (18.2)	45 (81.8)	0 (0.0)	10 (100.0)
TOTAL		1950	1118 (57.3)	832 (42.7)	420 (37.6)	698 (62.4)	44 (10.5)	376[b] (89.5)

a Site had a staffing issue. They had four nurses during the recruitment period. There were gaps of around 3 months between one nurse leaving and the next starting post.
b There are three missing screening logs, see CONSORT diagram, *Chapter 4*, *Figure 4*, for further detail.

TABLE 16 Reasons for ineligibility, by site

Site ID	Reason for ineligibility (*n*)														
	Aged < 18 years	Pre-existing diagnosis of diabetes mellitus	Participant has renal disease	Participant has known untreated renal artery stenosis	Participant has cholestasis, biliary obstructive disorders or severe hepatic impairment	Prior diagnosis of hepatitis C (+ve PCR result in previous 6 months)	Participant on unboosted atazanavir	Participant on on/has been on hormone therapy, anabolics and insulin sensitisers (previous 6 months)	Participant on/has been on other ARBs and/or ACE inhibitors (within 4 weeks before randomisation)	Suspected poor compliance	Pregnant/ lactating	Women of childbearing age (unless using reliable contraception that does not interact with their antiretroviral therapy)	Co-enrolment in other drug trials	Participant in a trial of an IMP likely to influence insulin sensitivity	Other reason not eligible
0006	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
0016	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0046	0	0	0	0	0	0	0	0	0	0	0	3	0	0	7
0050	0	2	5	0	0	4	3	0	0	6	5	2	0	0	28
0072	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
0076	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0080	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
0112	5	55	26	7	7	23	16	2	42	151	10	9	11	0	40
0145	0	0	1	0	1	1	0	1	0	0	0	0	0	0	3
0149	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
0155	0	0	0	0	0	0	0	0	7	3	1	1	0	0	3
0161	0	0	0	0	0	1	0	0	5	0	0	0	0	0	5
0187	0	0	2	0	0	1	3	0	0	7	1	0	0	0	11
0230	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
0241	0	1	0	0	1	0	0	0	1	0	0	0	1	0	4
0361	0	15	26	0	4	44	1	5	31	10	1	1	2	0	92
2575	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7478	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9446	0	7	12	0	6	4	0	4	12	25	1	1	1	0	13
TOTAL	5	80	73	7	19	78	23	13	99	202	19	17	15	0	208

+ve, positive; PCR, polymerase chain reaction.

TABLE 17 Reasons for exclusion

Reason	Number of patients
Aged < 18 years	5
Pre-existing diagnosis of diabetes mellitus	80
Participant has renal disease	73
Participant has known untreated renal artery stenosis	7
Participant has cholestasis, biliary obstructive disorders or severe hepatic impairment	19
Prior diagnosis of hepatitis C (i.e. positive PCR result in previous 6 months)	78
Participant on unboosted atazanavir	23
Participant on/have been on hormone therapy, anabolics and insulin sensitisers (previous 6 months)	13
Participant on/have been on other ARBs and/or ACE inhibitors (within 4 weeks before randomisation)	99
Suspected poor compliance	202
Pregnant/lactating	19
Women of childbearing age (unless using reliable contraception that does not interact with their antiretroviral therapy)	17
Co-enrolment in other drug trials	15
Participant in a trial of an IMP likely to influence insulin sensitivity	0
Other reason not eligible[a]	208

a Free-text field: alcohol problems, cannot commit to extra visits re travelling, multiple health issues currently under investigation, planning pregnancy, etc.

Baseline data

TABLE 18 Baseline CD4 cell count and HIV viral load by treatment arm

Characteristic	Treatment arm			
	Arm A (N = 105)	Arm B (N = 84)	Arm C (N = 82)	Arm D (N = 106)
CD4 cell count (cells/mm³)	(n = 102)	(n = 83)	(n = 78)	(n = 101)
Median (IQR); min.–max.	598 (480–756); 200–1400	580 (425–792); 131–1501	582 (440–770); 129–1467	593 (427–783); 62–1674
CD4 cell count and HIV viral load (%)	(n = 102)		(n = 81)	
Mean (SD); min.–max.	32.1 (7.7); 14.0–52.0	29.2 (8.6); 8.0–47.0	30.1 (9.3); 6.0–52.0	30.5 (7.9); 6.0–48.0
HIV viral load (copies/ml)	(n = 35)	(n = 17)	(n = 31)	(n = 34)
Median (IQR); min.–max.[a]	39 (0–40); 0–577	0 (0–39); 0–120	36 (0–44); 0–649	20 (0–39); 0–148
< 10, n (%)	2 (1.9)	1 (1.2)	2 (2.4)	1 (0.9)
< 20, n (%)	13 (12.4)	20 (23.8)	11 (13.4)	23 (21.7)
< 40, n (%)	50 (47.6)	38 (45.2)	35 (42.7)	43 (40.6)
< 45, n (%)	2 (1.9)	6 (7.1)	3 (3.7)	3 (2.8)
< 100, n (%)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)

max., maximum; min., minimum.
a Some data are presented in both continuous and categorical form as a result of there being upper and lower limits of measurement.

TABLE 19 Baseline liver function by treatment arm

Characteristic	Treatment arm			
	Arm A (*N* = 105)	Arm B (*N* = 84)	Arm C (*N* = 82)	Arm D (*N* = 106)
ALT (IU/l)	(*n* = 92)	(*n* = 75)	(*n* = 77)	(*n* = 96)
Median (IQR); min.–max.	24.0 (17.5–33.5); 9.0–80.0	26.0 (19.0–36.0); 6.0–142.0	27.0 (20.0–35.0); 10.0–84.0	25.0 (18.0–38.0); 8.0–305.0[a]
ALP (IU/l)	(*n* = 103)	(*n* = 83)	(*n* = 74)	(*n* = 102)
Median (IQR); min.–max.	88.0 (71.0–107.0); 30.0–371.0	85.0 (72.0–113.0); 40.0–403.0	77.0 (62.0–98.0); 32.0–179.0	80.0 (65.0–100.0); 35.0–309.0
Albumin (g/l)	(*n* = 102)	(*n* = 83)	(*n* = 81)	(*n* = 103)
Mean (SD); min.–max.	43.7 (4.1); 33.0–51.0	44.3 (3.5); 36.0–51.0	44.2 (3.2); 37.0–54.0	44.7 (3.8); 34.0–53.0
Total protein (g/l)	(*n* = 72)	(*n* = 59)	(*n* = 59)	(*n* = 69)
Mean (SD); min.–max.	74.5 (5.3); 63.0–87.0	73.7 (4.0); 66.0–84.0	74.2 (4.6); 65.0–85.0	73.4 (3.9); 65.0–84.0
Bilirubin (µmol/l)	(*n* = 100)	(*n* = 78)	(*n* = 76)	(*n* = 98)
Median (IQR); min.–max.[b]	6.0 (5.0–9.5); 2.0–67.0	7.0 (5.0–9.0); 3.0–82.0	8.0 (6.0–12.0); 3.0–100.0	7.0 (5.0–14.0); 2.0–68.0
< 2, *n* (%)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
< 3, *n* (%)	3 (2.9)	2 (2.4)	2 (2.4)	2 (1.9)
< 15, *n* (%)	1 (1.0)	2 (2.4)	1 (1.2)	4 (3.8)

max., maximum; min., minimum.
a Confirmed correct.
b Some data are presented in both continuous and categorical form as a result of there being upper and lower limits of measurement.

TABLE 20 Baseline full blood count by treatment arm

Characteristic	Treatment arm			
	Arm A (*N* = 105)	Arm B (*N* = 84)	Arm C (*N* = 82)	Arm D (*N* = 106)
Haematocrit (%)	(*n* = 70)	(*n* = 49)	(*n* = 50)	(*n* = 65)
Mean (SD); min.–max.	42.23 (3.29); 34.2–53.0	42.16 (6.51); 5.1–51.0	42.82 (3.18); 34.6–49.9	42.46 (5.69); 5.3–50.0
Haemoglobin (g/dl)		(*n* = 83)		
Mean (SD); min.–max.	143.77 (12.28); 114–171	144.16 (13.32); 107–173	146.73 (12.15); 114–177	145.72 (12.92); 80–171
Red blood cell count (10^{12}/l)	(*n* = 98)	(*n* = 79)	(*n* = 77)	(*n* = 97)
Mean (SD); min.–max.	4.55 (0.44); 3.47–5.63	4.62 (0.44); 3.23–5.59	4.69 (0.41); 3.68–6.06	4.60 (0.44); 3.10–5.79
White blood cell count (10^9/l)				(*n* = 105)
Median (IQR); min.–max.	5.98 (4.78–7.60); 3.5–15.3	5.61 (4.8–7.2); 3.0–13.8	5.56 (4.8–6.7); 2.04–12.9	5.7 (4.8–7.2); 2.8–14.4

TABLE 20 Baseline full blood count by treatment arm (*continued*)

Characteristic	Treatment arm			
	Arm A (*N* = 105)	Arm B (*N* = 84)	Arm C (*N* = 82)	Arm D (*N* = 106)
Platelets (10⁹/l)	(*n* = 104)			
Median (IQR); min.–max.	231.5 (198.5–271.5); 128–647	223.0 (193.0–252.0); 46–406	216.5 (182.0–266.0); 119–411	219.5 (185.0–262.0); 106–368
Mean cell volume (fl)	(*n* = 104)			
Mean (SD); min.–max.	93.40 (5.65); 77.4–111.1	92.87 (5.48); 73.6–104.0	92.47 (5.48); 81.4–110.2	94.37 (5.33); 81.0–111.0
Mean cell haemoglobin (pg)	(*n* = 80)	(*n* = 67)	(*n* = 60)	(*n* = 85)
Mean (SD); min.–max.	31.49 (3.92); 3.6–39.7	31.35 (2.06); 24.1–36.7	31.34 (1.91); 26.6–36.6	31.35 (3.68); 2.59–37.0
Mean cell haemoglobin concentration (g/dl)	(*n* = 68)	(*n* = 53)	(*n* = 53)	(*n* = 65)
Mean (SD); min.–max.	340.71 (11.83); 309–366	335.28 (12.97); 302–366	340.57 (13.03); 315–367	336.55 (12.48); 293–357
Neutrophils (10⁹/l)				
Median (IQR); min.–max.	3.15 (2.30–4.30); 1.16–12.60	2.90 (2.24–3.90); 1.10–9.70	2.90 (2.30–3.84); 0.83–8.70	3.00 (2.10–3.80); 0.88–10.00
Lymphocytes (10⁹/l)				
Median (IQR); min.–max.	1.90 (1.60–2.55); 0.89–4.10	2.13 (1.71–2.50); 0.93–5.02	2.00 (1.62–2.31); 0.53–3.70	1.91 (1.60–2.50); 0.90–4.20
Eosinophils (10⁹/l)	(*n* = 104)	(*n* = 82)		
Median (IQR); min.–max.	0.11 (0.10–0.20); 0.00–1.11	0.10 (0.10–0.20); 0.00–0.60	0.12 (0.10–0.20); 0.00–0.41	0.12 (0.10–0.20); 0.00–0.50
Basophils (10⁹/l)	(*n* = 101)	(*n* = 80)	(*n* = 81)	(*n* = 103)
Median (IQR); min.–max.	0.02 (0.00–0.05); 0.00–0.20	0.00 (0.00–0.04); 0.00–0.10	0.00 (0.00–0.03); 0.00–0.10	0.01 (0.00–0.06); 0.00–0.10
Monocytes (10⁹/l)				
Median (IQR); min.–max.	0.50 (0.34–0.60); 0.00–1.10	0.44 (0.30–0.60); 0.19–1.20	0.48 (0.38–0.60); 0.16–1.02	0.42 (0.31–0.60); 0.10–1.49

max., maximum; min., minimum.

Numbers analysed

TABLE 21 Number of patients with missed visits and missing data because of sample issues

Visit	Treatment arm				
	Arm A (*N* = 105)	Arm B (*N* = 84)	Arm C (*N* = 82)	Arm D (*N* = 106)	Total (*N* = 377)
No missing assessment visit	82	79	65	81	307
Complete longitudinal record	72	72	57	72	273
Study assessment at 12 weeks					
Missing	13	4	11	13	41
Data invalid[a]	3	1	2	5	11
Study assessment at 24 weeks					
Missing	15	2	11	20	48
Data invalid[a]	1	2	3	4	10
Study assessment at 48 weeks					
Missing	16	2	9	24	51
Data invalid[a]	5	4	6	3	18
Baseline					
Data invalid[a]	4	3	2	5	14

a Unfasted or haemolysed sample.

TABLE 22 Reasons for missingness or study withdrawal

Reason	Treatment arm				
	Arm A (*N* = 105)	Arm B (*N* = 84)	Arm C (*N* = 82)	Arm D (*N* = 106)	Total (*N* = 377)
Death	1	0	0	0	1
Loss to follow-up	6	2	5	5	18
Other reasons[a]	6	1	3	7	17
SAR	0	0	1	0	1
Treatment arm dropped	0	32	31	0	63
Withdrawal of consent for follow-up	1	0	3	4	8
Total	14	35	43	16	108

a Free-text field: patient moved to London – no forwarding address so unable to transfer patient; does not wish to continue the study because of organisational reasons; not able to commit to study; advice from study team following MRI incidental finding; to enter another clinical trial; decided to become pregnant, etc.

Interim analysis

TABLE 23 Summary statistics for HOMA-IR at baseline and 24 weeks by treatment arm

Summary statistic	Timeline							
	HOMA-IR at baseline				HOMA-IR at 24 weeks			
	Arm A (control)	Arm B (20 mg)	Arm C (40 mg)	Arm D (80 mg)	Arm A (control)	Arm B (20 mg)	Arm C (40 mg)	Arm D (80 mg)
Number of patients	39	45	35	35	39	45	35	35
Mean (SD); min.–max.	2.4 (2.0); 0.6–10.8	2.3 (1.6); 0.6–7.0	2.8 (3.9); 0.6–17.5	2.6 (2.7); 0.6–11.4	2.5 (1.9); 0.6–9.2	2.7 (1.9); 0.6–7.8	3.4 (4.4); 0.6–23.5	2.5 (1.7); 0.6–8.1
Median (IQR)	1.8 (1.0–3.5)	1.6 (1.2–2.8)	1.8 (1.2–2.5)	1.6 (1.2–2.9)	2.1 (1.2–3.2)	2.4 (1.2–3.3)	1.8 (1.4–3.4)	1.8 (1.3–3.1)
Number of patients randomised	48	49	47	45	48	49	47	45

max., maximum; min., minimum.

Homeostatic Model Assessment of Insulin Resistance at primary end point

Investigation of the extreme Homeostatic Model Assessment of Insulin Resistance value
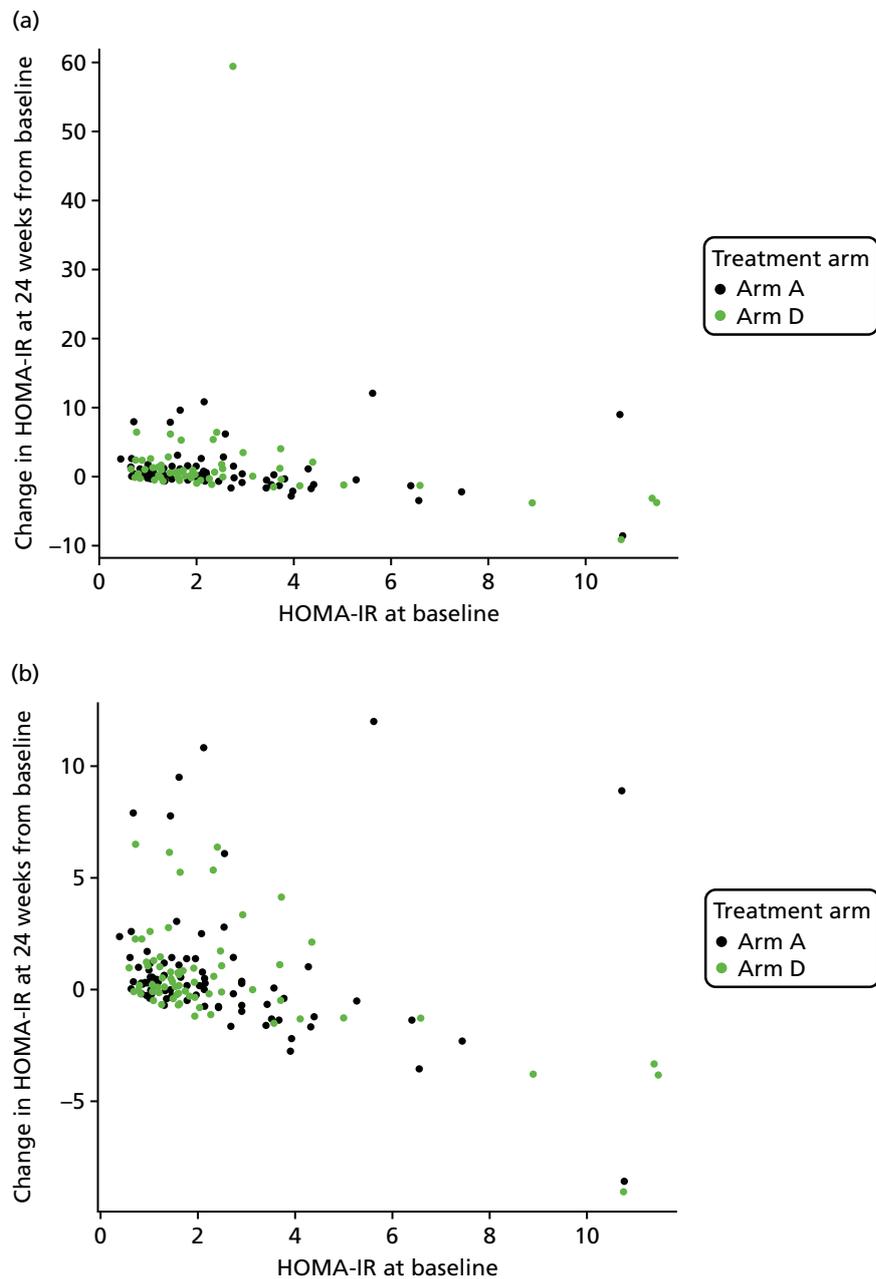
FIGURE 10 Change in HOMA-IR at 24 weeks from baseline against HOMA-IR at baseline. (a) all values; (b) values excluding patient 01552152.

Excluding the outlier patient

TABLE 24 Summary statistics for HOMA-IR at baseline and 24 weeks by treatment arm

Summary statistic	Time point			
	HOMA-IR at baseline		**HOMA-IR at 24 weeks**	
	Arm A (control)	**Arm D (80 mg)**	**Arm A (control)**	**Arm D (80 mg)**
Number of patients (%)	100 (95.2)	99 (93.4)	89 (84.8)	81 (76.4)
Mean (SD); min.–max.	2.49 (2.08); 0.41–10.78	2.54 (2.81); 0.59–16.85	2.99 (3.25); 0.62–19.6	2.72 (2.15); 0.60–8.77
Median (IQR)	1.81 (1.12–2.90)	1.62 (1.18–2.48)	2.09 (1.29–3.17)	1.99 (1.15–3.23)
Missing (%)	5 (4.8)	7 (6.6)	16 (15.2)	25 (23.6)
Number of patients randomised	105	106	105	106

max., maximum; min., minimum.

TABLE 25 Model estimates for log-HOMA-IR at 24 weeks, excluding patient with outlier HOMA-IR

Variable	Parameter estimate	Standard error	*t*-value for treatment
Intercept	0.458	0.126	–
Log-(HOMA-IR) at baseline	0.575	0.074	–
Ethnicity (non-black)	–0.012	0.123	–
Arm D vs. arm A	–0.034	0.099	–0.347

TABLE 26 Model estimates for log-HOMA-IR at 24 weeks, adjusted for weight change

Variable	Parameter estimate	Standard error	*t*-value for treatment
Intercept	0.400	0.126	–
Log-(HOMA-IR) at baseline	0.581	0.072	–
Ethnicity (non-black)	0.031	0.122	–
Weight change	0.050	0.016	–
Arm D vs. arm A	–0.039	0.097	–0.399

Sensitivity analysis 1

We fitted 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/arm A) and stratification factor (black/non-black).

TABLE 27 Model estimates for log-HOMA-IR at 24 weeks, imputed missing HOMA-IR

Variable	Parameter estimate	Standard error	*t*-value for treatment
Intercept	0.393	0.123	–
Log-(HOMA-IR) at baseline	0.575	0.073	–
Ethnicity (non-black)	0.030	0.120	–
Weight change	0.052	0.016	–
Arm D vs. arm A	–0.038	0.096	–0.393

The test statistic is –0.393, and as this value is not smaller than the critical value (–2.086), we failed to reject the null hypothesis (i.e. no difference between arm D and arm A).

Sensitivity analysis 2

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

TABLE 28 Model estimates accounting for received dose on log-HOMA-IR at 24 weeks

Variable	Parameter estimate	Standard error	95% CI	*p*-value
Intercept	0.408	0.132	0.149 to 0.667	0.0020
Log-(HOMA-IR) at baseline	0.589	0.077	0.438 to 0.741	< 0.0001
Ethnicity (non-black)	0.040	0.131	–0.218 to 0.297	0.7636
Arm D dose (unit: 1000 mg)	–0.010	0.009	–0.028 to 0.008	0.2885

The *p*-value (of 0.2885 > 0.05) implies that there is no effect of telmisartan after adjusting for dose. The test of endogeneity indicated that there was insufficient evidence to reject the null hypothesis of exogeneity (Durbin score, chi-squared(1) = 0.0234; $p = 0.8783$; Wu–Hausman $F(1,138) = 0.0226$; $p = 0.8807$), implying that dose is independent of the error and, thus, standard regression analysis is appropriate. The randomisation was an informative (strong) instrument in this analysis, as demonstrated by a high correlation between compliance and randomised treatment arm (0.9928) and a highly significant *p*-value (i.e. < 0.0001), rejecting the null hypothesis that randomised treatment is a weak instrument.

Same IV regression was carried out but additionally accounting for baseline HIV viral load. We assume that baseline HIV viral load was missing at random, and there were no other factors (i.e. other than HIV viral load) that influence whether or not patients provided compliance data.

TABLE 29 Model estimates accounting for received dose on log-HOMA-IR at 24 weeks, accounting for baseline HIV viral load

Variable	Parameter estimate	Standard error	95% CI	*p*-value
Intercept	0.431	0.167	0.103 to 0.759	0.0100
Dose (unit: 1000 mg)	−0.011	0.009	−0.029 to 0.008	0.2589
Log-HOMA-IR at baseline	0.591	0.078	0.439 to 0.743	< 0.0001
Ethnicity	0.040	0.133	−0.220 to 0.300	0.7639
HIV viral load	−0.001	0.003	−0.006 to 0.005	0.8288

In the next analysis, multiple imputation was used to impute missing compliance information prior to carrying out IV regression, with HIV viral load at baseline as the key predictor in the imputation model (i.e. imputed compliance information used for all participants who had missing compliance information but who had baseline HIV viral load data). Twenty imputations were generated per patient using predictive mean matching with baseline HIV viral load as predictor variable rather than including baseline HIV viral load in model.

TABLE 30 Model estimates accounting for received dose on log-HOMA-IR at 24 weeks using imputed compliance information for patients, with missing compliance information based on baseline HIV viral load

Variable	Parameter estimate	Standard error	95% CI	*p*-value
Intercept	0.458	0.125	0.213 to 0.704	< 0.001
Dose (unit: 1000 mg)	−0.003	0.009	−0.020 to 0.014	0.725
Log-HOMA-IR at baseline	0.575	0.073	0.432 to 0.718	< 0.001
Ethnicity	−0.013	0.122	−0.251 to 0.225	0.915

Quantitative Insulin Sensitivity Check Index and revised Quantitative Insulin Sensitivity Check Index at primary end point

TABLE 31 Summary statistics for QUICKI at baseline and 24 weeks by treatment arm

	Time point			
	QUICKI at baseline		QUICKI at 24 weeks	
Summary statistic	Arm A (control)	Arm D (80 mg)	Arm A (control)	Arm D (80 mg)
Number of patients (%)	100 (95.2)	99 (93.4)	89 (84.8)	81 (76.4)
Mean (SD); min.–max.	0.117 (0.0092); 0.097–0.142	0.118 (0.0092); 0.093–0.135	0.115 (0.0093); 0.092–0.134	0.116 (0.0099); 0.099–0.134
Median (IQR)	0.117 (0.111–0.124)	0.119 (0.113–0.123)	0.115 (0.110–0.122)	0.116 (0.110–0.124)
Missing (%)	5 (4.8)	7 (6.6)	16 (15.2)	25 (23.6)
Number of patients randomised	105	106	105	106

max., maximum; min., minimum.

TABLE 32 Summary statistics for Revised-QUICKI at baseline and 24 weeks by treatment arm

| Summary statistic | Time point | | | |
| | **Revised-QUICKI at baseline** | | **Revised-QUICKI at 24 weeks** | |
	Arm A (control)	**Arm D (80 mg)**	**Arm A (control)**	**Arm D (80 mg)**
Number of patients (%)	100 (95.2)	98 (92.4)	88 (83.8)	81 (76.4)
Mean (SD); min.–max.	0.132 (0.0168); 0.101–0.184	0.133 (0.0156); 0.096–0.178	0.132 (0.0176); 0.099–0.183	0.134 (0.0174); 0.103–0.187
Median (IQR)	0.13 (0.122–0.142)	0.132 (0.123–0.143)	0.129 (0.119–0.140)	0.131 (0.121–0.143)
Missing (%)	5 (4.8)	8 (7.5)	17 (16.2)	25 (23.6)
Number of patients randomised	105	106	105	106

max., maximum; min., minimum.

TABLE 33 Model estimates for QUICKI

Variable	Parameter estimate	Standard error	*t*-value for treatment
Intercept	0.0493	0.0085	–
QUICKI at baseline	0.5624	0.0704	–
Ethnicity (non-black)	–0.000035	0.0016	–
Weight change	–0.000656	0.0002	–
Arm D vs. arm A	0.000563	0.0013	0.4471

TABLE 34 Model estimates for Revised QUICKI

Variable	Parameter estimate	Standard error	*t*-value for treatment
Intercept	0.0638	0.0109	–
Revised QUICKI at baseline	0.4932	0.0784	–
Ethnicity (non-black)	0.0028	0.0031	–
Weight change	–0.0008	0.0004	–
Arm D vs. arm A	0.0017	0.0025	0.6882

Analysis of covariance model diagnostics of primary and secondary outcomes

The design has been constructed under the assumption that outcomes were normally distributed with a common standard deviation, σ. Levene's test for checking equal group variances, and histograms for checking normality were used.

Histograms to check normality for Homeostatic Model Assessment of Insulin Resistance at baseline and 24 weeks

(a)

(b)
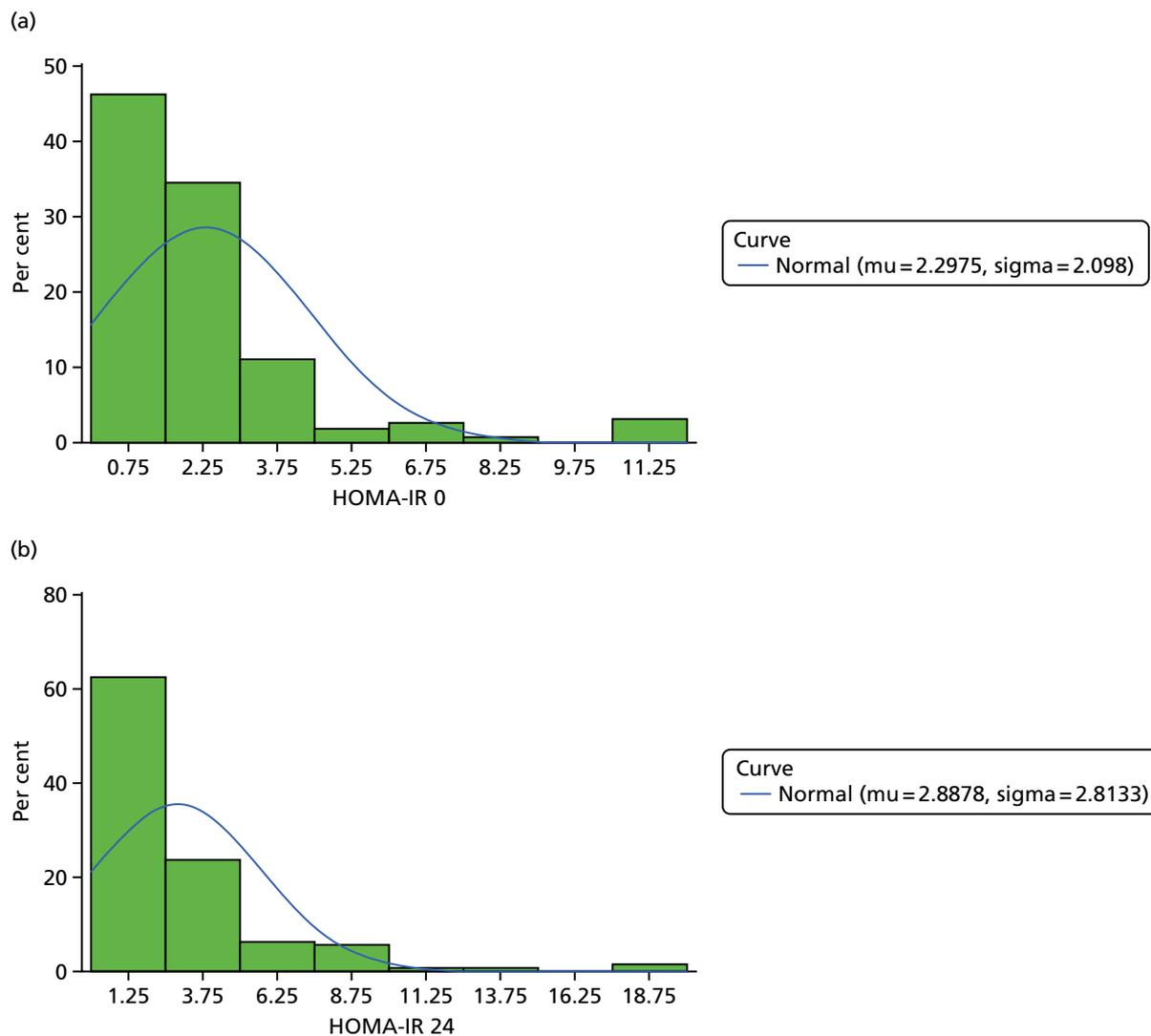
FIGURE 11 Normality of HOMA-IR (a) at baseline; (b) at 24 weeks; (c) log-transformed at baseline; and (d) log-transformed at 24 weeks. (*continued*)
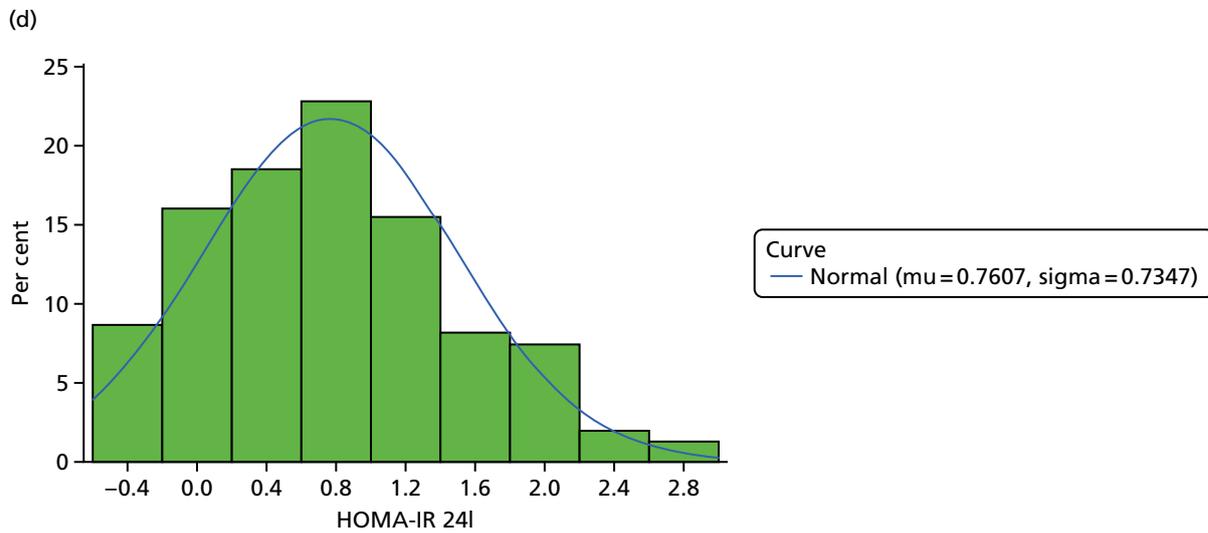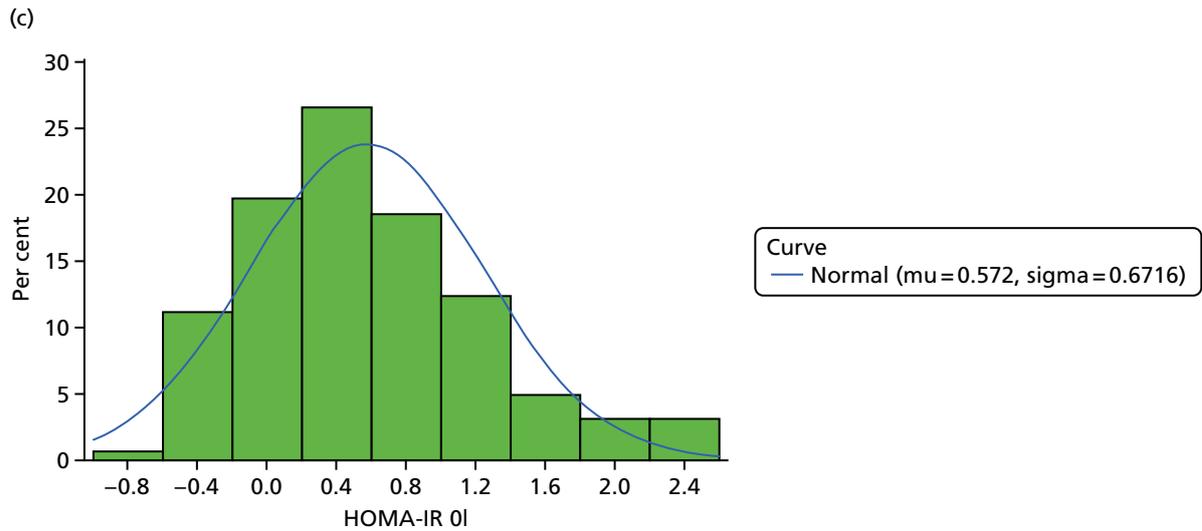
(c)

(d)

FIGURE 11 Normality of HOMA-IR (a) at baseline; (b) at 24 weeks; (c) log-transformed at baseline; and (d) log-transformed at 24 weeks.

TABLE 35 Levene's test to check equal group variances for Homeostatic Model Assessment of Insulin Resistance at baseline and 24 weeks

Source	df	Sum of squares	Mean square	F-value	p-value
Treatment arm	1	1588.3	1588.3	1.91	0.1684

df, degrees of freedom.
A p-value of > 0.05 implies the homogeneity of variance.

Histograms to check normality for Quantitative Insulin Sensitivity Check Index at baseline and 24 weeks

(a)

(b)
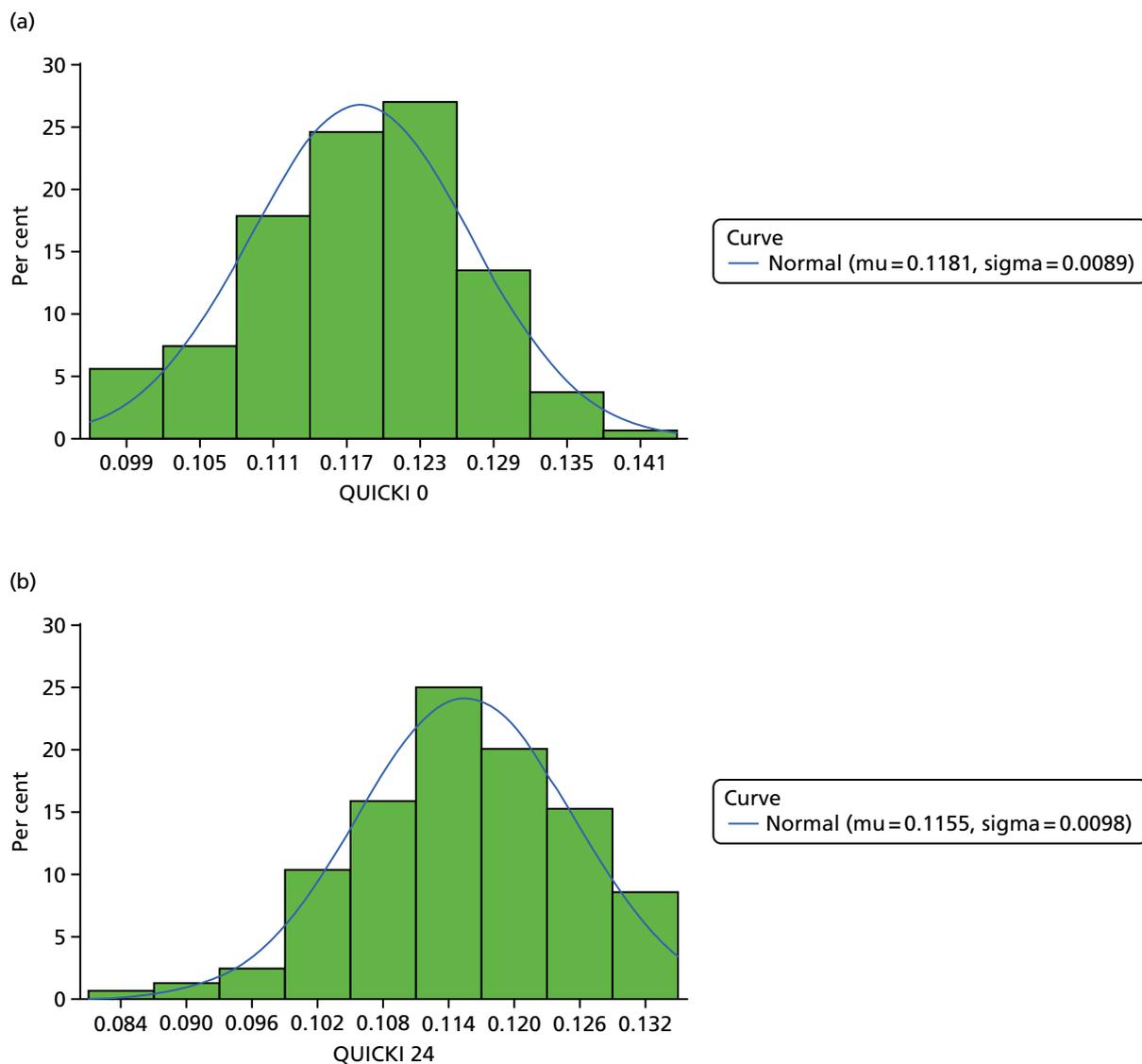
FIGURE 12 Normality of QUICKI at (a) baseline; and (b) 24 weeks.

TABLE 36 Levene's test to check equal group variances for Quantitative Insulin Sensitivity Check Index at baseline and 24 weeks

Source	df	Sum of squares	Mean square	F-value	p-value
Treatment arm	1	1.268×10^{-8}	1.268E-8	0.68	0.4125

Histograms to check normality for revised Quantitative Insulin Sensitivity Check Index at baseline and 24 weeks

(a)

(b)
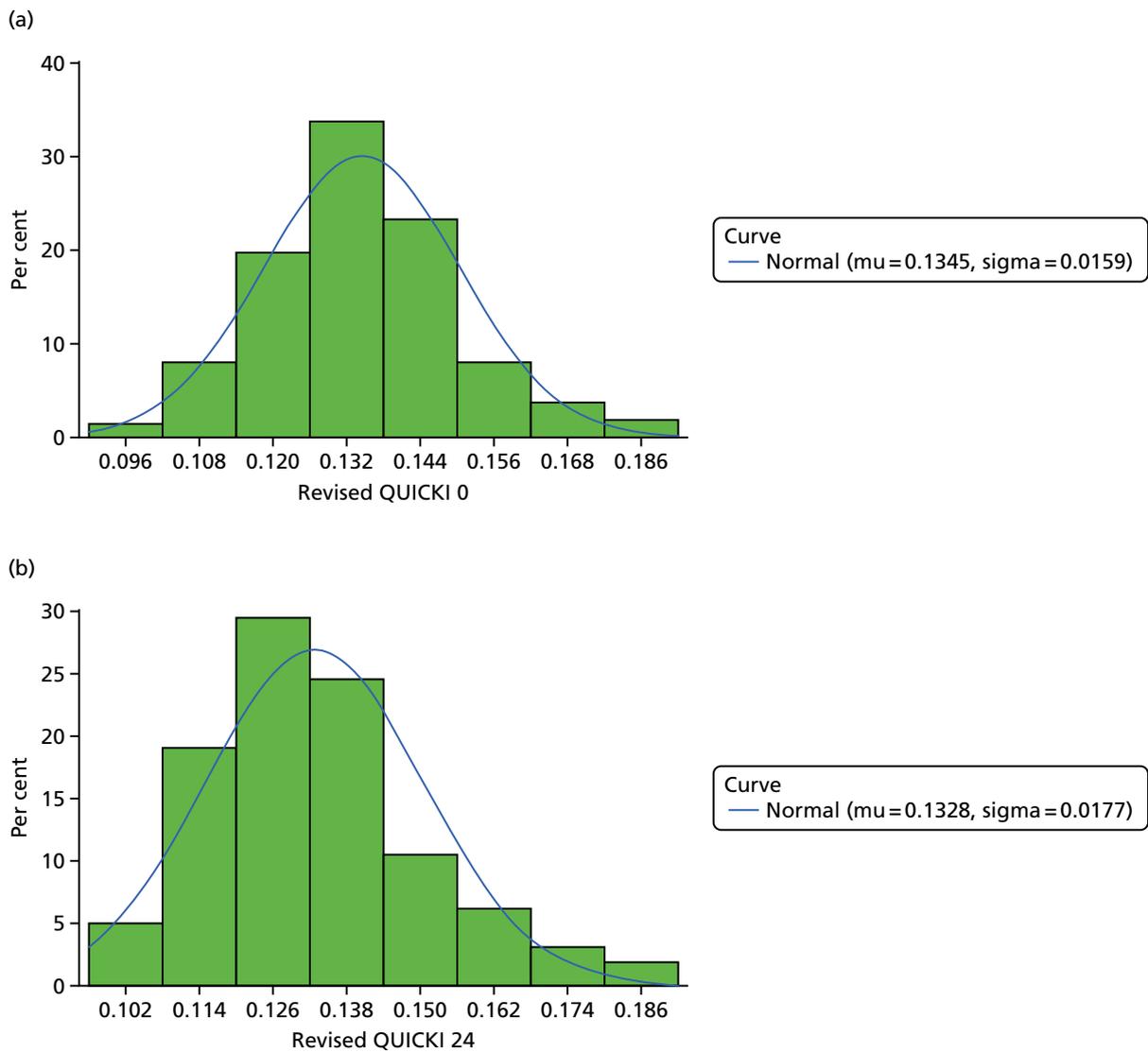
FIGURE 13 Normality of revised QUICKI at (a) baseline; and (b) 24 weeks.

TABLE 37 Levene's test to check equal group variances for revised Quantitative Insulin Sensitivity Check Index at baseline and 24 weeks

Source	df	Sum of squares	Mean square	F-value	p-value
Treatment arm	1	2.06×10^{-11}	2.06E-11	0.00	0.9928

Longitudinal analysis: profiles, model diagnostics and estimates

Homeostatic Model Assessment of Insulin Resistance

Histograms to check normality for Homeostatic Model Assessment of Insulin Resistance
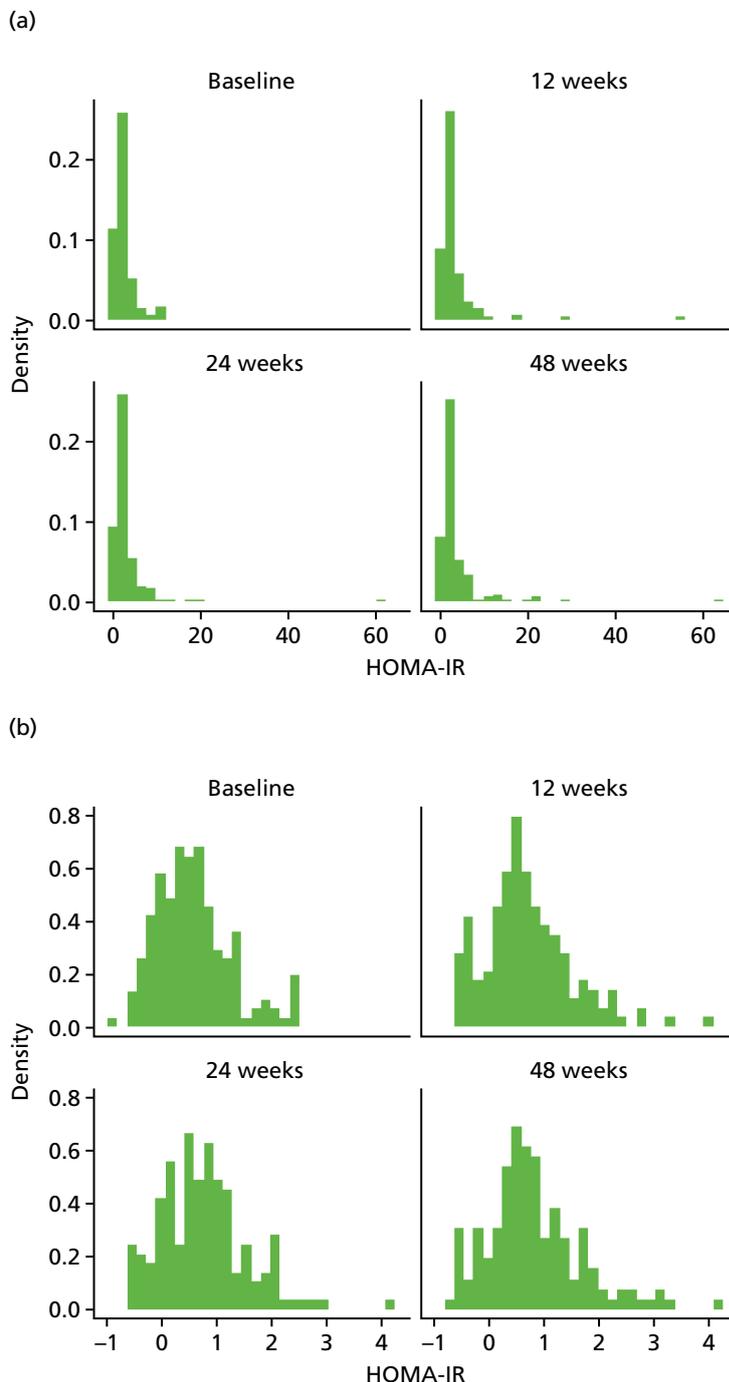
FIGURE 14 Normality of HOMA-IR. (a) original scale; and (b) log-transformed.

Three outlining HOMA-IR values were excluded from the longitudinal analysis [two from arm A (55.82720 at 12 weeks and 64.14336 at 48 weeks) and one from arm D (62.00064 at 24 weeks; this is the same value excluded at the primary analysis of HOMA-IR)].

The bivariate joint model included 321 patients and 812 records. The treatment effect [arm D: telmisartan (80 mg daily) compared with arm A: non-intervention (control)] on the longitudinal log-HOMA-IR is −0.083 (95% CI −0.247 to 0.082; $p = 0.3243$), implying that there is no significant difference between the treatments on HOMA-IR.
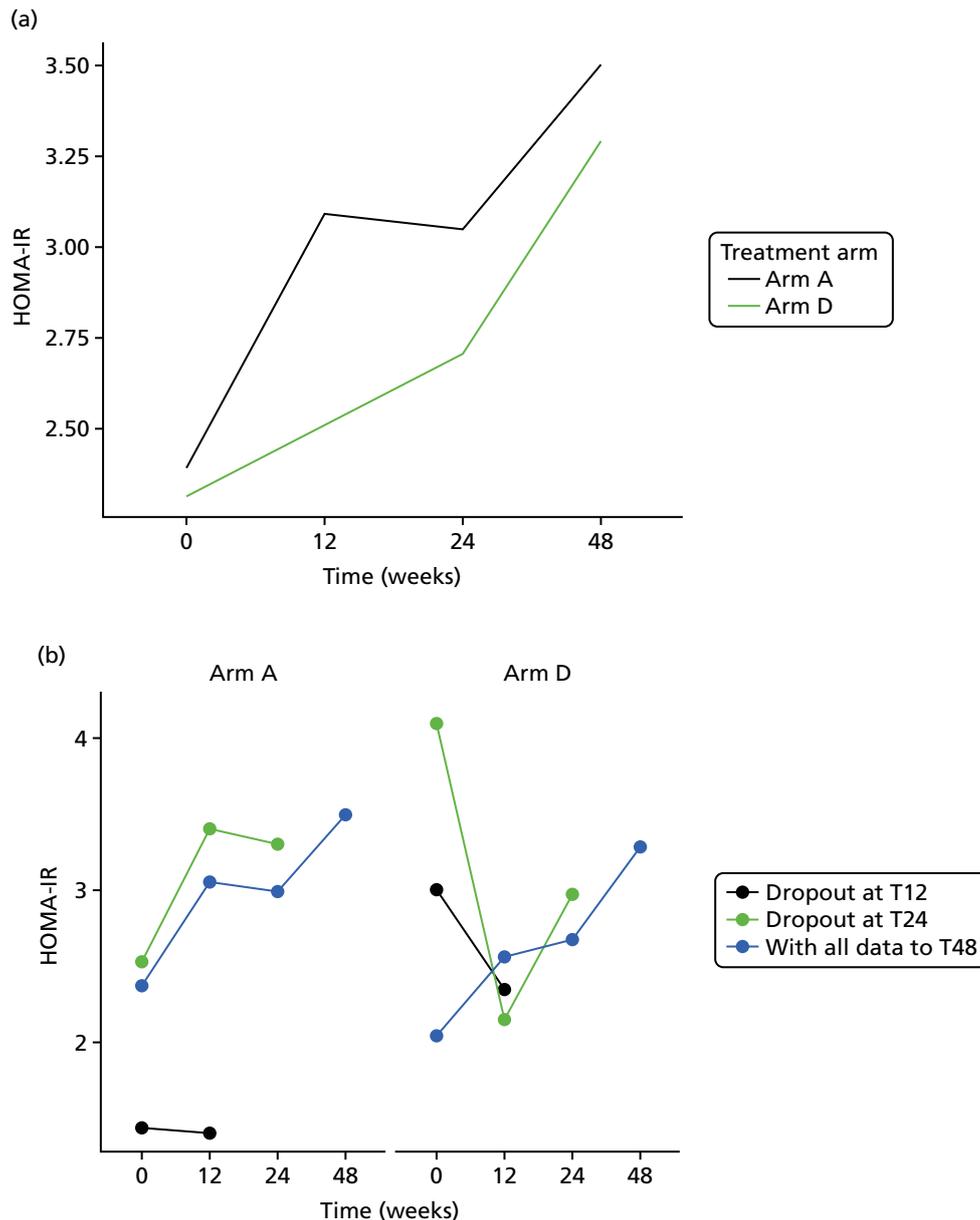
FIGURE 15 HOMA-IR mean profiles by treatment arm (original scale). (a) HOMA-IR profile plots; (b) HOMA-IR profile plots by dropout; and (c) HOMA-IR reverse-time profile plots. (*continued*)
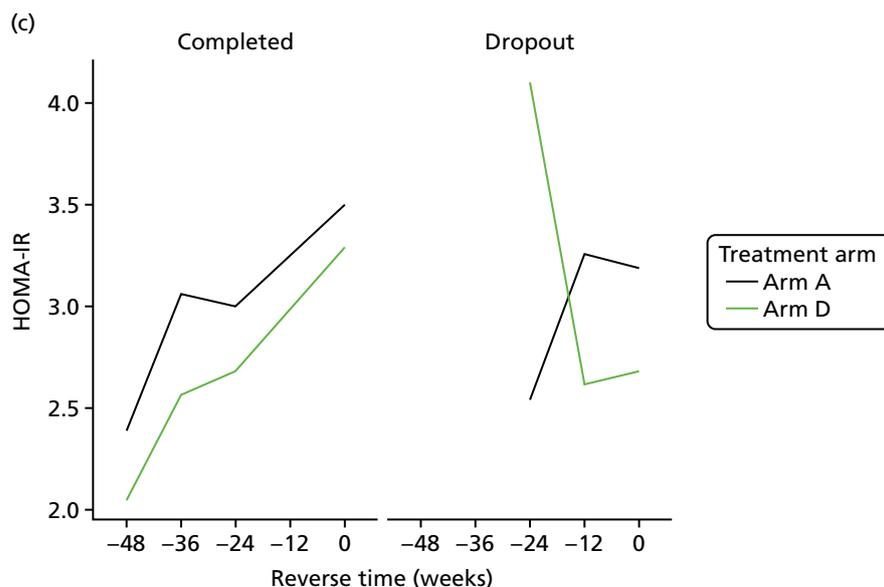
FIGURE 15 HOMA-IR mean profiles by treatment arm (original scale). (a) HOMA-IR profile plots; (b) HOMA-IR profile plots by dropout; and (c) HOMA-IR reverse-time profile plots.

TABLE 38 Joint model estimates: log-HOMA-IR

Component	Parameter	Estimate	95% CI	*p*-value
Longitudinal marker	Intercept	0.420	0.234 to 0.606	< 0.0001
	Time	0.003	0.001 to 0.006	0.0159
	Baseline marker	0.669	0.589 to 0.748	< 0.0001
	Treatment B vs. A	−0.084	−0.245 to 0.077	0.3043
	Treatment C vs. A	0.010	−0.172 to 0.193	0.9106
	Treatment D vs. A	−0.083	−0.247 to 0.082	0.3243
	Ethnicity	−0.107	−0.247 to 0.033	0.1343
Longitudinal weight	Intercept	1.047	−1.131 to 3.226	0.3459
	Time	0.022	−0.002 to 0.045	0.0686
	Baseline weight	0.987	0.965 to 1.008	< 0.0001
	Treatment B vs. A	0.458	−0.551 to 1.467	0.3741
	Treatment C vs. A	0.690	−0.367 to 1.746	0.2008
	Treatment D vs. A	0.117	−0.842 to 1.076	0.8111
	Ethnicity	−0.246	−1.055 to 0.562	0.5504
Dropout	Treatment B vs. A	−0.355	−1.270 to 0.561	0.4477
	Treatment C vs. A	−0.076	−0.976 to 0.824	0.8690
	Treatment D vs. A	0.081	−0.716 to 0.877	0.8427
	Ethnicity	−0.036	−0.847 to 0.775	0.9300
Association parameters	Marker	−0.262	−1.433 to 0.909	0.6611
	Weight	0.044	−0.208 to 0.296	0.7337

Quantitative Insulin Sensitivity Check Index

Histograms to check normality for Quantitative Insulin Sensitivity Check Index
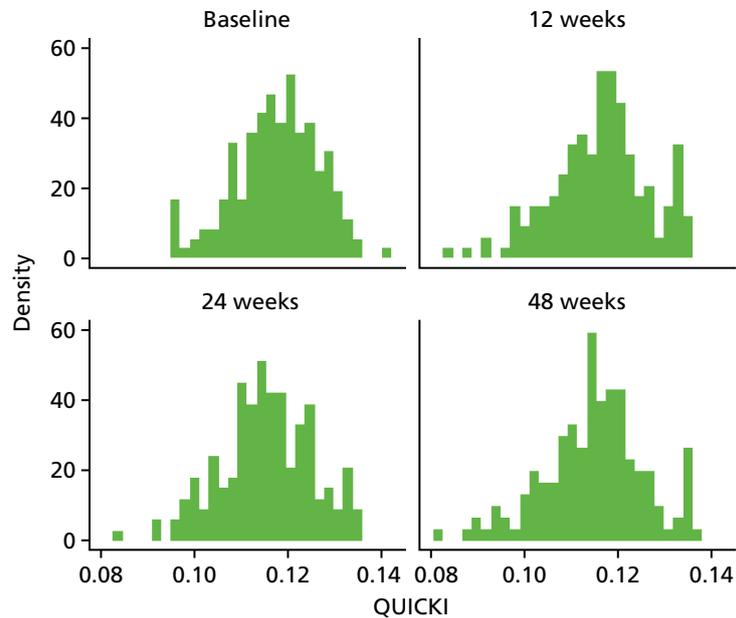
FIGURE 16 Normality of QUICKI (original scale).
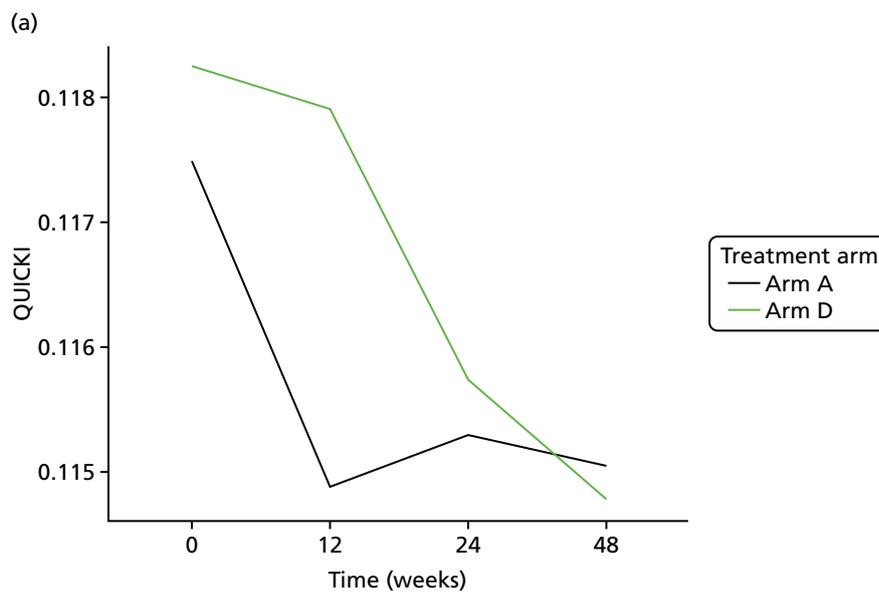
FIGURE 17 QUICKI mean profiles by treatment arm (original scale). (a) QUICKI profile plots; (b) QUICKI profile plots by dropout; and (c) QUICKI reverse-time profile plots. (*continued*)
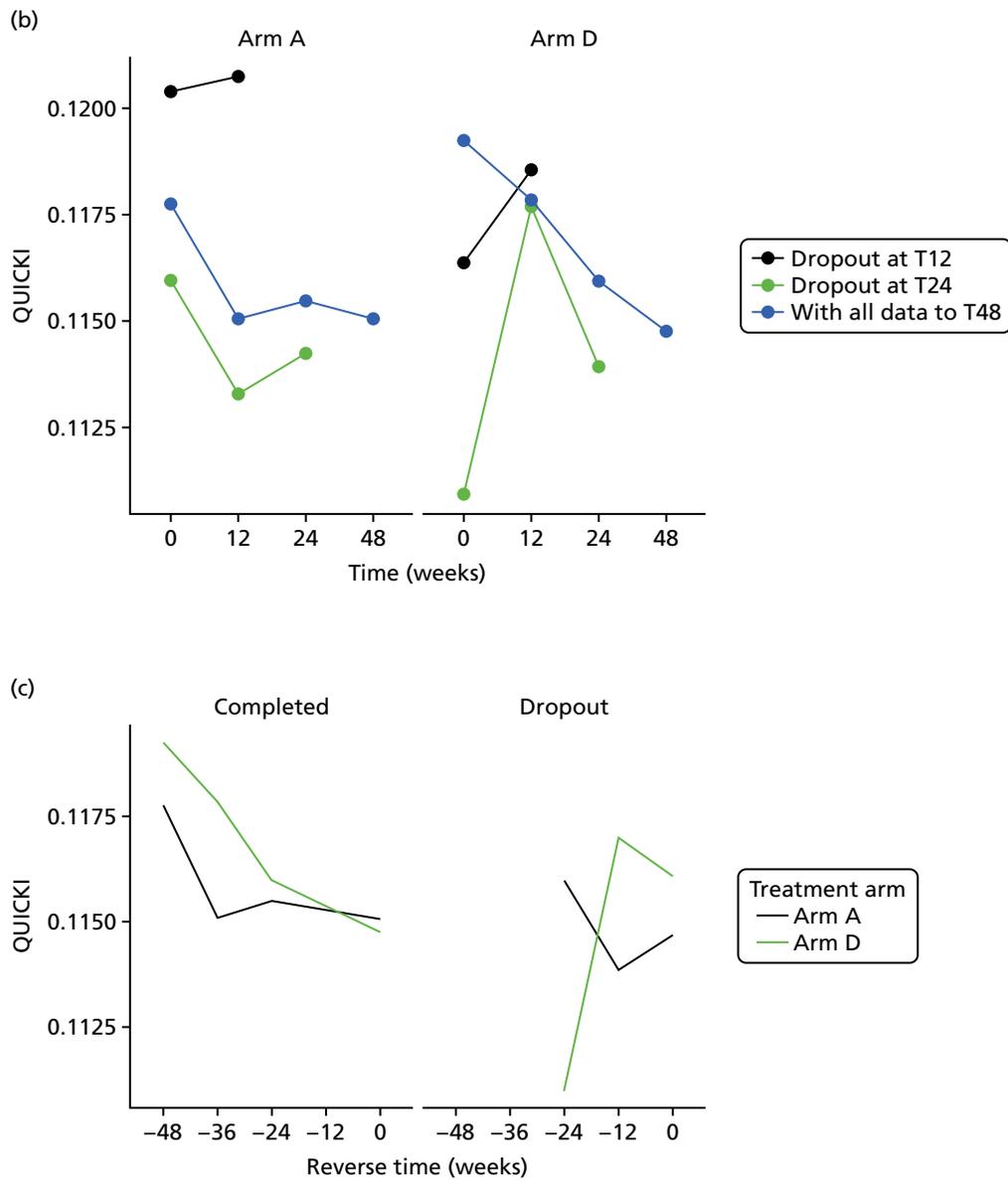
FIGURE 17 QUICKI mean profiles by treatment arm (original scale). (a) QUICKI profile plots; (b) QUICKI profile plots by dropout; and (c) QUICKI reverse-time profile plots.

TABLE 39 Joint model estimates: QUICKI

Component	Parameter	Estimate	95% CI	*p*-value
Longitudinal marker	Intercept	0.039	0.029 to 0.048	< 0.0001
	Time	0.000	0.000 to 0.000	0.0126
	Baseline marker	0.649	0.572 to 0.726	< 0.0001
	Treatment B vs. A	0.001	−0.001 to 0.003	0.2596
	Treatment C vs. A	0.000	−0.003 to 0.002	0.9125
	Treatment D vs. A	0.001	−0.001 to 0.003	0.3426
	Ethnicity	0.001	−0.001 to 0.003	0.2102
Longitudinal weight	Intercept	1.091	−1.066 to 3.248	0.3217
	Time	0.021	−0.002 to 0.045	0.0755
	Baseline weight	0.986	0.965 to 1.007	< 0.0001
	Treatment B vs. A	0.479	−0.533 to 1.490	0.3537
	Treatment C vs. A	0.704	−0.348 to 1.756	0.1898
	Treatment D vs. A	0.135	−0.823 to 1.093	0.7823
	Ethnicity	−0.253	−1.053 to 0.546	0.5344
Dropout	Treatment B vs. A	−0.354	−1.269 to 0.561	0.4485
	Treatment C vs. A	−0.075	−0.982 to 0.832	0.8714
	Treatment D vs. A	0.082	−0.716 to 0.879	0.8408
	Ethnicity	−0.037	−0.835 to 0.762	0.9279
Association parameters	Marker	18.535	−75.599 to 112.668	0.6996
	Weight	0.042	−0.210 to 0.295	0.7428

The bivariate joint model included 321 patients and 812 records. The treatment effect [arm D: telmisartan (80 mg daily) compared with arm A: non-intervention (control)] on the longitudinal QUICKI is 0.001 (95% CI −0.001 to 0.003; $p = 0.3426$), implying that there is no significant difference between the treatments on QUICKI.
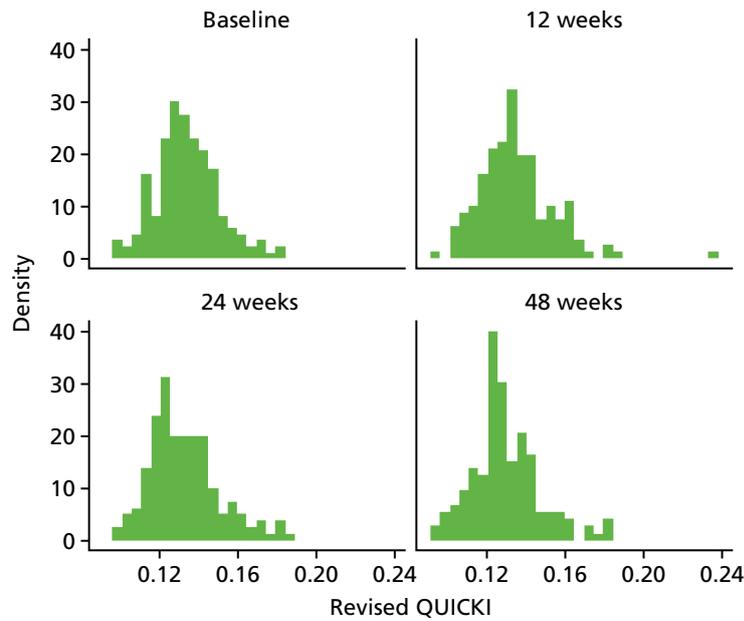
FIGURE 18 Normality of revised QUICKI (original scale).
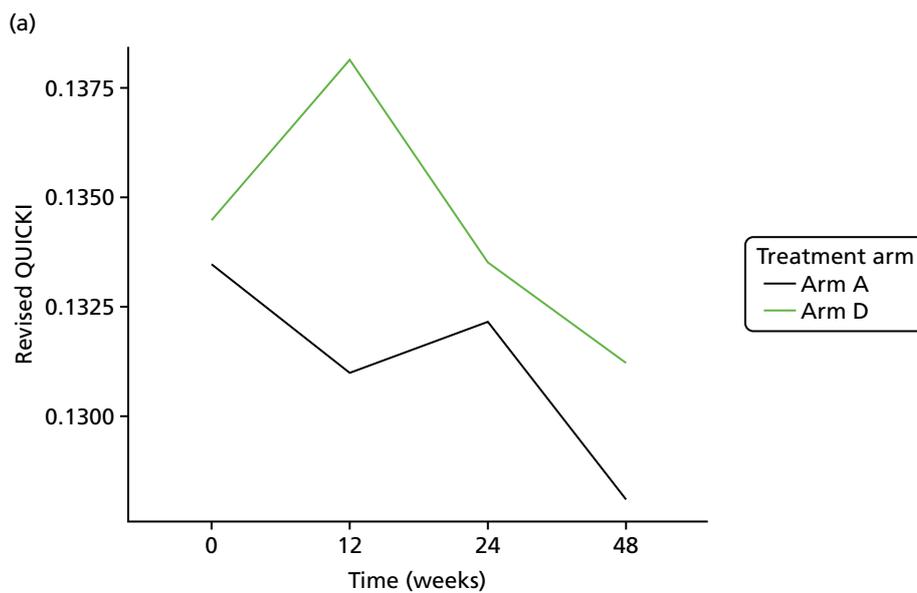
FIGURE 19 Revised QUICKI mean profiles by treatment arm (original scale). (a) revised QUICKI profile plots; (b) revised QUICKI profile plots by dropout; and (c) revised QUICKI reverse-time profile plots. (*continued*)
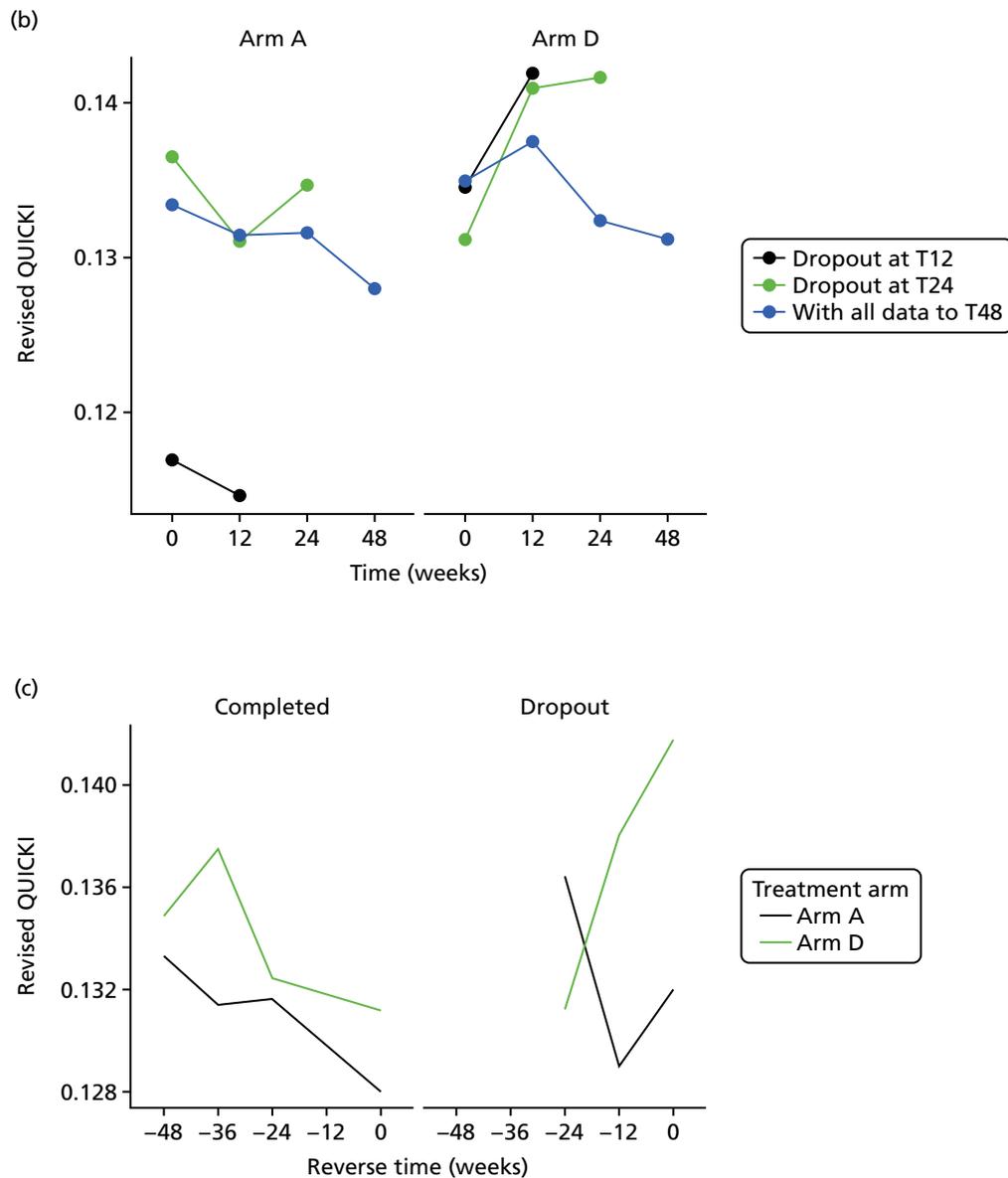
FIGURE 19 Revised QUICKI mean profiles by treatment arm (original scale). (a) revised QUICKI profile plots; (b) revised QUICKI profile plots by dropout; and (c) revised QUICKI reverse-time profile plots.

Revised Quantitative Insulin Sensitivity Check Index

Histograms to check normality for revised Quantitative Insulin Sensitivity Check Index

The bivariate joint model included 320 patients and 808 records. Revised QUICKI scores were fitted in their original scale.

The treatment effect [arm D (80 mg) compared with arm A (control)] on the longitudinal revised QUICKI was 0.004 (95% CI 0.000 to 0.008; $p = 0.0510$). As the p-value was just above 0.05, this implies a marginally significant difference between the treatments on revised QUICKI.

TABLE 40 Joint model estimates: revised QUICKI

Component	Parameter	Estimate	95% CI	*p*-value
Longitudinal marker	Intercept	0.058	0.046 to 0.070	< 0.0001
	Time	0.000	0.000 to 0.000	0.0402
	Baseline marker	0.550	0.473 to 0.627	< 0.0001
	Treatment B vs. A	0.003	−0.001 to 0.007	0.1023
	Treatment C vs. A	0.001	−0.003 to 0.005	0.5993
	Treatment D vs. A	0.004	0.000 to 0.008	0.0510
	Ethnicity	0.001	−0.002 to 0.004	0.5071
Longitudinal weight	Intercept	1.039	−1.087 to 3.164	0.3382
	Time	0.020	−0.003 to 0.044	0.0899
	Baseline weight	0.987	0.966 to 1.009	< 0.0001
	Treatment B vs. A	0.473	−0.493 to 1.438	0.3374
	Treatment C vs. A	0.690	−0.310 to 1.690	0.1765
	Treatment D vs. A	0.187	−0.748 to 1.123	0.6945
	Ethnicity	−0.250	−1.039 to 0.539	0.5340
Dropout	Treatment B vs. A	−0.364	−1.272 to 0.544	0.4319
	Treatment C vs. A	0.183	−0.633 to 0.999	0.6608
	Treatment D vs. A	0.078	−0.726 to 0.881	0.8496
	Ethnicity	−0.087	−0.845 to 0.671	0.8218
Association parameters	Marker	10.682	−47.031 to 68.395	0.7168
	Weight	0.028	−0.206 to 0.262	0.8153

Lipid profiles

High-density lipoprotein cholesterol

Histograms to check normality for high-density lipoprotein cholesterol
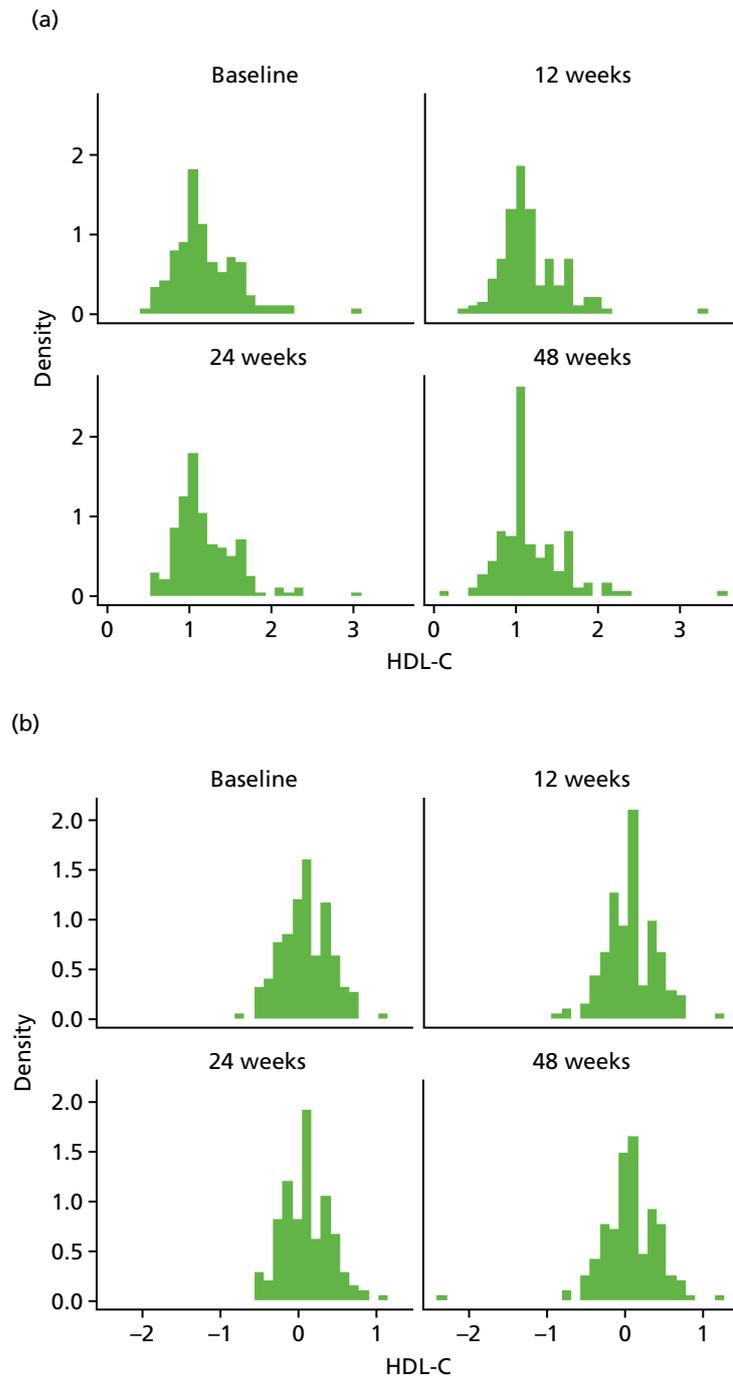
FIGURE 20 Normality of HDL-C. (a) original scale; and (b) log-transformed.
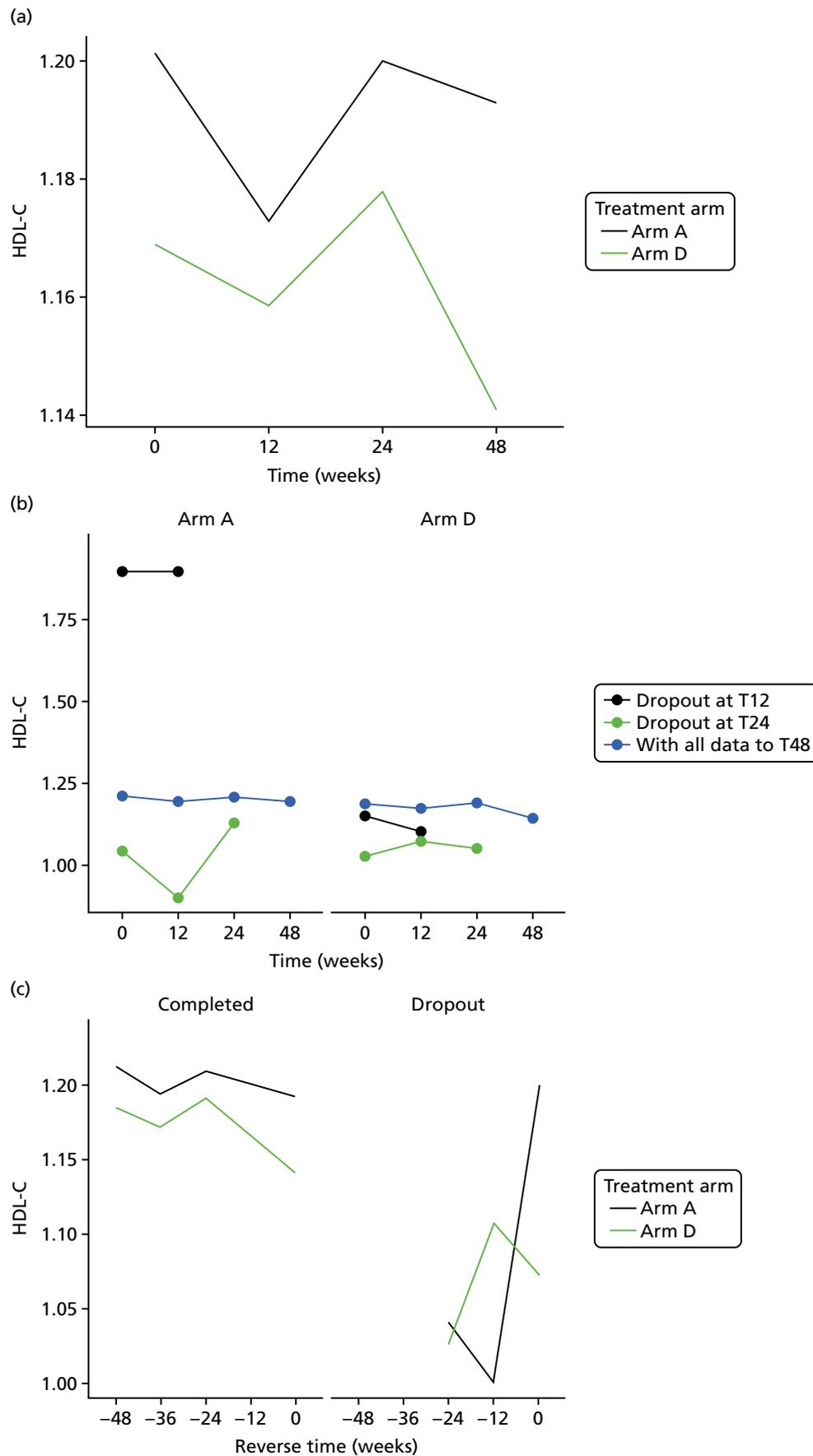
FIGURE 21 The HDL-C mean profiles by treatment arm (original scale). (a) HDL-C profile plots; (b) HDL-C profile plots by dropout; and (c) HDL-C reverse-time profile plots.

The bivariate joint model included 329 patients and 849 records. HDL-C scores were fitted in log-transformed scale for normality.

The treatment effect [arm D (80 mg) compared with arm A (control)] on the longitudinal log-HDL-C is 0.001 (95% CI –0.046 to 0.047), implying that there is no significant difference between the treatments on HDL-C.

TABLE 41 Joint model estimates: log-HDL-C

Component	Parameter	Estimate	95% CI	*p*-value
Longitudinal marker	Intercept	0.021	–0.034 to 0.076	0.4583
	Time	0.000	–0.001 to 0.001	0.6088
	Baseline marker	0.878	0.833 to 0.924	< 0.0001
	Treatment B vs. A	–0.012	–0.060 to 0.035	0.6089
	Treatment C vs. A	–0.038	–0.085 to 0.008	0.1086
	Treatment D vs. A	0.001	–0.046 to 0.047	0.9816
	Ethnicity	–0.018	–0.063 to 0.028	0.4455
Longitudinal weight	Intercept	0.285	–2.072 to 2.641	0.8129
	Time	0.019	–0.007 to 0.045	0.1537
	Baseline weight	0.994	0.971 to 1.017	< 0.0001
	Treatment B vs. A	0.477	–0.627 to 1.580	0.3972
	Treatment C vs. A	0.742	–0.415 to 1.899	0.2088
	Treatment D vs. A	0.075	–0.975 to 1.125	0.8881
	Ethnicity	–0.067	–0.945 to 0.811	0.8817
Dropout	Treatment B vs. A	0.089	–0.856 to 1.033	0.8540
	Treatment C vs. A	0.036	–0.986 to 1.058	0.9452
	Treatment D vs. A	0.329	–0.545 to 1.204	0.4608
	Ethnicity	–0.216	–1.078 to 0.646	0.6232
Association parameters	Marker	–0.638	–5.534 to 4.259	0.7986
	Weight	–0.046	–0.244 to 0.151	0.6465

Cholesterol

Histograms to check normality for cholesterol
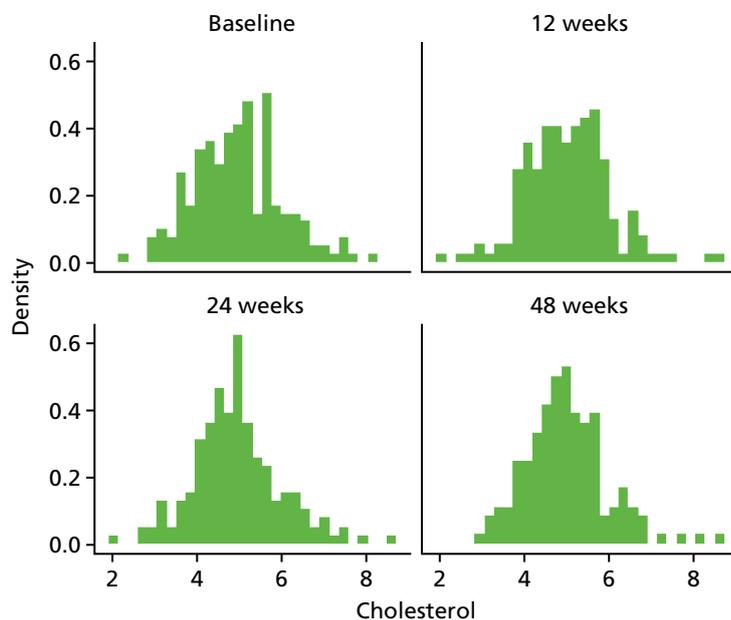
FIGURE 22 Normality of cholesterol (original scale).
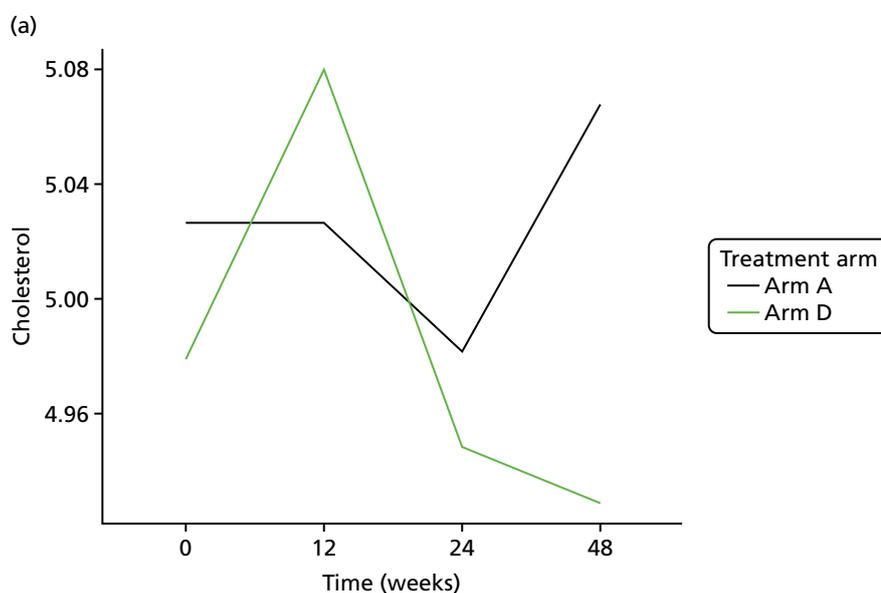
FIGURE 23 Cholesterol mean profiles by treatment arm (original scale). (a) cholesterol profile plots; (b) cholesterol profile plots by dropout; and (c) cholesterol reverse-time profile plots. (*continued*)
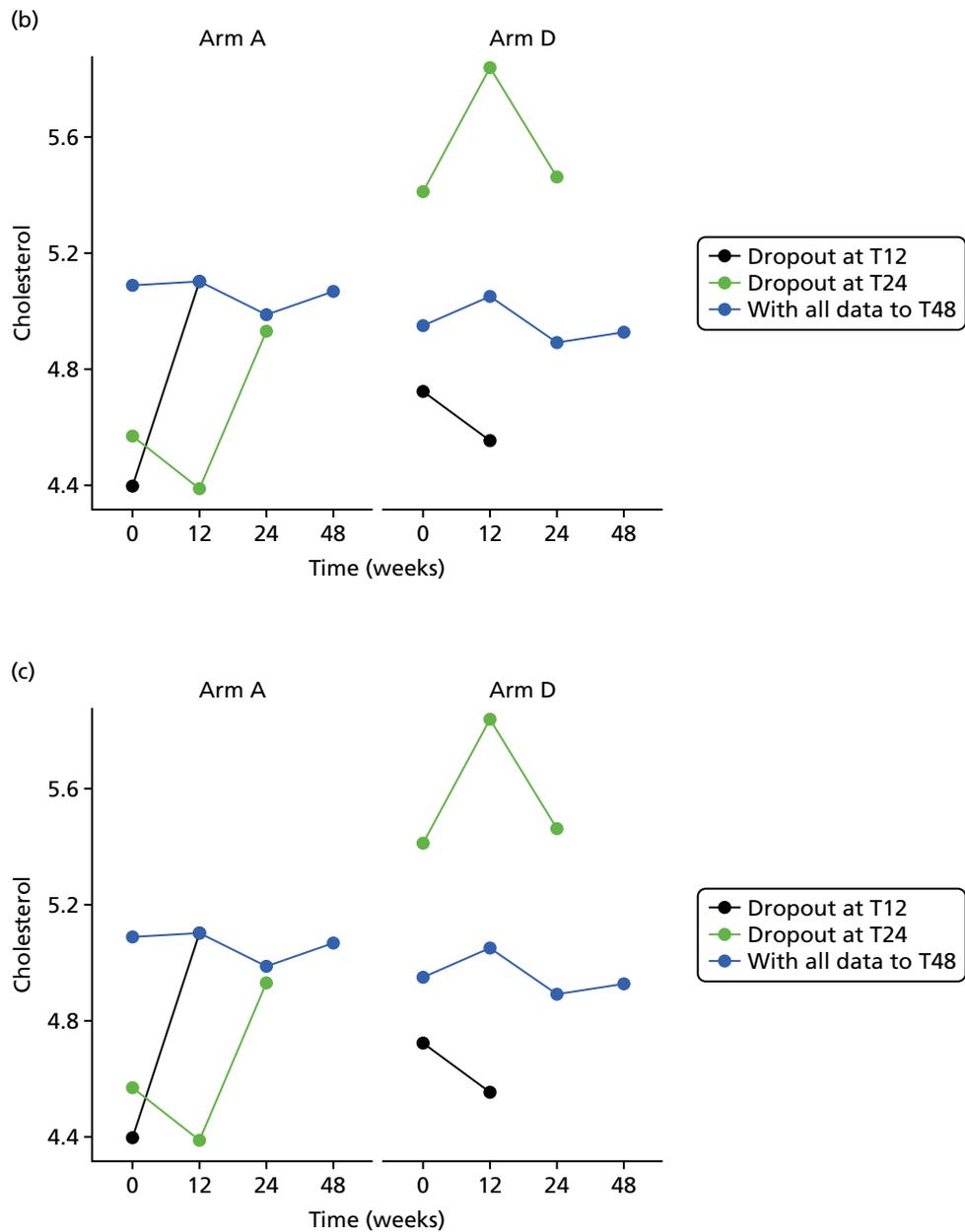
FIGURE 23 Cholesterol mean profiles by treatment arm (original scale). (a) cholesterol profile plots; (b) cholesterol profile plots by dropout; and (c) cholesterol reverse-time profile plots.

The bivariate joint model included 329 patients and 849 records. Cholesterol scores were fitted in their original scale.

The treatment effect [arm D (80 mg) compared with arm A (control)] on the longitudinal cholesterol is 0.013 (95% CI –0.173 to 0.199), implying that there is no significant difference between the treatments on cholesterol.

TABLE 42 Joint model estimates: cholesterol

Component	Parameter	Estimate	95% CI	*p*-value
Longitudinal marker	Intercept	1.325	0.965 to 1.684	< 0.0001
	Time	0.000	–0.002 to 0.003	0.8473
	Baseline marker	0.738	0.683 to 0.794	< 0.0001
	Treatment B vs. A	–0.046	–0.234 to 0.142	0.6326
	Treatment C vs. A	0.061	–0.117 to 0.238	0.5040
	Treatment D vs. A	0.013	–0.173 to 0.199	0.8904
	Ethnicity	–0.031	–0.201 to 0.139	0.7219
Longitudinal weight	Intercept	0.218	–2.106 to 2.541	0.8544
	Time	0.021	–0.005 to 0.046	0.1115
	Baseline weight	0.995	0.972 to 1.017	< 0.0001
	Treatment B vs. A	0.484	–0.617 to 1.586	0.3886
	Treatment C vs. A	0.746	–0.385 to 1.876	0.1960
	Treatment D vs. A	0.076	–0.954 to 1.105	0.8854
	Ethnicity	–0.090	–0.982 to 0.802	0.8433
Dropout	Treatment B vs. A	0.083	–0.872 to 1.038	0.8649
	Treatment C vs. A	0.027	–0.971 to 1.026	0.9576
	Treatment D vs. A	0.324	–0.549 to 1.197	0.4666
	Ethnicity	–0.215	–1.028 to 0.598	0.6042
Association parameters	Marker	–0.040	–1.197 to 1.118	0.9466
	Weight	–0.043	–0.249 to 0.163	0.6807

Triglycerides

Histograms to check normality for triglycerides
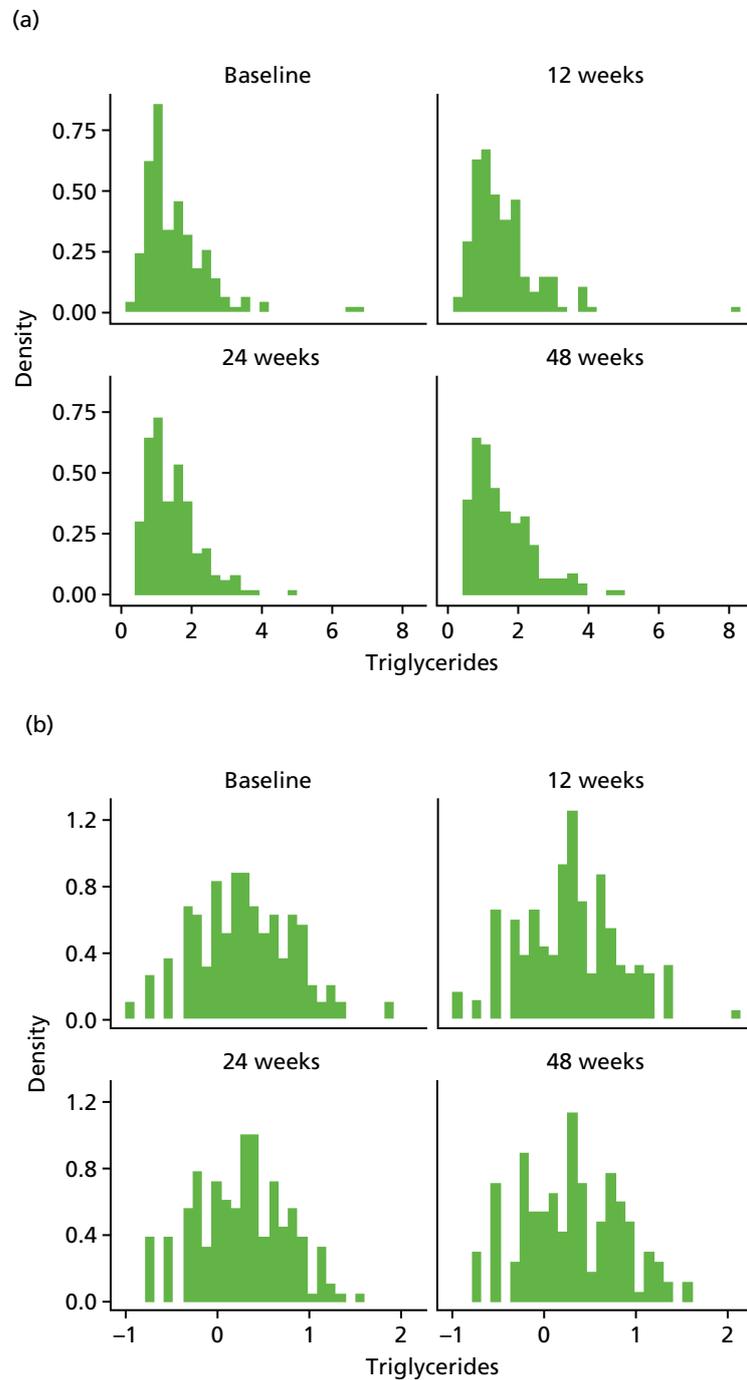
FIGURE 24 Normality of triglycerides. (a) original scale; and (b) log-transformed.
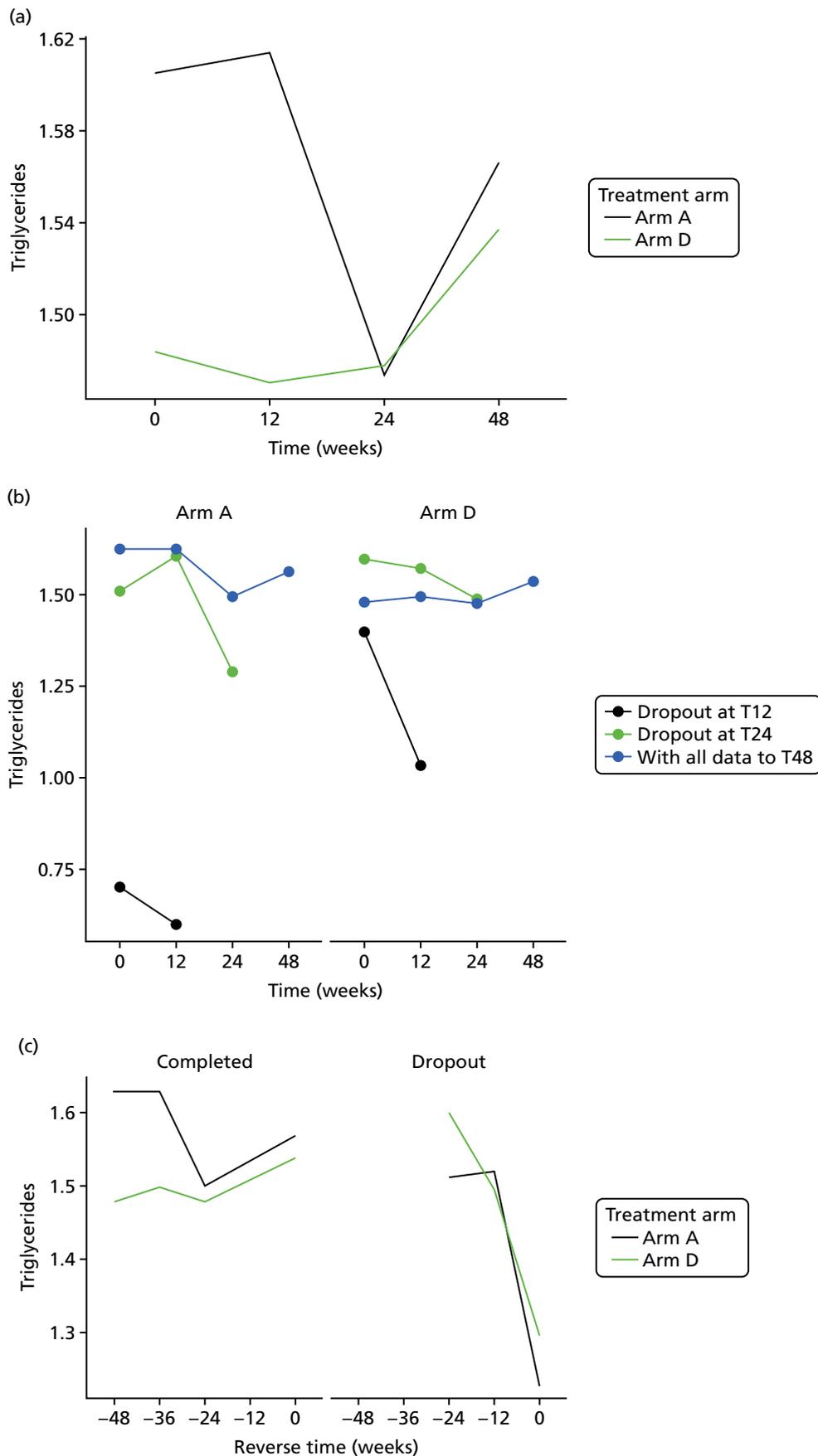
FIGURE 25 Triglycerides mean profiles by treatment arm (original scale). (a) triglycerides profile plots; (b) triglycerides profile plots by dropout; and (c) triglycerides reverse-time profile plots.

The bivariate joint model included 329 patients and 849 records. Triglycerides scores were fitted in log-transformed scale for normality.

The treatment effect [arm D (80 mg) compared with arm A (control)] on the longitudinal log-triglycerides is 0.030 (95% CI –0.056 to 0.116), implying that there is no significant difference between the treatments on triglycerides.

TABLE 43 Joint model estimates: log-triglycerides

Component	Parameter	Estimate	95% CI	*p*-value
Longitudinal marker	Intercept	0.018	–0.091 to 0.128	0.7450
	Time	0.001	–0.001 to 0.002	0.4220
	Baseline marker	0.779	0.713 to 0.845	< 0.0001
	Treatment B vs. A	0.002	–0.096 to 0.100	0.9614
	Treatment C vs. A	0.101	0.010 to 0.192	0.0291
	Treatment D vs. A	0.030	–0.056 to 0.116	0.4885
	Ethnicity	0.005	–0.089 to 0.099	0.9156
Longitudinal weight	Intercept	0.646	–1.688 to 2.980	0.5876
	Time	0.021	–0.004 to 0.046	0.0962
	Baseline weight	0.990	0.967 to 1.012	< 0.0001
	Treatment B vs. A	0.445	–0.602 to 1.491	0.4050
	Treatment C vs. A	0.676	–0.463 to 1.815	0.2448
	Treatment D vs. A	0.043	–0.953 to 1.039	0.9332
	Ethnicity	–0.088	–0.948 to 0.772	0.8412
Dropout	Treatment B vs. A	0.085	–0.876 to 1.046	0.8629
	Treatment C vs. A	0.027	–0.983 to 1.036	0.9588
	Treatment D vs. A	0.324	–0.547 to 1.195	0.4656
	Ethnicity	–0.219	–1.031 to 0.593	0.5967
Association parameters	Marker	–0.392	–3.779 to 2.996	0.8207
	Weight	–0.035	–0.269 to 0.199	0.7722

Low-density lipoprotein cholesterol

Histograms to check normality for low-density lipoprotein cholesterol
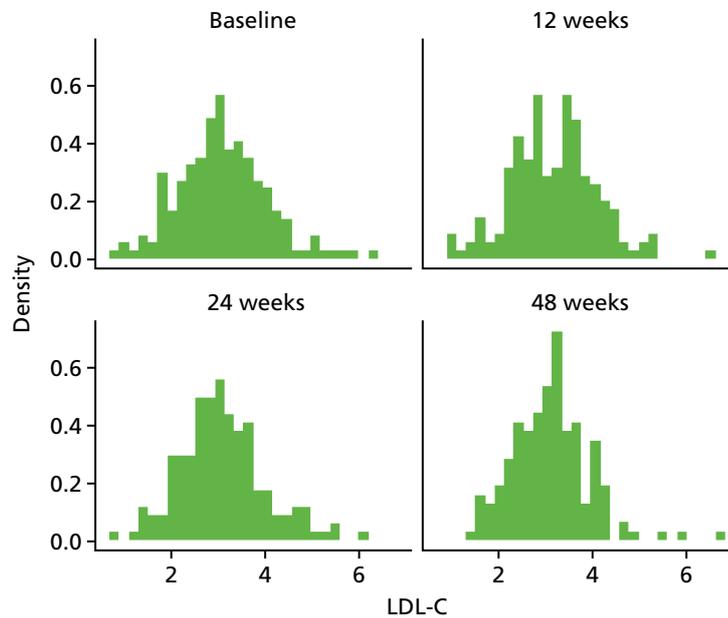
**FIGURE 26** Normality of LDL-C (original scale).
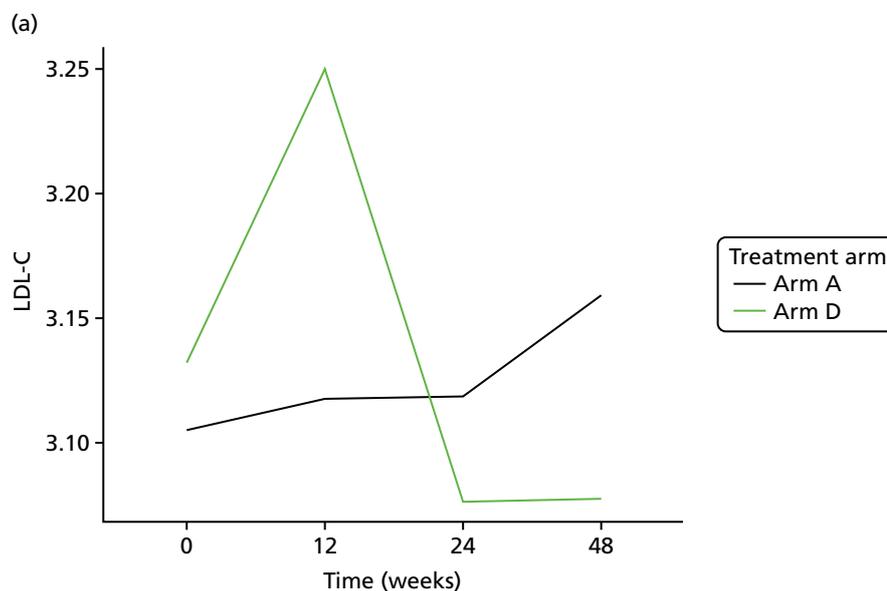
(a)

FIGURE 27 LDL-C mean profiles by treatment arm (original scale). (a) LDL-C profile plots; (b) LDL-C profile plots by dropout; and (c) LDL-C reverse-time profile plots. (*continued*)
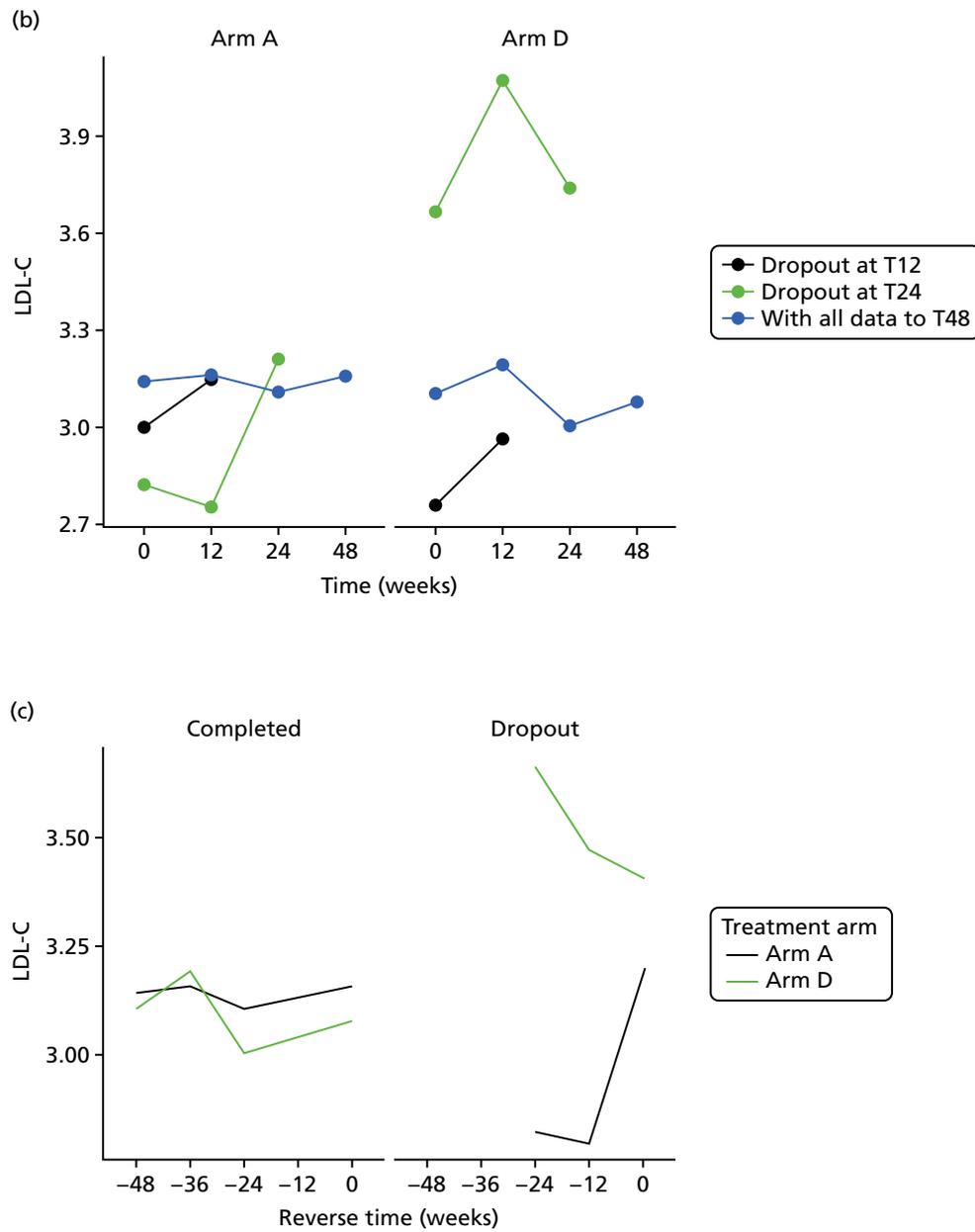
FIGURE 27 LDL-C mean profiles by treatment arm (original scale). (a) LDL-C profile plots; (b) LDL-C profile plots by dropout; and (c) LDL-C reverse-time profile plots.

The bivariate joint model included 324 patients and 833 records. LDL-C scores were fitted in original scale.

TABLE 44 Joint model estimates: LDL-C

Component	Parameter	Estimate	95% CI	*p*-value
Longitudinal marker	Intercept	0.787	0.539 to 1.035	< 0.0001
	Time	0.000	−0.002 to 0.002	0.9532
	Baseline marker	0.745	0.688 to 0.802	< 0.0001
	Treatment B vs. A	−0.008	−0.158 to 0.142	0.9127
	Treatment C vs. A	0.019	−0.135 to 0.172	0.8118
	Treatment D vs. A	0.000	−0.145 to 0.144	0.9946
	Ethnicity	0.029	−0.108 to 0.165	0.6820
Longitudinal weight	Intercept	0.223	−2.143 to 2.589	0.8536
	Time	0.021	−0.005 to 0.048	0.1170
	Baseline weight	0.995	0.971 to 1.018	< 0.0001
	Treatment B vs. A	0.427	−0.681 to 1.535	0.4505
	Treatment C vs. A	0.626	−0.579 to 1.832	0.3086
	Treatment D vs. A	0.065	−0.981 to 1.111	0.9027
	Ethnicity	−0.099	−1.003 to 0.806	0.8309
Dropout	Treatment B vs. A	−0.012	−0.970 to 0.946	0.9799
	Treatment C vs. A	−0.192	−1.232 to 0.848	0.7172
	Treatment D vs. A	0.222	−0.645 to 1.089	0.6161
	Ethnicity	−0.326	−1.101 to 0.448	0.4086
Association parameters	Marker	0.271	−1.151 to 1.693	0.7086
	Weight	−0.059	−0.253 to 0.135	0.5504

Plasma biomarkers

Adiponectin

Histograms to check normality for adiponectin
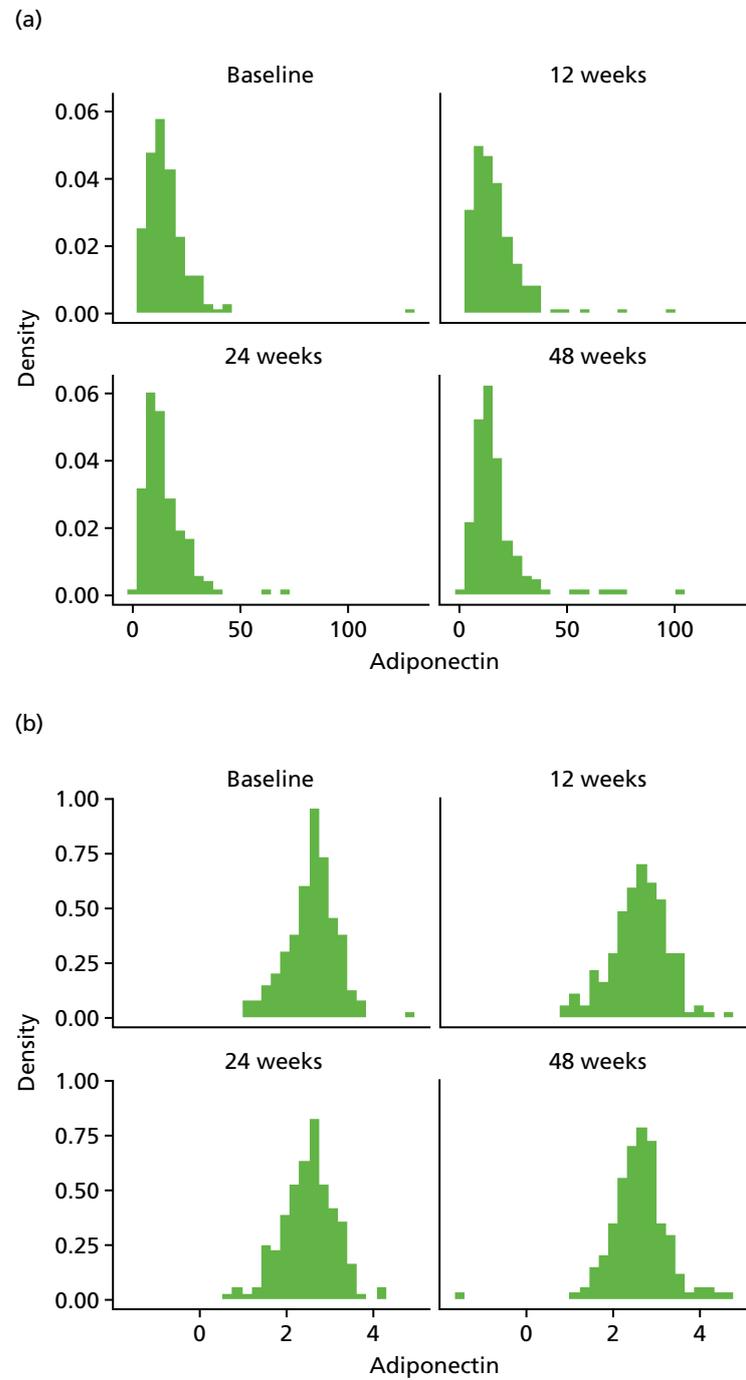
FIGURE 28 Normality of adiponectin. (a) original scale; and (b) log-transformed.
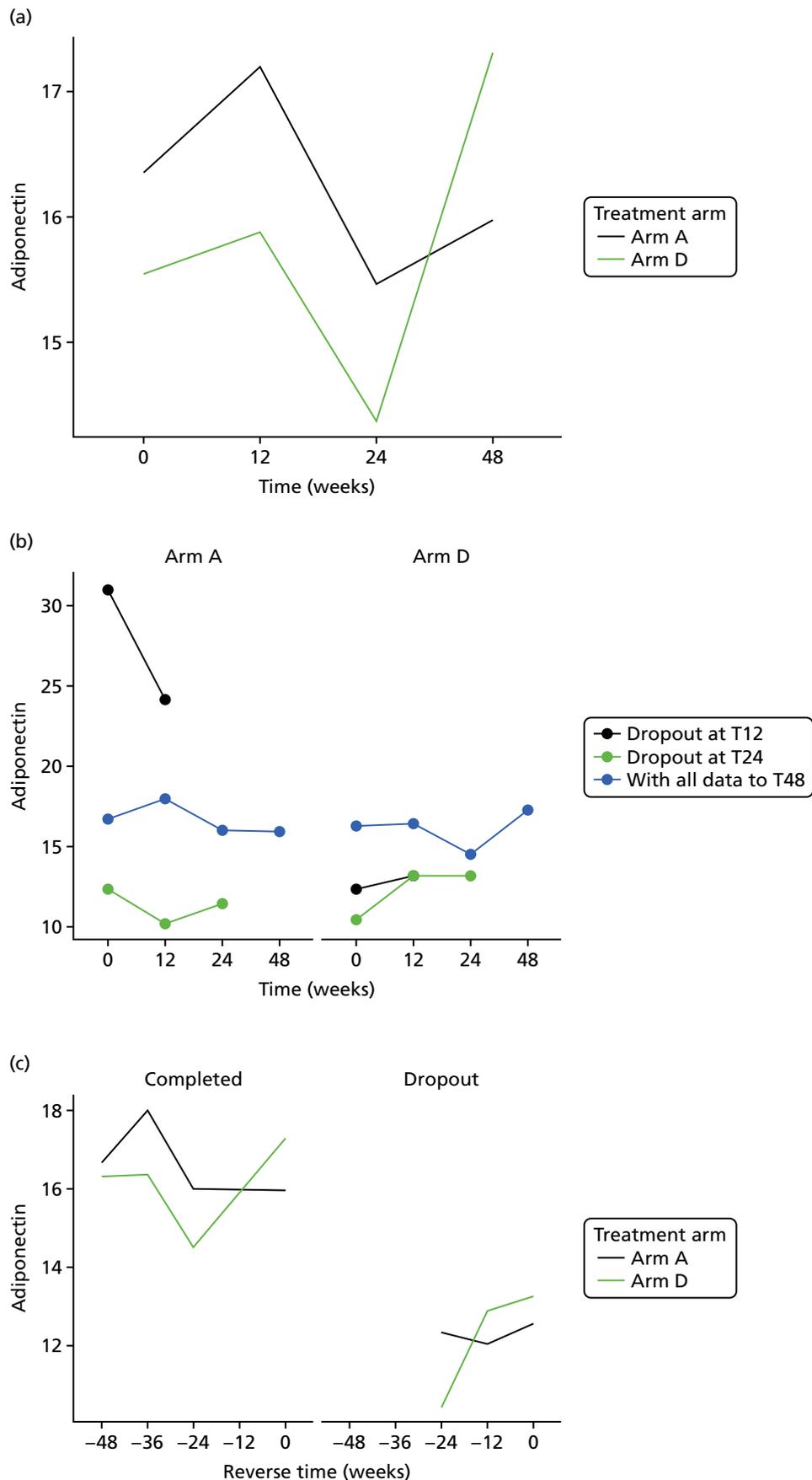
FIGURE 29 Adiponectin mean profiles by treatment arm (original scale). (a) adiponectin profile plots; (b) adiponectin profile plots by dropout; and (c) adiponectin reverse-time profile plots.

The bivariate joint model included 324 patients and 829 records. Adiponectin scores were fitted in log-transformed scale for normality.

The treatment effect [arm D (80 mg) compared with arm A (control)] on the longitudinal log-adiponectin is 0.035 (95% CI −0.078 to 0.148), implying that there is no significant difference between the treatments on adiponectin.

TABLE 45 Joint model estimates: log-adiponectin

Component	Parameter	Estimate	95% CI	*p*-value
Longitudinal marker	Intercept	0.555	0.297 to 0.812	< 0.0001
	Time	−0.001	−0.003 to 0.001	0.3345
	Baseline marker	0.787	0.709 to 0.865	< 0.0001
	Treatment B vs. A	0.072	−0.060 to 0.204	0.2846
	Treatment C vs. A	0.045	−0.077 to 0.168	0.4696
	Treatment D vs. A	0.035	−0.078 to 0.148	0.5420
	Ethnicity	−0.043	−0.161 to 0.075	0.4731
Longitudinal weight	Intercept	0.491	−1.739 to 2.720	0.6661
	Time	0.020	−0.003 to 0.043	0.0941
	Baseline weight	0.992	0.970 to 1.013	< 0.0001
	Treatment B vs. A	0.441	−0.608 to 1.489	0.4103
	Treatment C vs. A	0.683	−0.465 to 1.832	0.2437
	Treatment D vs. A	0.084	−0.932 to 1.100	0.8713
	Ethnicity	−0.054	−0.931 to 0.824	0.9046
Dropout	Treatment B vs. A	0.263	−0.665 to 1.190	0.5791
	Treatment C vs. A	0.023	−1.000 to 1.046	0.9649
	Treatment D vs. A	0.260	−0.625 to 1.146	0.5644
	Ethnicity	−0.059	−0.908 to 0.789	0.8912
Association parameters	Marker	0.415	−1.394 to 2.223	0.6529
	Weight	−0.034	−0.242 to 0.174	0.7467

Leptin

Histograms to check normality for leptin

(a)

(b)
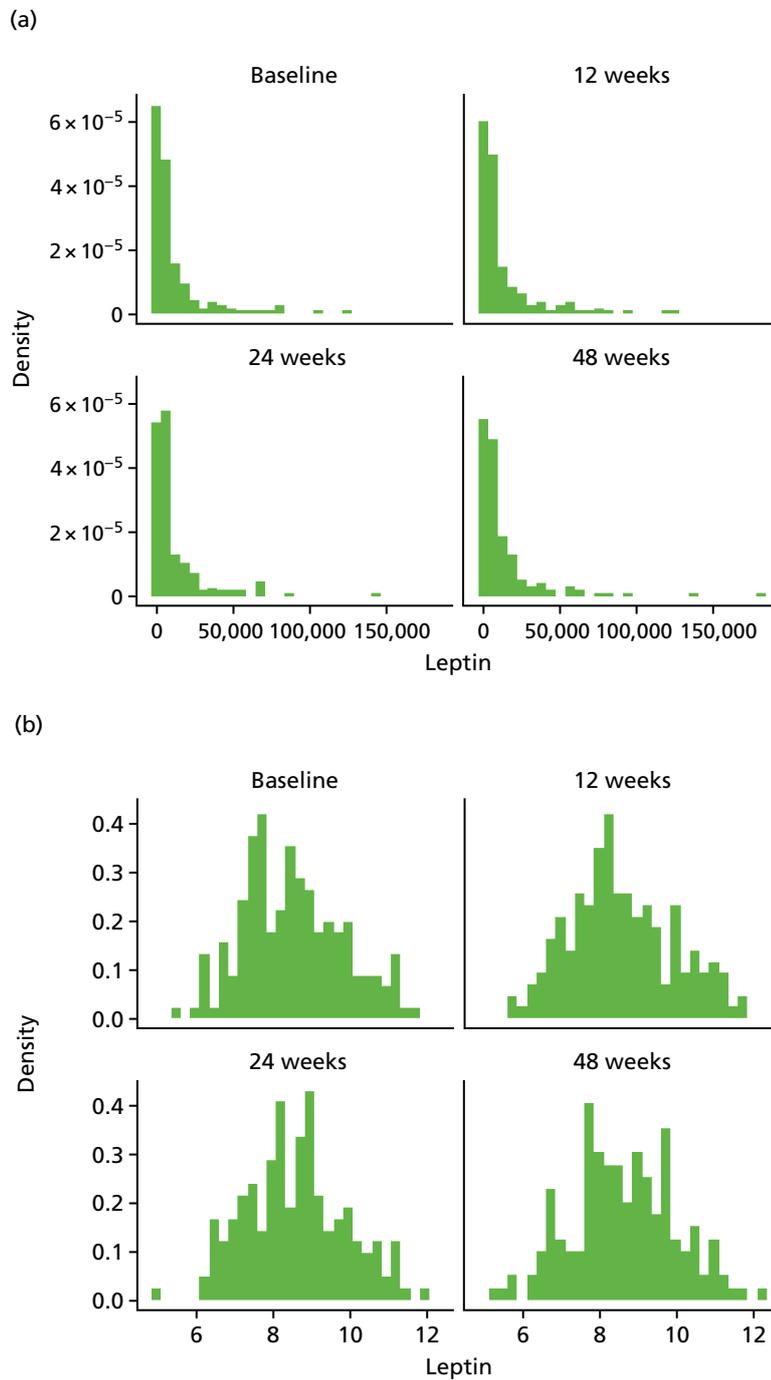
FIGURE 30 Normality of leptin. (a) original scale; and (b) log-transformed.
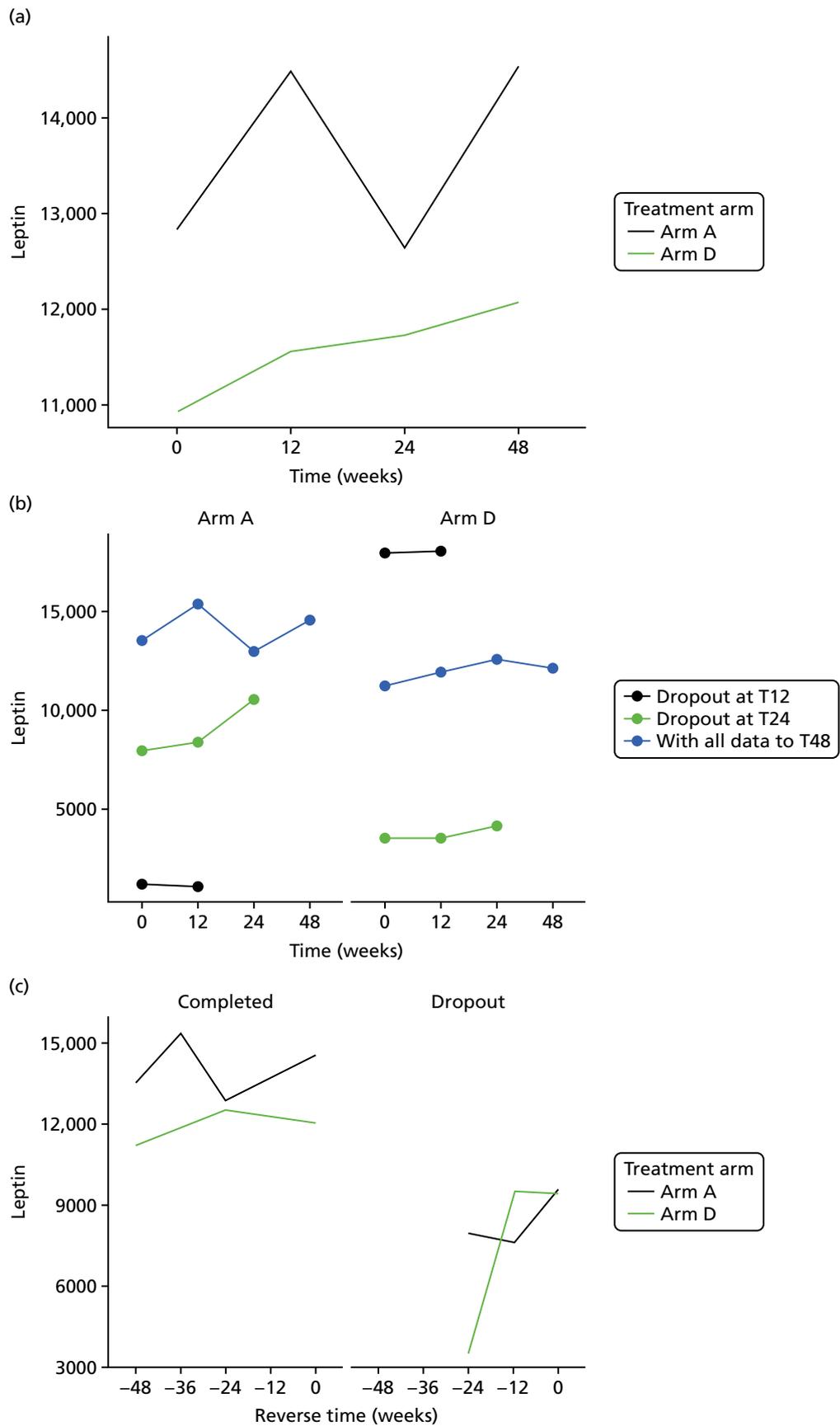
FIGURE 31 Leptin mean profiles by treatment arm (original scale). (a) leptin profile plots; (b) leptin profile plots by dropout; and (c) leptin reverse-time profile plots.

The bivariate joint model included 325 patients and 841 records. Leptin scores were fitted in log-transformed scale for normality.

The treatment effect [arm D (80 mg) compared with arm A (control)] on the longitudinal log-leptin is 0.004 (95% CI –0.179 to 0.187), implying that there is no significant difference between the treatments on leptin.

TABLE 46 Joint model estimates: log-leptin

Component	Parameter	Estimate	95% CI	*p*-value
Longitudinal marker	Intercept	0.893	0.419 to 1.367	0.0002
	Time	0.001	–0.002 to 0.003	0.6639
	Baseline marker	0.906	0.857 to 0.956	< 0.0001
	Treatment B vs. A	–0.010	–0.198 to 0.177	0.9132
	Treatment C vs. A	0.161	–0.038 to 0.359	0.1126
	Treatment D vs. A	0.004	–0.179 to 0.187	0.9664
	Ethnicity	–0.061	–0.226 to 0.105	0.4727
Longitudinal weight	Intercept	1.017	–1.224 to 3.258	0.3738
	Time	0.020	–0.008 to 0.048	0.1713
	Baseline weight	0.982	0.961 to 1.004	< 0.0001
	Treatment B vs. A	0.386	–0.671 to 1.443	0.4739
	Treatment C vs. A	0.840	–0.248 to 1.929	0.1302
	Treatment D vs. A	0.148	–0.817 to 1.113	0.7637
	Ethnicity	0.155	–0.682 to 0.991	0.7174
Dropout	Treatment B vs. A	–0.020	–1.047 to 1.007	0.9695
	Treatment C vs. A	0.244	–0.724 to 1.212	0.6213
	Treatment D vs. A	0.346	–0.569 to 1.260	0.4588
	Ethnicity	0.122	–0.773 to 1.016	0.7893
Association parameters	Marker	0.050	–1.425 to 1.524	0.9474
	Weight	–0.108	–0.433 to 0.218	0.5168

Interleukin 8

Histograms to check normality for interleukin 8
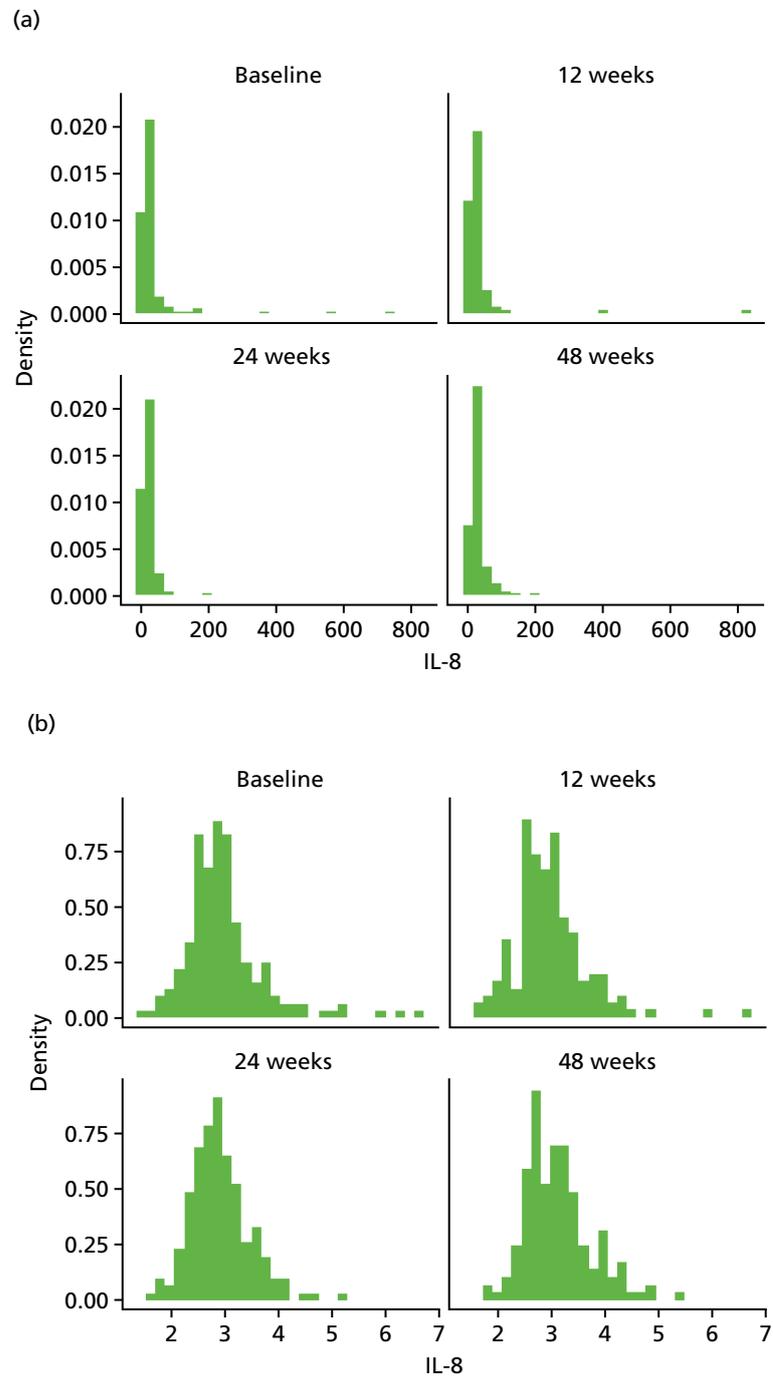
FIGURE 32 Normality of IL-8. (a) original scale; and (b) log-transformed.
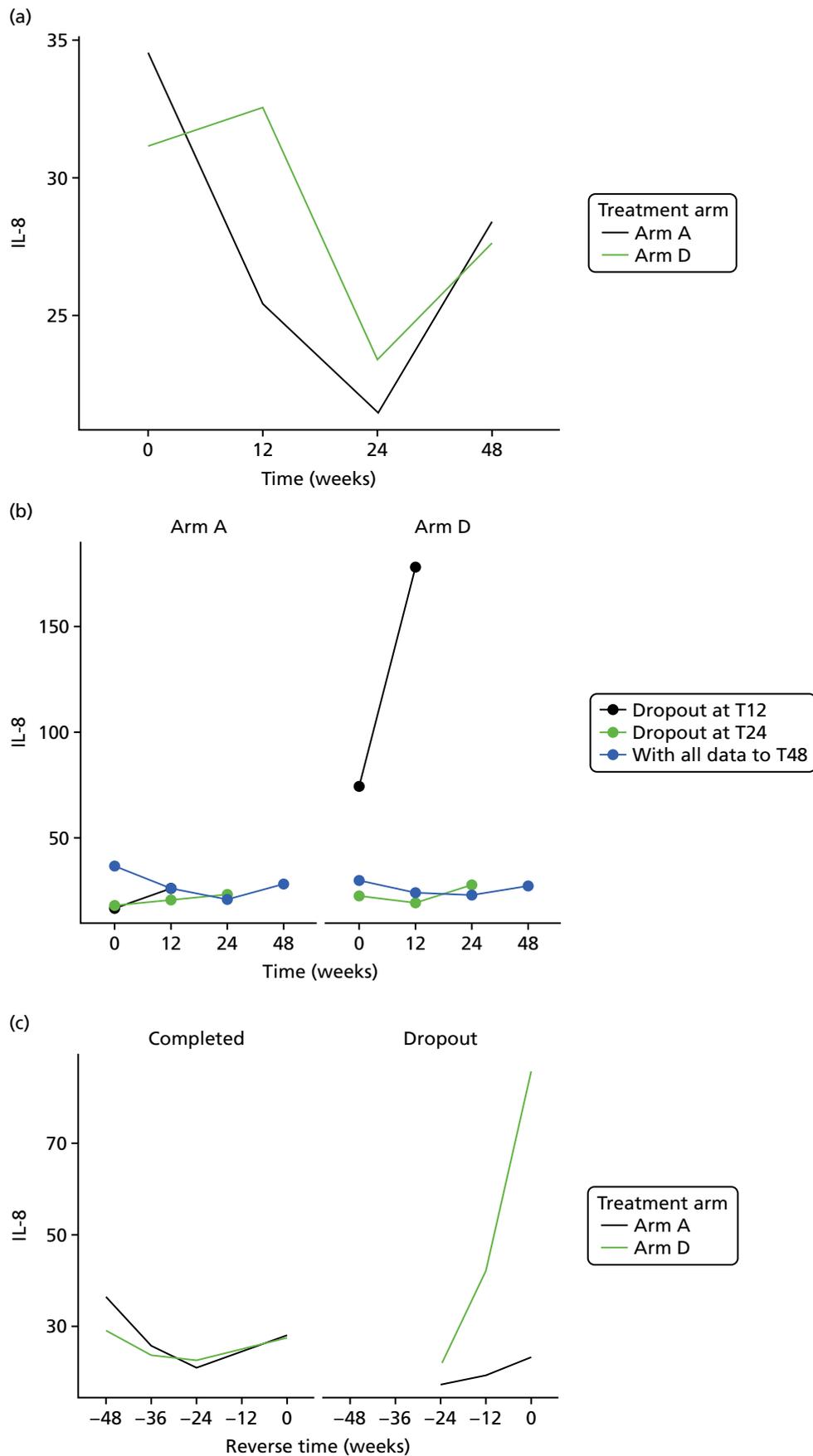
FIGURE 33 IL-8 mean profiles by treatment arm (original scale). (a) IL-8 profile plots; (b) IL-8 profile plots by dropout; and (c) IL-8 reverse-time profile plots.

The bivariate joint model included 327 patients and 845 records. IL-8 scores were fitted in log-transformed scale for normality.

The treatment effect [arm D (80 mg) compared with arm A (control)] on the longitudinal log-IL-8 is 0.041 (95% CI –0.111 to 0.193), implying that there is no significant difference between the treatments on IL-8.

TABLE 47 Joint model estimates: log-IL-8

Component	Parameter	Estimate	95% CI	*p*-value
Longitudinal marker	Intercept	1.851	1.594 to 2.107	< 0.0001
	Time	0.006	0.003 to 0.009	0.0004
	Baseline marker	0.297	0.246 to 0.348	< 0.0001
	Treatment B vs. A	0.021	–0.145 to 0.187	0.8029
	Treatment C vs. A	–0.112	–0.303 to 0.078	0.2480
	Treatment D vs. A	0.041	–0.111 to 0.193	0.5950
	Ethnicity	0.103	–0.042 to 0.249	0.1647
Longitudinal weight	Intercept	0.436	–1.841 to 2.712	0.7077
	Time	0.020	–0.002 to 0.043	0.0784
	Baseline weight	0.991	0.969 to 1.013	< 0.0001
	Treatment B vs. A	0.506	–0.525 to 1.537	0.3361
	Treatment C vs. A	0.689	–0.409 to 1.788	0.2188
	Treatment D vs. A	0.194	–0.807 to 1.195	0.7042
	Ethnicity	–0.018	–0.864 to 0.829	0.9675
Dropout	Treatment B vs. A	0.166	–0.776 to 1.108	0.7301
	Treatment C vs. A	0.027	–0.964 to 1.019	0.9568
	Treatment D vs. A	0.237	–0.648 to 1.122	0.6000
	Ethnicity	–0.353	–1.166 to 0.460	0.3948
Association parameters	Marker	–0.006	–1.347 to 1.335	0.9927
	Weight	–0.053	–0.254 to 0.148	0.6050

Tumour necrosis factor alpha

Histograms to check normality for tumour necrosis factor alpha
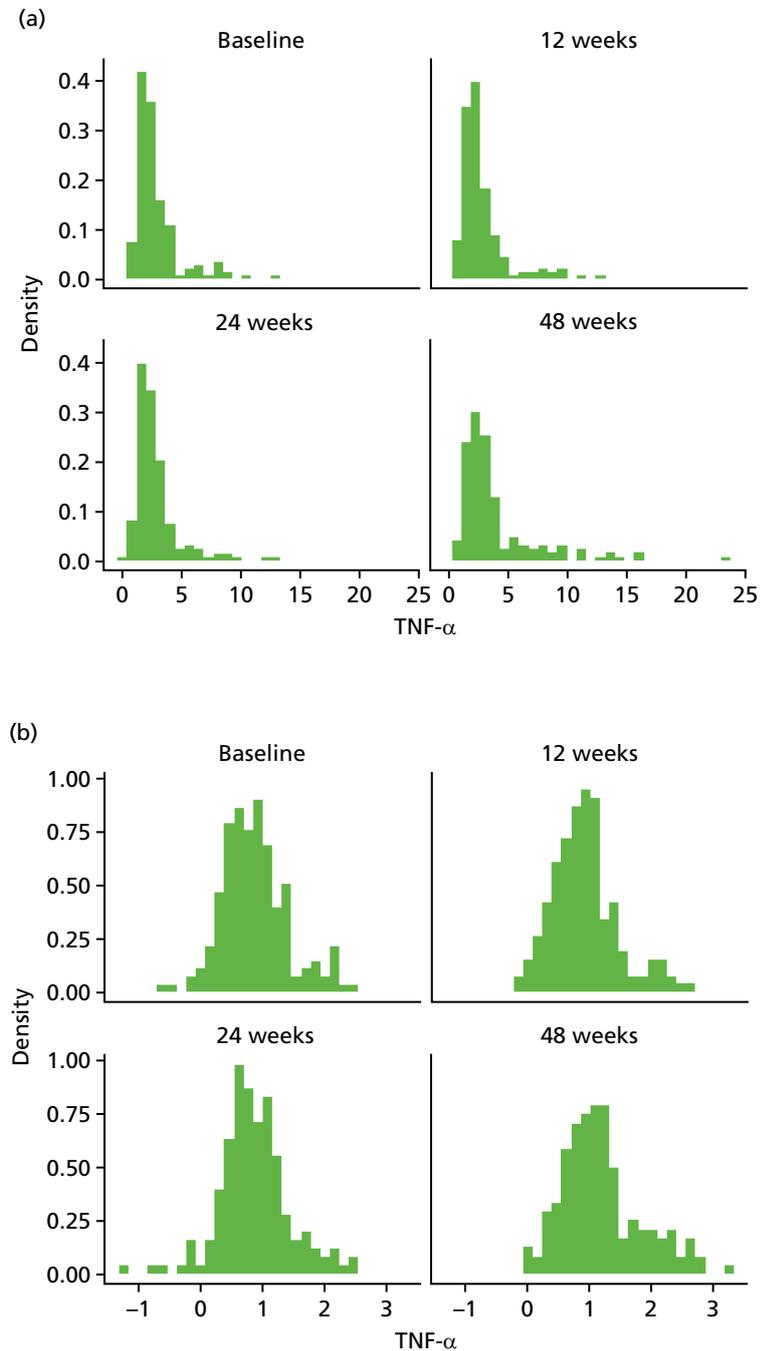
FIGURE 34 Normality of TNF-α. (a) original scale; and (b) log-transformed.
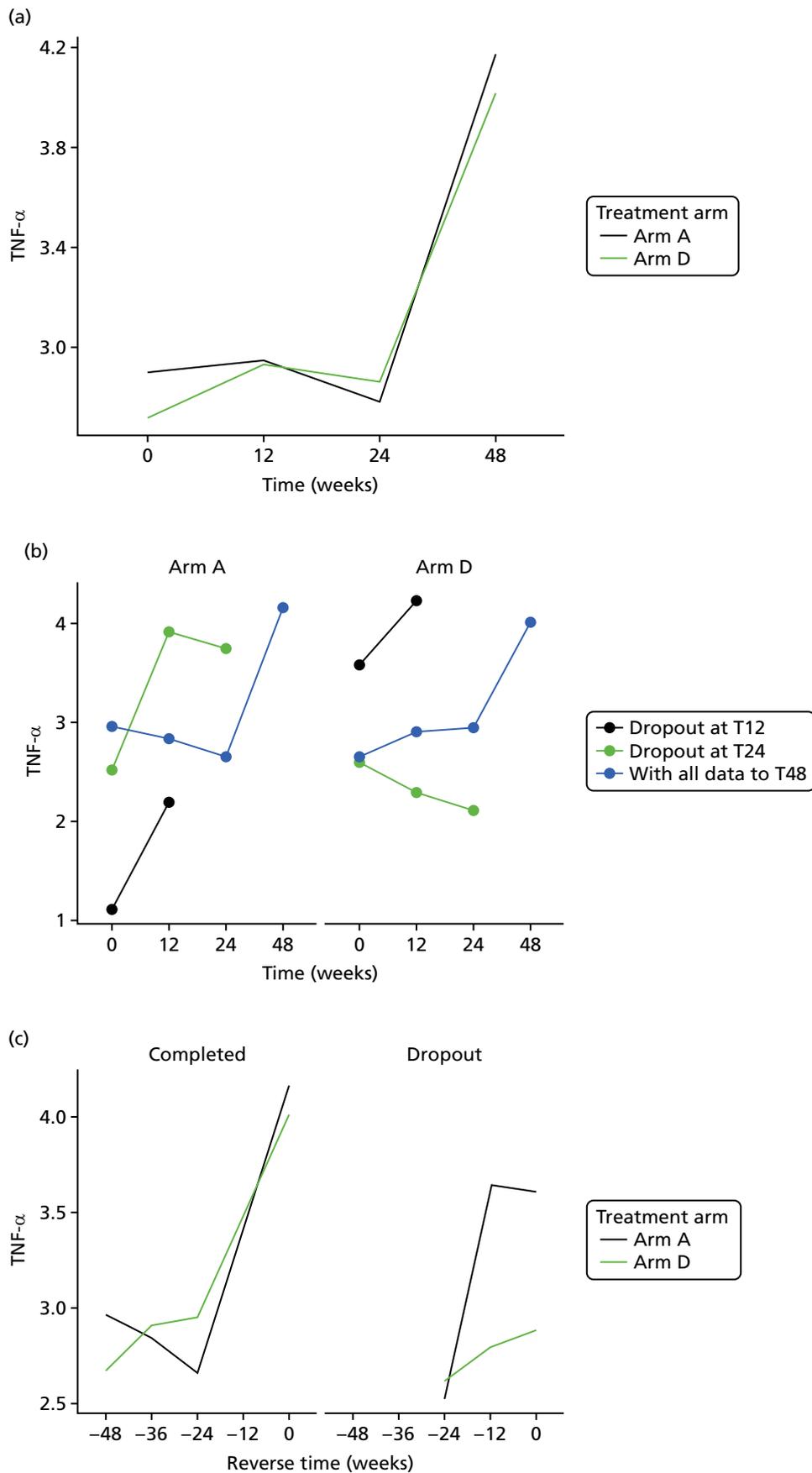
FIGURE 35 TNF-α mean profiles by treatment arm (original scale). (a) TNF-α profile plots; (b) TNF-α profile plots by dropout; and (c) TNF-α reverse-time profile plots.

The bivariate joint model included 325 patients and 838 records. TNF-α scores were fitted in log-transformed scale for normality.

The treatment effect [arm D (80 mg) compared with arm A (control)] on the longitudinal log-TNF-α is –0.025 (95% CI –0.133 to 0.082), implying that there is no significant difference between the treatments on TNF-α.

TABLE 48 Joint model estimates: log-TNF-α

Component	Parameter	Estimate	95% CI	*p*-value
Longitudinal marker	Intercept	0.154	–0.011 to 0.319	0.0682
	Time	0.007	0.004 to 0.009	< 0.0001
	Baseline marker	0.642	0.561 to 0.723	< 0.0001
	Treatment B vs. A	0.002	–0.119 to 0.122	0.9800
	Treatment C vs. A	–0.058	–0.197 to 0.080	0.4093
	Treatment D vs. A	–0.025	–0.133 to 0.082	0.6412
	Ethnicity	0.119	0.005 to 0.233	0.0415
Longitudinal weight	Intercept	0.433	–1.940 to 2.806	0.7208
	Time	0.020	–0.006 to 0.047	0.1374
	Baseline weight	0.992	0.970 to 1.014	< 0.0001
	Treatment B vs. A	0.492	–0.560 to 1.544	0.3591
	Treatment C vs. A	0.736	–0.392 to 1.864	0.2010
	Treatment D vs. A	0.107	–0.920 to 1.134	0.8381
	Ethnicity	–0.078	–0.979 to 0.824	0.8656
Dropout	Treatment B vs. A	0.169	–0.826 to 1.164	0.7392
	Treatment C vs. A	0.119	–0.902 to 1.140	0.8190
	Treatment D vs. A	0.425	–0.495 to 1.345	0.3653
	Ethnicity	–0.236	–1.052 to 0.579	0.5700
Association parameters	Marker	0.492	–1.269 to 2.252	0.5841
	Weight	–0.060	–0.259 to 0.139	0.5545

Resistin

Histograms to check normality for resistin
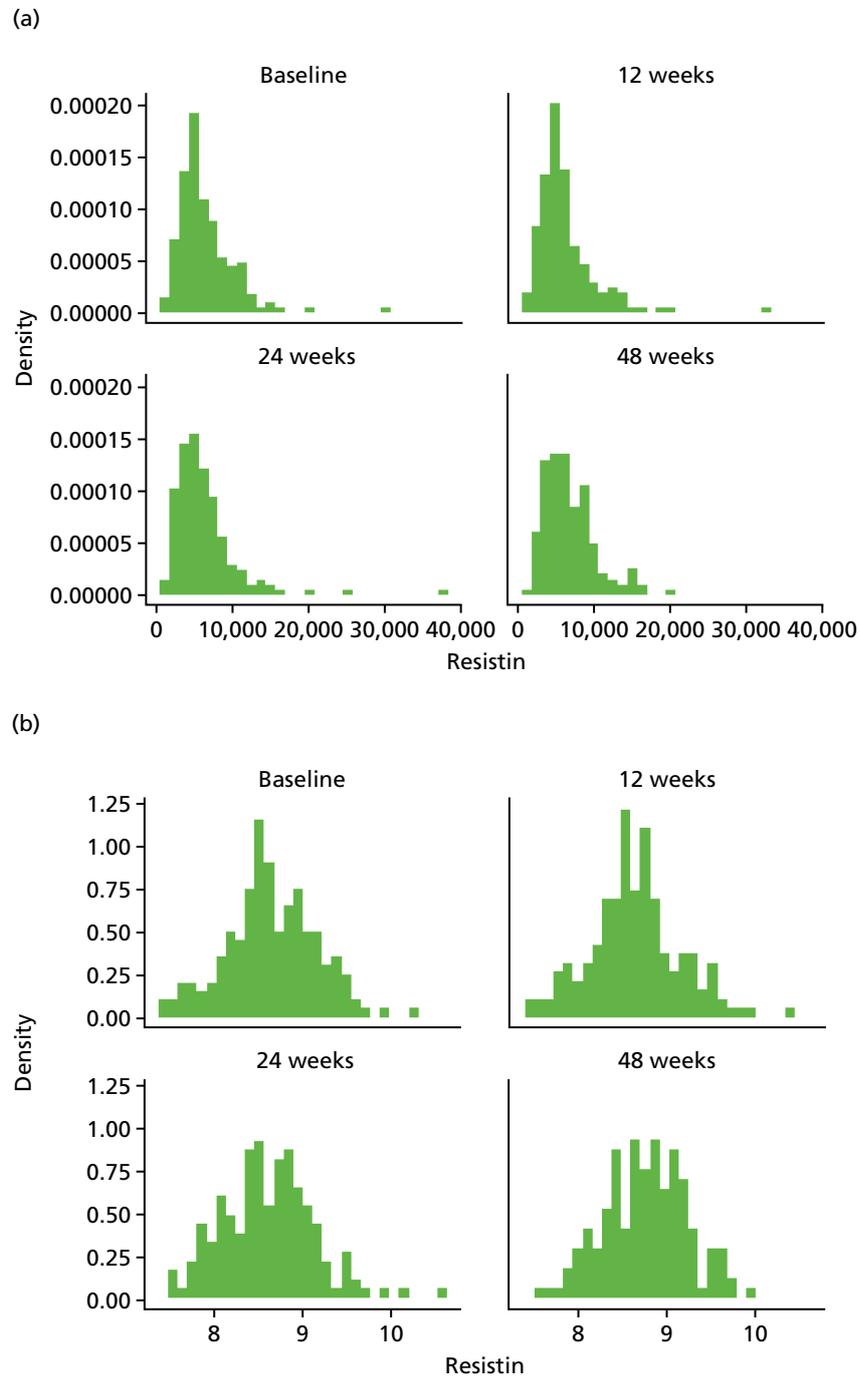
FIGURE 36 Normality of resistin (a) original scale; and (b) log-transformed.
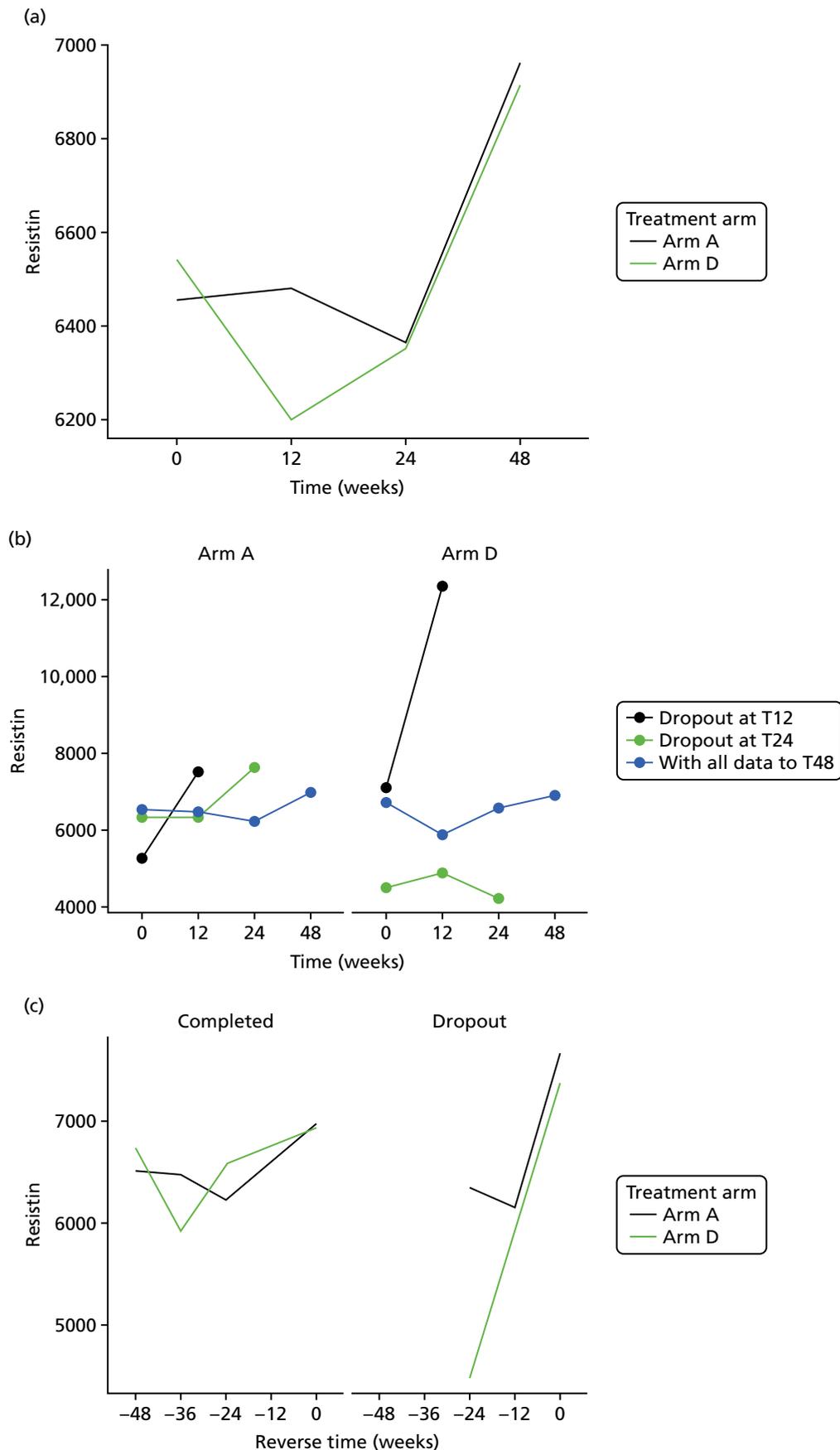
FIGURE 37 Resistin mean profiles by treatment arm (original scale). (a) Resistin profile plots; (b) resistin profile plots by dropout; and (c) resistin reverse-time profile plots.

The bivariate joint model included 326 patients and 841 records. Resistin scores were fitted in log-transformed scale for normality.

The treatment effect [arm D (80 mg) compared with arm A (control)] on the longitudinal log-resistin is –0.066 (95% CI –0.171 to 0.039), implying that there is no significant difference between the treatments on resistin.

TABLE 49 Joint model estimates: log-resistin

Component	Parameter	Estimate	95% CI	*p*-value
Longitudinal marker	Intercept	3.449	2.786 to 4.112	< 0.0001
	Time	0.004	0.002 to 0.005	< 0.0001
	Baseline marker	0.591	0.518 to 0.665	< 0.0001
	Treatment B vs. A	–0.021	–0.133 to 0.091	0.7126
	Treatment C vs. A	–0.020	–0.131 to 0.091	0.7211
	Treatment D vs. A	–0.066	–0.171 to 0.039	0.2201
	Ethnicity	0.038	–0.066 to 0.143	0.4699
Longitudinal weight	Intercept	0.265	–1.993 to 2.522	0.8182
	Time	0.021	–0.003 to 0.045	0.0877
	Baseline weight	0.994	0.972 to 1.016	< 0.0001
	Treatment B vs. A	0.436	–0.620 to 1.493	0.4180
	Treatment C vs. A	0.699	–0.394 to 1.793	0.2101
	Treatment D vs. A	0.076	–0.919 to 1.070	0.8816
	Ethnicity	–0.054	–0.907 to 0.799	0.9009
Dropout	Treatment B vs. A	0.174	–0.750 to 1.098	0.7125
	Treatment C vs. A	0.145	–0.798 to 1.087	0.7636
	Treatment D vs. A	0.263	–0.608 to 1.134	0.5545
	Ethnicity	–0.192	–1.075 to 0.691	0.6701
Association parameters	Marker	0.710	–0.679 to 2.099	0.3163
	Weight	–0.052	–0.251 to 0.148	0.6119

High-sensitivity C-reactive protein

Histograms to check normality for high-sensitivity C-reactive protein
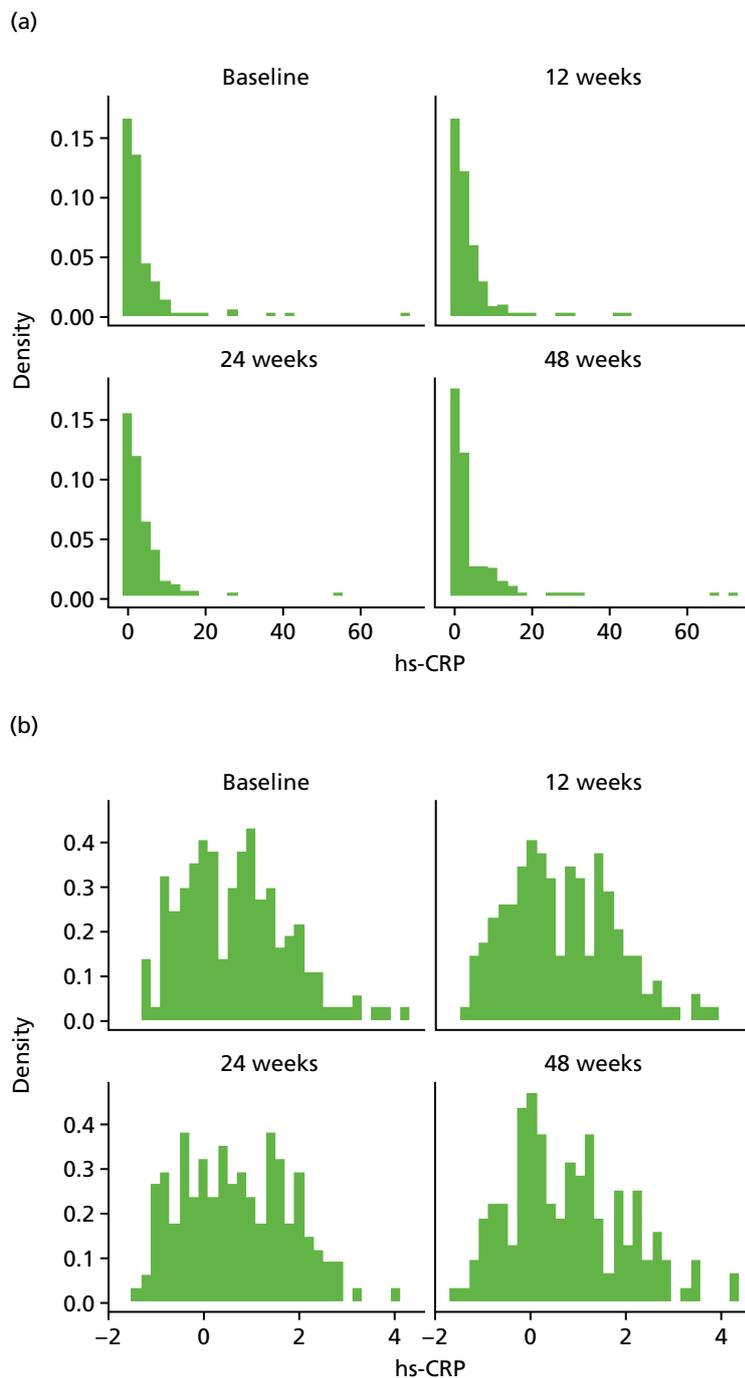
FIGURE 38 Normality of hs-CRP (a) original scale; and (b) log-transformed.
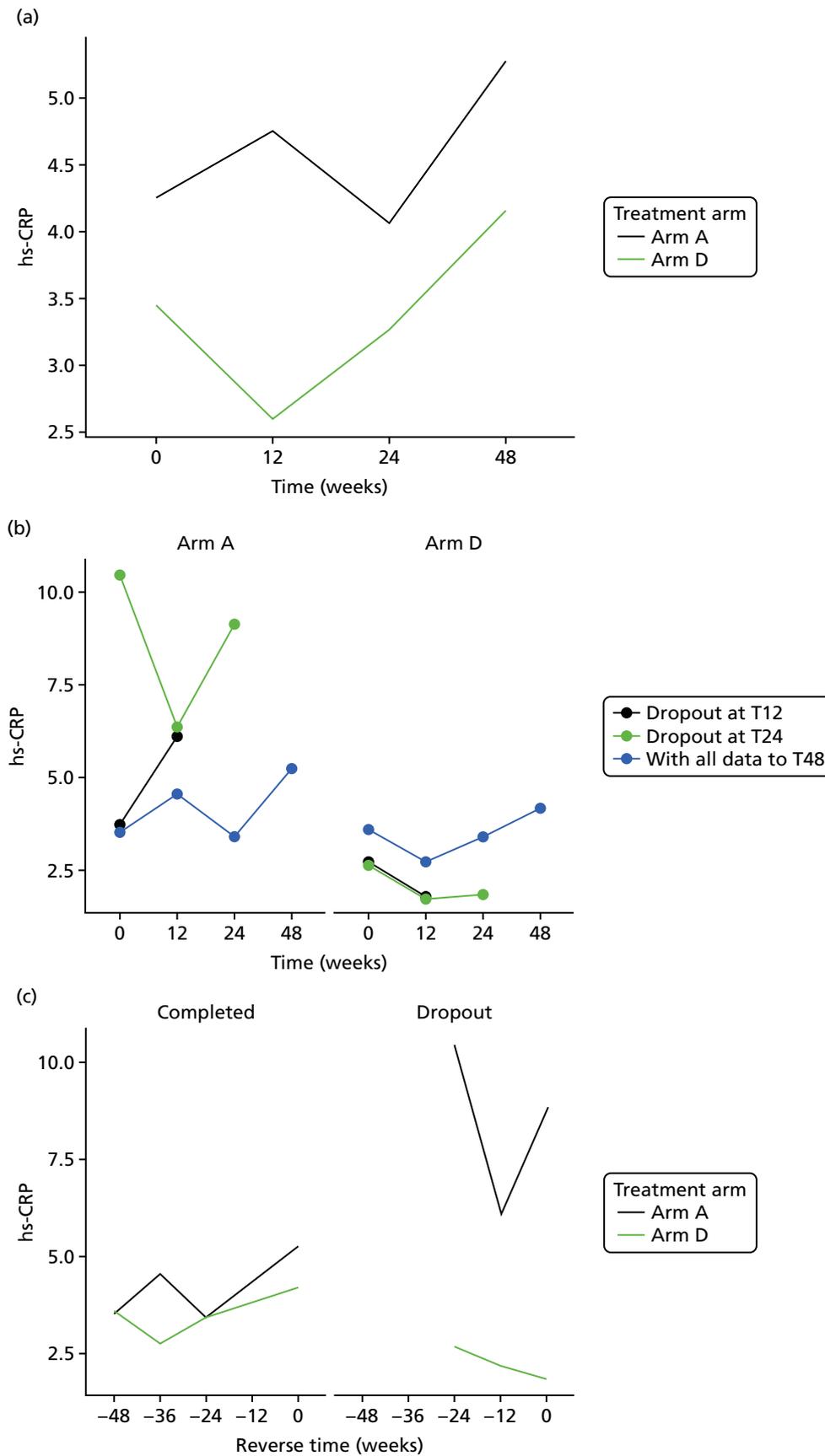
FIGURE 39 hs-CRP mean profiles by treatment arm (original scale). (a) hs-CRP profile plots; (b) hs-CRP profile plots by dropout; and (c) hs-CRP reverse-time profile plots.

The bivariate joint model included 328 patients and 845 records. The hs-CRP scores were fitted in log-transformed scale for normality.

The treatment effect [arm D (80 mg) compared with arm A (control)] on the longitudinal log-hs-CRP is statistically significant with an estimated effect of –0.222 (95% CI –0.433 to –0.011), implying that hs-CRP is significantly lower among those patients randomised to arm D (80 mg).

TABLE 50 Joint model estimates: log-hs-CRP

Component	Parameter	Estimate	95% CI	*p*-value
Longitudinal marker	Intercept	0.582	0.293 to 0.871	0.0001
	Time	0.001	–0.003 to 0.006	0.6069
	Baseline marker	0.612	0.527 to 0.697	< 0.0001
	Treatment B vs. A	–0.207	–0.444 to 0.030	0.0867
	Treatment C vs. A	–0.204	–0.443 to 0.036	0.0953
	Treatment D vs. A	–0.222	–0.433 to –0.011	0.0388
	Ethnicity	–0.278	–0.501 to –0.056	0.0141
Longitudinal weight	Intercept	0.378	–2.039 to 2.795	0.7593
	Time	0.020	–0.004 to 0.045	0.1074
	Baseline weight	0.993	0.969 to 1.016	< 0.0001
	Treatment B vs. A	0.489	–0.571 to 1.549	0.3656
	Treatment C vs. A	0.728	–0.419 to 1.875	0.2135
	Treatment D vs. A	0.091	–0.921 to 1.103	0.8599
	Ethnicity	–0.095	–0.972 to 0.782	0.8317
Dropout	Treatment B vs. A	0.086	–0.866 to 1.038	0.8592
	Treatment C vs. A	0.046	–0.931 to 1.024	0.9257
	Treatment D vs. A	0.321	–0.579 to 1.222	0.4841
	Ethnicity	–0.213	–1.014 to 0.588	0.6017
Association parameters	Marker	0.248	–0.732 to 1.228	0.6197
	Weight	–0.046	–0.234 to 0.142	0.6328

Substudies

Magnetic resonance imaging

TABLE 51 Summary statistics for the MRI and ^{1}H-MRS measurements at baseline and 24 weeks by treatment group

Summary statistic	Time point							
	Baseline				24 weeks			
	Arm A (control)	Arm B (20 mg)	Arm C (40 mg)	Arm D (80 mg)	Arm A (control)	Arm B (20 mg)	Arm C (40 mg)	Arm D (80 mg)
Internal visceral fat (dm³)								
Number (%)	8 (61.5)	7 (70.0)	6 (60.0)	8 (80.0)	8 (61.5)	7 (70.0)	5 (50.0)	8 (80.0)
Mean (SD); min.–max.	3.5 (1.1); 1.6–5.1	5.15 (2.20); 2.60–8.33	3.58 (2.70); 1.78–8.79	4.10 (2.71); 0.70–8.04	3.74 (1.43); 1.62–5.69	5.18 (2.67); 1.93–9.55	4.42 (2.06); 2.54–7.04	4.74 (2.59); 0.69–8.98
Median (IQR)	3.3 (2.8–4.2)	5.4 (2.8–7.2)	2.3 (2.0–4.2)	3.6 (1.6–5.6)	3.3 (2.9–4.7)	4.9 (2.5–7.5)	3.3 (2.9–6.2)	4.6 (2.4–5.8)
Missing (%)	5 (38.5)	3 (30.0)	4 (40.0)	2 (20.0)	5 (38.5)	3 (30.0)	5 (50.0)	2 (20.0)
Intrahepatic triglyceride content								
Number (%)	12 (92.3)	10 (100.0)	8 (80.0)	10 (100.0)	8 (62.0)	7 (70.0)	4 (40.0)	8 (80.0)
Mean (SD); min.–max.	8.2 (18.2); 0.4–64.8	6.7 (10.4); 0.4–30.7	1.9 (2.1); 0.3–6.4	2.2 (4.8); 0.1–14.0	3.0 (4.1); 0.1–12.8	7.3 (10.1); 0.2–25.1	1.2 (0.5); 0.7–1.7	1.6 (2.7); 0.3–6.9
Median (IQR)	1.7 (0.6–3.0)	1.6 (0.4–8.4)	1.2 (0.4–2.0)	1.0 (0.6–1.5)	1.8 (0.8–2.4)	2.5 (0.4–18.3)	1.3 (0.7–1.5)	0.6 (0.3–1.3)
Missing (%)	1 (7.7)	0 (0.0)	2 (20.0)	0 (0.0)	5 (38.0)	3 (30.0)	6 (60.0)	2 (20.0)

Summary statistic	Time point							
	Baseline				**24 weeks**			
	Arm A (control)	**Arm B (20 mg)**	**Arm C (40 mg)**	**Arm D (80 mg)**	**Arm A (control)**	**Arm B (20 mg)**	**Arm C (40 mg)**	**Arm D (80 mg)**
Intramyocellular triglyceride content (soleus)								
Number (%)	12 (92.3)	10 (100.0)	8 (80.0)	10 (100.0)	8 (62.0)	7 (70.0)	4 (40.0)	8 (80.0)
Mean (SD); min.–max.	19.5 (10.8); 6.2–41.8	19.0 (17.8); 6.1–65.1	12.6 (5.8); 5.0–22.4	17.3 (11.8); 7.4–44.5	19.5 (13.3); 5.2–40.0	17.1 (9.2); 7.7–33.7	22.2 (21.0); 4.8–51.9	16.6 (9.0); 8.2–33.6
Median (IQR)	17.8 (11.1–23.2)	12.4 (6.8–25.6)	11.8 (7.2–15.2)	13.7 (9.2–21.1)	16.7 (5.3–21.6)	15.8 (7.8–21.5)	16.1 (4.8–21.8)	14.5 (8.2–17.5)
Missing (%)	1 (7.7)	0 (0.0)	2 (20.0)	0 (0.0)	5 (38.0)	3 (30.0)	6 (60.0)	2 (20.0)
Intramyocellular triglyceride content (tibialis anterior)								
Number (%)	11 (84.6)	10 (100.0)	8 (80.0)	9 (90.0)	8 (62.0)	7 (70.0)	4 (40.0)	8 (80.0)
Mean (SD); min.–max.	6.3 (3.1); 0.0–11.0	8.1 (3.7); 1.4–13.9	5.3 (2.1); 3.0–9.6	7.8 (2.8); 3.0–11.0	8.1 (5.0); 2.6–18.6	10.2 (6.3); 2.5–17.7	5.1 (1.4); 3.8–6.6	7.4 (2.7); 3.4–11.2
Median (IQR)	5.9 (4.9–9.1)	8.6 (5.9–10.5)	4.9 (3.6–5.4)	7.7 (7.3–9.7)	7.4 (3.5–8.4)	9.8 (2.8–17.6)	4.9 (3.8–5.8)	7.8 (3.9–8.8)
Missing (%)	2 (15.4)	0 (0.0)	2 (20.0)	1 (10.0)	5 (38.0)	3 (30.0)	6 (60.0)	2 (20.0)

max., maximum; min., minimum.
Note
The main reason for missing MRI data at baseline is that MRI images were sent to Vardis (Vardis Limited, London, UK) for volume quantification mainly when images had been acquired at both time points (baseline and 24 weeks). However, there was one patient for whom baseline MRI volumes were estimated by Vardis, although the patient did not attend the 24-week follow-up visit.

TABLE 52 Summary statistics for the other MRI measures (external abdominal fat, total internal fat, total external fat and total body fat) at baseline and 24 weeks by treatment group

	Time point							
	Baseline				24 weeks			
Summary statistic	Arm A (control)	Arm B (20 mg)	Arm C (40 mg)	Arm D (80 mg)	Arm A (control)	Arm B (20 mg)	Arm C (40 mg)	Arm D (80 mg)
External abdominal fat (dm³)								
Number (%)	8 (61.5)	7 (70.0)	6 (60.0)	8 (80.0)	8 (61.5)	7 (70.0)	5 (50.0)	8 (80.0)
Mean (SD); min.–max.	5.0 (3.6); 1.7–12.2	6.4 (3.1); 2.6–10.9	4.1 (2.3); 1.3–6.7	3.4 (1.8); 0.8–6.7	5.1 (3.6); 1.2–12.1	6.7 (3.5); 2.2–11.1	5.06 (2.3); 1.8–7.5	3.8 (2.2); 0.8–8.0
Median (IQR)	3.8 (1.9–6.8)	6.1 (2.6–8.8)	4.7 (1.5–5.9)	3.2 (2.4–3.6)	3.8 (2.0–7.1)	7.4 (2.4–9.1)	5.0 (4.3–6.8)	3.2 (2.9–3.8)
Missing (%)	5 (38.5)	3 (30.0)	4 (40.0)	2 (20.0)	5 (38.5)	3 (30.0)	5 (50.0)	2 (20.0)
Total internal fat (dm³)								
Number (%)	8 (61.5)	7 (70.0)	6 (60.0)	8 (80.0)	8 (61.5)	7 (70.0)	5 (50.0)	8 (80.0)
Mean (SD); min.–max.	6.1 (1.6); 3.1–7.5	8.3 (2.7); 5.4–12.1	6.1 (3.7); 3.6–13.4	6.8 (4.1); 2.5–12.5	6.5 (1.9); 3.2–8.8	8.5 (3.2); 5.5–13.9	7.1 (2.5); 4.7–9.9	7.9 (3.3); 2.9–12.7
Median (IQR)	6.8 (4.7–7.0)	8.7 (5.8–10.8)	4.7 (3.9–6.3)	6.0 (3.0–9.4)	6.3 (5.0–7.9)	7.5 (5.6–11.9)	6.7 (4.9–9.5)	7.8 (5.0–9.3)
Missing (%)	5 (38.5)	3 (30.0)	4 (40.0)	2 (20.0)	5 (38.5)	3 (30.0)	5 (50.0)	2 (20.0)

| Summary statistic | Time point | | | | | | | |
| | **Baseline** | | | | **24 weeks** | | | |
	Arm A (control)	Arm B (20 mg)	Arm C (40 mg)	Arm D (80 mg)	Arm A (control)	Arm B (20 mg)	Arm C (40 mg)	Arm D (80 mg)
Total external fat (dm³)								
Number (%)	8 (61.5)	7 (70.0)	6 (60.0)	8 (80.0)	8 (61.5)	7 (70.0)	5 (50.0)	8 (80.0)
Mean (SD); min.–max.	18.1 (11.0); 8.1–41.1	20.4 (7.3); 9.7–30.3	13.3 (5.4); 5.6–17.6	12.2 (5.4); 5.0–22.8	18.3 (11.1); 6.5–40.0	20.9 (8.3); 8.7–32.3	16.4 (5.4); 7.6–20.9	13.3 (5.1); 5.5–22.4
Median (IQR)	15.0 (9.0–20.8)	22.3 (11.4–24.4)	16.0 (7.2–17.5)	12.0 (7.3–12.8)	14.9 (9.4–22.1)	22.7 (12.1–27.8)	16.9 (16.1–20.4)	12.6 (9.4–14.9)
Missing (%)	5 (38.5)	3 (30.0)	4 (40.0)	2 (20.0)	5 (38.5)	3 (30.0)	5 (50.0)	2 (20.0)
Total body fat (dm³)								
Number (%)	8 (61.5)	7 (70.0)	6 (60.0)	8 (80.0)	8 (61.5)	7 (70.0)	5 (50.0)	8 (80.0)
Mean (SD); min.–max.	24.2 (11.5); 11.2–47.7	28.6 (9.5); 15.5–41.2	19.4 (7.4); 9.5–29.5	19.0 (8.4); 7.5–32.1	24.8 (11.6); 9.6–45.9	20.4 (11.2); 14.1–44.2	23.5 (5.9); 14.3–29.9	21.1 (7.6); 8.1–31.7
Median (IQR)	21.5 (15.9–25.5)	31.0 (16.8–36.4)	20.6 (12.4–23.9)	19.8 (10.4–24.3)	22.2 (16.0–27.0)	30.1 (17.6–41.7)	25.8 (21.7–25.9)	21.5 (15.3–25.8)
Missing (%)	5 (38.5)	3 (30.0)	4 (40.0)	2 (20.0)	5 (38.5)	3 (30.0)	5 (50.0)	2 (20.0)

max., maximum; min., minimum.

TABLE 53 Model estimates for internal visceral fat (dm³) at 24 weeks (arm A, $n = 8$ patients; arm D, $n = 8$ patients)

Variable	Parameter estimate	Standard error	95% CI	p-value
Intercept (in dm³)	0.129	0.333	–0.604 to 0.861	0.7063
Baseline value of internal visceral fat (in dm³)	1.010	0.073	0.849 to 1.170	< 0.0001
Relative change in total external fat	4.161	1.423	1.029 to 7.293	0.0138
Change in weight (kg)	–0.034	0.063	–0.173 to 0.104	0.5941
Treatment arm D vs. control	0.038	0.287	–0.593 to 0.670	0.8961

TABLE 54 Model estimates for intrahepatic triglyceride content in liver at 24 weeks (arm A, $n = 8$ patients; arm D, $n = 8$ patients)

Variable	Parameter estimate	Standard error	95% CI	p-value
Intercept	1.359	0.375	0.542 to 2.177	0.0035
Baseline value of intrahepatic triglyceride content in liver	0.722	0.059	0.594 to 0.850	< 0.0001
Change in weight (kg)	0.365	0.102	0.141 to 0.588	0.0039
Treatment arm D vs. control	–1.714	0.492	–2.787 to –0.642	0.0045

TABLE 55 Model estimates for intramyocellular triglyceride content in the soleus and tibialis anterior at 24 weeks (arm A, $n = 8$ patients; arm D, $n = 8$ patients)

Variable	Intercept	Baseline value	Change in weight (kg)	Treatment D vs. control
Soleus and tibialis anterior[a]				
Approximately F	170.465	4.459	0.565	0.213
Numerator df	2	4	2	2
Denominator df	9	20	9	9
p-value	< 0.0001	0.0097	0.5873	0.8123
Soleus[b]				
Parameter estimate	2.222	0.902	–0.496	–2.567
Standard error	3.589	0.143	0.724	2.559
95% CI	–5.677 to 10.121	0.587 to 1.216	–2.089 to 1.097	–8.200 to 3.066
p-value	0.5480	< 0.0001	0.5070	0.3370
Tibialis anterior[b]				
Parameter estimate	9.882	–0.243	–0.060	–0.479
Standard error	3.087	0.420	0.522	2.472
95% CI	0.3087 to 16.678	–1.168 to 0.682	–1.089 to 1.210	–5.919 to 4.961
p-value	0.0080	0.5750	0.9100	0.8499

df, degrees of freedom.
a Multivariate test.
b Univariate models (ANCOVA).

Urinary biomarkers

Neutrophil gelatinase-associated lipocalin
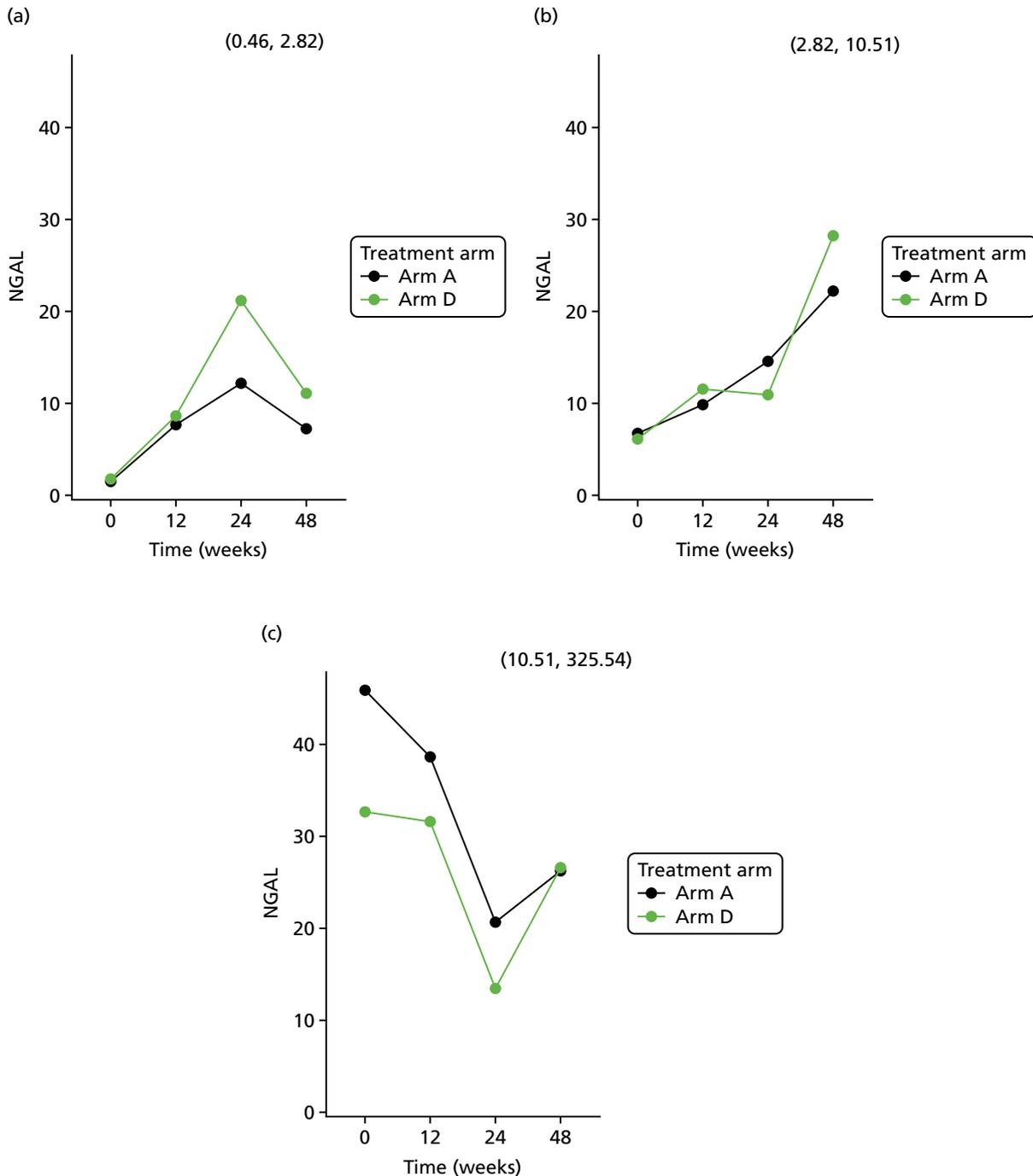
FIGURE 40 Longitudinal NGAL mean profiles for arm A (control) and arm D (80 mg) over tertile subgroups. (a) NGAL < 2.28 at baseline; (b) NGAL > 2.28 and < 10.51 at baseline; and (c) NGAL > 10.51 at baseline.

TABLE 56 Estimates from linear mixed-effect model for each subgroup for longitudinal NGAL

	Tertile											
	First				**Second**				**Third**			
Variable	**Parameter**	**SE**	**95% CI**	**_p_-value**	**Parameter**	**SE**	**95% CI**	**_p_-value**	**Parameter**	**SE**	**95% CI**	**_p_-value**
Intercept	2.271	0.469	1.345 to 3.197	< 0.0001	0.180	0.691	−1.184 to 1.543	0.7952	1.192	0.759	−0.309 to 2.693	0.1186
Time	0.005	0.004	−0.003 to 0.013	0.2545	0.006	0.004	−0.003 to 0.015	0.1854	0.003	0.004	−0.006 to 0.012	0.4670
Baseline NGAL	0.562	0.183	0.198 to 0.926	0.0028	0.480	0.227	0.031 to 0.930	0.0366	0.417	0.137	0.1460 to 0.688	0.0030
Age	−0.015	0.009	−0.032 to 0.002	0.0873	0.011	0.010	−0.008 to 0.030	0.2635	−0.002	0.010	−0.022 to 0.018	0.8741
Ethnicity	−0.057	0.249	−0.551 to 0.437	0.8194	0.094	0.275	−0.452 to 0.640	0.7336	−0.232	0.303	−0.833 to 0.368	0.4448
Sex (male)	−0.500	0.250	−0.997 to −0.004	0.0483	0.097	0.294	−0.486 to 0.681	0.7413	0.048	0.307	−0.562 to 0.657	0.8772
Treatment B vs. A	−0.511	0.224	−0.955 to −0.067	0.0247	0.075	0.234	−0.390 to 0.540	0.7490	−0.028	0.281	−0.585 to 0.528	0.9195
Treatment C vs. A	−0.300	0.240	−0.776 to 0.175	0.2133	−0.563	0.262	−1.084 to −0.043	0.0343	0.080	0.291	−0.498 to 0.658	0.7846
Treatment D vs. A	−0.215	0.207	−0.627 to 0.196	0.3018	−0.065	0.225	−0.512 to 0.382	0.7733	−0.347	0.275	−0.893 to 0.198	0.2093

SE, standard error.

Albumin-to-creatinine ratio
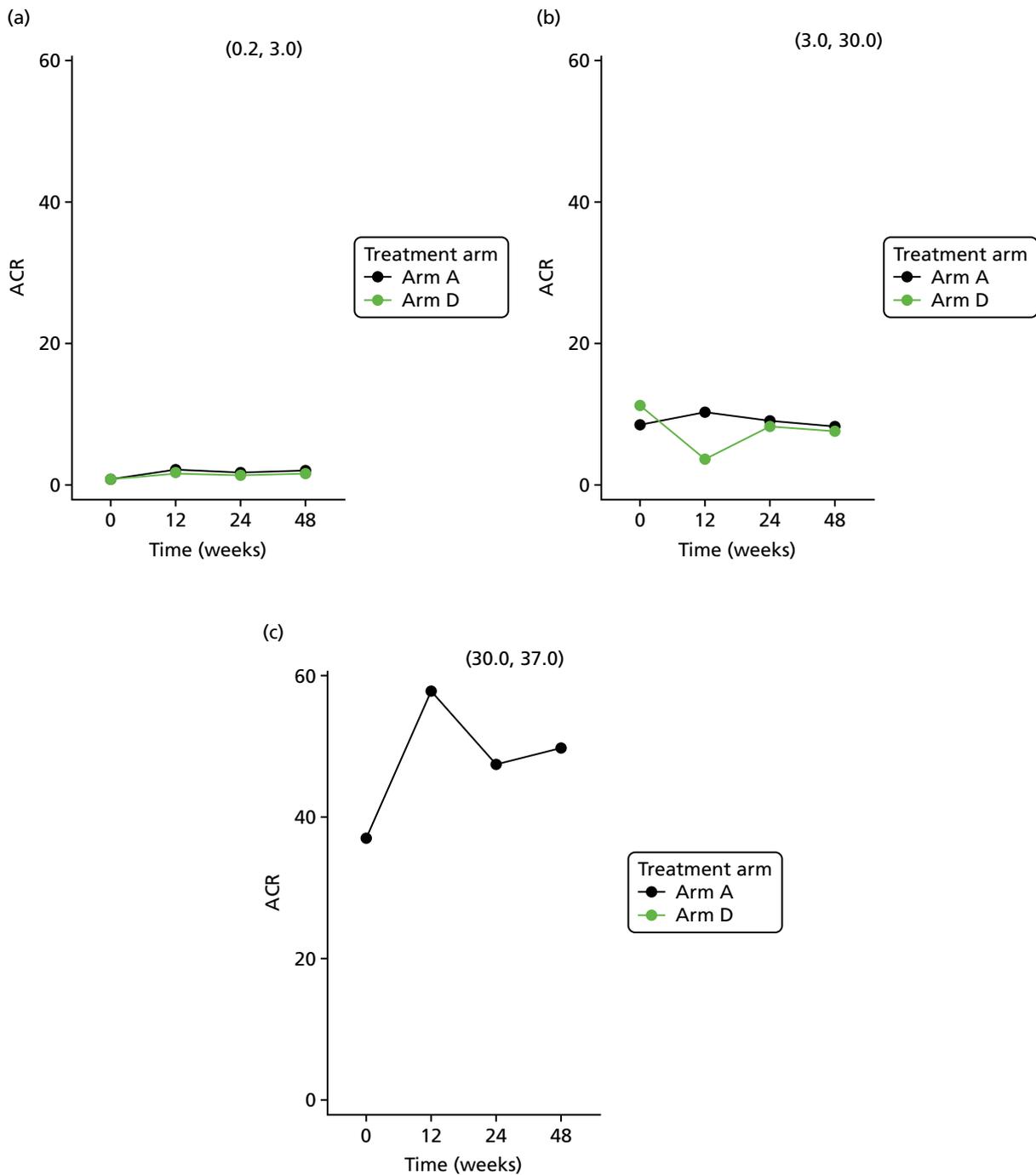
FIGURE 41 Longitudinal ACR mean profiles for arm A (control) and arm D (80 mg) over threshold subgroups. Note: the profile shown in ACR > 30 includes a single patient. (a) ACR < 3 mg/mmol at baseline; (b) ACR between 3 and 30 mg/mmol at baseline; and (c) ACR > 30 mg/mmol at baseline.

TABLE 57 Estimates from linear mixed-effect model for each subgroup for longitudinal ACR

| Variable | ACR | | | | | | | |
| | < 3 | | | | ≥ 3 | | | |
	Parameter	SE	95% CI	*p*-value	Parameter	SE	95% CI	*p*-value
Intercept	0.336	0.668	−0.999 to 1.672	0.6166	−1.779	0.908	−3.638 to 0.081	0.0601
Time	0.002	0.004	−0.005 to 0.009	0.5727	0.007	0.007	−0.006 to 0.021	0.2882
Baseline ACR	0.564	0.131	0.301 to 0.826	0.0001	0.877	0.221	0.406 to 1.347	0.0012
Age	−0.007	0.013	−0.032 to 0.018	0.5804	0.014	0.015	−0.018 to 0.046	0.3696
Ethnicity	0.182	0.245	−0.308 to 0.672	0.4616	1.159	0.403	0.300 to 2.019	0.0116
Treatment B vs. A	−0.320	0.223	−0.766 to 0.126	0.1567	−0.903	0.382	−1.718 to −0.088	0.0321
Treatment C vs. A	−0.111	0.258	−0.626 to 0.404	0.6676	0.643	0.480	−0.381 to 1.667	0.2008
Treatment D vs. A	−0.074	0.253	−0.578 to 0.431	0.7715	−0.665	0.303	−1.310 to −0.019	0.0443

SE, standard error.
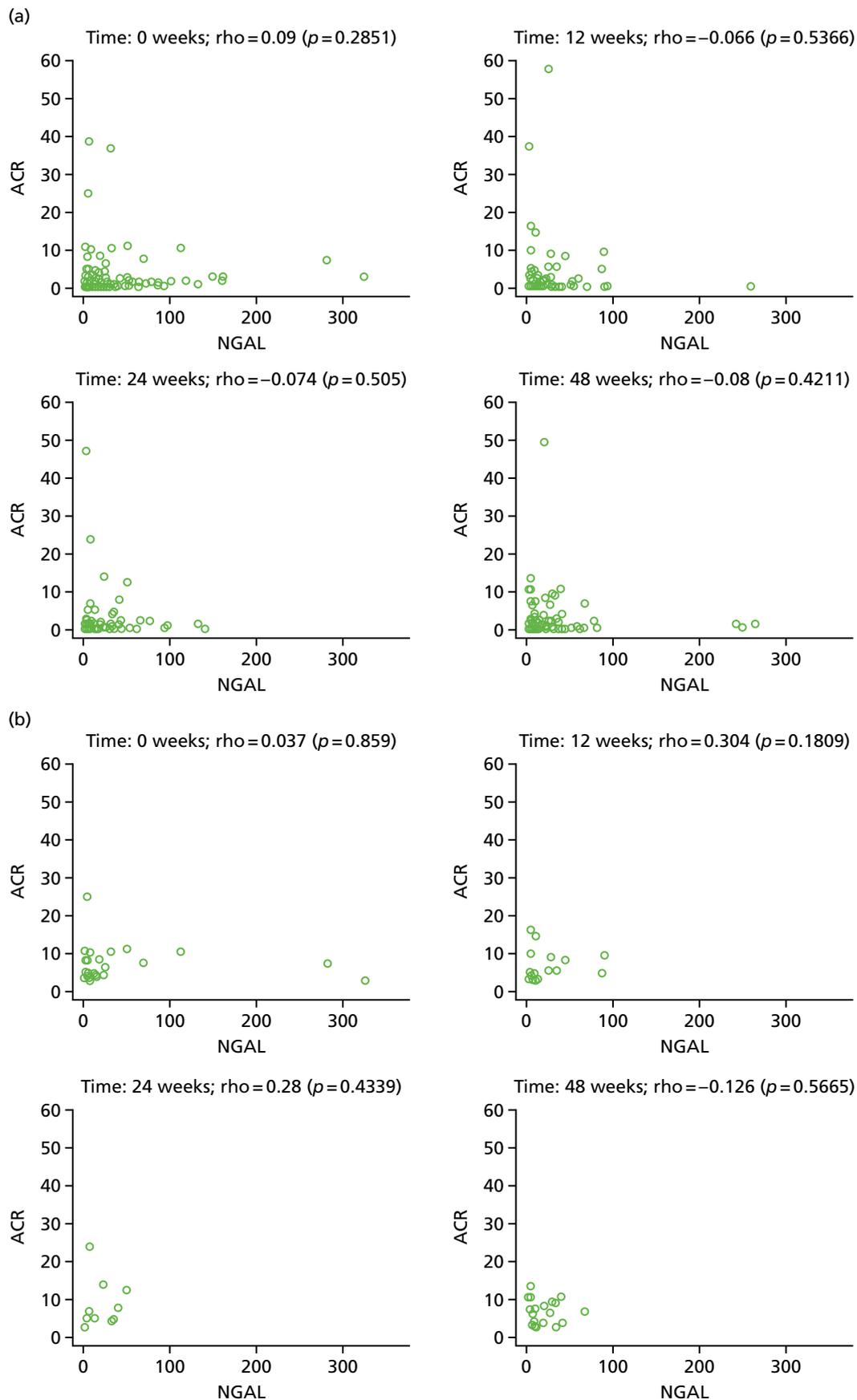
FIGURE 42 Scatterplots showing the correlation between NGAL and ACR at baseline and follow-up time points. (a) All pairs; and (b) ACR 3–30.

Safety data analysis

Adverse drug reactions by severity

The number of ARs and the number and percentage of patients affected in each category by treatment arm and by severity are provided in *Table 58*. For each patient, only the maximum severity experienced for each type of AR will be displayed.

TABLE 58 Adverse reactions by severity

AR	Severity	Arm B (20 mg) (*N* = 84)			Arm C (40 mg) (*N* = 82)			Arm D (80 mg) (*N* = 106)			Total randomised (*n* = 377)		
		Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients
Abdominal distension	Mild	0	0	0.0	2	2	2.4	1	1	0.9	3	3	0.8
	Moderate	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Abdominal pain upper	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Acute sinusitis	Mild	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Ageusia	Mild	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Amnesia	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Angioedema	Mild	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0

| AR | Severity | Treatment arm | | | | | | | | | | | |
| | | Arm B (20 mg) (N = 84) | | | Arm C (40 mg) (N = 82) | | | Arm D (80 mg) (N = 106) | | | Total randomised (n = 377) | | |
		Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients
Anxiety	Mild	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	1	1	1.2	1	1	0.9	2	2	0.5
	Severe	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
Arthralgia	Mild	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Asthenia	Mild	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Back pain	Mild	2	2	2.4	0	0	0.0	1	1	0.9	3	3	0.8
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Burning sensation	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Campylobacter gastroenteritis	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Chest pain	Mild	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Moderate	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Chromaturia	Mild	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Confusional state	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0

TABLE 58 Adverse reactions by severity (*continued*)

AR	Severity	Arm B (20 mg) (N = 84)			Arm C (40 mg) (N = 82)			Arm D (80 mg) (N = 106)			Total randomised (n = 377)		
		Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients
Constipation	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Cough	Mild	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Depressed mood	Mild	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Depression	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Diarrhoea	Mild	1	1	1.2	0	0	0.0	6	6	5.7	7	7	1.9
	Moderate	0	0	0.0	3	2	2.4	0	0	0.0	3	2	0.5
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Disturbance in attention	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Dizziness	Mild	6	6	7.1	4	4	4.9	13	13	12.3	23	23	6.1
	Moderate	0	0	0.0	2	2	2.4	2	2	1.9	4	4	1.1
	Severe	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
Double ureter	Mild	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Dry eye	Mild	0	0	0.0	0	0	0.0	2	1	0.9	2	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0

AR	Severity	Arm B (20 mg) (N = 84)			Arm C (40 mg) (N = 82)			Arm D (80 mg) (N = 106)			Total randomised (n = 377)		
		Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients
Dry mouth	Mild	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Dry skin	Mild	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Dysgeusia	Mild	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Dyspepsia	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	2	2	2.4	1	1	1.2	1	1	0.9	4	4	1.1
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Ear pain	Mild	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Ejaculation failure	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Epistaxis	Mild	0	0	0.0	0	0	0.0	2	2	1.9	2	2	0.5
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Faeces soft	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Fall	Mild	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0

TABLE 58 Adverse reactions by severity (*continued*)

| AR | Severity | Treatment arm | | | | | | | | | Total randomised (*n* = 377) | | |
| | | Arm B (20 mg) (*N* = 84) | | | Arm C (40 mg) (*N* = 82) | | | Arm D (80 mg) (*N* = 106) | | | | | |
		Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients
Fatigue	Mild	5	4	4.8	3	3	3.7	2	2	1.9	10	9	2.4
	Moderate	0	0	0.0	0	0	0.0	4	4	3.8	4	4	1.1
	Severe	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
Feeling cold	Mild	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Feeling hot	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Haematoma	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Haematuria	Mild	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Headache	Mild	3	3	3.6	5	5	6.1	5	5	4.7	13	13	3.4
	Moderate	2	2	2.4	1	1	1.2	5	4	3.8	8	7	1.9
	Severe	1	1	1.2	1	1	1.2	0	0	0.0	2	2	0.5
Hepatic enzyme increased	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Hyperhidrosis	Mild	1	1	1.2	1	1	1.2	0	0	0.0	2	2	0.5
	Moderate	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Hypertension	Mild	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0

| | | Treatment arm | | | | | | | | | | | |
| | | Arm B (20 mg) (*N* = 84) | | | Arm C (40 mg) (*N* = 82) | | | Arm D (80 mg) (*N* = 106) | | | Total randomised (*n* = 377) | | |
AR	Severity	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients
Hypotension	Mild	1	1	1.2	2	1	1.2	0	0	0.0	3	2	0.5
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Increased appetite	Mild	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Influenza	Mild	2	2	2.4	1	1	1.2	3	3	2.8	6	6	1.6
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Influenza like illness	Mild	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Insomnia	Mild	1	1	1.2	0	0	0.0	1	1	0.9	2	2	0.5
	Moderate	0	0	0.0	0	0	0.0	2	2	1.9	2	2	0.5
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Lacrimation increased	Mild	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Loss of consciousness	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Lower respiratory tract infection	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Malaise	Mild	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0

TABLE 58 Adverse reactions by severity (*continued*)

AR	Severity	Treatment arm											
		Arm B (20 mg) (N = 84)			Arm C (40 mg) (N = 82)			Arm D (80 mg) (N = 106)			Total randomised (n = 377)		
		Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients
Morbid thoughts	Mild	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Mouth ulceration	Mild	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Myalgia	Mild	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Nasopharyngitis	Mild	0	0	0.0	1	1	1.2	1	1	0.9	2	2	0.5
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Nausea	Mild	1	1	1.2	3	2	2.4	2	1	0.9	6	4	1.1
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Neck pain	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Neutropenia	Mild	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Onychomycosis	Mild	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Oropharyngeal pain	Mild	0	0	0.0	1	1	1.2	1	1	0.9	2	2	0.5
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0

AR	Severity	Arm B (20 mg) (N = 84)			Arm C (40 mg) (N = 82)			Arm D (80 mg) (N = 106)			Total randomised (n = 377)		
		Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients
Orthostatic hypotension	Mild	0	0	0.0	3	2	2.4	1	1	0.9	4	3	0.8
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Osteopenia	Mild	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Pain in jaw	Mild	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Palpitations	Mild	0	0	0.0	0	0	0.0	2	2	1.9	2	2	0.5
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Paraesthesia	Mild	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Photosensitivity reaction	Mild	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Pruritus	Mild	4	4	4.8	1	1	1.2	2	2	1.9	7	7	1.9
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Pulmonary fibrosis	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
Pyrexia	Mild	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0

TABLE 58 Adverse reactions by severity (*continued*)

| | | Treatment arm | | | | | | | | | | | |
| | | Arm B (20 mg) (*N* = 84) | | | Arm C (40 mg) (*N* = 82) | | | Arm D (80 mg) (*N* = 106) | | | Total randomised (*n* = 377) | | |
AR	Severity	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients
Rash	Mild	1	1	1.2	1	1	1.2	2	2	1.9	4	4	1.1
	Moderate	0	0	0.0	0	0	0.0	2	2	1.9	2	2	0.5
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Renal impairment	Mild	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Rhinitis	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Sinus congestion	Mild	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Sinusitis	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Somnolence	Mild	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Syncope	Mild	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Tension headache	Mild	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0

| AR | Severity | Treatment arm | | | | | | | | | Total randomised (*n* = 377) | | |
| | | Arm B (20 mg) (*N* = 84) | | | Arm C (40 mg) (*N* = 82) | | | Arm D (80 mg) (*N* = 106) | | | | | |
		Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients
Tongue coated	Mild	0	0	0.0	0	0	0.0	1	1	0.9	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Tremor	Mild	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Trigeminal neuralgia	Mild	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Upper respiratory tract infection	Mild	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Urinary tract infection	Mild	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Vision blurred	Mild	1	1	1.2	1	1	1.2	2	2	1.9	4	4	1.1
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Visual impairment	Mild	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Moderate	1	1	1.2	0	0	0.0	0	0	0.0	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Vomiting	Mild	0	0	0.0	1	1	1.2	1	1	0.9	2	2	0.5
	Moderate	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0

TABLE 58 Adverse reactions by severity (*continued*)

| | | Treatment arm | | | | | | | | | | | |
| | | Arm B (20 mg) (*N* = 84) | | | Arm C (40 mg) (*N* = 82) | | | Arm D (80 mg) (*N* = 106) | | | Total randomised (*n* = 377) | | |
AR	Severity	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients	Number of events	Number of patients	Percentage of patients
Weight increased	Mild	0	0	0.0	1	1	1.2	0	0	0.0	1	1	0.3
	Moderate	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
	Severe	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Grand total	Mild	41	20	23.8	47	18	22.0	65	27	25.5	153	65	17.2
	Moderate	7	6	7.1	18	8	9.8	36	21	19.8	61	35	9.3
	Severe	2	2	2.4	3	2	2.4	1	1	0.9	6	5	1.3

Patient 00162281 – arm D – dizziness (moderate and severe: included the severe AR).
Patient 01552036 – arm C – dizziness (mild and moderate: included the moderate AR).
Patient 00162174 – arm D – headache (mild and moderate: included the moderate AR).

Serious adverse events

TABLE 59 Serious adverse events

							Relationship				
SAE number	Description (PT)	Description (SOC)	Seriousness	Allocation	Severity	Expectedness	PI's assessment	Chief Investigator's assessment	Withdrew from study drug	Outcome	Patient status
1	Laceration	Injury, poisoning and procedural complications	Required hospitalisation	Arm C (40 mg)	Grade 4, potentially life-threatening	Unexpected	Unrelated	Unrelated	No	Resolved	Continuing in trial
2	Plasmablastic lymphoma	Neoplasms benign, malignant and unspecified (including cysts and polyps) Plasmablastic large B-cell lymphoma	Medically significant/ important	Arm C (40 mg)	Grade 4, potentially life-threatening	Unexpected	Unrelated	Unrelated	Yes	Ongoing at final follow-up	Withdrawn from treatment
3	Paraesthesia	Nervous system disorders	Required hospitalisation	Arm C (40 mg)	Grade 2, moderate	Expected	Probably	Probably	Yes	Resolved	Withdrawn from treatment
4	Mastitis	Infections and infestations	Required hospitalisation	Arm D (80 mg)	Grade 1, mild	Unexpected	Unrelated	Unrelated	No	Resolved	Continuing in trial
5	Infected bites	Infections and infestations	Required hospitalisation	Arm A (control)	Grade 3, severe	NA	NA	NA	No	Resolved	Continuing in trial
6	Hepatitis C	Infections and infestations	Medically significant/ important Hepatitis C	Arm C (40 mg)	Grade 3, severe	Unexpected	Unlikely	Unrelated	Yes	Resolved	Withdrawn from treatment
7	Haemoptysis	Respiratory, thoracic and mediastinal disorders	Required hospitalisation	Arm B (20 mg)	Grade 3, severe	Unexpected	Unrelated	Unrelated	No	Resolved	Continuing in trial
8	Skin cancer	Neoplasms benign, malignant and unspecified (including cysts and polyps) Skin cancer recurrence	Medically significant/important	Arm D (80 mg)	Grade 4, potentially life-threatening	Unexpected	Unrelated	Unrelated	No	Not resolved/ ongoing	Completed trial
9	Limb injury	Injury, poisoning and procedural complications	Required hospitalisation	Arm B (20 mg)	Grade 2, moderate	Unexpected	Unrelated	Unrelated	No	Resolved	Completed trial
10	Laceration	Injury, poisoning and procedural complications	Required hospitalisation	Arm A (control)	Grade 1, mild	NA	NA	NA	No	Resolved	Continuing in trial
11	Pneumonia	Infections and infestations	Required hospitalisation	Arm A (control)	Grade 2, moderate	NA	NA	NA	No	Resolved	Continuing in trial
12	Joint dislocation	Injury, poisoning and procedural complications	Required hospitalisation	Arm D (80 mg)	Grade 3, severe	Unexpected	Unlikely	Unrelated	Yes	Resolved	Withdrawn from treatment

TABLE 59 Serious adverse events (*continued*)

SAE number	Description (PT)	Description (SOC)	Seriousness	Allocation	Severity	Expectedness	Relationship PI's assessment	Chief Investigator's assessment	Withdrew from study drug	Outcome	Patient status
13	Groin pain	Musculoskeletal and connective tissue disorders	Required hospitalisation	Arm B (20 mg)	Grade 3, severe	Unexpected	Unrelated	Unrelated	No	Ongoing at final follow-up	Completed trial
14	Joint dislocation	Injury, poisoning and procedural complications	Required hospitalisation	Arm D (80 mg)	Grade 3, severe	Unexpected	Unlikely	Unrelated	Yes	Resolved	Continuing in trial
15	Convulsion	Nervous system disorders	Required hospitalisation	Arm A (control)	Grade 2, moderate	NA	NA	NA	No	Resolved	Continuing in trial
16	Chest pain	General disorders and administration site conditions	Required hospitalisation	Arm D (80 mg)	Grade 2, moderate	Unexpected	Unrelated	Unlikely	No	Resolved	Continuing in trial
17	Death	General disorders and administration site conditions	Required hospitalisation	Arm A (control)	Grade 5, death	NA	NA	NA	No	Fatal	Death
18	Abdominal pain upper	Gastrointestinal disorders	Required hospitalisation	Arm A (control)	Grade 2, moderate	NA	NA	NA	No	Resolved	Continuing in trial
19	Meningitis cryptococcal	Infections and infestations	Required hospitalisation	Arm D (80 mg)	Grade 2, moderate	Unexpected	Unrelated	Unrelated	No	Resolved	Continuing in trial
20	Gastroenteritis viral	Infections and infestations	Required hospitalisation	Arm D (80 mg)	Grade 2, moderate	Unexpected	Unrelated	Unrelated	No	Resolved	Continuing in trial
21	Pregnancy	Pregnancy, puerperium and perinatal conditions	Medically significant/ important Pregnancy	Arm D (80 mg)	[a]	Unexpected	Unrelated	Unrelated	Yes	Not resolved/ ongoing	Completed trial

NA, not applicable (patient is in the control group).

a This is a pregnancy-related SAE; therefore, the severity cannot be completed until the baby is born. The research team have sent in several file notes. The patient moved out of the area and they have been unable to contact her to find out the pregnancy outcome. They have also tried to contact the HIV team at the new hospital, but have received no response. The MHRA were contacted at the time and the trial co-ordinator was advised that they do not consider pregnancy to be a SAE.

Compliance with study drug schedule

TABLE 60 Compliance split by treatment

Variable and summary statistic	Treatment arm		
	Arm B (20 mg) (*N* = 84)	Arm C (40 mg) (*N* = 82)	Arm D (80 mg) (*N* = 106)
Total dose (mg) consumed according to the treatment diary	*n* = 48	*n* = 42	*n* = 64
Mean (SD), median; min.–max.	3215.4 (558.62), 3360; 296–3360	6347.4 (396.42), 6440; 4042–6440	11,829.8 (893.53), 12,040; 5160–12,040
n (%), missing	36 (42.8)	40 (48.8)	42 (39.6)
Total dose (mg) according to total number of returned pills	*n* = 70	*n* = 61	*n* = 93
Mean (SD), median; min.–max.	3290.4 (112.89), 3360; 2880–3360	6155.4 (413.91), 6440; 4680–6440	11,146.8 (1181.00), 11,840; 7620–12,040
n (%), missing	14 (16.7)	21 (25.6)	13 (12.3)
Discrepancies between these two estimates of total dose[a]	*n* = 43	*n* = 37	*n* = 62
Mean (SD), median; min.–max.	52.7 (601.34), 0.0; –392–3064	–234.3 (604.41), –120; –1120–2398	–964.5 (1534.06), –605.5; –3857–6720
n (%), missing	41 (48.8)	45 (54.9)	44 (41.5)
Average of these two estimates of total dose	*n* = 43	*n* = 37	*n* = 62
Mean (SD), median; min.–max.	3238.3 (297.51), 3330; 1828–3360	6217.7 (249.28), 6180; 5241–6440	11,340.8 (745.23), 11,512.8; 8520–12,040
n (%), missing	41 (48.8)	45 (54.9)	44 (41.5)

max., maximum; min., minimum.
a   Pill count – treatment diary.

TABLE 61 Baseline measures according to whether or not patients provided any compliance data

| Variable and summary statistic | Compliance data | |
	No (*N* = 36)	Some (*N* = 236)
Systolic blood pressure (mmHg)		
Mean (SD)	127.5 (13.0)	125.0 (15.0)
Median (IQR); min.–max.	126.5 (118.5–136.5); 105–161	122 (115–135); 92–172
Diastolic blood pressure (mmHg)		
Mean (SD)	76.0 (8.9)	79.2 (11.0)
Median (IQR); min.–max.	74 (70–81); 56–100	79 (71–87); 54–107
CD4 cell count (cells/mm³)		(*n* = 226)
Mean (SD)	702.4 (255.0)	603.1 (261.1)
Median (IQR); min.–max.	680 (556–846.5); 81–1417	566.5 (425–770); 62–1674
CD4 cell count and HIV viral load (%)		
Mean (SD)	31.0 (8.6)	29.8 (8.5)
Median (IQR); min.–max.	30 (27.5–34.5); 6–50	30 (24–36); 6–52
HIV viral load – copies/ml	(*n* = 13)	(*n* = 69)
Mean (SD)	16.8 (19.0)	40.6 (85.0)
Median (IQR); min.–max.[a]	3.5 (0–39); 0–39	26 (0–39); 0–649
< 10, *n* (%)	0 (0.0)	4 (1.7)
< 20, *n* (%)	2 (5.6)	52 (22.1)
< 40, *n* (%)	20 (55.6)	96 (40.9)
< 45, *n* (%)	0 (0.0)	12 (5.1)
< 100, *n* (%)	0 (0.0)	1 (0.4)
eGFR (ml/minute/1.73 m²)	(*n* = 18)	(*n* = 115)
Mean (SD)	76.7 (10.6)	80.5 (12.6)
Median (IQR); min.–max.[a]	77.2 (69–85); 53–90	79 (71–87); 56–122
< 60, *n* (%)	0 (0.0)	1 (0.4)
> 60, *n* (%)	4 (11.1)	66 (28.1)
> 90, *n* (%)	14 (38.9)	52 (22.1)

max., maximum; min., minimum.
a Some data are presented in both continuous and categorical form as a result of there being upper and lower limits of measurement.