9. Efficacy data

9.1 Primary efficacy assessment

- Reduction in insulin resistance (as measured by HOMA-IR) in telmisartan treated arm D after 24 weeks of treatment in comparison with control (following the interim decision, see Appendix 11.1).

HOMA-IR was calculated by

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

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

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

$$\text{HOMAIR\_24} = \text{HOMAIR\_0} + \text{treatment} + \text{stratification factor (Black/Non} - \text{Black)}$$

where HOMAIR_0 is the HOMAIR value at the baseline prior to randomisation and HOMAIR_24 is the HOMA-IR value at 24 weeks. The treatment variable is categorical with control as the reference level.

The test statistic is given by the t – values for each active dose treatment. The test statistic will be compared to 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.

Table 9-1 Summary statistics for HOMA-IR at baseline and 24 weeks by treatment group

	HOMA-IR at Baseline		HOMA-IR at 24weeks	
	Arm A Non intervention	Arm D Telmisartan (80mg daily)	Arm A Non intervention	Arm D Telmisartan (80mg daily)
N	100 (95.2%)	100 (94.3%)	89 (84.8%)	82 (77.4%)
Mean	2.5	2.5	3.0	3.4
Standard deviation	2.08	2.79	3.25	6.89
Min	0.4	0.6	0.6	0.6
Max	10.8	16.9	19.6	62.0
Median	1.8	1.6	2.1	2.0
Q1	1.1	1.2	1.3	1.1
Q3	2.9	2.5	3.2	3.6
Missing	5 (4.8%)	6 (5.7%)	16 (15.2%)	24 (22.6%)
N randomised	105	106	105	106

9.1.1 Checking for assumptions

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. Levene's test for checking equal group variances, and histogram for checking normality are used.

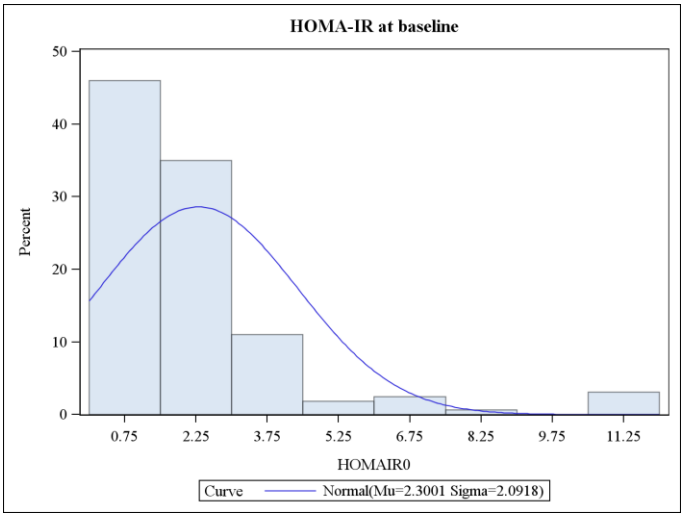
Levene’s test - check equal group variances

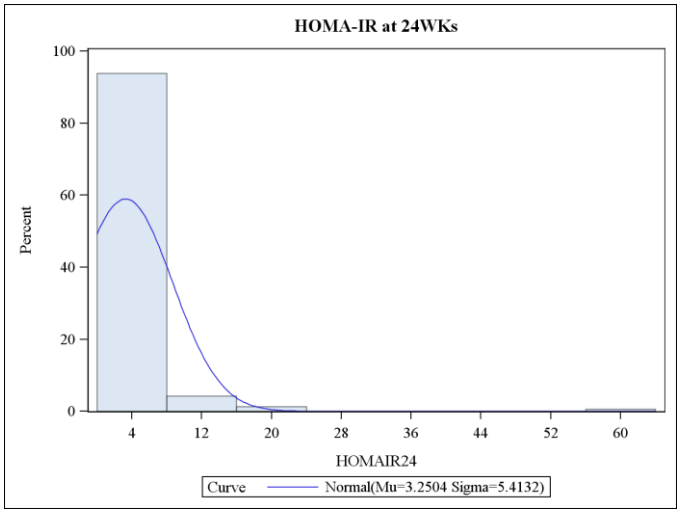
Table 9-2 Levene's Test for Homogeneity of HOMA-IR 24WK Variance

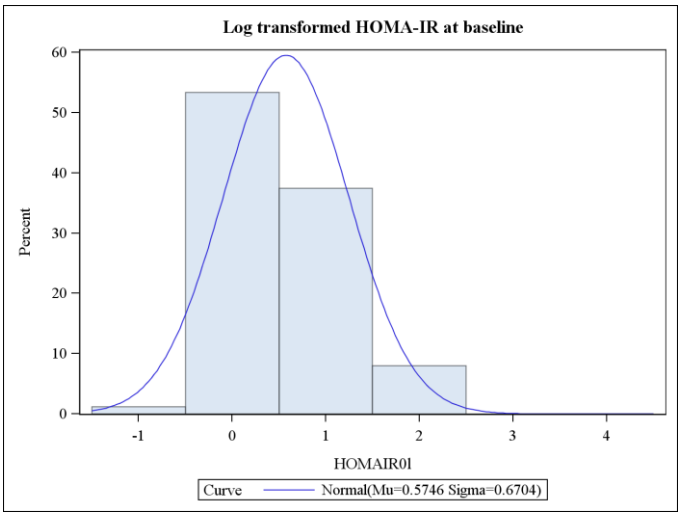
Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Treatment arm	1	59256.0	59256.0	0.8200	0.3676

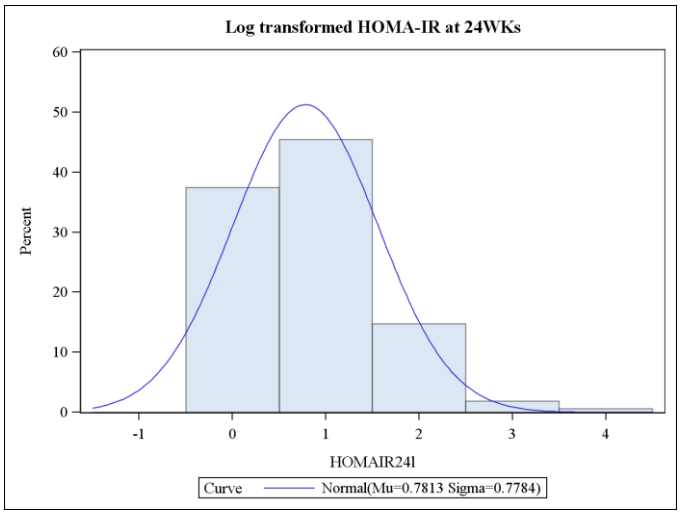
p-value > 0.05 implies the homogeneity of variance.

Histograms - check normality of HOMA-IR at baseline and 24 weeks









9.1.2 Estimates

85 patients from Arm A and 78 patients from D are included in this analysis who had both baseline and 24 week HOMA-IR measurements. Further details are shown in the CONSORT diagram in Section 2.

Table 9-3 Model estimates

Variable	Parameter Estimate	Standard Error	t – value for treatment	Test Statistic
Intercept	0.428	0.135	-	
Log HOMA-IR at baseline	0.594	0.079	-	
Ethnicity (Non-Black)	0.010	0.132	-	
Arm D versus Arm A	0.007	0.106	0.065	0.065

The test statistic is 0.065 and compared to the critical value of -2.086. As 0.065 is not smaller than the critical value we fail to reject the null hypothesis – i.e. no difference between Arm D and Arm A.

NOTE: In the original sample size calculation we used the model Y=(baseline - 24 week) and the test statistic based on (Y_24-Y_0) so that reducing HOMA-IR gives a positive value for the test statistic. Here we use an ANCOVA model as it is a more efficient approach given small group numbers and there is imbalance in baseline HOMA-IR. So, we used a model of the form Y_24 =Y_0 + treat + other covariates, means that the coefficient related to treatment is positive for an increase in HOMA-IR. Therefore we need to look at the negative of the test statistic (see Appendix 11.2 for Interim analysis). In the SAP for the final analysis we have (equivalently) changed the sign of the critical value and hence the test statistic directly from the ANCOVA can be used.

9.1.3 Primary efficacy assessment – sensitivity analysis 1

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

Table 9-4 Model estimates

Variable	Parameter Estimate	Standard Error	t – value for treatment	Test Statistic
Intercept	0.430	0.141	-	
Log HOMA-IR at baseline	0.532	0.083	-	
Ethnicity (Non-Black)	0.009	0.140	-	
Arm D versus Arm A	0.020	0.116	0.172	0.172

The test statistic is 0.172 and compared to the critical value of -2.086. As 0.172 is not smaller than the critical value we fail to reject the null hypothesis – i.e. no difference between Arm D and Arm A.

9.1.4 Primary efficacy assessment – sensitivity analysis 2

Planned analysis: The problem of non-ignorable missingness for HOMA-IR data is addressed through joint modelling of the longitudinal HOMA-IR and the time to dropout from the study (see details of the joint model in Section 9.3). In this analysis, patients who withdrew from the

study or had missing HOMA-IR for any other reason were considered as 'dropouts' and the time (t = 0, 12, or 24) they withdrew/missed is taken as the time of event (dropout). Those who did not dropout from the study before t = 24 or had complete record of HOMA-IR were censored at 24 weeks.

A joint model could not be fitted for HOMA-IR24 due to the following reasons:
The random-intercepts and random-slopes model failed as the number of random effects and parameters requiring estimation exceeds the total number of observation points. This is due to only a maximum of 2 follow-up measurements being available for each patient. Although fitting the joint model with random-intercepts only is in principle possible, it is precluded by the joineR software because it cannot initialise the parameter estimates for the baseline hazard function. This is because there are only 2 failure points available.

9.1.5 Primary efficacy assessment – sensitivity analysis 3

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

Table 9-5 Model estimates accounting for received dose on (log) HOMA-IR at 24 weeks

Variable	Parameter Estimate	Standard Error	95% confidence interval	p-value
Intercept	0.408	0.132	0.149, 0.667	0.0020
Log HOMA-IR at baseline	0.589	0.077	0.438, 0.741	<0.0001
Ethnicity (Non-Black)	0.040	0.131	-0.218, 0.297	0.7636
Arm D Dose (unit: 1000mg)	-0.010	0.009	-0.028 0.008	0.2885

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

Test of endogeneity: insufficient evidence to reject null hypothesis of endogeneity (Durbin score, chi2(1) = 0.023436, p value = 0.8783; Wu-Hausman F(1,138) = 0.02262 , p value = 0.8807), implying dose is independent of the error, thus standard regression analysis is appropriate.

Randomisation was an informative (strong) instrument in this analysis, as demonstrated by a high correlation between compliance and randomised treatment group (0.9928) and a highly significant p-value (<0.0001) rejecting the null hypothesis that randomised treatment is a weak instrument.