9. Efficacy data

9.3 Secondary efficacy endpoints: Longitudinal outcomes

- Change in lipid profile at T+12, T+24 and T+48 weeks (increase in HDL-c, reduction in total cholesterol, triglycerides and LDL-c) between telmisartan treated arm(s) and the control arm.

- Change in plasma concentrations of biomarkers (adiponectin, lipin, IL, TNF-α, Resistin and hs-CRP) at T+12, T+24 and T+48 weeks between telmisartan treated arm(s) and the control arm.

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

To identifying change in the expression of the markers in telmisartan treated arms remaining after the interim analysis in comparison to 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 marker is missing is taken as the time of dropout. Those who did not dropout from the study before t = 48 (had complete record of biomarker) were censored at 48 weeks.

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

$$Y(t) = \beta_0 + \beta_1 t + \boldsymbol{\beta_2 X} + W_1(t) + \varepsilon(t)$$

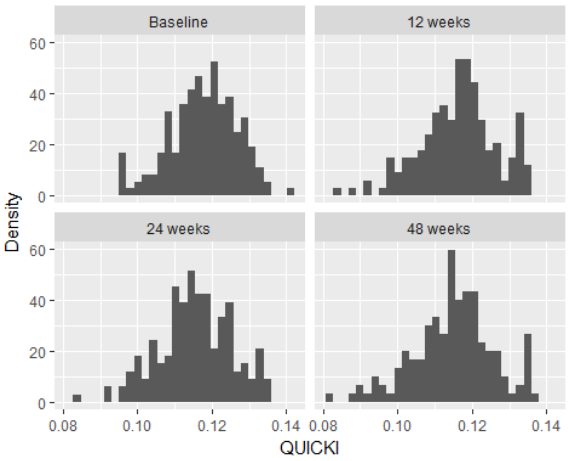
where $Y(t)$ is the marker measurement at time t where t = 12, 24, 48 weeks, and X includes categorical variables representing the treatment arm, stratification factor (Black/Non-Black) and marker at baseline as required. β_0, β_1 and $\boldsymbol{\beta_2}$ are regression coefficients related to intercept, slope and the covariates. $\varepsilon(t)$ denotes the measurement error process and assumes Gaussian distribution with mean zero and variance σ_e^2. The hazard for dropout is modelled by

$$\lambda(t) = \lambda_0(t)\mathrm{e}^{\gamma W_1(t) + \boldsymbol{\beta_3 X}}$$

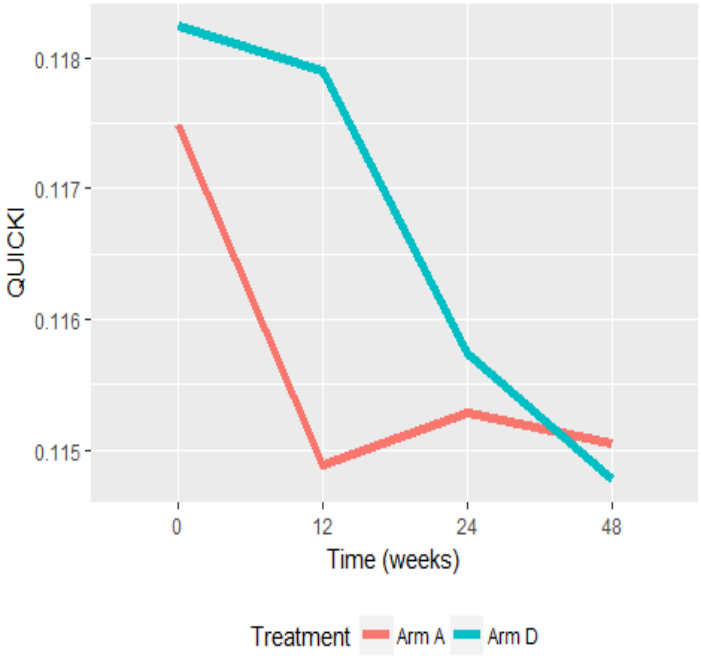
where $\lambda_0(t)$ is an unspecified baseline hazard and $\boldsymbol{\beta_3} = \{\beta_{31}, \beta_{32}\}$ and γ are regression coefficients related to covariates and association between dropout and longitudinal outcome over time (0, 48) weeks. We assume $W_1(t) = U_0 + U_1 t$, is an unobserved zero-mean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

NOTE: *The joint models fitted to the original data experienced some convergence issues, whether for the primary model fit or for the bootstrap standard error (SE) estimation. This was attributable to the slopes, which were on a much smaller magnitude than the other parameter estimates. In turn, this translated into a smaller variance component for the random slopes. To overcome this, we have scaled time for the joint models by factor 1/4. By scaling the time in the linear mixed model, the corresponding coefficient will be increased by the same factor, thus avoiding numerical issues in the estimation algorithm. The 95% confidence intervals are computed from 200 bootstrap samples.*

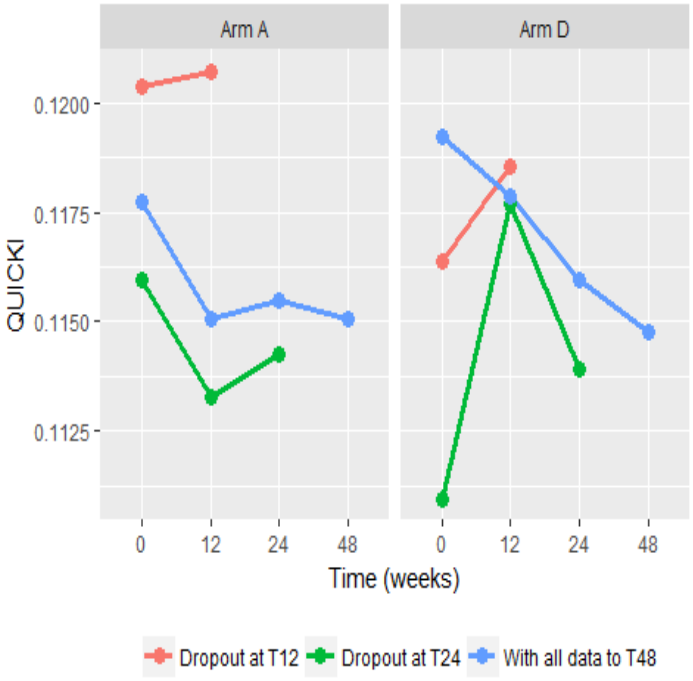
9.3.2 QUICKI



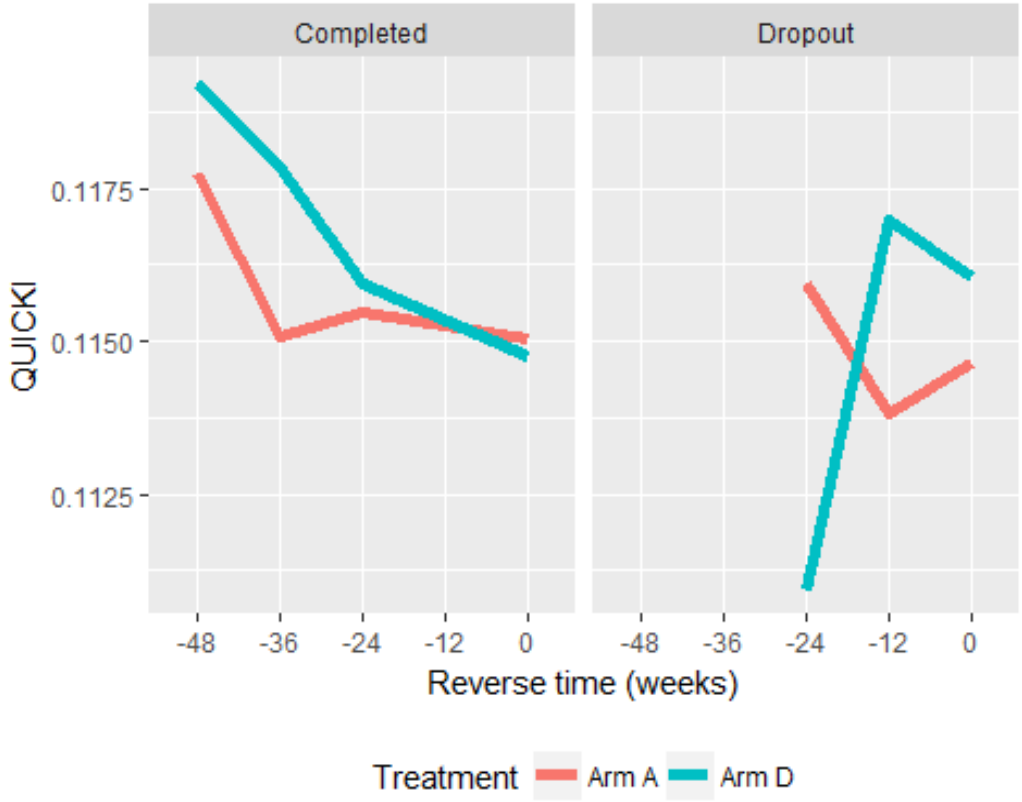
QUICKI histograms (original scale)



QUICKI profile plots **(original scale)**



QUICKI profile plots by dropout (original scale)



QUICKI reverse-time profile plots (original scale)

Estimates from the joint model

Number of observations: 477; Number of patients: 178

Component	Parameter	Estimate	95%Lower	95%Upper	P
Longitudinal	Intercept	0.392	0.228	0.584	<0.0001
	Time	-0.001	-0.003	0.000	0.3173
	Baseline	0.647	0.487	0.779	<0.0001
	Treatment	**0.008**	**-0.013**	**0.030**	**0.4671**
	Ethnicity	0.006	-0.020	0.030	0.6444
Dropout	Treatment	0.114	-0.638	0.848	0.7528
	Ethnicity	0.269	-0.578	1.915	0.8392
Association	gamma	4.618	-5.339	15.752	0.3593

Note: Unable to fit $W_1(t) = U_0 + U_1 t$ *model, so random-intercepts only model i.e.* $W_1(t) = U_0$ *is fitted.*

The treatment effect (Arm D: Telmisartan (80mg daily) compared to Arm A: Non intervention (control)) on the longitudinal QUICKI is 0.008 (95% CI:-0.013 to 0.030) implying that there is no significant difference between the treatments on QUICKI. These estimates are adjusted for the missing outcome data.