

11. Appendices

Interim analysis

A single linear regression model for log(HOMA-IR 24 weeks) was fitted simultaneously for the 3 dose arms vs control with stratification factor (Ethnicity = Black/Non-Black) and HOMA-IR at baseline (ANCOVA model). The test statistic for each dose arm vs control is given by the negative* of t-value corresponding to treatment effect.

Table 11-1: Model estimates and decision

Variable	Parameter Estimate	Standard Error	t – value for treatment	Test Statistic	Decision
Intercept	0.3799	0.1414	-	-	-
Log(HOMA-IR) baseline	0.5529	0.0681	-	-	-
Ethnicity	-0.0164	0.1228	-	-	-
Arm B versus Arm A	0.0486	0.1300	0.3738	-0.374	Drop arm B
Arm C versus Arm A	0.1009	0.1383	0.7297	-0.730	Drop arm C
Arm D versus Arm A	-0.0247	0.1386	-0.1778	0.178	Keep arm D

The decision was made as follows:

- If the largest of these statistics exceeds a critical value (equal to 2.782), this would mean that one active dose group shows a substantially higher mean reduction of 24 week HOMA-IR score than the control group, and therefore the study will be stopped and the corresponding dose will be recommended for further testing.
- If any active dose shows no improvement over control (i.e. has a negative measure of advantage) that active dose will be dropped from the second stage.
- If all three active doses satisfy this criterion, then the study will be stopped and no significant improvement over control will be claimed for any of the active doses.
- If some improvement over control is detected for at least one of the doses (i.e. if at least one test statistic is between 0 and 2.782), the study will progress to the second stage and the patients will be randomised between these dose(s) and control.

*In the sample size calculation we used the model $Y = (\text{baseline} - 24 \text{ week})$ 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 $Y_{24} = Y_0 + \text{treat} + \text{other covariates}$, 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 and use the decision as described in the SAP.

Interim decision

- **Drop arms B (20mg) and C (40mg).**
- **Progress to the second stage of the study. Randomise patients between dose arm D (80mg) and control.**