Soluble Epoxide Hydrolase Inhibition and Insulin Resistance

NCT03486223

Statistical Analysis plan from IRB approved version dated Date 8/11/2021

Statistical Analysis Plan:

The primary analysis will focus on the effect of GSK2256294 versus placebo on insulin sensitivity. Secondary endpoints will include the effect of GSK2256294 on insulin-stimulated FBF and renal blood flow; insulin-stimulated AKT phosphorylation in muscle and adipose tissue; tissue CD31 and VEGF expression; insulin-stimulated suppression of hepatic glucose production; plasma, muscle, adipose tissue sEH activity and EETs; and tissue and circulating adipokines and cytokines.

Sample Size and Power Calculation: In our prior study of the relationship between *EPHX2* Arg287Gln genotype and insulin sensitivity in obese individuals the insulin sensitivity index was 8.24±4.6 mg/kg/min per μU/mL*100 (mean±SD) in carriers of the 287Gln allele versus 3.54±1.3 mg/kg/min per μU/mL*100 in Arg/Arg homozygotes. Conservatively assuming a correlation of 0.5 between two measures of insulin sensitivity in the same subject, the study can detect a within-subject difference of 3.76 (80% of the above difference) or larger (with an SD for the within-subject difference of 4.6) with 80% power and 0.05 type 1 error rate with 34 subjects. The sample size was chosen to allow us to detect effects of treatment within racial or gender group. We need 16 per group to have 86% power to detect difference in insulin sensitivity noted above. Moreover, with 34 subjects, we have 80% power to detect a change in insulin-stimulated FBF of 0.9 mL/min/100 mL in the cross-over study, assuming a within-subject correlation coefficient of 0.5. We will have 80% power to see an increase in insulin signaling (ratio of pAKT to AKT) of 0.07 (0.91±0.13 versus 0.84±0.13 in Arg/Arg).

Data Analysis Plan: For the within-subject comparison of GSK2256294 versus placebo, we will use either a paired t-test or Wilcoxon-signed rank test. We do not expect a carry-over effect with the eight-week period between study days. Nevertheless, we will test for a carryover effect using the T-test approach proposed by Jones and Kenward. Should a carry over effect exist, we will either use period one data to estimate the treatment effect, or estimate the treatment effect using data from both periods with the understanding that the potential carry over effect may negatively bias the estimate of the treatment difference. Our conservatively planned sample size will help preserve study power. Although we also do not anticipate a period effect, we will use the T-test approach of Hills and Armitage to test for one.