Data Analysis Plan for assessing clinical efficacy and safety of ER niacin/laropiprant in the HPS2-THRIVE trial

1 Background

This Data Analysis Plan describes the strategy, rationale and statistical methods that will guide assessment of the clinical efficacy and safety of ER niacin/laropiprant in the HPS2-THRIVE trial. All analyses and reports will be prepared by the coordinating centre in the Clinical Trial Service Unit, University of Oxford ("study sponsor"). Early safety analyses were detailed in a separate Data Analysis Plan agreed in October 2011 prior to undertaking those pre-specified early safety analyses.

The HPS2-THRIVE randomized trial is comparing 2g extended-release (ER) niacin plus 40mg laropiprant daily versus placebo in 25,673 patients with pre-existing occlusive vascular disease. All participants are also taking effective background LDL-lowering treatment with 40mg simvastatin daily plus, depending on their baseline cholesterol level, 10mg ezetimibe daily. The LDL-lowering regimen was determined during the first part of a 2-4 month pre-randomization Run-in period. During the second part of the Run-in, participants were given active ER niacin (plus laropiprant): 1g daily for four weeks and then 2g daily for four weeks. At the Randomization visit at the end of the Run-in period, compliant and eligible participants were randomly allocated to receive 2g ER niacin plus 40mg laropiprant, or matching placebo. Post-randomization Follow-up visits were scheduled at 3, 6 and 12 months and then 6-monthly. The scheduled treatment period is intended to continue for a median of at least 4 years (i.e. 4 years after randomization of the first 12,500 participants).

2 Comparisons of 2g daily ER niacin/laropiprant versus placebo

All comparisons will involve comparing outcome during the scheduled treatment period among all those participants allocated at randomization to receive 2g daily ER niacin/laropiprant versus all those allocated to receive matching placebo (i.e. "intention-to-treat" analyses).[1-3]

2.1 Primary comparison

The primary comparison will be of the incidence of first major vascular event, defined as the first occurrence of non-fatal myocardial infarction or coronary death, non-fatal or fatal stroke, or any arterial revascularization procedure (including coronary and non-coronary angioplasty or grafting, and amputation for vascular disease).

2.2   Secondary comparisons

The secondary comparisons will be of the incidence of the first occurrence of:

(i)   major vascular events excluding haemorrhagic stroke

(ii)   major vascular events excluding both haemorrhagic stroke and any arterial revascularization procedure

(iii)   the separate components of the primary endpoint:

- major coronary events (defined as first occurrence of non-fatal myocardial infarction or coronary death);
- total stroke (fatal or non-fatal); and presumed ischaemic stroke (i.e. any stroke not confirmed to be haemorrhagic) and confirmed haemorrhagic stroke considered separately;
- any arterial revascularization procedure

(iv)   major vascular events separately in the first year after randomization (when little difference is anticipated) and in the later years of the scheduled treatment period

(v)   mortality, both overall and within particular categories of attributed causes of death (i.e. coronary disease, other cardiac disease, stroke, other vascular disease, neoplastic, hepatic, other medical, and non-medical causes)

(vi)   major vascular events in participants with and without a diagnosis recorded at baseline of:

- coronary heart disease;
- peripheral arterial disease;
- cerebrovascular disease; or
- diabetes mellitus

2.3   Tertiary comparisons

The tertiary comparisons will be of the incidence of first major vascular event:

(i)   in various categories of participant determined at baseline (with the cut-points typically chosen in order that there are substantial numbers of patients in each category and/or because they have some clinical or public health relevance):

- men and women;
- age (years): <65; ≥65 <70, ≥70[+];
- region: Europe and China;
- current, former and non-smokers;
- with and without treated hypertension;
- with and without diagnosed heart failure;
- diastolic blood pressure (DBP; mm Hg): <90; ≥90<100; ≥100;
- systolic blood pressure (SBP; mm Hg): <140; ≥140<160; ≥160;
- total cholesterol (mmol/L)*: <3.0; ≥3.0<3.5; ≥3.5;

- LDL-cholesterol (mmol/L)*: <1.5; ≥1.5<2.0; ≥2.0;
- HDL-cholesterol (mmol/L)*: <0.9; ≥0.9<1.1; ≥1.1;
- non-HDL cholesterol (mmol/L)*: <2.0; ≥2.0<2.5; ≥2.5;
- triglycerides (mmol/L)*: <1.0; ≥1.0<1.7; ≥1.7;
- apolipoprotein B (mg/dL)*: <60; ≥60<70; ≥70;
- apolipoprotein A1 (mg/dL)*: <140; ≥140<160; ≥160;
- lipoprotein (a) in approximate thirds*;
- HDL-cholesterol change (mmol/L) during run-in: <0.09; ≥0.09<0.24; ≥0.24;
- LDL-cholesterol change (mmol/L) during run-in: <0.25; ≥0.25<0.53; ≥0.53;
- prior statin use (years): none; <2; ≥2<5; ≥5;
- body mass index (kg/m^2): <25; ≥25<30; ≥30;
- waist circumference (cm): "normal" (men <94; women <80); "increased" (men ≥94<102; women ≥80<88); "excessive" (men ≥102; women ≥88);
- HbA1c in all participants (IFCC[4]: mmol/mol)*: <37; ≥37<48; ≥48; and, separately, in patients with diabetes recorded at baseline: <53; ≥53;
- glycaemic status: (i) "normoglycaemic" defined as: not diabetic and plasma glucose* <7.8 mmol/L if fasted <8 hours or <6.0 mmol/L if fasted ≥8 hours); (ii) "abnormal glucose tolerance" defined as: not diabetic and not "normoglycaemic"; and (iii) diabetes defined as: self-reported diabetes or hypoglycaemic use prior to randomization, or glucose ≥11.1 mmol/L if fasted <8 hours or ≥7.0 mmol/L if fasted ≥8 hours, or HbA1c ≥48 mmol/mol);
- with and without metabolic syndrome in all participants, defined as having three or more of: (i) abdominal obesity (waist circumference ≥102 cm in men, or ≥88 cm in women); (ii) triglycerides ≥1.7 mmol/L; (iii) HDL-C <1.04 mmol/L in men or <1.30 mmol/L in women; (iv) SBP≥130 mmHg or DBP≥85 mm Hg; (v) glucose ≥6.1 mmol/L after fasting ≥8 hours[5]
- estimated glomerular filtration rate (eGFR) derived using the CKD-EPI formula (mL/min/1.73^2): <60; ≥60;[6]
- urinary albumin:creatinine ratio (mg/mmol)*: "normal" (<3.4); "microalbuminuria" (≥3.4<34); "macroalbuminuria" (≥34);
- categories of alcohol intake (units per week): none; 1-20; ≥21;
  .

N.B. Unless otherwise stated those with missing values will be included in the group that includes the median.

*Blood and urine measurements are derived from samples obtained at the baseline assessment about 8 weeks prior to randomization while on background LDL-lowering therapy but not on ER niacin/laropiprant.

[+] Upper two categories also to be combined.

(ii)   in the presence and absence of particular treatments at baseline:

- simvastatin alone and ezetimibe/simvastatin combination;
- angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers;
- aspirin;
- non-steroidal anti-inflammatory drugs or coxibs;

- diuretics;
- calcium-channel blockers;
- beta-blockers.

2.4 Subsidiary comparisons of other outcomes and measures

A range of other outcomes and measures will also be compared:

(i)   Other outcomes of interest, including:
- cognitive function assessed by TICS-m questionnaire at the final visit: mean TICS-m score and proportions with score <22 (considered to be indicative of cognitive impairment);
- hospital admission for, or death from, heart failure;
- site-specific incident cancer (excluding non-melanoma skin cancer) within particular categories (i.e. gastrointestinal, respiratory, female breast, melanoma, genitourinary, haematological, other or not specified);
- coronary and non-coronary revascularization procedures;
- venous thromboembolism (i.e. fatal or non-fatal pulmonary embolism or deep vein thrombosis).

(ii)   Other measures of interest, including:
- systolic and diastolic blood pressure;
- body weight;
- estimated glomerular filtration rate;
- albuminuria;
- full blood count [FBC] (available in UK participants only): haemoglobin, white cell count and platelet count.

Based on differences in the change from baseline to 1 year (or 3 months for FBC) and baseline to final follow-up.

2.5 Additional safety outcomes

In addition to assessing the effect of allocation to ER niacin/laropiprant on efficacy and safety outcomes listed above, assessment will be made of other potential safety outcomes included in the Data Analysis Plan for early safety analyses. Where possible such events will be subdivided into serious and non-serious (although non-serious adverse events were only recorded when considered likely to be due to the study treatment; i.e. "reactions") and, where appropriate, subdivided by region:

(i)   Muscle-related outcomes:
- *myopathy:* defined as otherwise unexplained muscle symptoms with a creatine kinase (CK) >10x upper limit of normal [ULN];

- *rhabdomyolysis:* a subset of myopathy in which there is evidence of end-organ damage (e.g. doubling of serum creatinine compared to value at baseline) and significant muscle damage (e.g. CK >40xULN);

- *muscle enzyme elevations:* (i) highest post-randomization CK ≤5xULN; >5≤10xULN; >10≤40xULN; and >40xULN (with and without diagnosed

myopathy); and (ii) "incipient myopathy" defined as ALT >1.7x screening value and CK both >5x screening value and >3x ULN recorded within 7 days.

(ii)   Liver-related outcomes:

- *study drug-related hepatitis (i.e. hepatitis cause unknown)*: unrefuted report of non-infective hepatitis (defined as symptoms of liver disease and ALT or aspartate transaminase [AST] >5xULN, ALT/AST >3xULN with bilirubin >3xULN, or alkaline phosphatase [ALP] >3xULN) for which no alternative cause (such as infection) has been found.

- *hepatitis or abnormal liver function of unknown cause:* hepatitis cause unknown (as above), or ALT >10x ULN (cause unknown) or ALT 3x ULN + bilirubin ≥2x ULN (cause unknown)

- *liver enzymes elevations*: (i) highest post-randomization ALT >2≤3xULN; >3≤5xULN; >5≤10xULN; and >10xULN; (ii) two or more consecutive (i.e. within 2-10 days) ALT >3xULN; (iii) ALT >3xULN with bilirubin within 7 days ≥2x ULN; and (iv) ALT >3x with bilirubin ≥2x or ALT >10x ULN subdivided into those with and without an alternative identified cause.

  Analyses (i-iii) to be undertaken overall and sub-divided into those with or without myopathy (definite or incipient).

(iii)   Glucose-related outcomes:

- development of new diabetes (based on physician diagnosis or use of hypoglycaemic therapy) among all patients without diabetes recorded at baseline and, separately within that category, among those with and without abnormal glucose tolerance at baseline;

- microvascular complications of diabetes among those with diabetes recorded at baseline, defined as either: (i) retinopathy (i.e. reports of laser photocoagulation or diabetic eye disease); or (ii) nephropathy (i.e. fall in eGFR from baseline >20% and eGFR <60 mL/min/1.73m^2 on last post-randomization central sample, or new onset of albumin:creatinine ratio ≥34 mg/mmol or need for long-term renal replacement therapy or renal death);

- differences in HbA1c in all participants and, separately, in people with and without diabetes recorded at baseline, by time and overall using study average weighted for years at risk;

- worsened diabetic control among those with diabetes recorded at baseline defined as either: an increase in HbA1c >5 mmol/mol between baseline and end of study, or increased hypoglycaemic medication use defined as: either addition of insulin in those not on insulin at baseline; or use of an additional type of hypoglycaemic medication

- major and minor diabetes serious adverse events (events are considered major if admitted with coma or other complications with a report that the participant was significantly unwell assessed at the time of interview);

(iv)   Skin-related outcomes:
- overall and divided into flushing, rash, pruritis and other skin events (excluding skin cancer);

(v)   Gastrointestinal outcomes:
- overall and divided into indigestion; nausea or loss of appetite; diarrhoea; abdominal pain; or other GI symptom;

Exploratory safety analyses will also be undertaken of many other reported serious adverse events and non-serious adverse reactions (with due allowance made in their interpretation for the retrospective and exploratory nature of such analyses) and in subgroups defined in 2.3.

3   Details of analyses

3.1   Methods of analysis

The fundamental assessments of efficacy and safety will involve comparisons among all randomized patients in their originally allocated treatment group, irrespective of compliance, during the scheduled treatment period (i.e. "intention to treat" analyses).[2, 3] Analyses will be based on the first relevant unrefuted event of a particular type (i.e. either confirmed or not refuted during the adjudication process). All time-to-event analyses will be based on the first relevant event, and will use log-rank methods[3, 7] to calculate hazard ratios and P-values, except for risk ratios for myopathy which will use Cox regression analyses. The effect of full compliance with ER niacin/laropiprant will be estimated from the observed intention-to-treat effect on major vascular event risk of allocation to ER niacin/laropiprant and the average in-trial compliance with the randomized treatment. Where appropriate (e.g. for non-infective hepatitis and myopathy), these analyses will be annotated with the numbers actually taking their allocated study treatment before the event occurred. Comparisons of proportions of affected individuals will involve standard logistic regression methods.

3.2   Allowance for multiplicity of comparisons

No allowance will be made for multiplicity testing in the primary comparison. For secondary and, particularly, tertiary comparisons, allowance in their interpretation will be made for multiple hypothesis testing,[2, 3] taking into account the nature of events (including timing, duration and severity) and evidence from other studies. In addition to the pre-specified comparisons, many other analyses will be performed with due allowance for their exploratory and, perhaps, data-dependent nature. Conventionally, two-sided P-values (2P) <0.05 are often described as "significant". But, the larger the number of events on which a comparison is based and the more extreme the P-value (or, analogously, the further the lower limit of the confidence interval is from zero) after any allowance has been made for the nature of the particular comparison

(i.e. primary, secondary or tertiary; pre-specified or exploratory), the more reliable the comparison and, hence, the more definite any finding will be considered.

3.3 Tests for heterogeneity of effects

When a number of different subgroups are considered, chance alone may lead to there being no apparent effect in several subgroups in which the effect of treatment really is about the same as is observed overall. In such circumstances, "lack of direct evidence of benefit" is not good "evidence of lack of benefit", and clearly significant overall results would provide strong indirect evidence of benefit in some small subgroups where the results, considered in isolation, are not conventionally significant (or, even, perhaps, slightly adverse). [2, 3, 8] Hence, unless the proportional effect in some specific subcategory is clearly different from that observed overall, the effect in that subcategory is likely to be best estimated **indirectly** by applying the proportional effect observed among all patients in the trial to the absolute risk of the event observed among control patients in that category.[8] Tests for heterogeneity of the proportional effect on particular outcomes in specific subgroups will be used with allowance for multiple comparisons and for other differences between the subgroups (such as between group lipid differences) to determine whether the effects in those subgroups are clearly different from the overall effect. If such subgroups can be arranged in some meaningful order (e.g. baseline cholesterol subdivided into 3 similar sized groups of low, medium and high) then assessment of any trend in the proportional effects on outcome will be made.

3.4 Analyses of biochemical efficacy

Non-fasting blood samples were scheduled to be taken from all participants after about 1 year of median follow-up and at the final study visit, and from a randomly selected subset of 5-10% of randomized participants annually. For any participant selected for blood sampling who was alive at the time of the follow-up assessment but failed to provide a sample for any reason, values will be imputed based on their baseline values while taking background LDL-lowering therapy and their reported compliance. The main analyses will be of the effects of ER niacin/laropiprant versus placebo among all selected participants (irrespective of whether they remain compliant and attend scheduled follow-up visit; i.e. intention-to-treat) on:

- LDL-cholesterol
- HDL-cholesterol
- non-HDL-cholesterol
- triglycerides
- apolipoprotein B
- apolipoprotein A1
- lipoprotein (a)

Differences between allocated groups will be considered by time from randomization and a study-average difference (weighted for years at risk) calculated for each lipid component. These analyses will be undertaken by subgroups defined in 2.3.

References

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