Treatment of HDL to Reduce the Incidence of Vascular Events

Data Analysis Plan for early safety analyses

1 Background

This Data Analysis Plan describes the strategy and statistical methods which will guide the early safety analyses of ER niacin/laropiprant in the HPS2-THRIVE trial. As pre-specified in the Section 2.3.1 of the Protocol, these analyses are to be carried out on all randomized participants. All analyses and reports will be prepared in the coordinating centre at the Clinical Trial Service Unit of the University of Oxford, which is the study sponsor. The results of these analyses are to be reported in a peer-reviewed publication. (Clinical efficacy analyses are to be described in a subsequent Data Analysis Plan.)

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 patients are also taking effective background LDL-lowering treatment with 40mg simvastatin daily plus, depending on their cholesterol level, 10mg ezetimibe daily. The LDL cholesterol-lowering regimen was established during the first part of a 2-4 month pre-randomization Run-in period. Participants were then given active ER niacin/laropiprant during the second part of the Run-in: 1g daily for four weeks and then 2g daily for four weeks. At the end of the Run-in period, compliant and eligible patients were randomly allocated to receive 2g ER niacin/laropiprant or matching placebo at the Randomization visit. Post-randomization Follow-up visits are scheduled at 3, 6 and 12 months and then 6-monthly. The study is intended to continue until the median follow-up is at least 4 years (i.e. 4 years after randomization of the first 12,500 patients), by which time it is anticipated that at least 2300 patients will have had confirmed "major vascular events" (MVE; defined as non-fatal myocardial infarction or coronary death, non-fatal or fatal stroke, or revascularisation).

2 Safety and tolerability outcomes

The early safety and tolerability of ER niacin/laropiprant is to be assessed from the following information.

2.1 Serious adverse events (SAEs)

Certain SAEs are pre-specified in Section 2.3.1 of the Protocol to be included in the early safety assessments (regardless of whether or they are considered to be related to study treatment). Comparisons will be made between the randomized treatment groups of the numbers and proportions of participants with:

- *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 >40x ULN);

- *Study drug-related hepatitis:* an unrefuted report of non-infective hepatitis for which no alternative cause has been found on further investigation. To confirm hepatitis the following must be present:
  - (i) symptoms of liver disease; and
  - (ii) alanine transaminase (ALT) or aspartate transaminase (AST) >5x ULN; or ALT/AST >3x ULN with bilirubin >3x ULN or ALP >3x ULN

Other SAEs will not be included in these early safety analyses (and instead will be included in the main efficacy and safety analyses conducted at the end of the study), unless it is reported that they are thought with a reasonable probability to be related to study treatment or have lead to discontinuation of study treatment (see below).

2.2 Reported reasons for stopping study treatments

If a participant stops the LDL-lowering regimen started in the pre-randomization Run-in phase and/or stops the ER niacin/laropiprant or placebo treatment allocated at the Randomization visit, then the clinic staff are to record the reason(s). These early safety analyses will include comparisons between the randomized treatment groups of the numbers and proportions of participants who have stopped their study treatments overall and for particular reasons (with subdivisions according to whether the LDL-lowering treatment or randomized treatment have been stopped), as well as being subdivided by severity. Reasons will be grouped by body system or organ affected:

- skin-related (overall, and divided into flushing, rash and pruritus);
- diabetes-related (overall, and divided into new-onset diabetes and major and minor diabetes complications);
- gastrointestinal (overall, and divided into upper lower and other GI symptoms);
- cardiovascular (overall, and divided into presyncope/syncope, palpitations and other cardiovascular symptoms);
- musculoskeletal or abnormal CK;
- liver or abnormal ALT; and
- other and non-medical reasons.

If the number of events in any category is so few that it could lead to potential unblinding of individual participants, then this category will be grouped with another appropriate category or non-serious and serious categories will be merged.

2.3 Biochemical safety data

The Protocol specifies that each participant is to have blood ALT measured at every study visit and CK measured if the participant reports muscle symptoms or ALT is >1.5 xULN. In addition, results of liver and muscle enzymes from non-study laboratories and extra study visits are entered into the study database. The primary

analyses will be of results from routine study visits and secondary analyses of all values that are recorded (i.e. including Early Recall visit data and other values entered).

- *Liver enzyme elevations:* comparisons will be made between the randomized treatment groups of the numbers and proportions of participants with:

(i)   highest post-randomization ALT >2 ≤3x ULN; >3 ≤5x ULN; >5 ≤10x ULN; and >10x ULN;

(ii)   two or more consecutive (i.e. within 2-10 days) ALT >3x ULN;

(iii)   ALT >3x ULN without simultaneous myopathy (incipient [see below] or definite); and

(iv)   ALT >3x ULN with simultaneous bilirubin ≥2x ULN.

- *Muscle enzyme elevations:* For participants who have ever had a post randomization CK measure, comparisons will be made between the randomized treatment groups of the numbers and proportions of participants with:

(i)   highest post-randomization CK ≤5x ULN; >5 ≤10x ULN; >10x ULN; >40x (with and without diagnosed myopathy); and

(ii)   CK >5x ULN with simultaneous (within 7 days) ALT >1.5x ULN

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

These biochemical safety analyses will also be conducted by time (e.g. at 3, 6 and 12 month follow-up visits).

2.4 Exploratory analyses

Exploratory regression analyses will be conducted to identify baseline variables that predict safety outcomes of interest (e.g. myopathy, non-compliance at 1 year). Where appropriate, separate regression analyses of predictors will be undertaken within each treatment arm and within region.

In addition, exploratory analyses will be conducted in various subgroups, including: age (50-59, 60-69 & ≥70 years); gender; presence or absence of diabetes at baseline; baseline lipids; and geographical region (China and UK/Nordics) using appropriate tests for heterogeneity.

3 Details of analyses

3.1 Intention-to-treat analyses

The assessments of safety will involve comparisons among all randomized patients in their originally allocated treatment group (irrespective of compliance) during the treatment period up to the point of censoring for this analysis (i.e. "intention to treat" analyses). Where appropriate (i.e. for non-infective hepatitis and myopathy), these analyses will be annotated with the numbers actually taking their allocated study treatment before the event of interest occurred. Comparisons of proportions of affected individuals will involve standard logistic regression methods.

3.2 Allowance for multiplicity of comparisons

For these safety analyses, allowance in their interpretation will be made for multiple hypothesis testing, taking into account the nature of events (including timing, duration and severity) and evidence from other studies. 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. pre-specified or exploratory), the more reliable the comparison and, hence, the more definite any finding will be considered.