
HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events): A randomized trial of the long-term clinical effects of raising HDL cholesterol with extended release niacin/laropiprant

Does extended release (ER) niacin/laropiprant prevent vascular events in high-risk patients who are receiving intensive LDL-lowering treatment?

Large-scale randomized trials have demonstrated that lowering LDL cholesterol by about 1 mmol/L for 4-5 years reduces the risks of coronary events and of strokes by about one quarter. Furthermore, recent trials assessing more intensive versus standard statin regimens suggest further benefit with more intensive lowering of LDL cholesterol. Nevertheless, cardiovascular risk remains elevated even after some years of intensive LDL-lowering treatment. For example, in 2 recent trials, over 10% of CHD patients still suffered a major cardiovascular event during 4-5 years of intensive statin therapy. There is limited scope with current agents for much greater reductions in LDL cholesterol, but manipulating other aspects of lipid metabolism may well produce worthwhile reductions in occlusive vascular disease risk.

HDL cholesterol has long been known to have a strong inverse correlation with CHD risk. But, randomized trial evidence for beneficial effects from raising HDL cholesterol is limited. Most previous trials have been performed using fibrates, which raise HDL cholesterol only modestly, and those studies produced mixed results. One of the most effective HDL-raising agents is niacin, but the only previous large randomized trial of niacin was performed before the introduction of effective LDL-lowering treatments. Moreover, the tolerability of niacin has been limited by flushing and cutaneous side-effects, which appear to be mediated largely by prostaglandin D. Laropiprant (formerly MK-0524) is a selective prostaglandin D receptor antagonist that substantially reduces the frequency and intensity of niacin-induced flushing. Daily oral doses of the combined ER niacin/laropiprant 2 g have been well tolerated in early studies.

A streamlined international trial

The present study aims to assess the clinical effects of two tablets of ER niacin/laropiprant 1 g versus matching placebo tablets in 25,000 patients with pre-existing atherosclerotic vascular disease who are all receiving simvastatin 40 mg daily (plus, if indicated, ezetimibe 10 mg daily). Such large-scale recruitment will allow reliable assessment of the effects of raising blood HDL cholesterol on the risk of major vascular events among patients receiving effective LDL-lowering therapy (i.e. LDL cholesterol typically below 2 mmol/L [77 mg/dL]). An international collaboration, with a Central Coordinating Office in Oxford and 3 Regional Coordinating Centres in the UK, China and Scandinavia, will conduct the trial in about 200 hospitals. The study design is “streamlined”: extra work for collaborating doctors and hospitals has been kept to a minimum, and only essential data will be collected directly using computer-based systems.

HPS2-THRIVE Central Coordinating Office, Clinical Trial Service Unit,
Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK
Tel: +44(0)1865 743743, fax: +44 (0)1865 743985

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1 BACKGROUND

1.1 DOES RAISING HDL CHOLESTEROL PREVENT MAJOR VASCULAR EVENTS IN PATIENTS WITH VASCULAR DISEASE?

1.1.1 Residual vascular risk remains substantial even with intensive LDL-lowering treatment

Large-scale randomized trials have demonstrated that lowering LDL cholesterol concentration by about 1 mmol/L for 4-5 years reduces the risks of coronary events and of strokes by about one quarter.¹ Furthermore, recent trials assessing more intensive versus standard statin regimens suggest further benefit with more intensive lowering of LDL cholesterol.^{2 3} Nevertheless, cardiovascular risk remains elevated even after some years of intensive LDL-lowering treatment. For example, in 2 recent trials, over 10% of CHD patients still suffered a major cardiovascular event during 4-5 years of intensive statin therapy.^{2 3} There is limited scope with current agents for much greater reductions in LDL cholesterol, but manipulating other aspects of lipid metabolism may well produce worthwhile reductions in the risks of occlusive vascular disease.

1.1.2 Higher blood HDL cholesterol levels are associated with lower cardiovascular risk throughout the usual range

HDL cholesterol has long been known to have a strong inverse correlation with CHD risk.⁴⁻⁷ In the detailed Prospective Studies Collaborative (PSC) meta-analysis of 60 observational studies among 170,000 people involving 3020 deaths from CHD, each 0.2 mmol/L higher HDL cholesterol (e.g. 1.2 versus 1.0 mmol/L) was associated with about one-third lower risk of CHD death (figure 1).

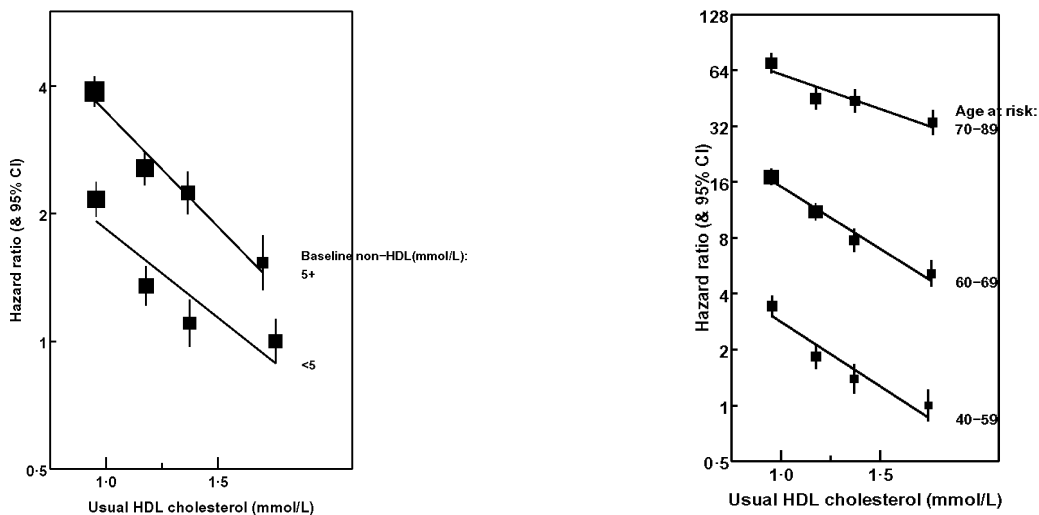


Figure 1: A strong negative association is seen between baseline HDL cholesterol and subsequent risk of death from coronary heart disease at both higher and lower levels of non-HDL cholesterol (left panel) and at different ages (right panel). Data from the Prospective Studies Collaboration, based on 3020 CHD deaths among 170,000 people with 1.3 million years of follow-up. Hazard ratios are relative to the lowest risk group in each panel (e.g. in left panel the group with the non-HDL <5.0 and HDL >1.5 mmol/L with “floating” risks).⁸

The strength of this relationship appeared to be similar at higher and lower levels of non-HDL cholesterol, and at different ages. Although there was no significant association between HDL cholesterol and stroke mortality in that meta-analysis, higher HDL cholesterol levels were clearly associated with a lower risk of other vascular deaths. Moreover, evidence from other sources that include both fatal and non-fatal strokes does indicate an inverse association between HDL cholesterol levels and stroke incidence.^{6,9}

No subject in the PSC meta-analysis of observational studies had evidence of vascular disease at baseline and few were taking lipid-lowering drugs. The Heart Protection Study (HPS) randomized trial of simvastatin provides an opportunity to explore the relationship between HDL cholesterol and the subsequent occurrence of major coronary events and strokes in high-risk patients with atherosclerotic vascular disease or diabetes.¹⁰ Among the statin-allocated participants in HPS, there was a continuous association between higher baseline HDL cholesterol and lower risk of such events, with no evidence of a threshold above which HDL cholesterol was not predictive of lower risk (figure 2).

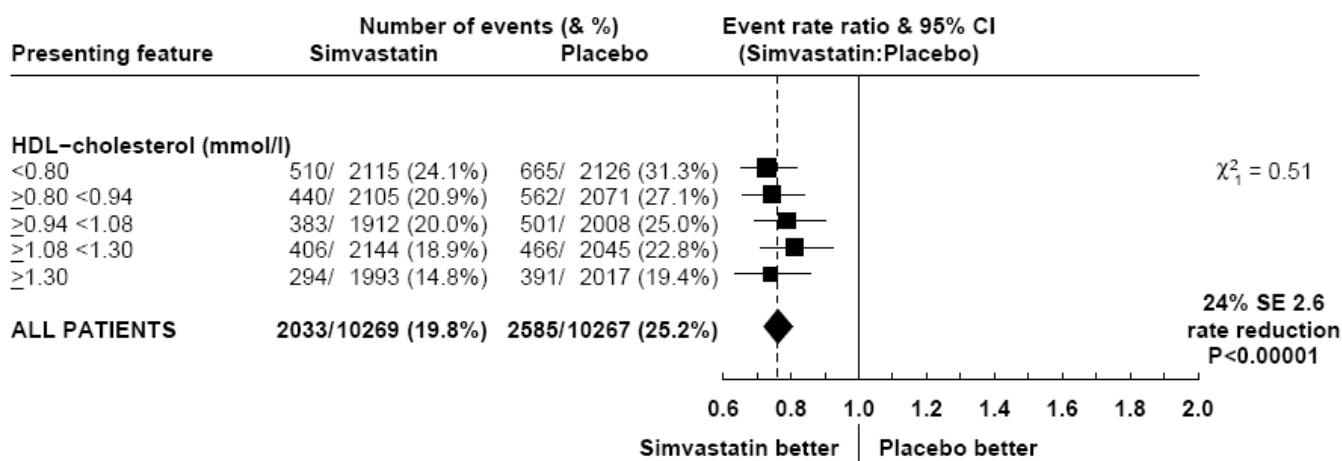


Figure 2. The effect of simvastatin on major vascular events (first major coronary event, stroke or arterial revascularization) in HPS participants subdivided by baseline HDL cholesterol

1.1.3 Niacin is effective at raising HDL cholesterol and apolipoprotein A-I levels

Randomized trial evidence for beneficial effects from raising HDL cholesterol is limited. Most previous trials have been performed using fibrates, which raise HDL cholesterol only modestly (5-10%), and those studies have produced mixed results.¹¹⁻¹⁵ One of the most effective HDL-raising agents is niacin. At a daily dose of 2g, niacin increases HDL cholesterol by about 20-25% and apolipoprotein A-I by about 10-15%,¹⁶ and these increases appear to add to those of statins (which increase HDL concentration by only about 5% and apolipoprotein A-I by about 0-5%).¹⁶ Niacin has only a modest LDL-lowering effect, typically only about 5% when added to a statin, but it can produce a further 30% reduction in plasma triglycerides.¹⁷

The only large randomized trial to have assessed the effects of niacin on clinical outcomes is the Coronary Drug Project (CDP).¹⁸ During the 5-8 year scheduled treatment period, a significant 19% reduction (odds ratio 0.81; 95% confidence interval 0.69-0.96) in non-fatal myocardial infarction or coronary death was observed among the 1119 men allocated niacin 3 g daily compared with the 2789 allocated placebo (26.0% vs 30.2%; p=0.005). Subsequently,

surviving patients were observed for an additional 9 years, and there was a significant 23% (95% CI: 11-33%) reduction in all-cause mortality by 15 years from randomization (52.0% vs 58.2%; p=0.0004).¹⁹ But, the CDP trial was conducted more than 30 years ago and before the introduction of effective LDL-lowering treatments (although there is no good reason to expect that any benefits of niacin would not be additional to those produced by a statin), and niacin is not widely used.

1.1.4 Minimising the side-effects of niacin use with concomitant use of laropiprant

The widespread use of niacin has been limited by poor tolerability, mainly due to flushing resulting from the cutaneous vasodilation that occurs in nearly all patients.²⁰ Slow-release formulations have been developed in an effort to reduce flushing and gastrointestinal side-effects, but those preparations were found to be associated with hepatotoxicity. More recently, an extended release (ER) formulation, Niaspan, has been developed that does not have increased toxicity compared to crystalline niacin.²¹ But, although the incidence of flushing with Niaspan is lower than with niacin, gradual escalation to therapeutically effective doses is required and many patients still experience flushing intermittently during chronic use. The flushing and cutaneous adverse effects associated with niacin appear to be partially or wholly mediated by prostaglandin D₂ release in the skin.²⁰

Laropiprant (formerly known as MK-0524) is an orally active, potent and selective prostaglandin D receptor antagonist that substantially reduces the frequency and intensity of niacin-induced flushing both in animal models and in man.²² Minimal toxicity has been observed in animal studies and co-administration with simvastatin and niacin had no meaningful effect on laropiprant blood levels. The apparent half-life of laropiprant is about 17 hours allowing once daily dosing. A Global Flushing Severity Score (GFSS) has been used to assess the frequency and severity of niacin induced flushing. Using this score, the concomitant use of laropiprant during the first week of niacin administration reduced the proportion of patients experiencing at least one day of moderate or greater flushing from around 60% to about 35% (compared to 10% on placebo). Furthermore, after about 6-8 weeks the proportion of days on which patients on the combination of laropiprant and ER niacin experienced moderate or severe flushing was similar to that among patients on placebo (figure 3). Consequently, the drop-out rate from these studies due to niacin induced flushing with the combination treatment was very low.

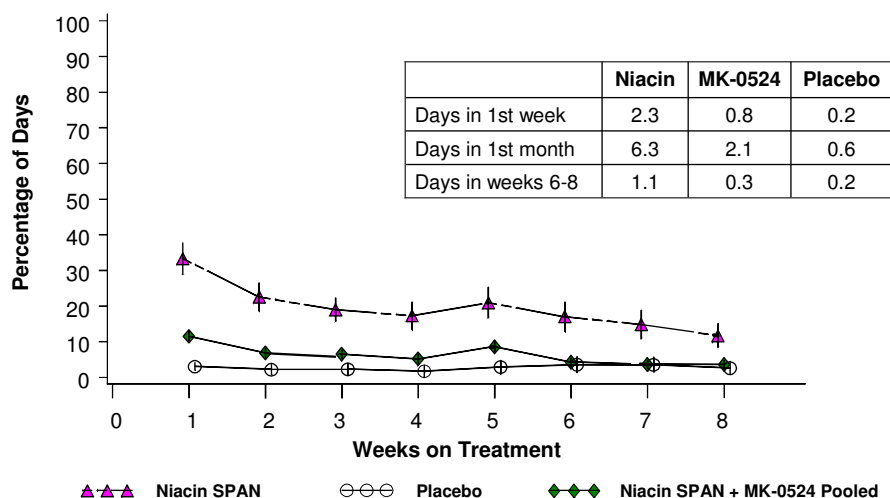


Figure 3. Laropiprant reduces the percentage of days with moderate/severe flushing (GFSS ≥ 4) over 6 to 8 weeks. (Merck data on file).

ER niacin/laropirant daily inhibits flushing associated with both initiation of treatment and with chronic use. About 10,000 people have so far been given laropirant or the combination tablet (not including the HPS2-THRIVE participants) and no safety concerns have arisen. Although not eliminating all the side-effects of niacin which also include gastrointestinal disturbance, liver function abnormalities, increases in blood glucose and hyperuricaemia, the combination tablet of ER niacin 1 g and laropirant 20 mg (denoted ER niacin/laropirant 1 g) is likely to be well tolerated. This combination now makes it practical to assess the use of niacin to raise blood HDL cholesterol in a large streamlined clinical outcome trial. Hence, HPS2-THRIVE aims to assess the effects of ER niacin/laropirant 2 g versus placebo in a large population of patients at high risk of atherosclerotic vascular disease events in whom LDL cholesterol has been reduced to below about 2.0 mmol/L (77 mg/dL).

1.1.5 Rationale for background intensive LDL cholesterol-lowering

Emerging trial evidence suggests that more intensive LDL-lowering therapy is well tolerated and produces larger cardiovascular benefits than standard LDL-lowering therapy.^{2,3} Hence, the present study aims to anticipate likely trends towards more intensive treatment by ensuring that participants achieve a total cholesterol level prior to being randomized of below about 3.5 mmol/L (135 mg/dL), which is equivalent to an LDL cholesterol of below about 2 mmol/L (77 mg/dL). This will have the advantage of reducing any need for lipid monitoring by participants' own doctors and of minimising any differential drop-in with LDL-lowering therapy between the two treatment arms (which might complicate interpretation of the results¹⁵). Simvastatin 40 mg daily is well tolerated and widely prescribed, but many high-risk patients will be on more intensive LDL-lowering regimens. Ezetimibe is an oral cholesterol absorption inhibitor that, in combination with statins, produces an additional relative reduction in LDL cholesterol of 15-20% (equivalent to about 3 doublings of the statin dose). Ezetimibe has been shown to be safe and well tolerated, and it is being widely prescribed.²³ To ensure that all participants are given sufficiently intensive LDL-lowering therapy, they will all receive simvastatin 40 mg daily and, if LDL cholesterol levels on this regimen are not considered to be sufficiently well controlled (i.e. an LDL cholesterol above about 2.0 mmol/L), ezetimibe 10 mg daily will be added.

2 PLAN OF INVESTIGATION

2.1 STUDY AIMS

The study will include 25,000 patients aged 50-80 years with pre-existing atherosclerotic vascular disease (plus concomitant diabetes in about 6000-7000) who are at particular risk of major vascular events. The primary aim is to assess the effect of raising HDL-cholesterol with ER niacin/laropiprant 2 g versus matching placebo on the time to first “major vascular event” (defined as non-fatal myocardial infarction or coronary death, non-fatal or fatal stroke, or revascularisation). LDL cholesterol levels will be controlled in all participants by simvastatin 40 mg plus, if required, ezetimibe 10 mg daily.

Secondary aims include assessment of the effects of ER niacin/laropiprant: on early safety outcomes; on the separate components of the primary endpoint; and on the primary endpoint within major baseline disease subgroups. Tertiary objectives include assessment of the effects of ER niacin/laropiprant: on the primary endpoint within subgroups defined by other baseline characteristics; on the incidence of new onset diabetes; on cognitive function; on changes in serum creatinine and HbA1c in all patients and, separately, among participants with diabetes at baseline; and on the incidence of diabetic microvascular complications (see Section 2.3).

2.2 TREATMENT COMPARISONS

2.2.1 Run-in period prior to randomization

At the initial Screening visit, participants will be assessed for eligibility and, if consenting, will be given simvastatin 40 mg daily or, if already on ezetimibe or a statin dose more potent than simvastatin 40mg, combination ezetimibe/simvastatin 10/40 mg daily. Other prescribed statin treatment will be stopped.

After about 4 weeks all participants given simvastatin 40mg daily (or at the Screening visit for those patients already on simvastatin 40mg daily), will have a Titration assessment with immediate dry chemistry assay of their cholesterol level. Those with total cholesterol levels ≥ 3.5 mmol/L will have ezetimibe 10 mg daily added, and will be seen 4 weeks later at their Run-in assessment for repeat dry chemistry assay of total cholesterol levels (Appendix 1). All other participants (i.e. those on simvastatin alone who have reached target cholesterol levels and those already on ezetimibe/simvastatin 10/40 mg) will proceed straight into their Run-in assessment. (Participants already on ezetimibe/simvastatin 10/40mg prior to screening will have the Run-in assessment at their Screening visit). At that assessment, participants will have baseline blood and urine sampling, and be provided with ER niacin/laropiprant 1 g daily for 4 weeks and then 2 g daily for the remaining 4 weeks of Run-in.

The Run-in period is to help ensure that only those likely to continue taking study treatment for an extended period are randomized and, in particular, to exclude patients for whom flushing or other side-effects due to niacin are a problem. The Run-in also allows LDL-lowering treatment to be tailored to individual participant’s needs. Following the Run-in assessment visit, the patients’ own doctor(s) will be informed of their total cholesterol or lipid profile on this tailored LDL-lowering regimen, so that they may decide whether it is appropriate for their patient to be randomized (see Section 3.4.4). By this process, many potential drop-outs should be excluded

before becoming part of the randomized comparison, with a consequent improvement in statistical sensitivity of the “intention-to-treat” analyses.

2.2.2 Randomization to HDL cholesterol-raising therapy versus placebo

The randomized HDL-raising therapy takes the form of two daily tablets, each containing ER niacin/laropiprant 1g versus matching placebo. In addition, all randomized patients will continue to take simvastatin 40 mg daily or, if indicated during the Run-in period, ezetimibe/simvastatin 10/40 mg daily. Study treatment will be provided in specially designed calendar-packs to facilitate long-term compliance.

2.3 ASSESSMENT OF OUTCOMES FOR ER NIACIN/LAROPIPRANT VERSUS PLACEBO

Two Data Analysis Plans will be agreed by the Steering Committee before any relevant data have been unblinded. The first of these will describe the early safety analyses that are to be carried out on patients who have completed at least 3 months of follow-up (see Section 2.3.1 below); and the second will describe the main and subsidiary efficacy analyses to be conducted at the end of the trial (see Section 2.3.2-5).

2.3.1 Early safety assessments for ER niacin/laropiprant

The safety of ER niacin/laropiprant 2g daily will be assessed during the first year of the study among all randomized patients with at least 3 months of follow-up. Safety outcomes will include:

- Myopathy (muscle symptoms with CK >10xULN*) and rhabdomyolysis (a subset of those with myopathy as defined in the Adverse Event SOP)
- Confirmed elevation of liver transaminases: aspartate or alanine transaminase (AST or ALT) >3xULN on 2 occasions within about one week
- Non-viral drug-related hepatitis
- Discontinuation of study treatment overall and by various causes, including known adverse effects of niacin (such as flushing and gastrointestinal symptoms)

2.3.2 Primary assessment of ER niacin/laropiprant at scheduled study end

The primary comparison will involve an “intention-to-treat” analysis among all randomized patients using the “logrank” test²⁴ of the effects of allocation to ER niacin/laropiprant versus placebo on **major vascular events** during the scheduled treatment period of a median of at least 4 years. A major vascular event (MVE) is defined as the composite of non-fatal myocardial infarction or coronary death; non-fatal or fatal stroke; or any revascularisation procedure (including coronary or non-coronary angioplasty or grafting)

* The upper limit of normal is defined by the laboratory or analyser used for the particular blood test.

2.3.3 Secondary assessments of ER niacin/laropiprant at scheduled study end

All secondary assessments will involve “intention-to-treat” analyses using the “logrank” test of the effects of allocation to ER niacin/laropiprant versus placebo during the scheduled treatment period on:

- (i) separate components of the primary endpoint:
 - major coronary events (i.e. 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 haemorrhagic stroke separately;
 - revascularisations
- (ii) mortality, both overall and within particular categories of causes of death (i.e. coronary heart disease; other cardiac; stroke; other vascular; neoplastic; hepatic; and other medical and non-medical causes)
- (iii) major vascular events in patients with and without:
 - coronary heart disease;
 - peripheral arterial disease;
 - cerebrovascular disease; or
 - diabetes mellitus

2.3.4 Tertiary assessments of ER niacin/laropiprant at scheduled study end

Tertiary assessments will involve “intention-to-treat” analyses using the “logrank” test of the effects of allocation to ER niacin/laropiprant versus placebo during the scheduled treatment period on:

- (a) major vascular events in various categories of patient determined at baseline:
 - men and women;
 - age <60; ≥60 <70; ≥70;
 - current, former and non-smokers;
 - diastolic blood pressure ≤90; >90≤100; and >100 mm Hg;
 - systolic blood pressure ≤140; >140≤160; and >160 mm Hg;
 - with and without metabolic syndrome;
 - with and without treated hypertension;
 - with and without heart failure;
 - tertiles of total cholesterol*;
 - tertiles of LDL-cholesterol*;
 - tertiles of HDL-cholesterol*;
 - tertiles of non-HDL cholesterol*;
 - tertiles of triglycerides*;
 - tertiles of apolipoprotein B*;
 - tertiles of apolipoprotein A-I*;
 - tertiles of HDL response during Run-in;
 - tertiles of fasting plasma glucose*;
 - tertiles of HbA1c (in all patients and, separately, in diabetic patients alone)*;
 - tertiles of body mass index;
 - tertiles of waist circumference;

- tertiles of urinary albumin:creatinine ratio;
- categories of alcohol intake;
- tertiles of cardiovascular risk

* based on samples obtained at the Run-in Assessment at -8 weeks

- (b) major vascular events in the presence and absence of particular treatments at baseline:
- simvastatin alone and ezetimibe/simvastatin combination;
 - angiotensin-converting-enzyme [ACE] inhibitors;
 - aspirin or other antiplatelet drug;
 - non-steroidal anti-inflammatory drugs or coxibs;
 - angiotensin-receptor blockers [ARBs];
 - diuretics;
 - calcium-channel blockers [CCBs];
 - beta-blockers

Additional analyses will be performed of the effects of treatment with ER niacin/laropiprant during the scheduled treatment period: on cognitive function assessed by questionnaire at the final visit; on hospital admission for, or death from, heart failure; on site-specific cancers; on development of new diabetes (based on physician diagnosis or new use of hypoglycaemic therapy) among all patients without diabetes at baseline and, separately, among those with and without impaired fasting glucose at baseline; and on any recorded changes in type or dose of hypoglycaemic medication; on microvascular and macrovascular complications of diabetes (as defined in the Data Analysis Plan); on changes in HbA1c and creatinine between the baseline visits and visits at 3 months (UK only), median of one year and at study end (all countries), overall and separately among those with and without diabetes and annually in a random sample; on changes in full blood count between the baseline visit and visits at 3 months and study end in UK participants only; on coronary and non-coronary revascularisation procedures; and on venous thromboembolism. As in the early safety analyses (see Section 2.3.1), possible side-effects of the randomly allocated treatment will also be assessed during the whole of the scheduled treatment period.

2.3.5 Biochemical efficacy of ER niacin/laropiprant during the scheduled treatment period

Biochemical efficacy will be assessed in non-fasting specimens in a random sample of 5-10% of participants annually, and in all patients after a median of about one year of follow-up and at their final visit. 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 their scheduled follow-up visit: i.e. intention-to-treat) on:

- HDL cholesterol
- triglycerides
- LDL cholesterol
- non-HDL cholesterol
- apolipoprotein B
- apolipoprotein A-I
- Lp(a)
- lipoprotein particle size

2.4 SAMPLE SIZE AND PREDICTED NUMBER OF EVENTS

Event rates in on-going and recently completed trials among patients with pre-existing occlusive vascular disease have been somewhat lower than originally anticipated, even when compared with the rates observed among statin-allocated patients in trials conducted during the 1990s. For example, among 12,000 MI patients randomized to simvastatin 80 mg versus 20 mg daily in the ongoing SEARCH trial, the overall *blinded* annual MVE rate is about 3.2%, compared with a rate of over 4% among apparently similar types of patient allocated simvastatin 40 mg daily in HPS.¹⁰ Similarly, two other trials involving patients with established CHD receiving intensive statin treatment have reported annual rates of the composite of coronary event or stroke of 1.7% and 2.4% respectively.^{2 3}

In HPS, the presence of cerebral or peripheral vascular disease alone, or of diabetes combined with occlusive vascular disease, were indicators of especially high risk.¹⁰ Patients with previous MI were also at higher risk, but those with angina alone had lower event rates. Similarly, among the MI patients in SEARCH, the addition of cerebral or peripheral vascular disease, or diabetes, is associated with high annual MVE rates (4.1% and 4.6% respectively). Hence, in the present study, patients are eligible only if they have a history of MI, cerebrovascular disease, peripheral vascular disease or, in those with diabetes, evidence of atherosclerotic vascular disease (including angina alone). Moreover, since event rates increase with increasing age, the lower age limit of 50 years is 10 years higher than in HPS. With this patient population, it is realistic to anticipate an annual MVE rate of at least 3%.

An average increase in HDL cholesterol of about 15-20% with ER niacin/laropiprant 2g daily might realistically translate into a 15-20% relative reduction in major vascular events (i.e. assuming that, as with LDL-lowering treatment, about half of the effect associated epidemiologically with long-term higher HDL cholesterol emerges within about 4-5 years). The reliable detection of such an effect might require a study with at least 2300 confirmed MVEs (see Table). Based on an approximate 3% per annum event rate, this can be achieved by randomising 20,000 high-risk patients and following them for a median of at least 4 years, or by increasing recruitment to 25,000 patients results could emerge about 4 months earlier. This would also provide 80% power at $2p < 0.05$ to detect a 15% reduction in risk separately among the 7000 diabetic patients assuming a slightly higher event rate (or other subgroups with similar numbers of events).

Table: Statistical power to detect 12%, 15% and 20% reductions in MVEs among 20,000 patients (assuming approx. 3% p.a. major vascular event rate in the control group).

Proportional reduction	Number of events (%) over 4 years		Power at $2p < 0.05$	Power at $2p < 0.01$
	Control 10,000	Active 10,000		
12	1200 (12%)	1060 (10.6 %)	>80%	>65%
15	1200 (12%)	1020 (10.2%)	>95%	>85%
20	1200 (12%)	960 (9.6%)	>99%	>99%

2.5 DATA AND SAFETY MONITORING

2.5.1 Recording and reporting of adverse events

2.5.1.1 Definition of Serious Adverse Events (SAE)

“Serious” adverse events are defined as those adverse events that:

- result in death;
- are life-threatening;
- require in-patient hospitalisation or prolongation of existing hospitalisation;
- result in persistent or significant disability or incapacity;
- result in congenital anomaly or birth defect;
- are cancer;
- are important medical events in the opinion of the responsible investigator (i.e. not life-threatening or resulting in hospitalisation, but may jeopardise the participant or require intervention to prevent one or other of the outcomes listed above); including, for the present study: myopathy; rhabdomyolysis; and hepatitis.

Pregnancies and overdoses of study medication are also to be recorded, regardless of any associated adverse events.

2.5.1.2 Reporting of Serious Adverse Events (SAE) and other relevant events

All serious adverse events (SAE) reported by participants at each follow-up visit will be recorded directly on the study computer-based data entry system (see Section 2.6.3). Clinic staff are to record whether any SAE is likely to be due to study treatment (see Section 2.5.1.3). Participants will also be asked specifically whether they have had any unexplained muscle pain or muscle weakness. Other adverse events not considered serious (as defined above) will be recorded if they lead to discontinuation of study treatment or are believed to be due to study treatment. SAEs that are potential study endpoints will undergo central review, verification and coding (see Section 3.8.1). Line-listings of all reported SAEs (blind to treatment allocation) will be provided on a monthly basis to Merck for regulatory purposes.

2.5.1.3 Reporting of Serious Adverse Reactions (SAR)

Any SAE that is considered, with a reasonable probability, to be due to study treatment is, potentially, a Serious Adverse Reaction (SAR). Reports of all such events are to be forwarded immediately to a clinician at the Regional Coordinating Centre (RCC) or Central Coordinating Office (CCO). The relevant clinician will obtain standard information, including participant study number, identity of reporting person, description of event, and reasons for attribution to study treatment. All such reports will then be forwarded urgently to the Clinical Coordinator (or their deputy), who will review the evidence for seriousness and relatedness, seek any additional information required, and assess expectedness based on study treatment data sheets. Any suspected SARs that are unexpected (Suspected Unexpected SARs: i.e. SUSARS) will be unblinded and, if on active treatment, reported immediately to Merck for regulatory authority submission, and to other relevant parties (including the Chairman of the Data Monitoring Committee and appropriate ethics committees), in accordance with study standard operating

procedures (SOPs). All valid expected SARS will be reported unblinded to the Chairman of the Data Monitoring Committee and blinded to Merck.

2.5.1.4 Unblinding of study treatment

There are 2 main situations in which unblinding of the treatment allocation (ER niacin/laropiprant or placebo) for an individual participant may be warranted:

- when knowledge of the treatment allocation could materially influence the immediate medical management (e.g. after overdose); and
- when the Clinical Coordinator reviews a report of a possible SAR (see Section 2.5.1.3).

Urgent unblinding is available via a 24-hour service at the Clinical Trial Service Unit (CTSU). Requests for unblinding will be reviewed urgently, and authorized, by the CCO on-call clinician.

2.5.2 Interim analyses: role of the Data Monitoring Committee

During the study, interim analyses of all serious adverse events and other study outcomes will be supplied regularly (e.g. 6-monthly) in strict confidence to the Chairman of the independent Data Monitoring Committee. In the light of these analyses and any other information considered relevant, the Data Monitoring Committee will advise the Steering Committee if, in their view, the randomized comparisons in the study have provided **both** (i) “proof beyond reasonable doubt”^{*} that for all, or some specific types of, patients prolonged use of ER niacin/laropiprant is clearly indicated or clearly contraindicated; **and** (ii) evidence that might reasonably be expected to influence materially the patient management of many clinicians who are already aware of the results of other relevant trials. The Steering Committee can then decide whether to modify the study, or to seek additional data. Unless this happens, the Steering Committee, collaborators, study participants, representatives of Merck, and all study staff (except those who provide the confidential analyses to the Data Monitoring Committee) will remain blind to the interim results on mortality and morbidity until the end of the study.

2.6 CENTRAL AND REGIONAL COORDINATION OF LOCAL CLINICAL CENTRES

The Study will be coordinated by the Central Coordinating Office (CCO) based at the Clinical Trial Service Unit (CTSU) of Oxford University, working with 3 Regional Coordinating Centres (RCCs) in the UK, China, and Scandinavia. It is anticipated that the distribution of participants among the three regions will be approximately 8500 from UK, 10,500 from China, and 6000 from Scandinavia. The RCCs will be based at CTSU for the UK, at the Fuwai-Oxford Centre for Cardiovascular Health in Beijing for China, and at the Merck Scandinavian Headquarters in Drammen, Norway, for the Nordic countries (Denmark, Norway, Finland and Sweden). Each RCC will be responsible for selection and funding of Local Clinical Centres (LCCs) within their region, and for the administrative support and monitoring of these LCCs. At each LCC, a Lead

^{*} Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but in general a difference of at least 3 standard deviations in an interim analysis of mortality or major morbidity would be needed to justify halting, or modifying, the study prematurely. This criterion has the practical advantage that the exact number of interim analyses is of little importance²⁶

Investigator and research nurse/doctor will be responsible for identification, recruitment, and follow-up (Appendix 2).

2.6.1 Training and monitoring

The study will be conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Research Practice (ICH-GCP), the EU Clinical Trial Directive and relevant local, national and international regulations. Prior to initiation of the study at any LCC, the RCC will confirm that the LCC has adequate facilities and resources to carry out the study (and, if considered necessary, a site visit will be undertaken). LCC Lead Investigators and study clinic staff will be provided with materials detailing relevant study procedures for LCCs, and clinic staff will be trained in study methods.

During the study, the relevant RCC and/or the CCO will arrange monitoring visits to study centres as considered appropriate based on perceived training needs and the results of central statistical monitoring of study data. The purpose of these visits will be to help LCC staff to resolve any local problems with the study, to ensure that the study is conducted according to the protocol, and to review study records, data quality and the completeness of follow-up. A report of each visit will be prepared by the study monitor and reviewed by RCC/CCO staff.

2.6.2 Supply of study materials

Study treatments will be manufactured, packaged, labelled and delivered to each LCC or RCC by Merck. An inventory of study drug supplies will be maintained on the study web-based IT system and will be monitored at the CCO. The LCC Lead Investigator will be responsible for making appropriate arrangements for the storage and dispensing of study treatments, and for the disposal of unused study drug in accordance with study SOPs.

2.6.3 Data management

All data in the study will be processed electronically using a set of custom-written applications. The LCC clinic staff will use a laptop-based application for performing LCC tasks (including: entering patient data at study visits; randomized treatment allocation; and basic local trial administration), with periodic synchronization of data to central databases. RCC and CCO staff will use a suite of administration applications to manage centres, including messaging between study staff, tracking serious adverse events and blood samples, and central statistical monitoring. Data transfers will be cryptographically secured, and all data will be stored securely. All accesses will require a unique username and password, and any changes to data will require the user to enter their username and password as an electronic signature. Staff will have access restricted to only that functionality and data that is appropriate to their role in the study.

2.6.4 Biological sample assay, transport and storage

2.6.4.1 *Dry chemistry assays in study clinics*

Dry chemistry analysers will be used in all LCC study clinics for eligibility checks at the Screening visit (ALT, CK and creatinine), for immediate total cholesterol measurement at the Titration and Run-in assessments, and for safety analyses during follow-up (ALT and CK).

Participants on simvastatin alone who have total cholesterol levels ≥ 3.5 mmol/L at their Titration assessment will have ezetimibe/simvastatin 10/40mg daily substituted for simvastatin alone. Following the Run-in assessment (Section 3.4), the participant's doctor will be informed of the cholesterol measurement on this tailored LDL-lowering regimen so that they may decide whether randomization is appropriate.

2.6.4.2 Sample handling in the UK

In the UK, blood for central laboratory assays will be collected in the LCC clinic into vacuum tubes and kept cool until the end of each clinic day before being couriered overnight in cool boxes to the central laboratory in CTSU. At the central laboratory, blood samples will be centrifuged and separated for any immediate assays (Appendix 3), and for long-term storage in liquid nitrogen of plasma and white cells. Urine samples collected in the LCC clinic will also be transferred overnight at the end of each clinic day for immediate assay and frozen storage (Appendix 3).

2.6.4.3 Sample handling in China and Scandinavia

In China and Scandinavia, blood for central laboratory assays will be collected in the LCC clinic into vacuum tubes and kept cool before being centrifuged and separated locally within a day of the clinic visit. Plasma and white cells will be put into bar-coded cryovials for immediate storage below -18°C (and transferred to below -40°C within 4 weeks). At appropriate intervals, these samples will be collected from the LCCs in China and Scandinavia (by the RCC and CCO respectively) and then transferred as necessary to the central laboratory for relevant assays and for long-term storage in liquid nitrogen. Urine samples collected in the LCC clinic will also be stored locally below -18°C at the LCC and then transferred together with the plasma and the white cells to the central laboratory for assay and frozen storage (Appendix 2).

2.6.5 Source documents and archiving

"Source documents" for the study constitute the clinic visit records (including blood and urine assay results) held in the study main data store, the additional information obtained on reported outcome measures and other relevant events, death certificates, and drug supply records. These documents will be retained for at least 15 years from the completion of the study in accordance with ICH-GCP. Merck and regulatory agencies will have the right to commission a confidential audit of such records in the CCO, RCCs, and LCCs provided this does not result in unblinding while the study is in progress.

2.6.6 Funding

This study has been initiated and designed by the independent investigators at the Clinical Trial Service Unit (CTSU) at Oxford University, and the data will be collected, analysed and published independently of the source of funding. Merck will provide a grant to CTSU at the University of Oxford, which will act as Sponsor of this study. This grant will support all central costs of the study, and regional and local costs in UK and China, while the regional and local costs in Scandinavia will be funded separately by Merck.

2.6.7 Indemnity

Merck will, at all times, indemnify the study investigators and study staff from claims that may be made against them for any injury sustained by a study participant as a consequence of participation in the study in accordance with this protocol. The indemnity will be outlined in detail in the agreements between the CCO, RCCs and LCCs (and, if required, in a letter from Merck).

2.6.8 Publications, reports and substudies

Draft copies of any manuscripts will be provided to the Steering and Data Monitoring Committees, the Lead Investigators at each LCC, and all other collaborators (including Merck) for review prior to their submission for publication. Papers will be written in the name of the Collaborative Group, with individual investigators named personally at the end of the report (or, to comply with journal requirements, in web-based material posted with the report). Responsibility for all study publications will rest entirely with the Steering Committee.

Proposals for substudies on patients randomized into the study will be welcomed, but must be approved by the Steering Committee before they begin. In considering such proposals, the Steering Committee will need to be satisfied that the proposed substudy is of a high quality, and that it will not compromise the main study in any way (for example by reducing the recruitment rate or compliance with study treatment).

3 SUMMARY OF PRACTICAL PROCEDURES

↓	<p>PRE-SCREENING PHASE</p> <ul style="list-style-type: none"> Identify potentially eligible patients (age 50-80 years with vascular disease) from medical records Invite to attend Screening clinic appointment in local study clinic
↓	<p>RUN-IN PHASE</p> <p>SCREENING VISIT</p> <p>All participants:</p> <ul style="list-style-type: none"> Medical history, relevant current treatment and other eligibility factors recorded Blood pressure measured Written informed consent sought from eligible and willing individuals Blood sample taken for dry chemistry assay of ALT, CK and creatinine Consenting patients asked to stop non-study statin or ezetimibe <p>Depending on participant's previously prescribed treatment:</p> <ul style="list-style-type: none"> Dry chemistry for total cholesterol Fasting blood sample for central laboratory glucose, HbA1c creatinine, detailed lipid assays and storage Urine for albumin/creatinine ratio and storage <p>Appointment scheduling and drug issuing depending on participant's LDL-lowering therapy +/- total cholesterol</p> <ul style="list-style-type: none"> If simvastatin 40 mg issued, next visit scheduled in 4 weeks (Titration visit) If ezetimibe/simvastatin 10/40mg issued, next visit in 4 weeks (Run-in assessment) If ER niacin/laropiprant (plus simvastatin 40mg +/- ezetimibe 10mg) issued, next visit in 8 weeks (Randomization visit) and patient's doctor (and/or investigator) informed about the total cholesterol level
↓	<p>TITRATION VISIT; <i>only for patients started on simvastatin 40mg daily at Screening</i></p> <p>All participants</p> <ul style="list-style-type: none"> Serious adverse events, compliance, and changes to non-study medication recorded Fasting blood sample for dry chemistry total cholesterol & ALT Fasting blood sample for central laboratory glucose, HbA1c creatinine, detailed lipid assays and storage Urine for albumin/creatinine ratio and storage <p>If total cholesterol ≥ 3.5 mmol/L:</p> <ul style="list-style-type: none"> Ezetimibe/simvastatin 10/40 mg issued and appointment scheduled in 4 weeks (Run-in assessment) <p>If total cholesterol < 3.5 mmol/L:</p> <ul style="list-style-type: none"> ER niacin/laropiprant plus simvastatin 40mg issued, next visit in 8 weeks (Randomization visit) Patient's doctor (and/or investigator) informed about the total cholesterol level
↓	<p>RUN-IN ASSESSMENT; <i>only for patients started on ezetimibe/simvastatin at Screening or Titration visit</i></p> <ul style="list-style-type: none"> Serious adverse events, compliance, and changes to non-study medication recorded Fasting blood sample for dry chemistry total cholesterol & ALT Fasting blood sample for central laboratory glucose, HbA1c creatinine, detailed lipid assays and storage Urine for albumin/creatinine ratio and storage Run-in treatment provided to eligible and consenting patients: <ul style="list-style-type: none"> Active ER niacin/laropiprant 1 g: 1 tablet daily for 4 wks then 2 tablets daily for 4 wks Simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg daily (as required) continued Randomization visit appointment scheduled for 8 weeks later Participant's doctor (and/or investigator) informed of total cholesterol level
↓	<p>RANDOMIZATION VISIT (0 MONTHS)</p> <ul style="list-style-type: none"> All non-study treatments and serious adverse events during Run-in recorded Final check of compliance and eligibility Height, weight, and waist circumference recorded Non-fasting blood sample taken for dry chemistry ALT, and for central lipid assay and frozen storage Randomization via study clinic computer Randomly allocated calendar-packed treatment provided to patient: <ul style="list-style-type: none"> Active ER niacin/laropiprant 1 g or matching placebo: 2 tablets daily Simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg daily continued Follow-up visit appointment scheduled for 3 months' time Participant's doctor informed of patient's randomization
↓	<p>FOLLOW-UP VISITS AT 3 and 6 MONTHS, THEN 6-MONTHLY</p> <ul style="list-style-type: none"> Serious adverse events, compliance, and changes to non-study medication recorded (plus blood pressure, waist and weight, measured at 1 year and final visit) Reasons for non-compliance and any non-serious adverse events attributed to study treatment recorded Non-fasting blood sample for safety assays (and, in 5% of participants annually and all participants at median 1 year and at final visit, for lipid assays, HbA1c, creatinine and frozen storage) Follow-up treatment pack dispensed, and next Follow-up visit scheduled
↓	<p>MONITORING OF SAFETY AND EFFICACY</p> <ul style="list-style-type: none"> Central monitoring of blood results and adverse events (with Early Recall visits to monitor any problems) Further details on relevant outcomes sought from participant's doctor (and, if necessary, other sources) Relevant events confirmed centrally blind to treatment allocation

3.1 ELIGIBILITY FOR THE STUDY

Patients are eligible for randomization into HPS2-THRIVE if: (i) inclusion criteria are satisfied whilst no exclusion criterion applies; and (ii) their own doctor does not consider there to be a definite indication for, or contraindication to, niacin.

3.1.1 Inclusion criteria

- History of myocardial infarction; or
- Cerebrovascular atherosclerotic disease (history of presumed ischaemic stroke, transient ischaemic attack or carotid revascularisation); or
- Peripheral arterial disease (i.e. intermittent claudication or history of revascularisation); or
- Diabetes mellitus with any of the above or with other evidence of symptomatic coronary heart disease (i.e. stable or unstable angina, or a history of coronary revascularisation or acute coronary syndrome).

3.1.2 Exclusion criteria

- Age <50 or >80 years at invitation to Screening;
 - Less than 3 months since presentation with acute myocardial infarction, coronary syndrome or stroke (but such patients may be entered later, if appropriate);
 - Planned revascularisation procedure within 3 months after randomization (but such patients may be entered later, if appropriate);
 - Definite history of chronic liver disease, or abnormal liver function (i.e. ALT >1.5xULN). (Note: Patients with a history of acute hepatitis are eligible provided this ALT limit is not exceeded);
 - Breathlessness at rest for any reason;
 - Severe renal insufficiency (i.e. creatinine >200 µmol/L);
 - Evidence of active inflammatory muscle disease (e.g. dermatomyositis, polymyositis), or CK >3xULN;
 - Previous significant adverse reaction to a statin, ezetimibe, niacin or laropiprant;
 - Active peptic ulcer disease;
 - Concurrent treatment with:
 - fibric acid derivative (“fibrate”)
 - niacin (nicotinic acid) at doses more than 100 mg daily
 - ezetimibe in combination with either simvastatin 80 mg, or atorvastatin 20-80 mg, or rosuvastatin 10-40 mg daily
 - any potent CYP3A4 inhibitor, including: macrolide antibiotics (erythromycin, clarithromycin, telithromycin); systemic use of imidazole or triazole antifungals (e.g. itraconazole, ketoconazole); protease inhibitors (antiretroviral drugs for HIV infection); and nefazodone
 - ciclosporin
 - amiodarone
 - verapamil
 - danazol
- (Note: Patients who are temporarily taking such drugs may be re-screened when they discontinue them, if considered appropriate.);
- Known to be poorly compliant with clinic visits or prescribed medication;

- Medical history that might limit the individual's ability to take trial treatments for the duration of the study (e.g. severe respiratory disease, history of cancer or evidence of spread within last 5 years other than non-melanoma skin cancer, or recent history of alcohol or substance misuse)

The study does not pre-specify any blood lipid thresholds in order to determine eligibility. Instead, the decision about whether a particular patient is potentially eligible for randomization is to be made by the patient's own doctor. Following the Run-in assessment, a participating patient's doctor would be provided with a total cholesterol value taken while the patient was using the LDL-lowering regimen (i.e. simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg daily) that would be supplied during the trial. The Steering Committee will review any relevant trial results or guidelines that emerge during the course of the study, and can re-consider the need for further communication with participants' and their doctors should this become appropriate.

3.2 SCREENING VISIT

3.2.1 Assessment of relevant medical history and eligibility

Potentially eligible individuals will be given information about the study and invited to attend a Screening Visit. At the Screening Visit, relevant medical history and other factors pertinent to eligibility will be recorded directly onto the Screening Visit Form on the study clinic IT system. The LCC clinic staff will check inclusion and exclusion criteria, and record relevant current medication and blood pressure. (N.B. Any potential problems that might require further investigation or treatment may be brought to the attention of the patient's own doctor by clinic staff.)

3.2.2 Invitation to participate and standardization of LDL-lowering therapy

Patients who appear to be eligible will have the study explained to them by the clinic staff, using the Patient Information Leaflet as a basis for discussion. Patients will have an opportunity to initiate discussion, and have time to think about their participation in the study, perhaps after discussing it first with their family, primary care physician, or a local physician. (Eligible patients who choose to do this will be asked to attend a repeat Screening visit within a few weeks.) Patients will be discouraged from participating if it is thought unlikely that they would be willing and able to continue attending Follow-up visits for at least 4 years.

Potentially eligible patients who agree to participate will be asked to provide written informed consent. Blood pressure will be measured and a blood sample taken for immediate dry chemistry analysis of ALT, creatine kinase (CK) and creatinine. Any prescribed statin therapy or ezetimibe will be stopped (although resin therapy may be continued). Eligible patients taking simvastatin 40 mg alone or in combination with ezetimibe 10 mg for at least 4 weeks prior to Screening will also have an immediate dry chemistry total cholesterol measured. Depending on their cholesterol level or on their previous LDL-lowering therapy, these patients would then be managed according to the Titration (Section 3.3.2) or the Run-in assessment (Section 3.4).

For all other eligible patients, the LCC clinic staff will dispense 5 weeks' supply of calendar-packed simvastatin 40 mg daily or, if already taking ezetimibe or more than the equivalent of simvastatin 40 mg (i.e. simvastatin 80 mg, atorvastatin 20-80 mg or rosuvastatin 10-40 mg),

calendar-packed ezetimibe/simvastatin 10/40 mg daily. (N.B. No patient will be given LDL-lowering therapy likely to be less effective than their current regimen.) For patients on oral anticoagulants, the managing doctor will be advised to check the international normalised ratio (INR) about one week after starting the study LDL-lowering therapy. An appointment will be made for the participant's next visit in about 4 weeks, and the participant will be asked to fast for that visit.

3.3 TITRATION VISIT

3.3.1 Reviewing eligibility and compliance

Only participants started on simvastatin 40 mg daily alone at the Screening visit will have this Titration visit. These patients will be asked if they have experienced myocardial infarction, arterial revascularisation, stroke, other serious adverse event (SAE) or any other significant problems since the Screening visit (if appropriate). Any SAE considered to be due to study treatment (i.e. possible serious adverse reaction [SAR]) is to be discussed immediately with a RCC/CCO clinician for expedited reporting (see Section 2.5.1.3). Changes to relevant non-study treatment will be sought, and compliance with the supplied simvastatin reviewed. Information will be recorded directly into the study clinic IT system (which is designed to obtain complete information and prompt appropriate actions).

3.3.2 Up-titration of LDL-lowering therapy (as required)

Compliant participants who have not experienced a vascular event or other significant problem since their Screening Visit, and are not on a contraindicated drug, will have a fasting blood sample taken for immediate dry chemistry measurement of total cholesterol in the clinic. Participants on simvastatin alone with total cholesterol <3.5 mmol/L will proceed straight into their Run-in Visit (see below: Section 3.4). Those with total cholesterol \geq 3.5 mmol/L will be provided with 5 weeks' supply of calendar-packed combination tablets of ezetimibe/simvastatin 10/40 mg daily (with the previously supplied simvastatin alone packs retrieved), and an appointment will be made for the Run-in Visit in about 4 weeks (with participants again asked to fast for that visit).

3.4 RUN-IN VISIT

3.4.1 Reviewing eligibility and compliance

All participants will have a Run-in assessment. If patients attend a Run-in visit after a Screening or Titration visit they will be asked if they have experienced myocardial infarction, arterial revascularisation, stroke, other SAE or any other significant problems since the previous visit. Any SAE considered to be due to study treatment (i.e. possible SAR) is to be discussed immediately with a RCC/CCO clinician for expedited reporting (see Section 2.5.1.3). Changes to non-study treatment will be sought, and compliance with the supplied simvastatin or ezetimibe/simvastatin reviewed. Information will be recorded directly onto the Run-in Visit Form on the study clinic IT. N.B. The Run-in assessment will be made at the same time as the Screening visit for those patients who either: (a) are already taking simvastatin 40 mg daily and

have a total cholesterol <3.5 mmol/l; or (b) are already taking ezetimibe/simvastatin 10/40 mg daily.

3.4.2 Collection of blood and urine samples

Compliant participants who have not experienced a vascular event or other significant problem since their previous study clinic visit, and are not on a contraindicated drug, will have a fasting blood sample taken for immediate dry chemistry measurement of total cholesterol and ALT in the clinic (and in the UK, for central full blood count). ALT must be $\leq 2 \times \text{ULN}$ to remain eligible. Samples will then be processed (Section 2.6.4.2 and 2.6.4.3) for later transportation to the central laboratory for detailed baseline assays (e.g. full lipid profile, glucose, creatinine, glycosylated haemoglobin and full blood count: Appendix 3) and long-term frozen storage. Urine samples will also be collected for central assay of albumin/creatinine ratio and long-term storage.

3.4.3 Continuing LDL-lowering treatment and starting ER niacin/laropiprant

All willing and compliant participants will be given a further 10 weeks' supply of their calendar-packed appropriate LDL-lowering therapy (i.e. simvastatin alone or ezetimibe/simvastatin as required). In addition, participants will be provided with 10 weeks of calendar-pack treatment containing active ER niacin/laropiprant 1 g tablets: one tablet daily for the first 4 weeks, and 2 tablets daily for the subsequent 4 weeks. An appointment will be made for the Randomization Visit in about 8 weeks.

3.4.4 Review of eligibility and LDL cholesterol control by patient's own doctor

The pre-randomization phase is intended to help identify, and exclude before randomization those patients who would be unlikely to comply with long-term study treatment and follow-up. The Run-in period also allows eligibility checks of relevant safety and lipid blood assays before deciding on randomization. The patient's doctor will be provided with the lipid values from the Run-in Visit following at least 4 weeks on the required LDL-lowering regimen (simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg daily) that would be supplied during the trial. The doctor would be asked to indicate whether, in his or her view, these blood results (or any other factor) make the patient unsuitable for entry into the randomized phase of the study.

3.5 RANDOMIZATION VISIT (0 MONTHS)

3.5.1 Final check of eligibility and compliance before randomization

Participants who attend their Randomization Clinic appointment will be asked if they have experienced myocardial infarction, arterial revascularisation (coronary or non-coronary), stroke, other SAE or any other significant problems during the Run-in period and whether any arterial revascularisation procedure is planned within 3 months. Any SAE considered to be due to study treatment (i.e. possible SAR) is to be discussed immediately with a RCC/CCO clinician for expedited reporting (see Section 2.5.1.3). Changes to non-study treatment will be sought, and compliance with Run-in treatment checked (at least 90% of scheduled study treatment should have been taken). Height, weight, and waist circumference will be measured. Details

will be recorded directly onto the Randomization Form on the clinic IT system (which is designed to obtain complete information and prompt appropriate actions). Compliant patients who have not experienced a vascular event or other significant problem during Run-in including new or unexplained muscle symptoms and are not on a contraindicated drug, will be asked if they are still willing to take study treatment for at least 4 years. If so, a non-fasting blood sample will be collected for immediate dry chemistry analysis of ALT (must be $\leq 2 \times \text{ULN}$ to remain eligible), and processed (see Section 2.6.4) for transportation to the central laboratory.

3.5.2 Random allocation of study treatment

Eligible and consenting individuals will be allocated ER niacin/laropiprant or placebo using a minimised randomization program on the clinic IT system that helps maximize balance between the treatment groups with respect to prognostically important variables (including age, gender, history of prior disease, smoking status, lipid levels, blood pressure, ethnic origin and history of prior statin use)²⁵. Patients will be allocated a numbered treatment pack containing a 7-month calendar-packed supply of one of the following study regimens:

- Two tablets daily of active ER niacin/laropiprant (each containing extended-release niacin 1 g combined with laropiprant 20 mg daily); or
- Two tablets daily of placebo ER niacin/laropiprant

The numbered treatment packs will be dispensed to the patient by the LCC clinic staff or by the local hospital pharmacy. Participants will also receive a 7-month supply of calendar-packed simvastatin 40 mg daily or ezetimibe/simvastatin 10/40 mg daily (as determined during Run-in). For patients on oral anticoagulants, the managing doctor will be advised to check the patient's international normalised ratio (INR) about one week after starting randomized therapy. An appointment for the first post-randomization Follow-up Visit will then be allocated by the study staff, with guidance from the clinic IT system. The patient's doctor(s) will be notified that the patient has been randomized into the study.

3.6 FOLLOW-UP VISITS (3 AND 6 MONTHS AND THEN 6-MONTHLY)

3.6.1 Recording adverse events and compliance

Following randomization patients are scheduled to attend Follow-up visits at 3 and 6 months, and then 6-monthly for a median of at least 4 years. At each visit, details of all hospital admissions, other SAEs, unexplained muscle pain or weakness, and non-serious adverse events attributed to study treatment will be sought. Any SAE considered to be due to study treatment (i.e. possible SAR) is to be discussed immediately with a RCC/CCO clinician for expedited reporting (see Section 2.5.1.3). Changes to non-study treatment will be recorded, and compliance with treatment reviewed. For patients who discontinue study treatment, the reasons for doing so will be recorded. At one year and at the final study visit, blood pressure, waist and weight will also be measured. Details will be recorded directly onto the Follow-up Form on the clinic IT system.

3.6.2 Blood sampling, and dispensing of study treatment

At each Follow-up visit, a non-fasting blood sample will be taken for immediate dry chemistry analysis of ALT. If ALT >3x ULN or symptoms suggestive of possible hepatitis (e.g. nausea, jaundice, lethargy or malaise) with ALT >2x ULN then additional liver function assays are to be done (see Section 3.7.1.1). Irrespective of new or unexplained muscle symptoms if ALT >1.5x ULN or participant has new or unexplained muscle pain then creatine kinase (CK) is to be measured. If a participant has muscle symptoms with ALT <1.5x ULN, myopathy is unlikely, but CK will be measured if any symptoms are present. Participants attending their first follow-up visit in the UK will also have a blood sample taken for central laboratory full blood count and HbA1c. Among a random 5% sample of patients annually, and all patients at median follow-up of one year and at the final visit, LCC Clinic staff will be prompted by the clinic IT system to take additional non-fasting blood and urine samples for central laboratory assays and storage (see Section 2.6.4). Provided continued study treatment remains appropriate, participants will be given a further 7-month supply of their allocated study treatment and any previously allocated treatment retrieved. An appointment will then be made for their next scheduled Follow-up visit in about 6 months.

3.6.3 Follow-up for randomized patients not attending study clinics

All study patients, irrespective of whether they continue to take study treatment, will be encouraged to attend routine Follow-up clinic visits. If, however, a patient becomes unwilling or unable to attend then LCC Clinic staff will telephone the patient at the time of each of their scheduled Follow-up clinics and complete the necessary Follow-up form on the clinic IT system. If this is not possible, then RCC staff will attempt to check a patient's progress by direct correspondence with the patient's own doctors. Participants who stop attending study visits will be asked to discontinue all study treatment (if safety monitoring of blood is no longer possible).

3.7 EARLY RECALL VISITS AND MODIFYING STUDY TREATMENT

3.7.1 Early Recall Visits: Monitoring significant biochemical or other problems

An Early Recall Visit may be arranged for any participant who requires review outside their planned visit schedule. Examples of circumstances where this may be necessary include the assessment of abnormal values in safety bloods from routine Follow-up visits, and review of symptoms believed by the participant to be related to study treatment. As at routine study visits, the results of blood tests performed at Early Recall visits will be entered by LCC staff into the clinic IT system and these will be monitored centrally by the clinical staff at the CCO and RCCs and in accordance with the study SOPs.

3.7.1.1 Monitoring elevated liver transaminases

Asymptomatic elevation of ALT >3xULN is to result in an Early Recall visit in 1 week, while ALT >2x but <3xULN is to be checked within about 3 weeks. In an asymptomatic patient with two consecutive ALT >3xULN study medication (ER niacin/laropiprant or placebo and simvastatin±ezetimibe) is to be stopped temporarily. Symptoms suggestive of hepatitis (e.g. nausea, jaundice, lethargy or malaise) with ALT >2xULN or any ALT >3xULN are to result in dry chemistry analysis of bilirubin and alkaline phosphatase and an Early Recall visit in 1 week.

If symptoms persist and repeat ALT $>2xULN$ then study medication (ER niacin/laropiprant/placebo and simvastatin±ezetimibe) is to be stopped temporarily. ALT is to be checked again at an Early Recall visit in about 6 weeks and study treatments stopped permanently if still $>3xULN$. On the other hand, if ALT $<3xULN$ then study treatments can be restarted after review by one of the RCC or CCO clinicians, with a further 2 Early Recall visits at 4-weekly intervals at which ALT must remain $<3xULN$ (otherwise study treatment is to be stopped permanently).

3.7.1.2 Monitoring elevated creatine kinase

Management of abnormal creatine kinase (CK) results is to be as follows:

CK $>10xULN$: Patients with CK $>10xULN$ plus unexplained muscle pain or weakness have myopathy (by definition), and will be instructed to stop all study medication (i.e. ER niacin/laropiprant/placebo and simvastatin±ezetimibe) permanently. An Early Recall visit is to be arranged within about 1 week for blood safety checks, with 3-weekly Early Recall visits (or referral to the participant's own doctor) until CK reverts to normal (i.e. $\leq 3xULN$). Appropriate advice will be provided to the managing doctors.

Asymptomatic CK $>10xULN$ will be checked within about one week while continuing study treatment. If repeat CK $<5xULN$ then study treatment may continue, but if CK remains $>10xULN$ both study treatments simvastatin±ezetimibe and ER niacin/laropiprant or placebo will be stopped permanently. CK is then to be checked again at an Early Recall visit in about 3 weeks to ensure a return to normal. Appropriate advice will be provided to the managing doctors.

CK $>5xULN$ but $\leq 10xULN$: Patients with CK $>5x$ but $\leq 10xULN$ plus unexplained muscle symptoms will have an Early Recall visit within about 1 week while continuing on study treatment. If repeat CK $<5xULN$ then study treatment may continue, but if repeat CK $>5xULN$ and muscle symptoms persist then both study treatments simvastatin±ezetimibe and ER niacin/laropiprant or placebo will be stopped permanently. CK is then to be checked again at an Early Recall visit in about 3 weeks to ensure a return to normal. Appropriate advice will be provided to the managing doctors.

Asymptomatic CK $>5xULN$ will be checked with about one week while continuing study treatment. If repeat CK $<5xULN$ then study treatment may continue, but if repeat CK $>5xULN$ then all study medication will be stopped temporarily. CK is then to be checked again at an Early Recall visit in about 3 weeks and both study treatments stopped permanently if CK is still $>3xULN$. On the other hand, if CK $\leq 3xULN$ then study treatments can be re-started after review by a CCO clinician, and at the discretion of the local investigator, with a further 2 Early Recall visits at 4-weekly intervals at which CK must remain $<3xULN$ (otherwise study treatments are to be stopped permanently).

3.7.2 Modifying study treatment

3.7.2.1 Temporary or permanent discontinuation of ER niacin/laropiprant (or placebo) and LDL-lowering therapy

If adverse events occur that are believed to be due to niacin then the dose of ER niacin/laropiprant (or matching placebo) may be reduced to 1 g (i.e. one tablet instead of two),

either permanently or (if considered appropriate) temporarily following successful rechallenge with 2 g. In addition, the ER niacin/laropirant (or placebo) and/or the LDL-lowering therapy (i.e. simvastatin±ezetimibe) may be permanently or temporarily discontinued if a significant elevation of liver transaminase or creatine kinase develops (see Section 3.7.1). The following events are also sufficient reason to discontinue ER niacin/laropirant (or placebo) and/or the LDL-lowering therapy permanently:

- Serious adverse event (SAE) considered likely to be due to one or more of the study treatments (see Section 2.5.1.3);
- Clear indication for niacin or fibrate in the view of the participant's own doctors. (N.B. Patients commencing other cholesterol-modifying drugs [e.g. resins or fish oil derivatives] or diets may remain on study treatment, unless such agents are believed to be clearly contraindicated by their own doctors);
- Use of agents that may be contraindicated in patients receiving simvastatin (e.g. a potent CYP3A4 inhibitor), which still allows the allocated ER niacin/laropirant (or placebo) to be continued;
- Any other situation where continuing study treatment is not considered to be in the patient's best interests by their own doctors or the Study clinical team; or
- At the request of the participant or their doctors, for whatever reason.

Whenever possible, the clinic IT system will prompt LCC Clinic staff to consider whether there are specific reasons for modifying either the ER niacin/laropirant (or placebo) or LDL-lowering therapy. Patients who have study simvastatin stopped may take non-study statin at the discretion of the local investigator and managing doctor, CCO clinicians will provide advice about this if requested.

3.7.2.2 Requirement for additional LDL-lowering treatment

Randomized participants who, in the opinion of their managing doctors, require more intensive LDL-lowering therapy than is being provided within the study (simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg daily) can stop that treatment and take an LDL-lowering regimen prescribed by their managing doctors. Alternatively, those who are taking simvastatin 40 mg alone can be changed to ezetimibe/simvastatin 10/40 mg at the request of their managing doctor. In such circumstances, the randomized ER niacin/laropirant (or placebo) should generally be continued.

3.7.3 Unblinding

An emergency unblinding facility will be accessible by telephone call to the CCO. In general, unblinding of patients is only likely to be necessary if knowledge of the treatment allocation could influence immediate patient management (for example, after overdose).

3.8 CONFIRMATION AND VERIFICATION OF STUDY OUTCOMES

3.8.1 Confirmation of all deaths and relevant non-fatal serious adverse events

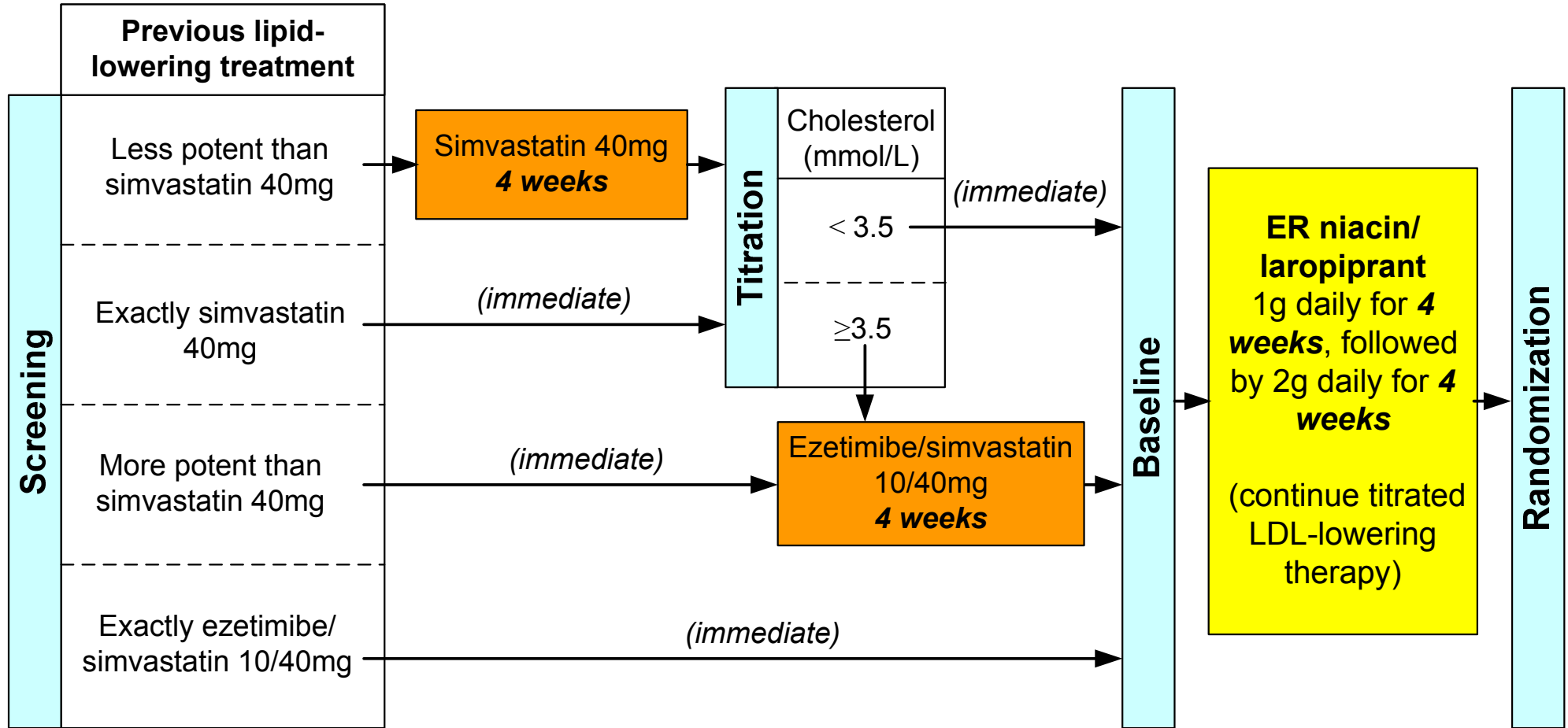
The RCCs will seek additional information about all reports of serious adverse events that might be relevant to the assessments of the efficacy or safety of the study treatments (in particular possible myocardial infarction, heart failure, stroke, revascularisation procedure, cancer, rhabdomyolysis or non-viral hepatitis) from the LCCs and other hospital records, from participant's own doctors and from any other appropriate sources. The RCC will also seek the certified cause of death and site-specific cancer for all randomized participants from national registries and other relevant sources. For each death reported, additional information will be obtained from the LCC hospital records and other appropriate sources. The RCC will be responsible for the review and provisional confirmation of these events and deaths using the study IT system in accordance with the study SOPs. Clinicians based centrally will review, blind to treatment allocation, the specified causes of all deaths and all serious adverse events provisionally confirmed as myocardial infarction, angina, stroke, revascularisation procedure, cancer, myopathy, rhabdomyolysis, or non-viral hepatitis.

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APPENDIX 1: FLOW CHART SHOWING TREATMENTS DURING RUN-IN



APPENDIX 2: ORGANISATIONAL STRUCTURE AND RESPONSIBILITIES

Principal Investigators

The Principal Investigators have overall responsibility for:

- The design and conduct of the Study
- Preparation of the Protocol and subsequent revisions
- Preparation of Standard Operating Procedures
- Design, testing and documentation of all computer systems
- Managing the CCO
- Organising meetings of the Steering Committee
- Publication of study reports

Steering Committee

The Steering Committee is responsible for:

- Agreement of the final Protocol
- Agreeing the Data Analysis Plans
- Reviewing progress of the study and, if necessary, agreeing changes to the protocol and/or Standard Operating Procedures to facilitate the success of the study
- Reviewing new studies that may be of relevance
- Review and approve sub-study proposals

Data Monitoring Committee

The independent Data Monitoring Committee is responsible for:

- reviewing unblinded interim data according to the schedule set out in the Protocol
- advising the Steering Committee if, in their view, the randomized comparisons in the Study have provided **both** (i) “proof beyond reasonable doubt” that for all, or some specific types, of patient, prolonged use of ER niacin/laropiprant is clearly indicated or clearly contraindicated; **and** (ii) evidence that might reasonably be expected to influence materially the patient management of many clinicians who are already aware of the main results of any other relevant trials.

Central Coordinating Office

The CCO is responsible for the overall coordination of the Study. Its functions include:

- Study planning, organisation of Steering Committee meetings
- Ensuring necessary regulatory approval
- Contractual issues with RCCs and budget administration
- Design, implementation and maintenance of IT systems for the study, including the CCO/RCC IT system for administration and the clinic IT system for direct data entry
- Provision of laptops for RCCs and LCCs and provision of IT support to RCCs
- Liaison with the Wolfson laboratory in CTSU for central laboratory assays and with other laboratories undertaking study analyses
- Establishing a satellite central laboratory at Fuwai Hospital, Beijing for HbA1c analyses from Chinese participants
- Provision of study materials
- Assistance with Ethics Committee applications
- Auditing and monitoring of overall progress of the study
- Monitoring of drug supply (in liaison with Merck, who will be responsible for drug distribution to each LCC)

- Responding to technical, medical and administrative queries from the RCCs
- Management of endpoint adjudication
- Pharmacovigilance
- Liaison with the Data Monitoring Committee and Merck, and (where appropriate) with regulatory authorities and other outside agencies
- Central laboratory assay of blood and urine samples at baseline, median follow-up of one year and at the final visit in all participants, and on 5-10% participants annually in between
- Long-term frozen storage of blood and urine samples

Regional Coordinating Centres

The responsibilities of the RCC, under the direction of the Regional Coordinator, will include:

- Contractual issues with LCCs and regional budget administration
- Recruitment and set-up of approximately 50-100 LCCs within the Region
- Obtaining central Ethics Committee approval where appropriate and assisting LCCs with local Ethics Committee applications
- Liaison with regulatory authorities as appropriate
- Training of LCC Clinic staff and Assistants
- Assisting LCC's with identification of suitable patients
- Distribution of study laptop computers and other study materials to LCCs
- Technical support to LCCs
- Monitoring of LCC's through visits (by the study monitor) and by responding to regular or occasional reports on regional progress prepared by the CCO
- Ensuring appropriate follow-up of abnormal ALT and CK results
- Ensuring appropriate confirmation of reported events in line with SOPs
- Responding to technical, medical and administrative queries from the LCCs
- Collection from LCCs of blood and urine samples for central analysis, and transport to the CCO
- Responding to medical and administrative queries within the Region
- Organisation of meetings of collaborators within the region

Local Clinical Centres

The responsibilities of the LCC Lead Investigator and LCC Clinic staff will include:

- Obtaining Local Ethics Committee approval (aided by the RCC)
- Obtaining local management approval where necessary
- Provision of adequate clinic space and access to appropriate hospital computer systems for identification of potentially eligible participants
- Liaising with consultant colleagues
- Conducting clinic procedures; managing and distributing study drugs (in conjunction with the hospital pharmacy), and maintaining the laptop computer, in accordance with the study protocol and standard operating procedures
- Ensuring adequate local laboratory facilities for safety monitoring, and if necessary freezer space for temporary sample storage
- Dealing with routine enquiries from patients and their families, in close collaboration with the RCC
- Obtaining appropriate information when requested to confirm potential primary and secondary study endpoints

APPENDIX 3: VISIT SCHEDULE AND PROCEDURES

	Screening Visit [§]	Titration ^{§ +}	Run-in [§]	Randomization Visit	3 month Visit	6 month Visits and then 6 monthly	Final Visit
Informed consent	X						
Medical history & assess eligibility	X						
Reconfirm eligibility		X	X	X			
Desk top safety bloods (ALT and, if muscle pain, CK)	X*	X [§]	X [§]	X [§]	X	X	X
Desk-top total cholesterol	X [^]	X	X				
Central laboratory lipids, & storage of plasma & cells			X	X		(X)	X
Central fasting plasma glucose			X				
Central creatinine and HbA1c			X		X [%]	(X)	X
Urine for central albumin/creatinine ratio & storage			X			(X)	X
Full blood count (UK patients only)			X		X		X
Height measured				X			X
Blood pressure, weight & waist measured	X			X		X [#]	X
Record endpoints and all SAEs		X	X	X	X	X	X
Monitor for AEs due to treatment					X	X	X
Dispense simvastatin or ezetimibe/simvastatin	X	X	X	X		X	
Dispense active ER niacin/laropiprant (1 g then 2 g)			X				
Dispense randomized ER niacin/laropiprant or placebo				X		X	
Cognitive assessment							X

[§] Denotes ALT, CK and creatinine at Screening visit. [%]UK patients only

⁺ Titration assessment only required for those taking simvastatin 40 mg daily

[§] Screening, Titration and Run-in can be separate visits or combined depending on the circumstances (see Appendix 1)

[#] Measured at one year visit [^] Only for those already taking simvastatin 40mg or ezetimibe/simvastatin 10/40mg

(X) Denotes measures made only at median of one year in all patients and in 5% sample annually

[§] Muscle symptoms during Run-in or at Randomisation render participants ineligible, so CK not to be measured.

APPENDIX 4: STUDY INVESTIGATORS

STEERING COMMITTEE (Major organisational and policy decisions)

Principal investigators	J Armitage (Clinical Coordinator), C Baigent, Z Chen & M Landray
Chairman	R Collins
Regional coordinators	Y Chen and L Jiang (China), T Pedersen (Scandinavia), M Landray (UK)
Other members	L Bowman, F Chen, R Haynes, C Knott, J Tobert, K Rahimi, P Sleight,
Lay member	D Simpson
Statistician	S Parish
Computing	A Baxter, M Lay
Administrative coordinators	C Bray, E Wincott
Merck representatives (non-voting)	G Moen, Y Mitchel, O Kuznetsova

DATA MONITORING COMMITTEE (Interim analyses and response to specific concerns)

Chairman	S MacMahon
Members	J Kjekshus, C Hill, TH Lam, P Sandercock
Statistician (non-voting)	R Peto

Study statistician providing unblinded analyses: J Hopewell

Central Coordinating Office
Clinical Trial Service Unit (CTSU), Richard Doll Building,
Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK
Tel: +44(0)1865 743743, fax: +44 (0)1865 743985
Email: thrive@ctsuo.ox.ac.uk