

## **HPS 3 / TIMI 55: REVEAL (Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification):**

**A large-scale, randomized placebo-controlled trial of the clinical effects of anacetrapib among people with established vascular disease**

### **Post-trial follow-up**

**EDMS #4762**

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## 1. BACKGROUND

The REVEAL trial has randomized over 30,000 participants aged 50 years or older with pre-existing atherosclerotic vascular disease between anacetrapib 100 mg daily and matching placebo for a median of about 4 years. The primary aim is to assess the effect of anacetrapib on the composite outcome of Major Coronary Event (MCE), defined as coronary death, myocardial infarction or coronary revascularization. The key secondary aim is to assess the effect of anacetrapib on coronary death, myocardial infarction or presumed ischaemic stroke. Other secondary, tertiary and exploratory assessments include analyses of cancer, cause-specific mortality, and other serious adverse events. Full details of the study design and analysis plan are provided in the main study protocol.

As described in the main study protocol, it has been planned from the outset that, wherever possible, extended follow-up of all surviving randomized participants would continue for several years beyond the final study visit in order to provide valuable information on the longer-term effects of the study treatment. This can be particularly informative for assessing effects on safety outcomes (e.g. cancers, neurodegenerative and cognitive disorders) that may only become evident many years after initiation of treatment. Furthermore, given the emerging evidence about the prolonged elimination phase of anacetrapib,<sup>1</sup> with drug detectable at low concentrations in the plasma for at least 5 years after discontinuation, extended follow-up in REVEAL is particularly important. This document describes the planned processes for collecting additional clinical information (in particular, with respect to safety of anacetrapib) following completion of the main treatment phase of the trial.

Strategies for post-trial follow-up have been used in a number of previous lipid treatment trials,<sup>2-12</sup> including the Heart Protection Study of simvastatin which was conducted by the Clinical Trial Service Unit at University of Oxford.<sup>2</sup>

## 2. PLAN OF INVESTIGATION

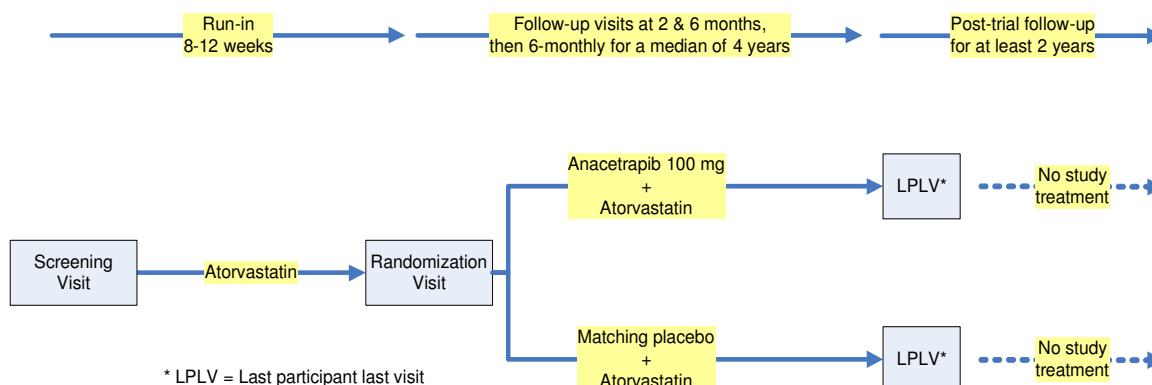
This plan was formulated and agreed in May 2016 while the Steering Committee, funders and investigators remain blind to the main trial results. Alterations to the plan may need to be made when the main trial results become available in 2017.

### 2.1. Eligibility

All surviving randomized participants will be eligible for post-trial follow-up.

### 2.2. Aims

As outlined in the main protocol, wherever possible, extended follow-up of all eligible randomized participants will continue for several years after the final main study visit in order to provide valuable information on the longer-term effects of anacetrapib (see Figure). During this time, participants will not receive any study medication. There will be a particular focus on clinical safety, including cause-specific mortality, cancer, and vascular events. Information on other reasons for hospitalization and other serious adverse events will be collected wherever feasible.



**Figure:** Outline of main study and post-trial follow-up schedule

### 2.3. Data Analysis Plan

Assessments will involve intention-to-treat comparisons among all randomized participants of the effects of allocation to anacetrapib versus placebo on vascular events, cancer, deaths, and other serious adverse events (where feasible) during extended follow-up. The main outcomes of interest are:

- i) Mortality (from all causes combined and, separately, within particular categories of causes, including cardiovascular and non-vascular causes);
- ii) Cancer at all sites (fatal or non-fatal), and site-specific cancers considered separately (excluding any known to pre-date randomization and non-melanoma skin cancers);
- iii) Cardiovascular events; and
- iv) Other serious adverse events (overall and, separately, by type).

In addition, exploratory assessments will be made of other possible effects of anacetrapib among particular subgroups of participants based on data recorded at the randomization visit (as specified in the main protocol), and on other serious adverse events during the extended follow-up period. A detailed data analysis plan will be developed and will focus on the analysis of data collected during the first 2 years of post-trial follow-up (i.e. last participant last visit plus 2 years).

### 2.4. Study duration and anticipated number of clinical events

Wherever possible, extended follow-up of all surviving randomized participants will continue for at least 2 years beyond the final study visit (last participant last visit) in order to provide valuable information on the longer-term effects of the study treatment. It is anticipated that if all surviving participants are followed-up for 2 years beyond the end of the main trial, then around 5800 participants will have suffered a major vascular event, 2500 will have developed a cancer, and 2900 will have died (see Appendix 1).

### **3. SUMMARY OF PRACTICAL PROCEDURES**

#### **3.1. Data collection**

Information on serious adverse events (including cause-specific mortality, cancers, and cardiovascular events) will be sought for all surviving and consenting REVEAL participants wherever possible (see Appendix 2). Follow-up will be by telephone with additional information collected by other means (e.g. linkage to routine data sources) depending on local circumstances (e.g. availability of national health registry data; see Appendix 3). The frequency and nature of assessments may be modified in the light of new information that emerges from the main trial or during the course of the post-trial follow-up period (e.g. to provide additional information about particular aspects of safety).

##### **3.1.1. 6-monthly follow-up assessments by telephone**

In all regions, follow-up assessments are to be made by telephone every 6 months, using similar procedures to those used for telephone follow-up in the main phase trial. At each assessment, participant contact details will be checked. Details of all SAEs will be sought (including specific questions about vascular events and cancers) and the answers recorded on the study's web-based IT system. Where direct contact with the participant is not possible, follow-up information may be collected through discussion with a relative or carer, the participant's routine physician, or through review of medical records. All assessments will be conducted by trained staff either at the Local Clinical Centre (LCC) or at the Regional Coordinating Centre (RCC) or delegated organization.

##### **3.1.2. Linkage to routine clinical databases**

Additional data are to be collected through linkage to available sources of health information, including electronic healthcare records systems, national registries and clinical audit databases (see Appendix 3). For example, in the UK information will be sought from the Health and Social Care Information Centre (HSCIC) on all hospital admissions, deaths and cancers.

##### **3.1.3. Blood sampling and analysis**

Blood samples (e.g. for analysis of lipids, lipoproteins, and plasma anacetrapib levels) may be taken in subsets of individuals (e.g. 5% random sample), subject to separate consent and ethics approval. Information on the residual treatment effects of anacetrapib on blood lipids and anacetrapib levels will inform the interpretation of the effects of anacetrapib on clinical events.

#### **3.2. Study Treatment and Unblinding**

At the final main study visit, all participants are to stop study treatment and are to be advised to contact their own doctor to discuss the appropriate use of LDL-lowering treatment as part of routine clinical care. During the post-trial period, no study treatment will be issued to participants. However, participants may receive LDL-lowering therapy from their own doctor as part of routine clinical care.

In order to minimize the potential for biased reporting of clinical events, participants and their doctors will not be unblinded to the original treatment allocation routinely. However, when knowledge of the original treatment allocation could materially influence the medical management of a participant, urgent unblinding is available on a 24-hour basis via the Central Coordinating Office (CCO) telephone service. Requests for unblinding will be reviewed urgently, and authorized, by the CCO on-call clinician.

### **3.3. Withdrawal of consent**

Participants are free to withdraw consent for some or all aspects of the study at any time. The decision to withdraw should be put in writing. This written information should specify which aspect(s) of the study consent is being withdrawn: for example, direct contact with the participant, collection of information from non-study doctors or use of routine data sources. (In accordance with FDA guidance, data that have already been collected and incorporated into the study database, including the results of laboratory assays, will continue to be processed.)

### **3.4. Confirmation and Verification of Clinical Events**

The RCCs will seek additional documentation (e.g. hospital notes, brain scan results, autopsy results) only about reports of SAEs that might be importantly relevant to assessment of the safety of the study treatment. Examples include cause of death (e.g. differentiating cancer, cardiovascular, and other causes of death) and type of stroke (e.g. distinguishing haemorrhagic from other forms of stroke). The RCC will be responsible for coordinating the collection of relevant supporting information (with assistance from the LCC, where appropriate), with clinicians based at or overseen by the CCO providing the final assessment. All review and processing of SAEs will be conducted in accordance with the study SOPs and will be blinded to the original study treatment allocation (anacetrapib or placebo).

## 4. REFERENCES

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## 5. Appendix 1 - Anticipated number of first events at end of main study and after an additional 2 years of follow-up

Region	Randomized	At end of main trial			At end of 2 years' post-trial		
		(median >4 years' follow-up)			(median >6 years' follow-up)		
		Major vascular event	Cancer	Death	Major vascular event	Cancer	Death
UK	8381	905	603	637	1274	860	931
Scandinavia	4168	467	250	167	665	363	247
Germany	1529	269	92	80	373	133	118
Italy	1660	193	93	93	273	134	137
North America	6082	1022	438	511	1404	623	745
China	8629	1277	276	483	1785	402	711
<b>Overall</b>	<b>30449</b>	<b>4133</b>	<b>1752</b>	<b>1971</b>	<b>5774</b>	<b>2515</b>	<b>2889</b>

**6. Appendix 2 – Visit Schedule and Procedures**

<b>Task</b>	<b>Activity</b>	<b>6-monthly assessments (by telephone)</b>	<b>Other remote assessments<sup>a</sup> (e.g. web, mail)</b>	<b>Blood sampling</b>	<b>Record linkage<sup>b</sup></b>
Demographics	Check and record contact details	✓	(✓) <sup>a</sup>		
Medication	Record current medication	✓	(✓) <sup>a</sup>		
Safety reporting	Record all serious adverse events	✓	(✓) <sup>a</sup>		
	Remote follow-up using routine data sources				(✓) <sup>b</sup>
Laboratory assessments	Lipids and lipoproteins			(✓) <sup>c</sup>	
	Storage for additional assays <sup>d</sup>			(✓) <sup>c</sup>	

<sup>a</sup> Alternative means of follow-up (e.g. mail, web- or smartphone based methods) may be used in order to ensure thorough, effective and efficient assessment of the effects of anacetrapib

<sup>b</sup> Where feasible, data are to be collected through linkage to available sources of health information, including electronic healthcare records systems, national registries and clinical audit databases.

<sup>c</sup> Blood samples to be collected in a subset of around 5% of surviving participants at a single time-point (subject to separate consent and ethics approval)

<sup>d</sup> Samples to be stored for additional assays (e.g. anacetrapib levels)



**7. Appendix 3 – Feasibility Assessment**

Country	Telephone follow-up			Linkage to routine data		
	Contact information	Serious adverse events	Deaths	Hospitalization	Cancer	Deaths
UK	✓	✓	✓	✓	✓	✓
Norway	✓	✓	✓	✓	✓	✓
Sweden	✓	✓	✓	✓	✓	✓
Denmark	✓	✓	✓	✓	✓	✓
Finland	✓	✓	✓	✓	✓	✓
Germany	✓	✓	✓	x	x	x
Italy	✓	✓	✓	x	x	x
USA	✓	✓	✓	x	x	x
Canada	✓	✓	✓	x	x	x
China	✓	✓	✓	x	x	x

\* Responsible organization: The entity (RCC – Regional Coordinating Centre; or LCC – Local Clinical Centre) responsible for conducting telephone follow-up with participants. Exact arrangements may vary according to local requirements