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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Version History

Version number	Date	Comment
1.0	18 May 2016	Version used for initial 2-year post-trial follow-up period in all regions
2.0	18 May 2020	Updated following completion of initial 2-year post-trial follow-up period to clarify process for further extended follow-up to be undertaken in UK only (all other regions of the trial to be closed)

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,[1] 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,[2-12] including the Heart Protection Study of simvastatin which was conducted by the Clinical Trial Service Unit at University of Oxford.[2]

2. PLAN OF INVESTIGATION

This plan was originally formulated and agreed in May 2016 while the Steering Committee, funders and investigators remained blind to the main trial results. The initial 2-year off-treatment post-trial follow-up period involved all regions of the trial and was completed in April 2019. Further extended follow-up continues for UK participants only. No further follow-up activities will be undertaken in other REVEAL regions.

2.1. Eligibility

All surviving randomized participants will be eligible for the initial 2-year post-trial follow-up. Any subsequent follow-up activity (after April 2019) will be restricted just to UK trial participants.

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.

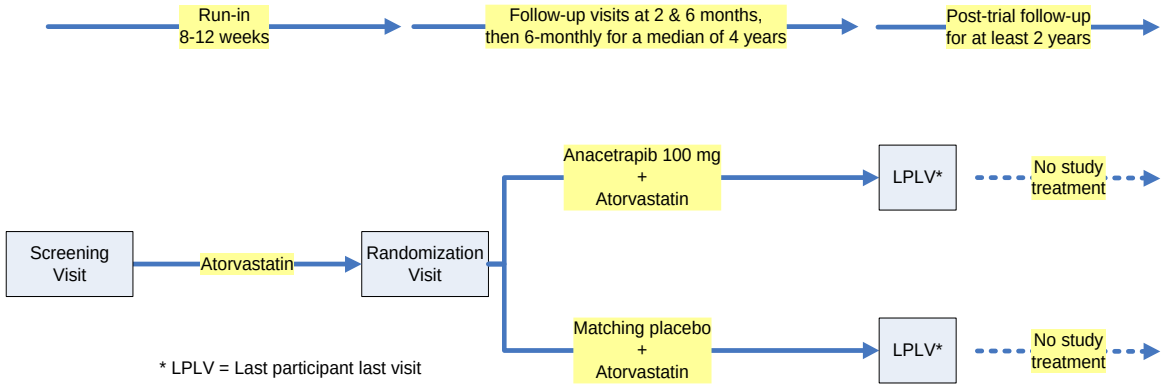

Figure: *Outline of main study and post-trial follow-up schedule*

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 focusing 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) was finalised and published on the trial website in July 2019 (https://www.revealtrial.org/REVEAL%20PTFU%20DAP%2030-07-19%20v1.pdf). At that point the Steering Committee, funders and investigators remained blind to results from the PTFU period.

For the ongoing extended follow-up to be undertaken in UK participants only, the main outcomes of interest will be as listed above. An updated data analysis plan for this extended follow-up will be published on the trial website in advance of any further analyses being undertaken. Subsequent analyses will be planned when median follow-up is at least 10 years (with further analyses possible at around 20 years of median follow-up).

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).
Following the initial 2-year post-trial period involving follow-up of participants from all REVEAL regions (which completed in April 2019), subsequent extended follow-up of UK participants only is planned for at least a further 15 years. No further follow-up is planned in other regions.

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 during the initial 2-year post-trial period was primarily 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). For the extended follow-up (beyond 2 years) in the UK information will be collected by means of linkage to routine medical databases such as those managed by NHS Digital and equivalent organisations in the devolved nations. 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 (initial 2-year post-trial period only)

In all regions, follow-up assessments were 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 were checked. Details of all SAEs were 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 was not possible, follow-up information could be collected through discussion with a relative or carer, the participant's routine physician, or through review of medical records. All assessments were 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. For example, in the UK information will be sought from medical databases (such as those managed by NHS Digital and equivalent organisations in the devolved nations) on all hospital admissions, deaths and cancers. This data linkage will provide the primary source of information for the extended follow-up to be undertaken in the UK only.

3.2. Study Treatment and Unblinding

At the final main study visit, all participants were to stop study treatment and 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 and the additional extended follow-up period in the UK 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

During the initial 2-year post-trial follow-up period, the RCCs were to 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). Each RCC was 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 were conducted in accordance with the study SOPs and blinded to the original study treatment allocation (anacetrapib or placebo).

During the extended follow-up period (UK only), SAE information will be provided by data linkage to relevant routine medical databases, such as those managed by NHS Digital and equivalent organizations. No additional confirmation and verification of events will be performed after the initial 2-year post-trial follow-up period.

4. ADMINISTRATIVE DETAILS

REVEAL was designed by the independent investigators at the Clinical Trial Service Unit (CTSU) at Oxford University in collaboration with the TIMI Study Group based at Brigham Women's Hospital, Harvard Medical School, Boston, and with Merck. The University of Oxford acts as the trial Sponsor worldwide. Merck provided funding for the design and overall conduct of the study. This funding covered the main trial and the initial 2-year post-trial follow-up period. The costs of the additional extended follow-up (UK only) will be covered by Oxford with no additional funding by Merck.
During the main study and throughout the initial 2-year post-trial follow-up period the responsibilities for safety reporting activities were agreed between Oxford and Merck and described in a study SOP ("Exchange of Adverse Experience Information between the University of Oxford and Merck Sharp & Dohme Corp"). Following the initial 2-year post-trial follow-up period, a formal End of Trial will be declared for all regions participating in REVEAL other than the UK. Merck have also advised the US FDA of a formal withdrawal of the Investigational New Drug Application (IND).

For the extended follow-up period (to be undertaken in the UK only) all trial responsibilities, including regulatory safety reporting requirements to the MHRA, and any required future updates to the clinicaltrials.gov record for REVEAL will be assumed by Oxford. Merck will have no further ongoing responsibilities within REVEAL. As agreed by the MHRA, the Annual Progress Report will serve as the DSUR for the annual submission provided by Oxford to MHRA for the REVEAL trial. A full DSUR is not required. Merck will no longer be involved in the production of any annual reports and the data provided will be trial specific.

The independent Steering Committee was responsible for drafting the main reports from the study and for review of any other reports. 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).

5. REFERENCES

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6. 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** (median >4 years' follow-up)			**At end of 2 years' post-trial** (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
Overall	**30449**	**4133**	**1752**	**1971**	**5774**	**2515**	**2889**

7. Appendix 2 – Visit Schedule and Procedures during initial 2-year post-trial follow-up period only

Task	Activity	6-monthly assessments (by telephone)	Other remote assessments[a] (e.g. web, mail)	Blood sampling	Record linkage[b]
Demographics	Check and record contact details	✓	**(✓)[a]**		
Medication	Record current medication	✓	**(✓)[a]**		
Safety reporting	Record all serious adverse events	✓	**(✓)[a]**		
	Remote follow-up using routine data sources				**(✓)[b]**

[a] 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

[b] 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.