Effects of Lomitapide on Carotid and Aortic Atherosclerosis in Patients Treated with Lomitapide in Usual Care

Protocol Number:	AEGR-733-028
Version / Date	Final Protocol: Version 1.7/ 2 Apr 2014
Name of Test Drug:	Lomitapide US: NDA 203858
Indication:	Adult patients with Homozygous Familial Hypercholesterolaemia (HoFH)
Sponsor:	Aegerion Pharmaceuticals, Inc. 101 Main Street, Suite 1850 Cambridge, MA 02142 1-617-500-7867
Responsible Medical Officer:	Helen Phillips, MD VP Medical Affairs, EMEA Telephone: **+44 (20) 8622 4100** Fax: **+44 (20) 8622 3200**

SPONSOR'S APPROVAL

This protocol has been approved by Aegerion Pharmaceuticals, Inc.

Sponsor's Signatory:

Dr Helen Phillips MD

Vice President, Medical Affairs EMEA

Signature: HSPhillips **Date:** 9th April 2014

INVESTIGATOR AGREEMENT

I have read this Aegerion Pharmaceuticals, Inc. Protocol No. AEGR-733-028:

Effects of Lomitapide on Carotid and Aortic Atherosclerosis in Patients Treated with Lomitapide in Usual Care

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representatives.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical/regulatory review of the study, without written authorisation from Aegerion Pharmaceuticals, Inc. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with ICH (International Conference on Harmonization) guidelines on GCP (Good Clinical Practice) and with the applicable regulatory requirements.

I understand that Aegerion Pharmaceuticals, Inc. may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to Aegerion Pharmaceuticals, Inc.

Signature:_____ **Date:**_____

Printed Name: _____

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Radiology
AE	adverse event
apo AI	apolipoprotein A-I
apo B	apolipoprotein B
Apo C-III	apolipoprotein C-III
AE(s)	adverse event(s)
BMI	body mass index
CFR	Code of Federal Regulations
CIMT	carotid intimal medial thickness
CTCAE	common terminology criteria for adverse events
DMP	data management plan
DICOM	digital imaging and communications in medicine
EC	Ethics Committee
eCRF	electronic case report form
EDC	electronic data capture
EU	European Union
FTP	file transfer protocol

Abbreviation	Definition
GCP	Good Clinical Practice
GVP	Good Pharmacovigilance Practices
HDL-C	high-density lipoprotein cholesterol
HIPAA	Health Insurance Portability and Accountability Act
HoFH	homozygous familial hypercholesterolaemia
HOMA	homeostasis model assessment
hs-CRP	high sensitivity C reactive protein
ICH	International Conference on Harmonization
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IL-6	interleukin - 6
IRB	Institutional Review Board
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
LOWER	Lomitapide Observational Worldwide Evaluation Registry
Lp (a)	lipoprotein (a)

Abbreviation	Definition
Lp-PLA2	Lipoprotein-associated phospholipase A2
MACE	major adverse cardiovascular events
MAH	Marketing Authorisation Holder
MeDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MITT	modified intent-to-treat
MRI	magnetic resonance imaging
MTP	microsomal triglyceride transfer protein
NC	North Carolina
NCI	National Cancer Institute
Non-HDL-C	non-high-density lipoprotein cholesterol
NSAR	non-serious adverse reaction
NMR	nuclear magnetic resonance
PD	proton density
PI	Primary investigator
PP	per-protocol
RMP	Risk Management Plan
SAE	serious adverse event

Abbreviation	Definition
SAP	statistical analysis plan
sE-selectin	soluble E-selectin
sICAM-1	soluble inter-cellular adhesion molecule – 1
sIL-6 receptor	Soluble interleukin-6 receptor
SOPs	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
sVCAM-1	Soluble vascular cell adhesion molecule – 1
TC	total cholesterol
TG	Triglycerides
TNF-α	tissue necrosis factor-alpha
TVWA	total vessel wall area
UBC	United BioSource Corporation
US	United States
VLDL	very-low-density lipoprotein
VLDL-C	very-low-density lipoprotein cholesterol

2. RESPONSIBLE PARTIES

Participating countries in this sub-study will include, but are not limited to, countries in North America and the European Union (EU).

The list of participating physicians is available upon request.

The Marketing Authorisation Holder (MAH) and sponsor (Aegerion Pharmaceuticals) contact persons are Ms. Angelique Winzenrieth, EU and Ms. Martha J. Carter, United States (US).

3. ABSTRACT

3.1 Title of Protocol

Effects of Lomitapide on Carotid and Aortic Atherosclerosis in Patients Treated with Lomitapide in Usual Care.

3.2 Rationale and Background

Lomitapide has been approved in the US and authorised in the EU for treatment of adult patients with homozygous familial hypercholesterolemia (HoFH). Due to the rarity of the disease, it is not feasible to study the potential effects of lowering LDL-C with lomitapide on the incidence of cardiovascular outcomes such as myocardial infarction, stroke and death from cardiovascular causes. Elevated LDL-C is generally accepted as a major risk factor for the onset and progression of atherosclerosis, and is implicated in the pathophysiological process underlying arterial wall atheroma. Patients with HoFH experience aggressive and premature vascular atherosclerosis, and lowering LDL-C is the primary goal of treatment.

Magnetic resonance imaging (MRI) studies in patients with established coronary and carotid atheroma have demonstrated that LDL-C reduction with statin therapy has resulted in a significant reduction in atheroma burden (Hayashi et al., 2010; Corti 2001; Migrino, et al., 2011). This sub-study will examine the hypothesis that LDL-C reduction with lomitapide results in regression and/or stabilisation of atheroma in the carotid artery and aorta. Such an effect, if demonstrated, would provide meaningful clinical data based on an 'intermediate outcome' that provides a biologically plausible link between LDL-C reduction and expectation of a reduction in the incidence of major cardiovascular events in this patient population.

3.3 Research Question and Objectives

The study is designed to evaluate the effects of lomitapide on carotid and aortic atherosclerosis in patients treated with lomitapide in usual clinical practice and who are enroled in the Lomitapide Observational Worldwide Evaluation Registry (LOWER).

Primary Objective:

- To assess the changes in atheroma burden as reflected by average carotid vessel wall area on MRI scanning following two years of treatment with lomitapide compared to baseline.

Secondary Objectives:

- To assess the changes in atheroma burden as reflected by changes in average aortic vessel wall area, average aortic and carotid vessel lumen area, total vessel area, wall thickness, normalized wall index and standard deviation of wall thickness on MRI following two years of lomitapide treatment compared to baseline.
- To assess the changes in atheroma burden as reflected by changes in average aortic and carotid vessel wall area, lumen area, total vessel area, wall thickness, normalized wall index and standard deviation of wall thickness following one year and five years of lomitapide treatment compared to baseline.
- To assess changes in LDL-C and other lipoproteins at one, two and five years of lomitapide treatment compared to baseline and the correlation of these laboratory evaluations with the change from baseline in MRI parameters of carotid and aortic atheroma.

Exploratory Analyses:

- To evaluate major plaque compositional features including the necrotic lipid area, fibrous cap thickness and calcium area. These plaque composition analyses will be performed at imaging time points if sufficient data exist with respect to both the size and frequency of the plaques.
- To assess changes in markers of inflammatory and cardiovascular processes at one, two, and five years of lomitapide treatment compared to baseline, and to correlate these changes with the change from baseline in MRI parameters of carotid and aortic atheroma.

3.4 Study Design

This is a multi-centre long-term open-label non-comparative study to assess changes in carotid and aortic atherosclerosis in patients being treated with lomitapide. Patients from countries in the EU, the US and Canada who are being treated with lomitapide and are enroled in LOWER, will be invited by the LOWER enroling physician to participate in this substudy. Each LOWER enroling physician will be instructed to invite consecutive patients who meet the eligibility criteria. Sites will be asked to keep a log of the patients invited identified only by Identification (ID) number, indicating those who declined participation or did not meet eligibility criteria. Patients who agree to participate will be referred to a regional study site to further assess eligibility. The regional study sites selected will have the resources to perform all study related procedures including patient screening and enrolment, MRI imaging, blood draws and processing, patient follow-up, and data storage and transfer. These sites will be selected on a regional basis and may include sites that are also enroled in LOWER.

Upon enrolment in the sub-study, patients will immediately have a baseline integrated vascular MRI assessment and laboratory tests. If the patient is already being treated with lomitapide, a baseline MRI must occur within 3 months of initiating treatment. Additional assessments will be performed at years one, two and five after enrolment. All MRI images will be sent to a central Imaging Core Laboratory for qualitative and quantitative image analysis.

3.5 Sample Size

Based on published information from a randomized, placebo-controlled study on change in carotid vessel parameters as assessed by MRI (Fayad, et.al, 2011), the standard deviation of percent change from baseline to 24 months in carotid vessel wall area was estimated to be 22%. Detection of a 10% change from baseline to 24 months in carotid vessel wall area, at a two-sided α-level of 0.05 with 80% power, requires 40 evaluable patients. In order to obtain 40 evaluable patients at the two-year primary endpoint, at least 57 patients with a baseline readable MRI will be enroled. The 57 patients to be enroled accounts for a dropout rate of 15% over the two-year period and a 15% unreadable/unusable MRI rate.

Based on the experience of the central Imaging Core Laboratory in a study of 130 enroled subjects, only 112 had matched images of adequate quality across all time points over a 2

year period, leading to the assumption of a 15% unreadable or unusable MRI rate (Fayad, et.al, 2011).

After 20 evaluable patients have two-year MRI evaluations, a sample size re-estimation will be performed. Additional information about this analysis is described in Section 8.5.5.

3.6 Eligibility Criteria

3.6.1 Inclusion Criteria

- Adult patients (age ≥18 years) who are enroled in LOWER
- Patients who are either:

  Initiating treatment with lomitapide at the time of enrolment in this study,

  or

  Initiated treatment with lomitapide within 3 months prior to enrolment in this study

- Patients who have the ability to understand the requirements of the study, and provide written informed consent to comply with the requirements for periodic MRI assessments and laboratory monitoring.

3.6.2 Exclusion Criteria

- Patients with a prior history of carotid angioplasty, carotid stenting, or carotid atherectomy
- Patients with a contraindication to MRI examination (i.e., brain aneurysm, implanted neural stimulator, implanted cardiac pacemaker, pacemaker wires or defibrillator, prosthetic heart valves, cochlear implant, ocular foreign body, or other implanted body)
- Patients who have undergone a coronary stenting procedure in the preceding three weeks prior to enrolment
- Patients prone to claustrophobia or known anxiety disorders that will interfere with the ability to acquire quality MRI scans

- Patients with an implanted insulin pump
- Patients with metal shrapnel or bullet wounds
- Patients with a body mass index (BMI) > 40 kg/m^2 (since it may be difficult to position comfortably with the MRI scanner)
- Patients who work with metal lathes (unless an orbit x-ray performed prior to the enrolment MRI scan has been done to rule out metal fragments in the eye)

3.7 Data Collection

Data will be collected through an electronic data collection (EDC) system. The database will be housed at the Study Coordinating Centre (SCC) on a physically and logically secure computer server maintained by the SCC in accordance with written security policies. Patient identifying information will not be included in the database, but must be maintained in a secure fashion at the treating physician's site.

For patients enroled in this study, all of their individual data collected in LOWER that are relevant to this study will be transferred into the study database as described in a separate Data Management Plan (DMP). Therefore, patient demographic data, medical history, and lomitapide exposure data will not be collected in this study.

Results of the MRI imaging will be electronically transferred from the regional site to the central Imaging Core Laboratory. After the central Imaging Core Laboratory completes their assessment of the data, the results will be transferred to the SCC's database on a periodic basis.

3.8 Statistical Methods

A formal statistical analysis plan (SAP) will provide complete details of all statistical analysis and data presentation.

4. AMENDMENTS AND UPDATES

None

5. MILESTONES

MILESTONE	PLANNED DATE
Start of data collection	01 March 2014
End of data collection	01 October 2019
Annual reports	Every year starting on 31 January 2015 (as per agreed Risk Management Plan (RMP))
Registration in the EU PAS register	To Be Determined
Final report of study results	01 December 2019

6. RATIONALE AND BACKGROUND

HoFH is a serious, life-threatening disease caused by mutations in both alleles that encode the low-density lipoprotein receptor (LDLR), or proteins known to affect LDLR functionality leading to severe impairment or complete absence of LDLR function. LDLR dysfunction results in four- to ten-fold elevations in LDL-C where patients develop premature atherosclerosis and coronary heart disease and can have cardiovascular events and complications such as myocardial infarction (MI) or aortic stenosis in the first decade of life. The primary goal of therapy for patients with HoFH involves controlling hypercholesterolemia and thereby delaying the progression of cardiovascular disease. Unfortunately, patients with HoFH are minimally responsive to conventional lipid lowering medications, which work directly or indirectly through up regulation of the LDLR. Therefore, in patients with HoFH, effects from other classes of lipid lowering agents (e.g., statins, bile acid sequestrants, and cholesterol absorption inhibitors) are limited and almost always insufficient.

Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor treatment for patients with HoFH. MTP plays a key role in the assembly of apolipoprotein B (apo B)-containing lipoproteins in the liver and intestine. Inhibition of MTP reduces secretion of very-low-density lipoprotein (VLDL) and chylomicrons and thus reduces circulating concentrations of plasma cholesterol. Thus, lomitapide has a mechanism of action that is independent from the LDLR.

In the HoFH population, there is a high burden of atherosclerosis and cardiovascular complications. Lipid-lowering therapy is associated with delayed cardiovascular events and prolonged survival in this patient population (Raal et al. 2011). However, there are no large randomised controlled clinical outcome trials in patients with HoFH treated with lomitapide, and data for HoFH are extrapolated from studies in different (combined) populations. Despite the limited data, there is an expectation of a possible cardiovascular benefit with the observed LDL-C lowering effect of lomitapide. However, the long term clinical benefit of lomitapide has not yet been shown. Collection of long term cardiovascular outcome data can be achieved indirectly by long-term monitoring (~ five years) of vascular outcomes using appropriate and scientifically validated imaging techniques or other vascular surrogate endpoints such as endothelial function.

Aegerion is conducting a postmarketing observational study, LOWER, to further characterize the outcomes of patients treated with lomitapide. Although LOWER will evaluate long-term survival and will collect data on major adverse cardiac events (MACE) occurring in patients treated with lomitapide, it is not possible to require MRI imaging in an observational study that follows patients as per usual care. A controlled, randomized study with hard clinical endpoints to confirm the cardiovascular benefit of lomitapide would be difficult or even unethical.

Magnetic resonance imaging (MRI) studies in patients with established coronary and carotid atheroma have demonstrated that LDL-C reduction with statin therapy has resulted in a significant reduction in atheroma burden (Hayashi et al., 2010; Corti 2001; Migrino 2011). Therefore, active long-term monitoring of cardiovascular benefits based on surrogate endpoints of vascular outcomes using MRI to measure atherosclerosis burden is planned as a sub-study of LOWER. At least 57 patients who are enroled in LOWER and are being treated at sites participating in this study will be invited to participate. This study will evaluate the effect of lomitapide treatment for up to five years on carotid and aortic plaque burden measured by integrated vascular MRI. This study will examine the hypothesis that LDL-C reduction with lomitapide results in regression and/or stabilisation of atheroma in the carotid artery and aorta. Such an effect, if demonstrated, would provide meaningful clinical data based on an 'intermediate outcome' that provides a biologically plausible link between LDL-C reduction and expectation of a reduction in the incidence of major cardiovascular events in this patient population.

6.1 Appropriateness of Efficacy Assessments

There is strong evidence demonstrating the correlation between the effect of slowing or regression of arterial plaque burden by various therapeutic interventions with the reduction in atherothrombotic ischemic events in patients with coronary heart disease. High-resolution MRI has proven feasible for non-invasive carotid artery imaging to accurately measure the thickening of vessel wall (Corti, et al., 2001; Lee, et al., 2008), and demonstrated a strong correlation between the MRI-based carotid total vessel wall area (TVWA) and maximal wall thickness and the standard carotid intimal medial thickening (CIMT) measured by B-mode echo (Mani et al., 2006). In addition, MRI is superior to CIMT measurement allowing direct visualization of the bifurcation region of the carotid artery with greater vessel wall thickness, whereas CIMT usually only

evaluates the sections of carotid artery above or below the bifurcation with smaller vessel wall thickness. MRI is also the modality of choice for visualizing atherosclerotic disease in the ascending, descending thoracic and abdominal aorta. Furthermore, MRI measurements of plaque burden have now been used in multicentre trials that use imaging as an endpoint to evaluate atherosclerotic plaque burden (Fayad et al., 2011).

7. RESEARCH QUESTION AND OBJECTIVES

The study is designed to evaluate the effects of lomitapide on carotid and aortic atherosclerosis in patients treated in clinical practice by collecting direct evidence of the antiatherosclerotic effect of lomitapide on vessel wall morphology.

The primary objective of this study is:

- To assess the changes in atheroma burden as reflected by average carotid vessel wall area on MRI scanning following two years of treatment with lomitapide compared to baseline.

Secondary objectives of this study are:

- To assess the change in atheroma burden as reflected by changes in average aortic vessel wall area, average aortic and carotid vessel lumen area, total vessel area, wall thickness, normalized wall index and standard deviation of wall thickness on MRI following two years of lomitapide treatment compared to baseline.
- To assess the change in atheroma burden as reflected by changes in average aortic and carotid vessel wall area, lumen area, total vessel area, wall thickness, normalized wall index and standard deviation of wall thickness following one year and five years of lomitapide treatment compared to baseline.
- To assess changes in LDL-C and other lipoproteins at one, two and five years of lomitapide treatment compared to baseline and the correlation of these laboratory evaluations with the change from baseline in MRI parameters of carotid and aortic atheroma.

Exploratory analyses of this study are:

- To evaluate major plaque compositional features including the necrotic lipid area, fibrous cap thickness and calcium area. These plaque composition analyses will be performed at imaging time points if sufficient data exist with respect to both the size and frequency of the plaques.

- To assess changes in markers of inflammatory and cardiovascular processes at one, two, and five years of lomitapide treatment compared to baseline, and to correlate these changes with the change from baseline in MRI parameters of carotid and aortic atheroma.

8. RESEARCH METHODS

8.1 Study Design

This is a multi-centre long-term open-label non-comparative study to assess changes in carotid and aortic atherosclerosis in patients being treated with lomitapide. Patients from the European Union (EU), the United States (US) and Canada who are being treated with lomitapide and are enroled in LOWER will be invited by the LOWER enroling physician to participate in this substudy. Each LOWER enroling physician will be instructed to invite consecutive patients who meet the eligibility criteria. Sites will be asked to keep a log of the patients invited identified only by Identification (ID) number, indicating those who declined participation or did not meet eligibility criteria. Patients who agree to participate will be referred to a regional site to further assess eligibility.

The regional study sites selected will have the resources to perform all study related procedures including patient screening and enrolment, MRI imaging, blood draws and processing, patient follow-up, and data storage and transfer. These sites will be selected on a regional basis and may include some sites that are also enroled in LOWER.

After the regional site confirms patient eligibility and the patient provides informed consent for the vascular sub-study, the patient will be scheduled to have a baseline integrated vascular MRI assessment as well as laboratory assessments. If the patient is already being treated with lomitapide, a baseline MRI must occur within three months of initiating treatment. Additional MRI assessments will be performed at years one, two and five after enrolment. All MRI images will be sent to a central Imaging Core Laboratory for qualitative and quantitative image analysis.

8.2 Setting

The study will include, but not be limited to, regional study sites in the EU, the US and Canada. Patients to be recruited for this study are those who are enroled in LOWER from these geographic areas. Since lomitapide was first approved in the US, US sites and patients are expected to be the first to be enroled in LOWER. In order to have a wide representation of countries and patients in this study, no more than 50% of patients will be enroled from the US. Once a LOWER patient has indicated he/she is interested in participating in this sub-study, the SCC will work with the central Imaging Core Laboratory to identify the regional study site where the patient can be directed to

participate in this sub-study. Integrated vascular MRI assessments must be done at regional study sites identified for this sub-study that are pre-qualified and trained to perform the required testing. All study-related requirements will occur at the regional study site.

8.2.1 Patient Eligibility

The target study population will include patients for whom the decision to prescribe commercially available lomitapide has been made and who have been enroled in LOWER. Consecutive patients within each prescriber's practice who are enroled in LOWER and meet the enrolment criteria for this sub-study and provide informed consent will be invited to enrol into this sub-study and will be followed at the specified intervals at the regional study site.

8.2.1.1 Inclusion Criteria

- Adult patients (age ≥18 years) who are enroled in LOWER
- Patients who:

  Are initiating treatment with lomitapide at the time of enrolment in this study,

  or

  Have initiated treatment with lomitapide within 3 months prior to enrolment in this study

- Patients who have the ability to understand the requirements of the study, and provide written informed consent to comply with the requirements for periodic MRI assessments.

8.2.1.2 Exclusion Criteria

- Patients with a prior history of carotid angioplasty, caotid stenting, or carotid atherectomy
- Patients with a contraindication to MRI examination (i.e., brain aneurysm, implanted neural stimulator, implanted cardiac pacemaker, pacemaker wires or defibrillator, prosthetic heart valves, cochlear implant, ocular foreign body, or other implanted body)

- Patients who have undergone a coronary stenting procedure in the preceding three weeks prior to enrolment
- Patients prone to claustrophobia or known anxiety disorders that will interfere with the ability to acquire quality MRI scans
- Patients with an implanted insulin pump
- Patients with metal shrapnel or bullet wounds
- Patients with a body mass index (BMI) > 40 kg/m^2 (since it may be difficult to position comfortably with the MRI scanner)
- Patients who work with metal lathes (unless an orbit x-ray performed prior to the enrolment MRI scan has been done to rule out metal fragments in the eye)

8.2.2 Regional Study Site Qualifications

In the US, only individuals that are not on the FDA debarred list will be selected for participation. In addition to the FDA debarred list, other lists will be checked for investigators that will be excluded from participation (i.e. Disqualified/Restricted/Assurances List, Notice of Initiation of Disqualification Proceedings and Opportunity to Explain, Public Health Service listing).

For countries outside the US (e.g., EU), comparable lists might be prohibited according to local law. In these countries, the above mentioned evaluation will be performed as applicable.

In order for a regional study site to become qualified to provide MRI imaging for this study, it must meet the following criteria:

- Agree to follow the study imaging protocol
- Receive training
- Perform an acceptable test scan
- Be certified to meet the specifications for the study by a representative from the central Imaging Core Laboratory prior to performing study-related imaging
- Perform study MRIs on a 1.5T or 3 Tesla MR scanner made by Siemens, General Electric, or Philips

- Have, or be approved to purchase and installed by the first time patient is enroled, the required equipment as described below:
    - Aorta: Phased array body/cardiac coil (of 4 channels or more) or equivalent coil determined in consultation with the central Imaging Core Laboratory for imaging of the aorta (anterior and posterior elements)
    - Carotid: Bi-lateral 4- or more channel multi-channel phased array carotid coil or equivalent coil determined in consultation with the central Imaging Core Laboratory
    - Cardiac gating and pulse gating system compatible with respective vendor platform
    - Capability to transfer imaging data by Secure FTP (file transfer protocol) to a location external to site firewall or send the images to the central Imaging Core Laboratory by courier

In addition, the regional study site must perform all other activities associated with being an investigational site, including patient screening and enrolment, MRI imaging, blood draws and processing, patient follow-up, and data storage and transfer.

8.3 Variables

8.3.1 Patient Data Collection

For patients enroled in this substudy, all of their relevant individual data collected in LOWER will be included in the study database. The relevant data points will be transferred into the study database as described in a separate data management plan (DMP). Therefore, patient demographic data, medical history, and lomitapide exposure data will not be necessary to collect again in this study. A Central Laboratory will be used for this study.

8.3.1.1 Regional Study Site Enrolment Visit

At the LOWER enrolment visit, after the patient has provided written consent to participate in LOWER, the LOWER enroling physician (or designee) will provide an overview of this vascular imaging study to each patient. The LOWER enroling physician will notify the SCC of interested patients. The SCC will then notify the regional study

site. The regional study site will contact the patient to assess eligibility and obtain informed consent. For patients who are not located near the regional site, verbal informed consent will be obtained first by phone with written informed consent obtained at the baseline visit, prior to any procedures being performed. Enroled patients will have a baseline MRI scan at the regional study site prior to initiating lomitapide therapy or within three months after initiating lomitapide therapy.

The following will be collected at the enrolment visit:

- Date of written informed consent
- Confirmation of eligibility criteria
- Laboratory tests (lipoprotein, inflammatory and cardiovascular biomarkers)
    - Lipoprotein biomarkers
        - Total cholesterol (TC)
        - High density lipoprotein (HDL-C)
        - Low density lipoprotein (LDL-C)
        - Triglycerides (TG)
        - Apolipoprotein B (apo B)
        - Apolipoprotein A-I (apo AI)
        - Lipoprotein (a) (Lp(a))
        - Apolipoprotein C-III (Apo C-III)
        - LDL sub-fractions using nuclear magnetic resonance (NMR) technology
    - Inflammatory and cardiovascular biomarkers
        - High sensitivity C reactive protein (hs-CRP)
        - Serum amyloid A (SAA)
        - Soluble Inter-cellular Adhesion Molecule-1 (sICAM-1)
        - Interleukin 6 (IL-6)
        - Lipoprotein Associated Phospholipase 2 (LpPLA2)
        - Soluble Vascular Cell Adhesion Protein 1 (sVCAM-1)
        - Soluble E-selectin (sE-selectin)

- Fasting glucose and insulin and calculate HOMA (Homeostasis Model Assessment)
- Baseline MRI

8.3.1.2 Baseline MRI Scan

In order to be eligible for this study, a patient must have his/her baseline MRI scan within three months after initiating therapy with lomitapide. The baseline MRI should ideally be scheduled as soon as possible after enrolment and prior to initiation of lomitapide therapy.

Patients must have a baseline MRI scan that is deemed evaluable with an acceptable image quality of carotid arteries (both left and right carotid arteries) and aorta as determined by the central Imaging Core Laboratory in order to proceed to the follow up visits. All MRI scans must be immediately sent to the central Imaging Core Laboratory for qualitative image analysis. The central Imaging Core Laboratory will provide a rapid turnaround (within one week) of the image quality evaluation. The image quality evaluation will be sent to the regional study site as well as to the SCC so that, in the event that a repeat MRI is required, the site can contact the patient to return for additional scans.

Each regional study site will provide data to the central Imaging Core Laboratory following the guidelines set forth in the MRI Imaging Facility Charter (Section 8.3.2). The central Imaging Core Laboratory will notify the regional study site and the SCC that the MRI is acceptable, or if a repeat MRI is required. The SCC will request that the regional study site Investigator or his/her designee either complete the notification form if the testing was completed or contact the patient and schedule a repeat MRI. An MRI image deemed acceptable by the central Imaging Core Laboratory must be confirmed within three months of the patient starting lomitapide treatment. If delays result in the imaging being done outside of the three month window since starting lomitapide treatment, the patient will not be eligible to continue in the study.

The central Imaging Core Laboratory will transfer analysed results to SCC in a pre-specified format and time-frame as specified in the DMP.

8.3.1.3 Follow-up MRI Imaging Visits

Patients must receive the required MRI scans at one, two and five years after enrolment. Scans should be obtained within a window of -1 month- 2+ months around these data collection time points. If the MRI is not performed within the specified time frame (-1 month-2+ months of the estimated date for the one, two and five year MRIs), then the SCC will notify the regional study site and this will be documented as a protocol deviation. Regional study site staff will assist the patient in scheduling an appointment for the MRI imaging.

8.3.1.4 Patient Follow-up for Laboratory Assessments

Blood for the laboratory assessments required for this study should be collected by the regional study site at the time of the patient's MRI scan at one, two, and five years after enrolment in the study (-1 month-2+months). Blood will be processed as described in a separate laboratory manual and will be sent to the Central Laboratory for analysis.

The specific laboratory assessments for lipoprotein, inflammatory and cardiovascular biomarkers are:

<u>Lipoprotein biomarkers</u>

- Total cholesterol (TC)
- High density lipoprotein (HDL-C)
- Low density lipoprotein (LDL-C)
- Triglycerides (TG)
- Apolipoprotein B (apo B)
- Apolipoprotein A-I (apo AI)
- Lipoprotein (a) (Lp(a))
- Apolipoprotein C-III (Apo C-III)
- LDL sub-fractions using NMR technology

<u>Inflammatory and cardiovascular biomarkers</u>

- High sensitivity C reactive protein (hs-CRP)
- Serum amyloid A (SAA)

- Soluble Inter-cellular Adhesion Molecule-1 (sICAM-1)
- Interleukin 6 (IL-6)
- Lipoprotein Associated Phospholipase 2 (LpPLA2)
- Soluble Vascular Cell Adhesion Protein 1 (sVCAM-1)
- Soluble E-selectin (sE-selectin)
- Soluble interleukin-6 receptor (sIL-6 Receptor)
- Fasting glucose and insulin and calculate HOMA (Homeostasis Model Assessment)

8.3.1.5 Patient Withdrawal

Patients may withdraw from the study at any time at their own request. They may also be withdrawn at any time at the discretion of the regional study site Investigator or Sponsor if the patient's baseline MRI scan is deemed unreadable or for administrative reasons.

Patients who inform their regional study site Investigator of their intent to prematurely withdraw from the study will be asked to have a final MRI scan prior to withdrawal (unless the most recent MRI was done within three months prior to the withdrawal from the study). The regional study site Investigator will record the reason for withdrawal on the End of Study form.

Sites may not enrol additional patients to replace those who withdraw early from the study.

The study may retain and continue to use any data collected before withdrawal of consent in accordance with the original patient consent form.

8.3.1.6 Discontinuation of Lomitapide

Lomitapide may be discontinued at the request of the patient and his/her treating physician at any time during the study. If the patient discontinues lomitapide treatment, then he/she will be encouraged to have an MRI performed if the most recent MRI was more than three months prior to discontinuation of lomitapide, and to have MRI scans at approximately one and two years after discontinuing lomitapide. The Study SCC will remind the regional study site two months prior to the expected MRI dates so that the patient can be scheduled for the imaging.

8.3.2 MRI Imaging Facility Charter

A Charter will be developed by the central Imaging Core Laboratory to provide details on the imaging processes at the regional study site and at the central Imaging Core Laboratory. The guidelines set forth in the MRI Imaging Facility Charter include the following:

- MRI protocol which will describe the requirement specifications for imaging
- Image acquisition at the various sites including site qualification, acquisition methodology as well as methods of transfer of imaging data to the central Imaging Core Laboratory
- The image interpretation and analysis at the central Imaging Core Laboratory
- The central Imaging Core Laboratory systems validation procedures and documentation

8.3.3 Steering Committee

A Steering Committee will be established prior to initiation of the sub-study and will include a subset of the members of the LOWER Steering Committee such as clinicians and scientists with expertise in HoFH, cardiology, and biostatistics. The Steering Committee will also include a representative from the central Imaging Core Laboratory. The Steering Committee will be responsible for reviewing the sub-study data over time and making recommendations to Aegerion regarding the study conduct, as well as assist in study execution and interpretation and in publication planning.

8.4 Study Size

Based on published information from a randomized, placebo-controlled study on change in carotid vessel parameters as assessed by MRI (Fayad, et.al, 2011), the standard deviation of percent change from baseline to 24 months in carotid vessel wall area was estimated to be 22%. Detection of a 10% change from baseline to 24 months in carotid vessel wall area, at a two-sided α-level of 0.05 with 80% power, requires 40 evaluable patients. In order to obtain 40 evaluable patients at the two-year primary endpoint, at least 57 patients with a baseline readable MRI will be enroled. The 57 patients to be enroled accounts for a dropout rate of 15% over the two-year period and a 15% unreadable/unusable MRI rate.

After 20 evaluable patients have two-year MRI evaluations, a sample size re-estimation will be performed only if the conditional power of the Z-test statistic falls within the promising zone as defined by Mehta and Pocock (Mehta et. al., 2011). Further information regarding this analysis (including maximum allowable sample size) is described in Section 8.5.5. If the conditional power does not fall within the promising zone, no sample size re-estimation will be performed and the study will continue as planned (Mehta, et.al, 2011).

Should patient enrolment be much lower than anticipated, Aegerion Pharmaceuticals will propose additional measures to increase patient enrolment including opening the sub-study to other countries or regions if necessary.

8.5 Statistical Methods

A formal statistical analysis plan (SAP) will provide complete details of all statistical analyses and data presentation.

8.5.1 Efficacy Endpoints

The primary objective of the study is to assess the change in carotid atheroma as reflected by carotid vessel wall area on MRI scanning following two years of treatment with lomitapide. The endpoint used to address this objective will be the percent change in carotid vessel wall area from baseline to two years on lomitapide therapy, where percent change is calculated as 100*{WA(24)-WA(0)}/WA(0). WA(x) denotes wall area at either baseline (x=0) or 24 months (x=24). The mean area obtained from the left and right carotid arteries will be used in the primary analysis; additional analyses will consist of individual results from the left and right arteries separately. Refer to Section 8.5.2 for the derivation of wall area measurements.

The secondary objectives of the study are:

- To assess the changes in atheroma burden as reflected by changes in average aortic vessel wall area, average aortic and carotid vessel lumen area, total vessel area, wall thickness, normalized wall index and standard deviation of wall thickness on MRI following two years of lomitapide treatment compared to baseline.

- To assess the changes in atheroma burden as reflected by changes in average aortic and carotid vessel wall area, lumen area, total vessel area, wall thickness, normalized wall index and standard deviation of wall thickness following one year and five years of lomitapide treatment compared to baseline.
- To assess changes in LDL-C and other lipoproteins at one, two and five years of lomitapide treatment compared to baseline and the correlation of these laboratory evaluations with the change from baseline in MRI parameters of carotid and aortic atheroma.

8.5.2 Efficacy Measurements

Carotid and aortic plaque burden will be measured as follows: The fat-suppressed black-blood fast spin echo proton density or T2 weighted images will be analyzed with a semi-automated algorithm to segment the inner lumen boundary and outer vessel wall area at the adventitial layer. Subtraction of the lumen area from the outer vessel wall area provides the vessel wall area. Mean carotid vessel wall area is obtained from the analysis of the serial images that cover the bilateral common carotid arteries. Mean aortic wall areas are obtained in three segments: the ascending aorta, the descending thoracic aorta and descending abdominal aorta. Average vessel wall area (mm^2) = sum of wall area for each slice/total number of slices will be computed. The images will be matched for locations across visits using anatomical landmarks.

Total carotid plaque burden derived from MRI is reported from the individual carotid arteries as well as the average vessel wall area of both left and right carotid arteries.

Exploratory endpoints will include the lumen area, total vessel area, standard deviation of wall thickness and the normalized wall index. Mean wall thickness measurements are obtained using the centerline method and are obtained for each slice separately and averaged. Measurements are obtained from both carotids and the aortic segments described previously for wall area measurements. The normalized wall index (NWI) is the ratio of the vessel wall area divided by the total vessel area.

Carotid Plaque Composition - The axial multi-contrast proton density (PD), T1 and T2 weighted) black-blood images obtained in the carotid will be analyzed with a semi-automated algorithm to determine inner and outer vessel wall boundaries as well as major plaque compositional features determined from the contrast patterns across each of the

three images acquired at the same location. The major features include the necrotic lipid area, fibrous cap thickness and calcium area. These are quantified as either present or absent by subjective analysis.

8.5.3 Analysis Populations

8.5.3.1 Modified Intent-to-Treat (MITT) Population

The modified intent-to-treat (MITT) population consists of all enroled patients with a readable baseline MRI. The terminology "readable MRI" is an image that can be read and interpreted by the central Imaging Core Laboratory for the study. The primary analysis of efficacy will use this population. Imputation methods as outlined in Section 8.5.6 will be used for missing data for the 2-year MRI evaluation for the mITT patient population.

8.5.3.2 Per-protocol (PP) Population

The per-protocol (PP) population consists of all enroled patients who adhere to the protocol-specified study requirements. These patients will include those for whom a baseline MRI and a two-year MRI exist and are readable. Patients in the PP population must also satisfy additional explicit criteria for eligibility that will be included in the SAP prior to the start of this study. The PP population may generally be considered a complete-case population.

8.5.3.3 Safety Population

The safety population consists of all enroled patients who have received at least one dose of lomitapide.

8.5.4 Statistical Analysis

8.5.4.1 Baseline Evaluations and Disposition

Demographic and baseline disease characteristic data will be collected as part of LOWER and summarized for patients enroled in this study. Data to be tabulated will include demographic information such as sex, age, and race, as well as information on variables which may be potential confounders including medications, procedures, comorbidities (including hypertension) and conditions (including smoking status, alcohol use, and

diabetes) that can affect atheroma progression. The number of study subjects included in each analysis population will be summarized, including the number who withdraw from the study or discontinue lomitapide and the reasons for withdrawal or discontinuation.

8.5.4.2 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is the percent reduction from baseline in carotid vessel wall area at the two-year evaluation. The primary analysis will be a one-sample t-test on the within-subject percent reduction in average carotid vessel wall area using the MITT population. Given that these patients have substantial cardiovascular disease, it is unlikely that reduction in atheroma burden would occur over time in the absence of lipid-lowering therapy. Further, it is logical to believe that any reduction in carotid vessel wall area would be of benefit to the patient, and that this reduction would accompany the anticipated reduction in LDL-C from lomitapide therapy. Based on the sample size calculation, the null hypothesis to be tested is that the percent reduction in carotid vessel wall area is 0%, versus the alternative that the reduction is 10% or more; however, it is also important to consider the minimal detectable difference that may be achieved. The minimal detectable difference would range from 3% to 4.2%, with achieved sample sizes in the range between 40 and 57 subjects. The minimal detectable difference represents the lower bound of the two-sided, 95% confidence interval calculated when data are available for analysis and presumes the targeted 10% point estimate for reduction in carotid vessel wall area has been achieved, and the standard deviation is consistent with the estimated 22% used as the basis for the sample size calculations. It is believed that the absence of progression as determined by excluding a change in atheroma size of >3% would be clinically important.

Descriptive statistics will also be presented, including the sample number, mean, median, standard deviation, minimum and maximum values, as well as a two-sided, 95% confidence interval. Absolute data values, including arithmetic change from baseline, will be presented descriptively, in addition to percent change from baseline.

This analysis will be conducted when two-year carotid vessel wall area measurements have been obtained from all study subjects, including potentially imputed values from MITT subjects missing the two-year measurement. Missing observations at the two-year time point will be estimated using a multiple imputation (MI) procedure, as outlined in Section 8.5.6. The missing data will be estimated as the absolute value of the MRI

measurement, and this imputed value will be used for calculation of percent change from baseline.

Exploratory analyses of the potential impact of covariates such as age, sex and baseline atheroma burden on the primary endpoint will also be performed. These analyses will help determine if the percent reduction from baseline in carotid vessel wall area at the two-year evaluation is influenced by these covariates. In addition, the potential influence of confounding factors will be evaluated through descriptive, univariate analyses. Multivariate analyses to evaluate the potential for interactions among the various confounding variables will not be performed, since the sample size limitations may not allow this to be done with precision. These confounding variables are factors that could influence change in atheroma burden over time, and will include:

- Changes in existing therapies or procedures or the administration of new therapies or procedures that may influence the progression of atheroma
- Co-morbidities including cardiovascular disease, hypertension, diabetes mellitus, and obesity
- Smoking status and alcohol use

Changes in factors while on study will be included in these analyses as long as there is at least 6 months between the change and the MRI data obtained at 2 years.

8.5.4.3 Secondary Efficacy Endpoint Analysis

The analysis of secondary endpoints is intended to support the secondary objectives of the study. In order to add credibility to the results of key secondary endpoint analyses, an adjustment for multiplicity of endpoints will be applied. Key secondary efficacy endpoints include the percent change from baseline to one and five years on therapy for carotid and aortic vessel wall area, and carotid and aortic vessel wall thickness. The same method of analysis as used for the primary efficacy endpoint will be used for secondary efficacy endpoints. The multiplicity adjustment will be applied as follows: First, secondary endpoints will only be candidates for statistical significance following a statistically significant result for the primary endpoint of two-year percent change in carotid wall area. Subsequently, the p-values from the separate tests of significance of each key secondary endpoint are ranked from smallest to largest. If the largest p-value is

<0.05, then all secondary endpoints will be declared statistically significant. If the largest p-value is ≥0.05, then the next-largest p-value is tested at a significance level of 0.025, and if significant then that endpoint and all remaining endpoints are declared statistically significant. The procedure continues in this fashion, using significance levels of 0.05/3 and so on (Hochberg, 1988).

Additional secondary endpoints will include laboratory evaluations for LDL-C, and other lipoprotein biomarkers at one, two and five years of lomitapide treatment and the correlation of these laboratory evaluations with the change from baseline in MRI parameters of carotid and aortic atheroma. An additional secondary analysis will be performed on atheroma parameters from patients who have discontinued lomitapide therapy and who have a final MRI approximately one year after discontinuing lomitapide. These additional endpoints will not be subject to multiplicity adjustment, with statistical analyses considered to be descriptive.

Lipoprotein biomarkers include:

- Total cholesterol (TC)
- High density lipoprotein (HDL-C)
- Low density lipoprotein (LDL-C)
- Triglycerides (TG)
- Apolipoprotein B (apo B)
- Apolipoprotein A-I (apo AI)
- Lipoprotein (a) (Lp(a))
- Apolipoprotein C-III (Apo C-III)
- LDL sub-fractions by NMR technology

As a supportive analysis to the primary endpoint results, the percent change from baseline to one year on lomitapide therapy will be analyzed in the same manner as the primary time-point of two year MRI data. To control for potential multiplicity effects, statistical significance of the one year data will only be claimed if the primary two year data is statistically significant.

The exploratory analyses to look at the potential impact of covariates as described above will also be performed for key secondary endpoints.

8.5.4.4 Exploratory Endpoint Analysis

The analysis of exploratory endpoints will be descriptive only. Exploratory endpoints will consist of lumen area, total vessel area, standard deviation of wall thickness and the normalized wall index, at baseline, one, two, five years and one year post discontinuation of lomitapide if available. Exploratory endpoints will also include laboratory evaluations of biomarkers for inflammatory and cardiovascular processes. Correlation analysis will be performed between changes in these potential biomarkers and the change from baseline in MRI parameters of carotid and aortic atheroma.

The major plaque compositional features will include the necrotic lipid area, fibrous cap thickness and calcium area. These are quantified as either present or absent by subjective analysis, and will be analysed as categorical data through summary statistics of number and percentage of positive and negative results. These plaque composition analyses will be performed if sufficient data exist with respect to both the size of the plaques as well as frequency.

Inflammatory and cardiovascular biomarkers include:

- High sensitivity C reactive protein (hs-CRP)
- Serum amyloid A (SAA)
- Soluble Inter-cellular Adhesion Molecule-1 (sICAM-1)
- Interleukin 6 (IL-6)
- Lipoprotein Associated Phospholipase 2 (LpPLA2)
- Soluble Vascular Cell Adhesion Protein 1 (sVCAM-1)
- Soluble E-selectin (sE-selectin)
- Soluble interleukin-6 receptor (sIL-6 Receptor)
- Fasting glucose and insulin and calculate HOMA (Homeostasis Model Assessment)

8.5.4.5 Safety

Safety specific to this sub-study will be evaluated for adverse events (AEs) and serious adverse events (SAEs) associated with the MRI procedures and clinical laboratory monitoring, using the safety population.

All other safety information, including MACE events, will be obtained from the data collected as part of each patient's participation in the global lomitapide registry, LOWER. A summary of study drug exposure, including the durations of the therapy and doses, and the proportions of patients with modifications in therapy, will be produced.

Adverse events for the sub-study safety population, collected as part of the LOWER study, will be summarized by the Medical Dictionary for Regulatory Activities (MeDRA) system organ class and preferred term. Separate tabulations will be produced for all treatment emergent AEs, treatment-related AEs (those considered by the LOWER enroling physician as at least possibly drug related), SAEs, and discontinuations due to AEs. By-patient listings will be provided for deaths, SAEs, and events leading to discontinuation of treatment.

Descriptive statistics will be provided for clinical laboratory data, presented as both actual values and changes from baseline relative to each on-study evaluation and to the last evaluation on study, as well as shifts relative to normal ranges.

8.5.5 Interim Analysis

When two-year MRI evaluations are available for 20 evaluable patients, an interim analysis will be performed to determine whether an increase in sample size is warranted following the Mehta and Pocock procedure. Mehta and Pocock showed that if the conditional power falls within the promising zone, the sample size may be increased up to a pre-specified maximum with no impact on the type I error rate and, as a result, no further adjustment needs to be made to the final adjusted two-sided significance level of 0.05.

The sample size re-estimation is planned to occur upon evaluation of two-year MRIs for 20 (50% of the minimum required sample size) evaluable patients. The pre-specified maximum number of evaluable patients if the sample size is increased is 60. The promising zone was calculated using the methods of Mehta and Pocock to be between 41% and 80%. The number of additional evaluable patients required to achieve 80% power will be calculated using the formula presented by Mehta and Pocock:

$$\tilde{n}_2' = \left[\frac{n_1}{z_1^2}\right]\left[\frac{z_{\alpha/2}\sqrt{n_2} - |z_1|\sqrt{n_1}}{\sqrt{n_2 - n_1}} + z_\beta\right]^2$$

Where:

n_1 is the number of patients required for the interim analysis (n_1=20),

$\tilde{n}_2'$ is the number of additional patients required to achieve 80% power ($\tilde{n}_2' \leq 20$)

z_1 is the Z-statistic from the interim analysis,

n_2 is the originally planned number of patients included in the final analysis (n_2=40),

$z_{\alpha/2}$ is the Z-statistic corresponding to half of the final adjusted two-sided alpha level of 0.05,

z_β is the Z-statistic corresponding to study power of 80%

There will be no adjustments such that the sample size would decrease. Should the conditional power at the interim analysis fall below the lower bound of the promising zone, no sample size re-estimation will take place. Should the conditional power at the interim analysis fall above 80%, the trial will continue as originally planned to a final sample size of at least 40 evaluable patients.

8.5.6 Missing Observations

It is unlikely that patients would withdraw from the trial due to the nature of this disease; however, this possibility must be addressed. Patients will be strongly encouraged to continue in the study, and if withdrawal is necessary, they will be encouraged to obtain an MRI prior to discontinuation. Missing data for the primary endpoint of carotid vessel wall area (CVWA) obtained at 2 years, due to an unavailable or unreadable MRI at year 2, is also possible. To help minimize unreadable MRI results, patients with follow up MRIs that are considered unreadable will be requested to have a repeat MRI performed within the 2 month window. A thorough evaluation will be performed prior to data analysis, to determine the causes for any unavailable MRI results at 2 years. In particular, the possibility that missing MRI results are related to response to lomitapide therapy will be evaluated, in order to determine if MRI data are missing at random or not. For patients with no available readable MRI at 2 years, the following imputation method will be used.

For patients that could reasonably be considered to have data missing at random, such as resulting from inability to travel to the MRI center, a standard multiple imputation technique, using the predictive characteristics of complete cases (patients with 2-year

MRI data), will be used to account for these missing data in analysis. These predictive characteristics will include, for example, age, sex, lipid measurements over time, MRI results obtained prior to 2 years, etc. For patients whose data cannot reasonably be determined to be missing at random, an approach to multiple imputation will be used wherein the value to be used in each iteration of the method will be a random selection of a data point from the set of values from all patients with an available percent reduction from baseline in carotid vessel wall area at the two-year evaluation who have shown an increase in CVWA (worsened). This approach would therefore apply a conservative value that also would not artificially decrease variability.

Similar methods will be used for the assessment of, and imputation for, secondary endpoints as appropriate.Sensitivity analyses of the primary endpoint will be performed to assess the effect of missing data on the two-year endpoint, including repeated measure mixed model procedures and complete-case analysis.

An additional consideration is the fact that the primary efficacy analysis will take place using two-year MRI data, whereas the study will be conducted over a five-year period. Therefore it is possible that two-year MRI results may be missing but five-year results may be available. In this case, a second MI procedure may be performed to impute missing two-year MRI data by inclusion of five-year results in the methodology, once five-year data are available.

Missing safety information may also be imputed as appropriate, such as inference of the timing of an adverse event based on incomplete date information.

8.5.7 Inter- and Intra-Observer Variability

All MRI image analyses will be performed by trained image analysts who have experience with vessel wall images. All analysts have to pass rigorous tests and have to be internally certified for performing vessel wall analysis by the central Imaging Core Laboratory. The qualification procedure for each analyst involves directed training from the laboratory director or previous analyst followed by a test of the reproducibility of their analysis on a test data set consisting of at least 10 subjects (each with a minimum of 16 imaging slices). Inter-observer reproducibility is assessed by using an intra-class correlation (ICC) and Bland-Altman analysis to look for bias. An ICC > 0.9 with minimal bias on Bland-Altman analysis compared to the previous analyst is required for certification.

As part of this imaging study, to maintain quality of analysis, 10% of all subject data (acquired within the calendar year as part of the study) will be analyzed twice by the primary analyst for the study as well as by a second reader. Both inter- and intra-observer variability metrics will be obtained using a procedure similar to reader qualification (ICC + bland Altman analysis) each year. The primary analysis is deemed acceptable if the ICC for both inter- and intra- observer variability assessments is > 0.90 with minimal bias. If this metric is not achieved, all data acquired during the calendar year as part of this protocol will be reanalyzed. The reproducibility metrics will then be reassessed. This procedure is repeated until the acceptance criteria for data robustness are met.

All data sent to the central Imaging Core Laboratory for analysis will be evaluated for image quality. All image analyses will be performed on a dedicated, validated workstation for vessel wall morphometric analysis. The analysis system is validated by performing imaging on a phantom of size and validating the imaging metrics derived. All data handling steps and workflow are also validated prior to any subjects being enroled in the study using dummy data (phantom validation script). A system validation report will be available as part of the MRI Facility Imaging Charter developed for this protocol. An audit trail for the entire data workflow through the core laboratory will be maintained in the form of a paper log. All imaging data are stored on encrypted hard drives (data repository for study) that also have version control enabled to maintain data integrity. All procedures used will be described in MRI Facility Imaging Charter to be developed specifically for this study.

8.6 Data Management

8.6.1 Electronic Data Capture (EDC) System

The database will be housed at the SCC on a physically and logically secure computer server maintained by the SCC in accordance with written security policies. The EDC system meets approved established standards for the security of health information and is validated. The system also meets the International Committee on Harmonisation (ICH) guideline E6R1 regarding electronic study data handling and is available for audit upon request. The system is developed in accordance with a rigorous system development life cycle and quality program, which insures compliance with regulatory agency guidelines including 21 Code of Federal Regulations (CFR) Part 11, Health Insurance Portability

and Accountability Act (HIPAA) in the US and Annex 11 in the EU. Patient confidentiality will be strictly maintained. Patient identifying information will not be included in the database, but must be maintained in a secure fashion at the treating physician's site.

Electronic Case Report Forms (eCRFs) and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the SCC and records retention for the study data will be consistent with standard operating procedures (SOPs).

The SCC maintains high data quality standards and utilizes processes and procedures to repeatedly ensure that the data are as clean and as accurate as possible when presented for analysis. Data quality is enhanced through a series of programmed data quality checks that automatically detect and prevent the entry of out-of-range or anomalous data. A remote data quality audit will be performed at various times throughout the study on collected data.

8.6.2 Statistical Software

All analyses will be performed using SAS® for Windows statistical software (SAS Institute, Cary, North Carolina (NC)) version 9.2 or higher using validated implementations of each application or SAS custom programming.

8.6.3 Data Entry

All reported data from the regional study site will be entered via a secure web-based EDC study database. Site personnel will be provided with secure usernames and passwords in order to enter study data into the EDC system. All sites will be fully trained in using the EDC system, including eCRF completion guidelines.

All participating sites will only have access to view and enter the data for their own patients.

Staff at the central Imaging Core Laboratory will electronically transfer data to the SCC for inclusion in the study database. Transfers will take place at periodic pre-specified intervals.

A data manager will perform concurrent review during the course of the data collection period. The data manager will generate ad-hoc queries to sites or the central Imaging

Core Laboratory when required, and the site management team will follow-up to request completion of such queries.

8.7 Quality Control

8.7.1 Site Training and Initiation

A meeting will be held to train the regional study site Investigators and their site staff on the study requirements and use of the EDC system. Site management personnel will contact each site to review site initiation procedures. Ongoing site management will occur throughout the entire duration of the study. Additional outreach and training including on-site visits will occur for sites to target regional sites needing remedial training and to address quality control concerns prior to analysis.

8.7.2 Regional Study Site MRI Qualification and Training

For investigators wishing to serve as regional sites, the central Imaging Core Laboratory staff will conduct a feasibility assessment to confirm the regional imaging facility's interest and qualifications and ensure the facility meets the specifications as described in the MRI Imaging Site Charter (Section 8.3.2). Staff from the central Imaging Core Laboratory will then conduct training at each new regional MRI site regional site to ensure that they are able to perform the imaging necessary for this study and will certify the site for participation. The SCC will also evaluate the regional study site to be sure the staff can perform the patient enrolment process and the required assessments and data collection activities required for the study.

Each regional study site training visit will be conducted by personnel from the central Imaging Core Laboratory and will include the following:

- Introductory meeting with the study site Investigator (if possible) and/or site coordinator
- Introductory meeting with imaging technologist, site radiologist, and/or other personnel involved in imaging aspects of the study
- Imaging equipment, facilities review/check (scanner, coils, interface, software version)
- American College of Radiology (ACR)/ equivalent accreditation review
- Phantom testing for scanner calibration (if required)

- Loading/compiling of appropriate study protocol specific for scanner
- Set up for volunteer scan, patient and coil positioning, scan logistics
- Discussion of imaging protocol and test scan on volunteer
- Review of test scan data, discussion of possible artefacts, protocol adjustments, contingency approaches, image quality requirements, other miscellaneous items
- FTP transfer account set up and test, data transfer issues, logistics, data transmittal forms requirements, filling instructions
- Site visit close out procedures, discussion of any other issues, and approval of site

8.8 Data Quality Assurance and Quality Control

The study will be conducted in accordance with the design and specific provisions of this protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

The regional study site Investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Sponsor and documented approval from the IEC/IRB, except where necessary to eliminate an immediate hazard(s) to the study participants. The regional study site Investigator will promptly report to the IEC/IRB and the Sponsor any changes in research activity and all unanticipated problems involving risk to human subjects or to others.

Prior to the initiation of the study, the regional study site Investigator and site personnel will be trained on the study. Training will include a detailed discussion of the protocol, Schedule of Study Assessments and eCRF completion. Sites will be given a workbook for reference regarding completion of the eCRF and directions for collecting data.

All non-MRI study data will be entered via the eCRF by trained site staff. All eCRF information will be imported directly into the EDC system. Any necessary corrections will be made to the database and documented via addenda, queries, source data clarification forms or an audit trail. Monitoring will occur at regularly scheduled intervals at the study site to allow for verification by sampling of source documents and comparing these with information recorded on the eCRFs. In addition, eCRFs will also be monitored remotely during the course of study participation, as specified in the Study Monitoring Plan.

The database will be housed on a physically and logically secure computer server maintained in accordance with written security policies. The EDC system meets approved established standards for the security of health information and is validated per 21CFR Part 11and Annex 11. The system also meets the International Conference on Harmonisation (ICH) guideline E6R1 regarding electronic study data handling and is available for audit upon request. Patient confidentiality will be strictly maintained. Patient identifying information will not be included in the database, but must be maintained in a secure fashion at the regional study site.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored and records retention for the study data will be consistent with standard procedures.

A test data transfer will be performed and will be evaluated against study specific requirements to ensure all data transfer requirements were met. A Data Validation Plan will detail how the data and data structure will be validated, including the need to conduct code review. Validation of the test data will ensure the integrity of the data structure itself is intact and that all data mapping is correct according to the requirements. Upon successful completion of the test transfer and finalization of the transfer requirement, ongoing quality control (QC) will be performed on the data. The QC process includes but is not limited to:

- File size check
- Total numbers of records in the data file
- Edit checks

Standard Operating Procedures (SOPs) for data base lock will be followed to ensure that data has been processed according to project-specific requirements. Final validation and plausibility checks will be run against the frozen data as defined in the edit specifications and/or final validation plan. Resolution of any issues will be documented.

8.8.1 Site Monitoring

Site management will be more frequent during enrolment and decrease during the subject follow-up period due to more limited site involvement. All inbound calls from the regional study sites will be triaged immediately and all calls (inbound and outbound) will

be tracked, including inquiry type, regional study site ID, query resolution and regional study site feedback.

The SCC has a highly trained, experienced staff responsible for site communication.

In-house site management or central monitoring will be used to manage regional study sites during the study period.

The central Imaging Core Laboratory will determine if re-training is necessary for any of the MRI facilities based on the quality of the images received.

8.9 Limitations of the Research Methods

8.9.1. Comparator Population

The primary limitation of the study design is that it is uncontrolled and potential subjects are not randomized under equipoise to either lomitapide treatment or a control agent. However, this is an inevitable consequence of the fact that this is a sub-study coordinated with an observational study (LOWER). The paired data, within-subject analysis will provide an estimate of the effect of lomitapide, which will then require comparison to historical or literature references for validation. Further, a positive correlation of reduction in vessel wall area with reduction in LDL-C will contribute meaningfully to an understanding of the potential long-term benefit of the previously seen reductions in LDL-C achieved with lomitapide.

Because of the severity of the hypercholesterolaemia associated with HoFH and its resultant effects on overall health and life expectancy, it is anticipated that many patients with the condition who are candidates for lomitapide will receive it once it is marketed in their region. This is typical for new biopharmaceuticals introduced for the treatment of rare diseases. Therefore, patients who do not receive lomitapide would be an inappropriate comparator group because these patients will likely be different as a group than those who are candidates to receive lomitapide.

8.9.2. Selection Bias

There are several ways in which selection bias may occur. The first is that the LOWER enrolling physician selectively invites patients into the sub-study. However, to avoid this type of section bias, the LOWER enroling physician will be asked to invite consecutive patients who are enroled in LOWER and to provide reasons why patients were not selected or declined participation.

Another reason for selection bias is that due to the unmet medical need of patients with HoFH, the most severe patients will be those initially treated with lomitapide. Since this sub-study will begin as soon as possible after lomitapide availability in a given country and the initiation of LOWER, these patients will also be the first to be invited into this sub-study. This may be a benefit since patients with the most severe disease are most likely to show a therapeutic effect of lomitapide on atheroma burden. These patients may also be more compliant and more motivated to stay on treatment compared to those with less severe disease.

Thirdly, the sub-study will be conducted in select countries that are a subset of countries also participating in LOWER, i.e., countries in the EU, the US, and Canada. These countries have high standards of medical care and more experience with the disease which will serve as the back drop for treatment with lomitapide. Other countries participating in LOWER have more heterogeneous approaches to care. Excluding these countries may introduce selection bias. However, it is not likely to have a large impact on study outcome.

The characteristics of patients enrolled in the sub-study will be compared with the overall LOWER population to examine if the sub-study population is representative.

8.9.3. Confounding

Confounding is an important consideration, since it is possible that factors other than treatment could influence reduction in carotid vessel wall thickness. Therefore, additional exploratory analyses may be performed to investigate the influence of factors that may become apparent during the course of the study.

8.10 Other Aspects

8.10.1 Regulatory Authorities

The approved protocol will be submitted to Regulatory Authorities in accordance with the regulations of the countries involved in the study.

8.10.2 Protocol Modifications

Amendments to the protocol may only be made by Aegerion Pharmaceuticals. All protocol amendments must be signed and dated by the treating physician, and, if required, submitted and approved by the Regulatory Authorities and Institutional Review Board/Independent Ethics Committees (IRB/IEC), prior to implementation of the amendment**.**

8.10.3 Records Retention

The regional study site must maintain all essential documents until notified by Aegerion Pharmaceuticals and in accordance with all local laws and regulations.

Aegerion Pharmaceuticals and the SCC will follow their applicable SOPs regarding retention of records.

8.10.4 Compensation to Physicians

Study site Investigators will be compensated for time spent in completing study requirements consistent with local prevailing conditions. This compensation schedule will be determined in accordance with national and local IRB/IEC guidelines and fair market value for the work performed.

8.10.5 Compensation to Patients

Patients will be reimbursed for their time and expense to travel to regional study sites to perform study-related procedures, consistent with local prevailing conditions.

9. PROTECTION OF HUMAN SUBJECTS

9.1 Informed Consent

The regional study site will discuss the study, determine eligibility and obtain informed consent. In cases where the patient does not live near the regional study site, informed consent will first be obtained verbally over the phone. Once the patient arrives at the regional study site, prior to any data collection under this protocol, a written informed consent or privacy statement must be signed by the patient, in accordance with local practice and regulations. A copy of the informed consent form, signed and dated by the patient, must be given to the patient. Confirmation of a patient's informed consent must also be documented in the patient's medical records prior to any data collection under this protocol. The informed consent form must not be altered without the prior agreement of the relevant IRB/IEC and Aegerion Pharmaceuticals.

In order to ensure patient confidentiality, patients will be assigned a unique identifying number, which will be based on the numbering system used in the LOWER study. The key matching ID numbers with patient names will be maintained by the site, and only the unique identifier will be recorded on the data collection forms with the patient initials. To assist patients in scheduling appointments for MRIs, the site will maintain the patient's name and contact information. The treating physician and their site staff will securely store this information separately from other study information.

In any presentations or in publications of the results of the study, the patients' identities will remain anonymous and confidential. Aegerion Pharmaceuticals, its designee(s), and various government health agencies may inspect the records of the study. Every effort will be made to keep the patients' personal medical data confidential.

9.2 Ethics Committee or Institutional Review Board

Prior to the collection of any study related data, IRB/IEC approval of the protocol, informed consent and all patient enrolment materials will be obtained in each country and for each site, as applicable.

The study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki, applicable privacy laws, and local regulations for each

participating site. An IRB/IEC will review and approve the protocol before any patient is enroled. Appropriate informed consent will be obtained from participating patients.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1 Events Associated with the MRI Evaluations and Laboratory Assessments

If an AE related to the MRI procedure or laboratory assessments occur, the regional study site should report this event to the SCC within 24 hours of identification.

If upon the regional study site Investigator's review of the MRI report, he/she identifies an AE, that event should be reported to the SCC within 24 hours of identification.

Other AEs occurring in patients enroled in LOWER will be collected according to the requirements set forth by the LOWER protocol and do not need to be reported specifically under this protocol.

10.2 Definitions

The definitions to follow are in accordance with those outlined in the current protocol and in the Guideline on Good Pharmacovigilance Practices (GVP).

10.3 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

10.4 Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
    - Note: The term "life-threatening" refers to an event which, in the view of the treating physician, places the subject at immediate risk of death from the time of the event as it occurred; it does not refer to an event which hypothetically might have caused death had it been more severe.

- Requires inpatient hospitalisation or prolongation of an existing hospitalisation.
- A pre-existing event or condition that results in hospitalisation should be recorded on the medical history eCRF. If the onset of an event occurred before the subject entered the trial (e.g., any pre-planned hospitalisation for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalisation would not lead to an AE being classified as serious unless, in the view of the treating physician, hospitalisation was necessary due to a worsening of the pre-existing condition.
- Results in persistent or significant disability/incapacity.
    - Note: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions, in the opinion of the treating physician.
- Is a congenital anomaly/birth defect.
- Is an important and significant medical event (medically significant) that may not be immediately life threatening or resulting in death or hospitalisation but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.
- Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse event.

10.5 Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is an AE that is assessed as suspected, serious and unexpected. Unexpected means that the nature or severity of the AE is not consistent with the applicable product information (e.g., investigator's brochure for an unauthorized investigational product or summary of product characteristics for an authorized product).

10.6 Severity

The severity refers to the intensity of an AE according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4. In cases where CTCAE do not apply, severity of the reported AE should be rated as mild,

moderate, or severe; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed by the treating physician for each AE recorded on the eCRF.

10.7 Relationship

The relationship of lomitapide to an AE will be determined by the regional study site investigator. The regional study site Investigator should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to lomitapide, indicating "yes" or "no" accordingly. The regional study site Investigator should indicate whether the event is considered to be related to the MRI scan or other study procedures; if so, he/she will assign a relationship.

Not Related: The AE is not related to lomitapide if there is evidence that clearly indicates an alternative explanation. If the patient has not received lomitapide, the timing of the exposure to lomitapide and the onset of the AE are not reasonably related in time, or other facts, evidence or arguments exist that strongly suggest an alternative explanation, then the AE is not related.

Related: The administration of lomitapide and AE are considered reasonably related in time and the AE could be explained either by exposure to the study drug or by other causes, or no alternative explanation has been identified. The following factors should be taken into consideration:

- Temporal relationship of event onset to the initiation of lomitapide.
- Course of the event, considering especially the effects of dose reduction.
- Discontinuation of lomitapide, or reintroduction of lomitapide (where applicable).
- Known association of the event with lomitapide or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1 Reporting to Regulatory Agencies

All reports will be submitted to the regulatory authorities based on agreed upon timeframes. The information provided will include enrolment and participation metrics by country as well as rates of readable MRIs.

11.2 Use of Information and Publications

All data generated from this study are the property of Aegerion Pharmaceuticals. Aegerion Pharmaceuticals shall have the right to publish such data and information without approval from the sites. Aegerion will establish a uniform procedure for analyzing, publishing, and disseminating findings from this study. Co-authors of publications may include participating physicians, Aegerion personnel, members of the central Imaging Core Laboratory, members of the Steering Committee, and/or other relevant thought leaders who contribute substantially to the publication. Data from planned interim analyses will be published by Aegerion at time points deemed appropriate based on study progress. Publications will adhere to the International Committee of Medical Journal Editors (ICMJE) guidelines.

Study data may not be published by participating sites without review and authorisation by Aegerion.

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