# Global Lomitapide Pregnancy Exposure Registry

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| **Protocol Number:** | AEGR- 733-027 |
| **Version / Date** | Draft Protocol: Version 3.0 / 21 Nov 2013 |
| **Name of Test Drug:** | Lomitapide<br>US: NDA 203858<br>EU: MAA EMEA/H/C/002578/0000 |
| **Indication:** | Adult patients with Homozygous Familial Hypercholesterolaemia (HoFH) |
| **Sponsor:** | Aegerion Pharmaceuticals, Inc.<br>101 Main Street, Suite 1850<br>Cambridge, MA 02142<br>1-617-500-7867 |
| **Responsible Medical Officer:** | Helen Phillips, MD<br>VP Medical Affairs, EMEA<br>Telephone: **+44 (20) 8622 4100**<br>Fax: **+44 (20) 8622 3200** |

# EU Protocol Details in Accordance with CHMP Guidance for the Format and Content of the Protocol of Non-interventional Post-Authorisation Safety Studies (PASS)

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| **Title** | Global Lomitapide Pregnancy Exposure Registry |
| **Protocol version identifier** | Version 3.0 |
| **Date of last version of protocol** | 21 Nov 2013 |
| **EU PAS register number** | ENCEPP/SDPP/5329 |
| **Active substance** | Lomitapide |
| **Medicinal product** | Lojuxta® |
| **Product reference** | H0002578 |
| **Procedure number** | EU: H/C002578/0000 |
| **Marketing authorisation holder(s)** | Aegerion Pharmaceuticals<br>37-39, Avenue Ledru Rollin<br>75012 Paris |
| **Joint PASS** | No |
| **Research question and objectives** | To evaluate the outcomes of pregnancy in women treated with lomitapide at any time within 30 days prior to first day of Last Menstrual Period (LMP) or during pregnancy. The outcomes of primary interest are major congenital anomalies. |
| **Country(-ies) of study** | Patients will be enroled from (but not limited to) countries in North America and Europe |
| **Author** | Helen Phillips, MD<br>VP Medical Affairs EMEA |
| **Marketing authorisation holder(s)** | Aegerion Pharmaceuticals, Inc.<br>37-39, Avenue Ledru Rollin<br>75012 Paris, France |
| **MAH contact person** | Ms. Angelique Winzenrieth |

# 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:** HPhillips **Date:** 27th November 2013

# INVESTIGTOR AGREEMENT

I have read this Aegerion Pharmaceuticals, Inc. Protocol No. AEGR-733-027:

Global Lomitapide Pregnancy Exposure Registry

I have fully discussed the objectives of this trial 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 trial, 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 trial according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the trial in accordance with ICH guidelines on GCP and with the applicable regulatory requirements.

I understand that Aegerion Pharmaceuticals, Inc. may decide to suspend or prematurely terminate the trial 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 trial I will communicate my intention immediately in writing to Aegerion Pharmaceuticals, Inc.

**Signature:**_____ **Date:** _____

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## 1. LIST OF TABLES

## 2. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE(s) | Adverse Event(s) |
| CC | Coordinating Centre |
| CDC | Centers for Disease Control and Prevention |
| CRFs | Case Report Forms |
| eCRFs | Electronic Case Report Forms |
| EDC | Electronic Data Capture |
| EDD | Estimated Date of Delivery |
| EU | European Union |
| FDA | Food and Drug Administration |
| HCP | Healthcare Provider |
| HIPAA | Health Insurance Portability and Accountability Act |
| HoFH | Homozygous Familial Hypercholesterolaemia |
| ICBDM | International Clearinghouse for Birth Defects Monitoring |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |

| Abbreviation | Definition |
|---|---|
| LDL-C | Low Density Lipoprotein-Cholesterol |
| LDL-R | Low Density Lipoprotein- Receptor |
| LMP | Last Menstrual Period |
| MACDP | Metropolitan Atlanta Congenital Defects Program |
| MTP | Microsomal Triglyceride Transfer Protein |
| NOAEL | No-observed-adverse-effect level |
| PER | Pregnancy Exposure Registry |
| PI | Package Insert |
| PK | Pharmacokinetic |
| PRCA | Pregnancy Root Cause Analysis |
| REMS | Risk Evaluation and Mitigation Strategy |
| RMP | Risk Minimization Plan |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SPC | Summary of Product Characteristics |
| SOPs | Standard Operating Procedures |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| UK | United Kingdom |

| Abbreviation | Definition |
|---|---|
| ULN | Upper Limit of Normal |
| US | United States |
| USPI | United States Prescribing Information |

## 3. RESPONSIBLE PARTIES

The MAH and Sponsor contact persons are Ms. Angelique Winzenrieth (EU) and Ms. Martha J. Carter (US), respectively.

# 4. ABSTRACT

## 4.1 Title

Global Lomitapide Pregnancy Exposure Registry version 2.0, 19Aug2013.

## 4.2 Rationale and Background

Lomitapide, a microsomal triglyceride transfer protein (MTP) inhibitor, was approved as Juxtapid® in the United States on December 21, 2012 and was authorized as Lojuxta® in the European Union on July 31, 2013. The approved indications in the two regions are quite similar and are described in Section 7. Homozygous Familial Hypercholesterolaemia (HoFH) is a serious, life-threatening disease caused by mutations in both alleles that encode the low density lipoprotein receptor (LDL-R), or proteins known to affect LDLR functionality. Subjects with HoFH typically have 4-10 fold elevations in LDL-C and 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. Untreated, subjects generally do not survive past age 30 (Raal, et al., 2011).

Due to its rarity and early mortality, the prevalence of HoFH is not well characterized. No studies accurately quantify the prevalence or incidence of the disease. The frequency of HoFH has been calculated to be 1 in 1 million in the general population based upon the estimated prevalence of the heterozygous state (1 in 500). In geographic regions with a presumed founder effect the prevalence has been observed to increase up to 10 in 1 million (Goldstein, et al., 1973; Goldstein, et al., 2001). A molecular diagnosis is not typically undertaken at the clinical practice level because, although over 1600 known mutations of the LDLR gene have been reported, unrecognized alleles lead to an inability to confirm the diagnosis and false negative reporting in 15-20% of cases (DeMott, et al., 2008; Varret, et al., 2007). In addition, genotyping is not widely available, is costly, may not be reimbursed, and does not influence treatment decisions. Consequently, HoFH is commonly diagnosed based on LDL-C levels, family history and clinical manifestations.

Women of reproductive age are among those affected by HoFH. Pregnancy is an event of special interest (ESI) in women exposed to lomitapide for 2 reasons. First, there are no reliable data on the use of lomitapide in pregnant women. Lomitapide may cause foetal harm when administered to a pregnant woman based on findings of teratogenicity in animal studies. Second, lomitapide may induce diarrhoea and vomiting due to its mechanism of action and decrease the

absorption of oral contraceptives, thereby increasing the risk of unintended pregnancy. Lomitapide MTP inhibition causes triglyceride accumulation not only in the liver but also in the intestine. Presumably, diarrhoea develops as a consequence of this mechanism of action (Samaha et al., 2008). The reduced bowel transit time may affect the absorption of concomitant oral contraceptives.

The lomitapide US Prescribing Information (PI) and the EU Summary of Product Characteristics (SPC) include a contraindication for use during pregnancy and instructions that females of reproductive potential should have a negative pregnancy test before starting lomitapide and should use effective contraception during therapy with lomitapide.

The Global Lomitapide Pregnancy Exposure Registry (PER) will be conducted in all countries that are included in LOWER (Lomitapide Observational Worldwide Evaluation Registry) Protocol AEGR-733-025. Information on any spontaneous and literature reports of pregnancies with lomitapide exposure in patients who are not enroled in LOWER or the PER will be added to the PER analyses once the pregnancies have been followed to outcome by the Aegerion Safety Department or its designee.

The PER will collect data on any pregnancies that occur in women exposed to lomitapide in the 30 days prior to conception or during pregnancy. Women residing in countries where the larger companion registry ("LOWER", protocol AEGR-733-025) is being offered who become pregnant will be offered to enrol into this PER and will be followed to pregnancy outcome. Due to the rarity of HoFH and the contraindications for lomitapide use during pregnancy, it is anticipated that the PER will collect a small number of pregnancies. All eligible pregnancies will be accepted; the pregnancies that are recorded in and reported from the PER will provide valuable information on birth outcomes following exposure to lomitapide. While the outcomes of primary interest are major congenital anomalies, full descriptions of all pregnancies and birth outcomes will be provided in the planned annual reports.

### 4.3 Research Question and Objectives

To evaluate the outcomes of pregnancy in women treated with lomitapide at any time within 30 days prior to the first day of Last Menstrual Period (LMP) or during pregnancy. The outcomes of primary interest are major congenital anomalies.

### 4.4 Study Design

This is a global, longitudinal, observational study. Data will be collected at enrolment and periodically during pregnancy from prescribers, gynaecologists, paediatricians and other Health Care Providers (HCPs) who may be caring for the patient during the pregnancy or caring for the child. HCPs will be contacted during the pregnancy (each trimester), within 4 weeks after the estimated delivery date (EDD), and for paediatric follow-up at 12 weeks of age and at 12 months of age. In the US and in other countries where patient contact is possible, data will also be collected directly from patients during each trimester, at the EDD, and, for paediatric patients, at 12 weeks and 12 months.

Primary data collection will be completed using electronic case report forms (eCRFs) completed by the PER Coordinating Centre (CC) personnel. Medical records will be requested for all pregnancy outcomes and birth defects. Pregnancy outcomes and birth defects will be verified, whenever possible, by review of medical records.

### 4.5 Population

Patients to be enroled in the PER include:

- Pregnant females:
    - exposed to lomitapide at any time within 30 days prior to first day of the LMP or during pregnancy.
    - willing to provide written informed consent and release medical records.

### 4.6 Variables

Data will be captured on eCRFs. Information included in the patient's medical record will be collected by the PER to verify the data provided by the patient and the HCP(s). The primary outcomes of interest are major congenital anomalies. Additionally, the following pregnancy outcomes will be captured and reported: live birth; spontaneous abortion/miscarriage; induced abortion; and foetal death/ stillbirth.

### 4.7 Data Sources

The PER CC will conduct outreach (further described in Section 9.3.4.1.1) to identify women who have become pregnant while being treated with lomitapide. Eligible patients will be enroled in the study through the CC by their treating physician and followed through pregnancy

outcomes and the final assessment (such as the evaluation of the infant if a live birth). In the US and other countries where it is permissible, patients may also self-enrol.

Data concerning patient history, pregnancy outcomes, and infant assessment will be collected at the indicated time points (enrolment, per trimester, prenatal follow-up, pregnancy outcome, and infant follow-up –up to 12 months) and entered into the PER Electronic Data Capture (EDC) system by CC personnel.

### 4.8 Study Size

The PER will collect lomitapide-exposed prospectively reported pregnancies and will also include retrospective reports of exposed pregnancies while the main registry ("LOWER", Protocol AEGR-733-025) remains open in the US. Additionally, reports of pregnancy and birth defects from post-marketing adverse event reports (spontaneous reports) and from published medical literature will be summarized within the annual PER study reports.

### 4.9 Data Analysis

A formal statistical analysis plan (SAP) will include details of all planned analyses and presentation of PER data. Since this is an observational study, descriptive analyses will be provided. Descriptive statistics will comprise the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables; and n and percent for categorical variables. Data will be presented for all patients enroled in the PER. An analysis of all PER participants combined will be provided. Separate analyses will also be conducted for prospective and retrospective reports. All data will be pooled for an additional analysis that includes spontaneous and literature reports from patients not participating in the PER. The proportion of pregnancies and births that have been lost to follow-up will also be calculated and reported. The primary outcome is major congenital abnormalities.

## 5. AMENDMENTS AND UPDATES

None

## 6. MILESTONES

| MILESTONE | PLANNED DATE |
|---|---|
| Start of data collection | At time of first reported pregnancy after opening of the Lomitapide Observational Worldwide Evaluation Registry (LOWER) |
| End of data collection | EU: Open<br>Non-EU: At the closure of LOWER, which is planned for 01 March 2028<br>Note: any pregnancies that are on-going at the time of registry closure will be followed to outcome, with live births followed for an additional 12 months. Ongoing infant follow-up will be completed as well. |
| Annual reports | Annually during the life of the PER |
| Registration in the EU PAS register | To Be Determined |
| Final report of study results | EU: Open<br>Non-EU: 6 months after database lock (no later than 01 September 2028) |

## 7. RATIONALE AND BACKGROUND

Lomitapide, a microsomal triglyceride transfer protein (MTP) inhibitor, was approved as Juxtapid® in the United States on 21Dec2012 and was authorized as Lojuxta® in the European Union on 31Jul2013. The approved indications in the two regions are quite similar and are included in the table below:

| REGION | APPROVED INDICATION |
|---|---|
| EU | Indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH).<br>Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinemia and secondary causes of hypercholesterolemia (e.g., nephrotic syndrome, hypothyroidism) must be excluded. |
| US | Indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).<br>Limitations of Use: The safety and effectiveness of JUXTAPID have not been established in patients with hypercholesterolemia who do not have HoFH. The effect of JUXTAPID on cardiovascular morbidity and mortality has not been determined. |

HoFH is a serious, life-threatening disease caused by mutations in both alleles that encode the low-density lipoprotein receptor (LDL-R), or proteins known to affect LDL receptor functionality. Subjects with HoFH typically have 4-10 fold elevations in low-density lipoprotein cholesterol (LDL-C) and develop premature atherosclerosis and coronary heart disease and can have cardiovascular events and complications such as myocardial infarctions or aortic stenosis in the first decade of life. Untreated, subjects generally do not survive past age 30 (Raal, et al. 2011). Due to its rarity and early mortality, the prevalence of HoFH is not well characterised. No studies accurately quantify the prevalence or incidence of the disease. The frequency of HoFH has been calculated to be 1 in 1 million in the general population based upon the estimated prevalence of the heterozygous state (1 in 500). In geographic regions with a presumed founder effect the prevalence has been observed to increase up to 10 in 1 million (Goldstein, et al., 1973; Goldstein, et al., 2001). Women of reproductive age are among those affected by HoFH.

Pregnancy is an ESI in women exposed to lomitapide for 2 reasons. First, there are no reliable data on the use of lomitapide in pregnant women. Lomitapide may cause foetal harm when administered to a pregnant woman based on findings of teratogenicity in animal studies.

Lomitapide was teratogenic in rats in the absence of maternal toxicity at an exposure (AUC) estimated to be less than that in humans at 60 mg. There was no evidence of embryofoetal toxicity in rabbits at 3 times the maximum recommended human dose (MRHD) of 60 mg based on body surface area. Embryofoetal toxicity was observed in rabbits in the absence of maternal toxicity at ≥6.5 times the MRHD. In ferrets, lomitapide Aegerion was both maternally toxic and teratogenic at <1 times the MRHD.

Second, lomitapide may induce diarrhoea and vomiting due to its mechanism of action and decrease the absorption of oral contraceptives, thereby increasing the risk of unintended pregnancy. Lomitapide MTP inhibition causes triglyceride accumulation not only in the liver but also in the intestine. Presumably, diarrhoea develops as a consequence of this mechanism of action (Samaha et al., 2008). The reduced bowel transit time may affect the absorption of concomitant oral contraceptives.

The lomitapide US Prescribing Information (PI) and the EU Summary of Product Characteristics (SPC) include a contraindication for use during pregnancy and instructions that females of reproductive potential should have a negative pregnancy test before starting lomitapide and use effective contraception during therapy with lomitapide.

The PER will be conducted in all countries that are included in the Lomitapide Observational Worldwide Evaluation Registry (LOWER), Protocol AEGR-733-025. Information on any spontaneous or literature reports of pregnancies with lomitapide exposure from patients who are not enroled in the PER will be added to the PER analyses once the pregnancies have been followed to outcome by the Aegerion Safety Department or its designee.

The PER will collect data on any pregnancies that occur in women exposed to lomitapide in the 30 days prior to conception or during pregnancy. Due to the rarity of HoFH and the contraindications for lomitapide use during pregnancy, it is anticipated that the PER will collect few pregnancies; however, all eligible pregnancies, whether retrospective or prospective, will be enroled. The pregnancies that are recorded in and reported from the PER will provide valuable information on birth outcomes following exposure to lomitapide. While the outcomes of primary interest are major congenital anomalies, full descriptions of all pregnancies, birth outcomes, and loss-to-follow-up will be provided in the planned annuals reports; the descriptions will include birth weight, gestational age, whether the delivery was a multiple birth, and age at diagnosis of any paediatric abnormalities.

# 8. RESEARCH QUESTION AND OBJECTIVES

The PER will evaluate the outcomes of pregnancy in women treated with lomitapide at any time within 30 days prior to first day of Last Menstrual Period (LMP) or during pregnancy. The outcomes of primary interest are major congenital anomalies.

# 9. RESEARCH METHODS

## 9.1 Study Design

This PER is a global, longitudinal, observational cohort study of women who were exposed to lomitapide at any time within 30 days prior to the first day of their LMP or during pregnancy. The outcomes of primary interest are major congenital anomalies. The PER will include pregnancies identified from any country where LOWER is conducted. Information on spontaneous and literature reports of pregnancies with lomitapide exposure from patients who are not enroled in the PER will be added to the PER analyses once the pregnancies have been followed to outcome by the Aegerion Safety Department or its designee. Information on any spontaneous reports of birth defects or literature reports of birth defects that are identified while the PER is open will also be included in the PER analyses.

No study medication will be provided as part of this long term, observational study. The treating physician will make all treatment decisions according to his or her usual practices and will provide prescriptions for his or her patients, as appropriate. The only addition to usual practice is the collection and structured documentation of data from the patient and/or her HCPs. There are no protocol mandated procedures or diagnostic tests.

CC personnel will obtain information from HCPs and/or eligible patients and record data in an EDC system. Data sources for the international study will include HCPs (e.g., gynaecologists, obstetricians, paediatricians, midwives, and primary care practitioners) and patients in countries where direct contact with patients is permitted, such as in the US. Data will be collected at patient enrolment, each trimester, at 6-7 months of gestation, within 4 weeks after the estimated date of delivery (EDD), and for paediatric follow-up at 12 weeks and 12 months of age.

## 9.2 Setting

Subjects will be accepted from all countries where LOWER is being conducted. Physicians who are treating adult patients with lomitapide will be informed about the PER and invited to notify the CC of any patient who meets the eligibility criteria.

To raise awareness of the PER amongst prescribers and patients, information about it will be disseminated through a variety of mechanisms which may include educational materials, labeling, and follow-up on spontaneous reports of pregnancy.

### 9.2.1 Patient Eligibility

Inclusion criteria are broad and exclusion criteria are limited in order to include a representative population of patients taking the product in usual clinical practice.

### 9.2.2 Inclusion Criteria

The eligibility criteria for patients enroled in the PER are:

- Adult (≥18) pregnant females exposed to lomitapide at any time within 30 days prior to first day of the LMP or during pregnancy.
- Patients who have the ability to understand the requirements of the study.
- Patients who have provided written consent for participation.

A patient may first provide oral consent on a recorded line if she is enroling herself. The CC will then send the patient a consent form for signature, to be returned in a provided postage-paid envelope. Following completion of oral consent, collection of enrolment data will proceed. If a physician obtains informed consent, the physician will indicate to the CC that verbal consent was obtained. The physician will then be sent a consent form for completion by the patient at her next visit.

### 9.2.3 Exclusion Criteria

Patients who are unable or unwilling to provide written informed consent or assent are not eligible to participate in the PER.

### 9.2.4 Prospective and Retrospective Pregnancy Definitions

In order to reduce the bias that may occur when outcome information is known prior to enrolment, eligible women are advised to enrol in the PER as soon as their pregnancy is known, preferably in the first trimester before the condition of the foetus has been assessed through prenatal testing. In order to determine the impact of such a bias, pregnancy reports and outcomes will be classified as either prospective or retrospective and will be analysed separately.

The criteria for prospective pregnancies are:

> Prospective pregnancies will include patients who are enroled after exposure to lomitapide but before the outcome of the pregnancy is known. An exception will be made that women who have undergone prenatal testing that could provide knowledge of the outcome of pregnancy will be considered as a prospective report if the outcome of the testing is normal.
>
> Note: Because early prenatal testing is so prevalent, it may be difficult to achieve adequate numbers of prospectively identified patients if all pregnancies with prior prenatal testing are excluded from the prospective analysis. Therefore, the primary analysis includes pregnant women enroled prior to outcome but after a prenatal test as long as the test does not indicate an abnormality. However, this practice could potentially bias the results by lowering the overall risks of birth defects. To examine this possible source of bias, the analysis will also be conducted excluding the subgroup of women who reported negative prenatal testing at the time of enrolment.

All other patients will be counted as retrospective pregnancies.

The retrospective and prospective pregnancies will be collected in a similar fashion, but treated separately as part of any analyses or reports.

### 9.3 Variables

The primary outcomes of interest are major congenital abnormalities. Also reported will be pregnancy outcomes, such as induced abortion and foetal loss; the plans for classifications of these outcomes are given below. The PER's definition of pregnancy losses and birth defects is consistent with that used in the Metropolitan Atlanta Congenital Defects Program (MACDP) (National Center for Birth Defects and Developmental Disabilities, 2004). All pregnancy outcomes will be reviewed based on earliest exposure to lomitapide.

#### 9.3.1 Pregnancy Outcomes

Pregnancy outcomes will be classified into one of the following mutually exclusive categories: spontaneous abortion/miscarriage; induced abortion; foetal death/stillbirth; or live birth. Other PER outcomes of interest are: ectopic pregnancy; maternal death; and neonatal death. The PER will attempt to assess all outcomes for the presence of birth defects.

#### 9.3.1.1 Spontaneous Abortion/Miscarriage

The PER defines any loss of a foetus due to natural causes at less than 20 weeks gestation (with gestational age measured from the first day of the LMP) as a spontaneous abortion. If available, data from gross or pathological examination of the abortus or foetus will be evaluated for structural or chromosomal defects.

#### 9.3.1.2 Induced Abortion

The PER defines an induced abortion as any induced or voluntary foetal loss during pregnancy. If available, data from gross or pathologic examination of the abortus or foetus will be evaluated for structural or chromosomal defects.

#### 9.3.1.3 Foetal Death/Stillbirth

Foetal death or stillbirth refers to foetuses born dead at ≥20 weeks gestation or weighing ≥500 g. Foetal death occurring at ≥20 weeks, but <28 weeks gestation is considered an early foetal loss. Foetal death occurring at ≥28 weeks is considered a late foetal loss. If available, data from gross or pathologic examination of the abortus or foetus will be evaluated for structural or chromosomal defects. The PER will make the final classification between foetal death/stillbirth and spontaneous abortion based on gestational age and weight. If these parameters are not available, the PER will accept the classification indicated by the HCP.

#### 9.3.1.4 Live Birth

A live birth refers to a complete expulsion or extraction from its mother of a surviving neonate breathing or showing any other evidence of life, such as heartbeat, umbilical cord pulsation, or definite movement of voluntary muscles, whether the umbilical cord has been cut or the placenta is attached.

#### 9.3.1.5 Ectopic Pregnancies

Any reported ectopic pregnancy will be sub-classified in the respective pregnancy outcome including induced abortion, maternal death, live birth, or spontaneous pregnancy loss.

### 9.3.2 Birth Defects

The PER adopts the term “birth defect” for an abnormality usually referred to as “congenital abnormality.” A description of the definition of birth defects is provided in Annex 3.

#### 9.3.2.1 Major Birth Defects

Criteria for major birth defects will be those used in the MACDP. The MACDP defines a case as one having at least 1 major structural birth defect or syndrome. It uses a defect collection and coding system known commonly as "BPA" codes that was established by the British Paediatric Association (BPA), World Health Organization, and modified by the CDC (National Center for Birth Defects and Developmental Disabilities, 2004). The system is divided into "codable" and "conditional" defects. Codable defects are usually significant structural malformations or genetic syndromes. Additional details are provided in Annex 3.

### 9.3.3 Effectiveness of Risk Minimisation

Measures of the effectiveness of risk minimisation such as rates of prescribing of contraceptives for women of reproductive potential will be estimated from the companion lomitapide observational cohort study (LOWER). The lomitapide Registry will provide estimates of the types and rates of contraceptive use among women of reproductive age who are being treated with lomitapide. In addition, the lomitapide PER will provide the distribution of self-reported methods of contraception among the women who are PER participants.

#### 9.3.3.1 Pregnancy Root Cause Analysis

A pregnancy root cause analysis (PRCA) will be conducted for every pregnancy that is reported to the PER. Questionnaires will seek to better understand the circumstances of the pregnancy and the patient's and/or HCP's knowledge of the information in the product label concerning pregnancy and the importance of birth control. The PRCA will be conducted with the HCP or, in countries where this is permissible, directly with the patient.

CC staff will use a standardised questionnaire to document the patient's use of birth control and her receipt of information about lomitapide, including the risk of teratogenicity and the need to use highly reliable birth control and possible loss of effectiveness of oral contraceptives due to diarrhoea or vomiting and need for additional contraception. This information, together with other metrics, will be used to determine whether changes need to be made to processes and educational materials to make them more effective in minimising the risk of teratogenicity.

### 9.3.4 Data Collection

Data collection and entry in the EDC system will be done by the PER CC. Data collection forms are designed to gather data needed for the study that have been documented as part of usual care

of the patient. If the HCP is unable or unwilling to provide the necessary data over the phone, a hard copy form will be sent to the HCP office for completion and return faxing to the CC.

#### 9.3.4.1 Data Collection Details

##### 9.3.4.1.1 PER Awareness

Active outreach will occur to solicit reports of women exposed to lomitapide during pregnancy. The CC will use various options to make HCPs and patients aware of the PER, such as:

- Discussion by the enroling physician of the PER with female patients of reproductive potential during enrolment in LOWER
- Reminder to physicians participating in the lomitapide Registry to encourage their patients who become pregnant to join the PER, i.e., including eligible patients not enroled in the lomitapide Registry
- Reminder to prescribers who enrol patients in any lomitapide Named Patient or Compassionate Use/Expanded Access Programs
- Notification of all prescribers of lomitapide where known
- Where appropriate, reference to the PER in product labeling aimed at prescribers and patients
- Notification of HoFH education and support groups
- FDA pregnancy registry website
- Toll-free telephone number printed on applicable patient materials

##### 9.3.4.1.2 Enrolment Procedures

Reporting of pregnancy exposures to lomitapide is voluntary. Pregnancies should be reported as early as possible, before prenatal testing has been performed.

The CC will maintain toll-free telephone lines and toll-free faxes to facilitate patient enrolment, data collection, and data queries.

The PER participants will originate from the following sources:

- Patient self-referral through telephone contact with the CC (US and other countries where permissible)
- Prescriber or other HCP referrals
- Pregnancies reported to Aegerion directly from countries where LOWER is ongoing

#### 9.3.4.1.2.1 Countries Allowing Direct Patient and HCP Contact

##### 9.3.4.1.2.1.1 Direct Patient Reports

In countries, such as the US, that allow for direct patient reports, the CC will explain the purpose and scope of the PER to the patient, obtain verbal consent for participation (if consent has not already been obtained by the HCP), and send the patient a Consent Form, Release of Medical Information (RMI) form and a PER Information Sheet. In some cases, the CC will send information to the patient's HCP as an intermediary. Enrolment data will be collected at the time of the initial report; however, no additional data will be collected until the patient has returned the signed consent form to the CC.

##### 9.3.4.1.2.1.2 Reports from HCPs

HCPs will explain the purpose and scope of the PER to the patient, obtain her consent for participation, and notify the CC. The CC will complete the patient enrolment form, or send it to the HCP for completion. The CC will also provide the HCP with a Consent Form and an RMI form to be completed by the patient and returned to the CC (for obtaining information from other HCPs if necessary) and a PER Information Sheet .

#### 9.3.4.1.2.2 Countries Allowing Only HCP Contact

Unless allowed by national and local regulation, there will be no direct reports from patients.

### 9.3.4.2 PER Contact Schedule

In countries that allow contact with the patient and the HCP, during the course of the pregnancy the CC will contact the patient once per trimester. In countries with contact restricted to HCPs, during the course of the pregnancy the CC will contact the patient's HCP once per trimester.

Regardless of country of origin of the report, the patient's HCPs will be contacted at 6 to 7 months of gestation for the Prenatal Follow-Up and within 4 weeks after the EDD for Pregnancy Outcome Follow-Up. The infant's HCP will be contacted by the enroling HCP or by the CC when the infant is 12 weeks of age and at 12 months of age for paediatric follow-up.

The data collection schedule is outlined in Table 1 and Table 2.

**Table 1: Data Collection Schedule in Countries with Data Collection Restricted to HCPs**

| DATA COLLECTION | REGISTRATION BY LOMITAPIDE PRESCRIBER WITH CC | CC CONTACT WITH THE HCP AT EACH TRIMESTER | 6 TO 7 MONTHS OF GESTATION FOR THE PRENATAL FOLLOW-UP | CC CONTACT WITH PRACTITIONER(S) AT THE PREGNANCY OUTCOME FOLLOW-UP WITHIN 4 WEEKS AFTER THE EDD | HCP OR CC CONTACT WITH THE INFANT'S HCP AT THE PAEDIATRIC FOLLOW-UP AT 12 WEEKS OLD AND 12 MONTHS OLD[1] |
|---|---|---|---|---|---|
| Consent | X | | | | |
| Patient Demographics and Pregnancy History | X | | | | |
| Lomitapide Use | X | X | X | X | X (if mother is nursing) |
| Concomitant Medications | X | X | X | X | X |
| Medical History | X | | | | |
| Pregnancy Outcome | | | | X | |
| Paediatric History and Examinations | | | | X | X |
| Serious Adverse Events (Pregnancy-Related) | | X | X | X | X |

[1] The 12-week follow up should be conducted +/- one week.

**Table 2: Data Collection Schedule in Countries with Data Collection from Patients or HCPs**

| DATA COLLECTION | REGISTRATION/ ENROLMENT | CC CONTACT WITH THE PATIENT AT EACH TRIMESTER | CC CONTACT WITH THE PATIENT'S HCP(S) AT THE PRENATAL FOLLOW-UP, 6 TO 7 MONTHS OF GESTATION | CC CONTACT WITH THE HCP(S) AT THE PREGNANCY OUTCOME FOLLOW-UP[1] WITHIN 4 WEEKS AFTER THE EDD | CC CONTACT WITH THE INFANT'S HCP AT THE PAEDIATRIC FOLLOW-UP AT 12 WEEKS AND 12 MONTHS OLD[2,3] |
|---|---|---|---|---|---|
| Consent[4] | **X** | | | | |
| Patient Demographics and Pregnancy History | **X** | | | | |
| Contact Information | **X** | **X** | **X** | | |
| Lomitapide Use | **X** | **X** | **X** | **X** | **X** **(if mother is nursing)** |
| Concomitant Medications | **X** | **X** | **X** | **X** | **X** |
| Medical History | **X** | | | | |
| Pregnancy Status/ Outcome | | **X** | **X** | **X** | |
| Paediatric History and Examinations | | | | **X** | **X** |
| Serious Adverse Events (Pregnancy Related) | | **X** | **X** | **X** | **X** |

[1] The CC will contact the patient's HCP earlier in the pregnancy for outcome data if the patient reports an adverse pregnancy outcome or an induced abortion.
[2] The CC will contact the infant's HCP. The HCP will be designated either at registration/enrolment or during one of the previous collection time periods.
[3] The 12-week follow up should be conducted +/- one week.
[4] The CC will first obtain verbal informed consent. The CC will then mail the patient a Consent Form and Release of Medical Information form to sign and return.

#### 9.3.4.3 Patient Withdrawal

Patients may withdraw from the PER at any time at their own request. They may also be withdrawn at any time at the discretion of the HCP for administrative reasons. Note: discontinuation of lomitapide treatment is not a reason for withdrawal from the PER.

Patients who inform the CC or their HCP of their intent to prematurely withdraw from the PER will be asked a brief series of questions in an Exit Interview to determine the pregnancy status and to document the reason for withdrawal.

If the patient withdraws from the PER and also withdraws consent for disclosure of future information, no further assessments will be taken and no additional data will be collected beyond the Exit Interview. The PER may retain and continue to use any data collected before withdrawal of consent in accordance with the original patient consent form.

##### 9.3.4.3.1 Losses to Follow-up

Multiple attempts (at least 4 attempts) to obtain information about the outcome of pregnancy will be made within 3 months following EDD before the patient is considered lost to follow-up. Similarly, multiple attempts will be made to obtain infant follow-up at 12 months after birth. The CC will contact the enroling HCP using multiple follow-up mechanisms (i.e., mail, fax, telephone, or e-mail) based on prior success and/or HCP preference to minimise the occurrence of missing data. In the US, if the CC is unable to solicit the outcome of the pregnancy or the infant status at 12 months from the HCP, the patient may be contacted for outcome information. In areas where it is possible to match against birth and death records, a final check will be made for comparison against vital statistics records.

### 9.4 Data Sources

As described in Section 8.3, the PER follows data collection strategies used in established population-based birth outcome registries. The below-listed variables will be collected; they include those in the FDA's Pediatric and Maternal Health Staff's (PMHS) Recommended Data Elements for Collecting Pregnancy Exposure Data, and additional variables specific to lomitapide use and HoFH medical history. Primary data collection will be accomplished via eCRFs completed by the CC staff. Medical records will be requested for all pregnancy outcomes and birth defects. Pregnancy outcomes and birth defects will be verified, whenever possible, by review of medical records.

**General**

- Patient identifier or patient name and contact information where patient contact is possible
- Name of reporter at initial contact
- Date of initial contact
- Dates of any follow-up contacts
- Telephone number of reporter
- Additional contact names and phone numbers (if reporter is the patient)

**Maternal Information**

- Source of information (e.g., obstetrician, pregnant woman, other)
- Birth date
- Race
- Occupation
- Pre-pregnancy weight
- Maternal medical history (e.g., vaccination history, hypertension, diabetes, seizure disorder, thyroid disorder, allergic disorders, heart disease including congestive heart failure, connective disease, autoimmune disease, hepatitis, known risk factors for adverse pregnancy outcomes including environmental or occupational exposures, other).
- Obstetric History
    - Number of pregnancies and outcome of each (live birth, spontaneous abortion, induced abortion, ectopic pregnancy, molar pregnancy)
    - Previous maternal pregnancy complications
    - Previous foetal/neonatal abnormalities and type
- Current Pregnancy
    - Date of last menstrual period
    - Complications during pregnancy (including any adverse drug reactions such as reports of infection or fever) and dates
    - Number of foetuses
    - Labor/delivery complications

- Disease course(s) during pregnancy and any complications
- Nursing history
- Exposure to radiation, pesticides and chemicals during pregnancy
- History of HoFH and method of diagnosis
- Indication for lomitapide use
- Lomitapide treatment regimen (directly from patient whenever possible otherwise from HCP as reported by the patient)
  - Start date
  - Stop date
  - Duration of use
  - Changes in dose
  - Whether lomitapide was discontinued at the time of pregnancy identification
    - If not, changes in pattern of lomitapide use during pregnancy
- Apheresis
- Other medical product exposures (prescription drugs, OTC products & dietary supplements) including contraceptive use
  - Name
  - Dosage & route
  - Date of first use & duration
  - Indication

- Recreational drug use (e.g., tobacco, alcohol, illicit drugs) and amount
- Family History (specify type, maternal/paternal, etc.):
  - Spontaneous abortions
  - Anomalies/malformations
  - Multiple foetuses/births
  - Family history of HoFH and, if applicable, basis for diagnosis in parents
  - Other relevant family medical history

**Neonatal information**

- Initial
    - Source of information (e.g., obstetrician, paediatrician, mother)
    - Date of receipt of information
    - Date of birth or termination
    - Gestational age at birth or termination
    - Gestational outcome (live born, foetal death/stillborn, spontaneous abortion, induced abortion)
    - Sex
    - Pregnancy weight gain of mother
    - Obstetric complications (e.g., pre-eclampsia, premature labour, premature delivery)
    - Pregnancy order (singleton, twin, triplet)
    - Results of neonatal physical examination including
        - Anomalies diagnosed at birth or termination
        - Anomalies diagnosed after birth (including age at diagnosis)
        - Weight at birth indicating whether small, appropriate, or large for gestational age
        - Length at birth
        - Condition at birth (including, when available, Apgar scores at 1 and 5 minutes, umbilical cord vessels and gases, need for resuscitation, admission to intensive care nursery)
        - Neonatal illnesses, hospitalizations, drug therapies
- Follow-up:
    - Source of information (e.g., paediatrician, mother)
    - Date of receipt of information
    - Anomalies diagnosed since initial report (including age at diagnosis)
    - Developmental assessment
    - Infant illnesses, hospitalizations, drug therapies

### 9.4.1 Steering Committee

A Steering Committee will be established prior to initiation of the PER and will include clinicians and scientists with expertise in HoFH, obstetrics, teratology, paediatrics, epidemiology and biostatistics. Committee members will provide subject matter expertise for the program. The Steering Committee will adjudicate endpoints and be responsible for reviewing the data from the PER over time and making recommendations to the Sponsor regarding its conduct, and will assist in study interpretation.

## 9.5 Study Size

HoFH is an ultra-rare disease. The prevalence of defects in both alleles of the LDL-R (homozygous) has been calculated to occur in ~1 in 1 million persons based on the estimated prevalence of 1 in 500 for the more common heterozygous FH, which is characterised by less severe hypercholesterolaemia.

Every attempt will be made to recruit eligible participants to this PER using methods found to be effective in similar pregnancy exposure registries. However, the number of women who will be candidates for inclusion with an eligible pregnancy cannot be accurately estimated.

Any pregnancies reported in previous clinical studies with HoFH or spontaneous or literature reports of pregnancies with known outcomes will be considered retrospective reports and will be included in the PER and analyzed separately. Any prospective pregnancies reported spontaneously (i.e., from patients not enroled in the PER) will be handled by the Aegerion Safety Department or its designee. These reports will be included in a pooled analysis of all reports.

## 9.6 Data Management

### 9.6.1 Electronic Data Capture (EDC) System

The database will be housed at the CC on a physically and logically secure computer server maintained by the CC 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 CFR Part 11 and 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 clinical database, but must be maintained in a secure fashion by the physician. In countries where direct patient contact is possible, the CC will maintain the patient identifying data, including contact information, separately from the clinical data with limited access only by authorised study personnel.

Electronic CRFs (eCRFs) and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the CC and record retention for the study data will be consistent with standard operating procedures.

The CC 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.

### 9.6.2 Statistical Software

All analyses will be performed using SAS® for Windows statistical software (SAS Institute, Cary, NC) version 8.2 or higher using validated implementations of each application or SAS custom programming.

### 9.6.3 Data Entry

All data will be entered by the CC via a secure web-based EDC study database. All CC personnel will use secure usernames and passwords and will be fully trained in using the EDC system, including eCRF completion guidelines.

A data manager will perform concurrent review during the course of the data collection period. The data manager will generate ad-hoc queries for the CC to call HCPs when required. Further detail relating to data collection, processing, linking, protection, and reporting will be described in the Data Management Plan and/or Statistical Analysis Plan.

## 9.7 Data Analysis

Complete analytical specifications, including tables and listings, will be included in the Statistical Analysis Plan (SAP), which will be prepared separately. All statistical analyses will be coordinated by Aegerion or designee.

Data will be presented for all patients enroled in the PER. An analysis of all PER participants combined will be provided. Separate analyses will also be conducted for prospective and retrospective reports. All data will be pooled for an additional analysis that includes spontaneous and literature reports from patients not participating in the PER. The proportion of pregnancies and births that have been lost to follow-up will also be calculated and reported. The primary outcome is major congenital abnormalities. Data will be presented using descriptive statistics using number and percent for categorical endpoints, n, mean, standard deviation (SD), standard error (SE) of mean, median, minimum (min), maximum (max) for continuous endpoints. The primary analyses will also present 95% confidence intervals (CI). Details of the analysis and table shells will be included in the SAP.

### 9.7.1 Potential Biases

As reporting of pregnancies will be totally voluntary, it is possible that even in prospectively reported pregnancies, potential bias could exist. For example, high-risk pregnancies may be more likely to be reported.

The calculation of risk of birth defects will exclude foetal losses (spontaneous abortions, induced abortions, or foetal deaths) for which no birth defects have been detected as they may introduce a classification bias. It is unknown what percentage of these pregnancies consists of potentially normal outcomes or birth defects. The PER will attempt to obtain information on birth defects detected at the time of foetal loss. However, the reporting HCP may not know the defect status of the aborted foetus. Evaluating spontaneous pregnancy losses is problematic for a number of reasons. First, the number of pregnancy losses in the general population is not well established. Early losses generally occur frequently and losses decrease as pregnancy progresses. Collecting information on pregnancy losses is difficult in this voluntary PER when enrolment time or initial contact with PER cannot be regulated. Spontaneous losses are likely to occur before the pregnancy is recognized. Even if the pregnancy is recognized, it may not be reported to the PER if the spontaneous loss occurred prior to PER enrolment.

Every effort will be made to obtain the outcome of every reported pregnancy. However, enroled patients for whom pregnancy outcome information is unobtainable will be considered lost to follow-up. It is possible that outcomes from pregnancies lost to follow-up could differ from those with documented outcomes. Because of differences in follow-up and reporting patterns, it is currently not possible to assess with any certainty what impact the potential biases of the loss to follow-up may have on the analysis. However, efforts at comparing some of the

characteristics of each group will be conducted in an attempt to address this potential source of bias.

As lomitapide is indicated for individuals 18 years and older, data from females who become pregnant under the age of 18 will not be included; however, the number of excluded pregnant females will be reported in study reports.

### 9.7.2 Estimates of Incidence of Birth Defects

For the primary analysis, the incidence of birth defects reported to the PER is calculated by dividing the number of birth defects by the total number of live births. Pregnancy losses with reported birth defects at ≥20 gestation weeks are included in the numerator to increase sensitivity and to allow comparison with the US national population-based birth defect surveillance system (CDC MACDP) that uses this convention.

A secondary analysis, including pregnancy losses with reported birth defects occurring at <20 gestation weeks in the calculation of risk, will be conducted. The analysis of birth defects outcomes will be stratified by earliest trimester of exposure, maternal age, and other maternal risk factors, as appropriate. Statistical analysis will consider maternal age as it influences the rate of chromosomal abnormalities.

Ninety-five percent confidence intervals for birth defect rates will be calculated to assess the degrees of confidence. The prevalence in exposed pregnancies will be compared with the prevalence observed in the population-based birth defect data sources. The strength of evidence for lack of elevated levels of major birth defects in pregnancy exposures to lomitapide will be assessed by comparing the observed proportion of birth defects in the PER with rates from the external birth defect data sources, using a chi-square test.

## 9.8 Quality Control

### 9.8.1 Coordinating Centre Staff Training and Initiation

CC staff will be fully trained on the study requirements and use of the EDC system with retraining should the EDC be modified during the existence of the PER.

### 9.8.2 Data Quality Assurance

Data quality will be monitored including annual reviews by an Aegerion or designee team member including a senior scientist with prior experience in the evaluation of PER data.

Necessary modifications will be suggested and, as appropriate, submitted as a request to the appropriate Regulatory Authorities.

### 9.9 Limitations of the Research Methods

The PER is observational epidemiologic research with limitations inherent in a non-randomized design.

#### 9.9.1 Comparison Population

Outcomes data will be compared to published rates such as those from the MACDP.

#### 9.9.2 Other Aspects

##### 9.9.2.1 Regulatory Authorities

The protocol will be submitted to applicable regulatory authorities in accordance with the regulations of the countries involved in the study.

##### 9.9.2.2 Protocol Modifications

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

## 10. PROTECTION OF HUMAN SUBJECTS

### 10.1 Informed Consent

Written consent will be obtained from all PER participants. When a patient reports her own pregnancy to the PER, in countries where direct patient contact is allowed, the CC will first obtain verbal consent in order that enrolment information can be documented for sending a consent form and RMI form to the patient for signature.

### 10.2 Data Privacy

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.

### 10.3 Independent 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, 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. This non-interventional study will be conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology. When applicable, an IRB/IEC will review and approve the protocol before any patient is enroled. Appropriate informed consent will be obtained from participating patients.

## 11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

### 11.1 Definitions

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

### 11.2 Adverse Event

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.

### 11.3 Serious Adverse Event

A Serious Adverse Event (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 investigator, 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.

Required inpatient hospitalisation or prolongation of an existing hospitalisation.

A pre-existing event or condition that results in hospitalization 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 investigator, 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 investigator.

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.

### 11.4 Suspected Unexpected Serious Adverse Reaction

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

### 11.5 Severity

The severity refers to the intensity of an adverse event 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 investigator for each adverse event recorded on the eCRF.

### 11.6 Relationship

The relationship of lomitapide to an AE will be determined by the reporting HCP. HCPs 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.

Not Related: the AE is not related to lomitapide if there is evidence that clearly indicates an alternative explanation. If the subject 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 and 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.

# 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

## 12.1 Reporting to Regulatory Agencies

Interim reports will be submitted to the regulatory authorities, as required, based on agreed upon timelines. A final report will be submitted to the regulatory authorities within 6 months after database lock.

## 12.2 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 reporting HCPs.

## 13. REFERENCES

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3. Food and Drug Administration. Guidance for Industry: Establishing Pregnancy Exposure Registries. US Dept of Health and Human Services, Food and Drug Administration, Rockville, Maryland 2002.

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13. Varret M, Abifadel M, Rabès JP, Boileau C. Genetic heterogeneity of autosomal dominant hypercholesterolaemia. Clin Genet. 2008 Jan;73(1):1-13. Epub 2007 Nov 16. Review. PubMed PMID: 18028451

14. World Medical Organization. Declaration of Helsinki. British Medical Journal. 1996 Dec 7;313(7070):1448-1449.

## ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

| NUMBER | DOCUMENT REFERENCE NUMBER | DATE | TITLE |
|---|---|---|---|
| 2 | Number | 13Mar2013 | ENCePP Checklist for Study Protocols |
| 3 | Number | Date – Not Applicable | Birth Defect Definitions |

# ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

**ENCePP Checklist for Study Protocols (Revision 1)**

| **Section 1: Research question** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 1.1 Does the formulation of the research question clearly explain: | ☒ | ☐ | ☐ | 18-19 |
| 1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue) | ☒ | ☐ | ☐ | 20 |
| 1.1.2 The objectives of the study? | | | | |
| 1.2 Does the formulation of the research question specify: | | | | |
| 1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | 20 |
| 1.2.2 Which formal hypothesis(-es) is (are) to be tested? | ☐ | ☐ | ☒ | |
| 1.2.3 If applicable, that there is no *a priori* hypothesis? | ☐ | ☐ | ☒ | |

Comments: This is an observational study with descriptive analyses and no hypothesis testing.

| **Section 2: Source and study populations** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 2.1 Is the source population described? | ☒ | ☐ | ☐ | 20 |
| 2.2 Is the planned study population defined in terms of: | | | | |
| 2.2.1 Study time period? | ☒ | ☐ | ☐ | 17 |
| 2.2.2 Age and sex? | ☒ | ☐ | ☐ | 21 |
| 2.2.3 Country of origin? | ☒ | ☐ | ☐ | 2 |
| 2.2.4 Disease/indication? | ☒ | ☐ | ☐ | 18 |
| 2.2.5 Co-morbidity? | ☐ | ☐ | ☒ | |
| 2.2.6 Seasonality? | ☐ | ☐ | ☒ | |
| 2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 21 |

Comments: There are broad eligibility criteria solely based on pregnancy status and treatment with lomitapide. The PER will remain open indefinitely in the EU; in non-EU countries the PER will close to enrolment when the LOWER closes.

| **Section 3: Study design** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated? | ☒ | ☐ | ☐ | 22-24 |
| 3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design) | ☒ | ☐ | ☐ | 20 |
| 3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year) | ☐ | ☐ | ☒ | |
| 3.4 Is sample size considered? | ☐ | ☐ | ☒ | |
| 3.5 Is statistical power calculated? | ☐ | ☐ | ☒ | |

Comments: A separate Statistical Analysis Plan will be prepared. All reported eligible pregnancies will be collected.

| **Section 4: Data sources** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: | | | | |
| 4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc) | ☒ | ☐ | ☐ | 29-32 |
| 4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc) | ☒ | ☐ | ☐ | 29-32 |
| 4.1.3 Covariates? | ☒ | ☐ | ☐ | 29-32 |
| 4.2 Does the protocol describe the information available from the data source(s) on: | | | | |

| **Section 4: Data sources** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☒ | ☐ | ☐ | 29-32 |
| 4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 29-32 |
| 4.2.3 Covariates? (E.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.) | ☒ | ☐ | ☐ | 29-32 |
| 4.3 Is the coding system described for: | | | | |
| 4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10) | ☐ | ☒ | ☐ | |
| 4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events) | ☐ | ☒ | ☐ | |
| 4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System) | ☐ | ☒ | ☐ | |
| 4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other) | ☐ | ☒ | ☐ | |

The above details will be described in the Data Management Plan and/or Statistical Analysis Plan, as appropriate.

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure) | ☒ | ☐ | ☐ | 19 |
| 5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study) | ☒ | ☐ | ☐ | 35-36 |
| 5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use) | ☐ | ☒ | ☐ | |
| 5.4 Is exposure classified based on biological mechanism of action? | ☐ | ☐ | ☒ | |
| 5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured? | ☐ | ☐ | ☒ | |

Comments: Exposure data are collected from the reporting HCP or the patient.

| **Section 6: Endpoint definition and measurement** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 6.1 Does the protocol describe how the endpoints are defined and measured? | ☒ | ☐ | ☐ | 21-24 |
| 6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study) | ☒ | ☐ | ☐ | 35-36 |

Comments: The Steering Committee will review all possible reports of congenital anomalies.

| **Section 7: Biases and Effect modifiers** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 7.1 Does the protocol address: | | | | |
| 7.1.1 Selection biases? | ☒ | ☐ | ☐ | 35 |
| 7.1.2 Information biases? | ☒ | ☐ | ☐ | 35 |
| (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods) | | | | |
| 7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders) | ☒ | ☐ | ☐ | 35-36 |
| 7.3 Does the protocol address known effect modifiers? | ☐ | ☒ | ☐ | |
| (e.g. collection of data on known effect modifiers, anticipated direction of effect) | | | | |
| 7.4 Does the protocol address other limitations? | ☒ | ☐ | ☐ | 37 |

Comments:

| |
|---|
| |

| **Section 8: Analysis plan** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 8.1 Does the plan include measurement of absolute effects? | ☐ | ☐ | ☒ | |
| 8.2 Is the choice of statistical techniques described? | ☐ | ☐ | ☒ | |
| 8.3 Are descriptive analyses included? | ☒ | ☐ | ☐ | 34-35 |
| 8.4 Are stratified analyses included? | ☒ | ☐ | ☐ | 36 |
| 8.5 Does the plan describe the methods for identifying: | | | | |
| 8.5.1 Confounders? | ☐ | ☒ | ☐ | |

| **Section 8: Analysis plan** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 8.5.2 Effect modifiers? | ☐ | ☒ | ☐ | |
| 8.6 Does the plan describe how the analysis will address: | | | | |
| 8.6.1 Confounding? | ☐ | ☒ | ☐ | |
| 8.6.2 Effect modification? | ☐ | ☒ | ☐ | |

Comments: A Statistical Analysis Plan will be developed that will include the items above as appropriate.

| **Section 9: Quality assurance, feasibility and reporting** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving) | ☒ | ☐ | ☐ | 33-34 |
| 9.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 36-37 |
| 9.3 Does the protocol describe quality issues related to the data source(s)? | ☒ | ☐ | ☐ | 29 |
| 9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment) | ☒ | ☐ | ☐ | 16 |
| 9.5 Does the protocol specify timelines for | | | | |
| 9.5.1 Study start? | ☒ | ☐ | ☐ | 17 |
| 9.5.2 Study progress? (e.g. end of data collection, other milestones) | ☒ | ☒ | ☐ | 17 |
| 9.5.3 Study completion? | ☒ | ☐ | ☐ | 17 |
| 9.5.4 Reporting? (i.e. interim reports, final study report) | ☒ | ☐ | ☐ | 17 |

| **Section 9: Quality assurance, feasibility and reporting** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 9.6 Does the protocol include a section to document future amendments and deviations? | ☒ | ☐ | ☐ | 16 |
| 9.7 Are communication methods to disseminate results described? | ☒ | ☐ | ☐ | 41 |
| 9.8 Is there a system in place for independent review of study results? | ☒ | ☐ | ☐ | 33 |

Comments:

The PER will remain open indefinitely in the EU; in non-EU countries the PER will close to enrolment when the LOWER closes.

| **Section 10: Ethical issues** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described? | ☒ | ☐ | ☐ | 37-38 |
| 10.2 Has any outcome of an ethical review procedure been addressed? | ☐ | ☐ | ☒ | |
| 10.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 37-38 |

Comments: Ethical review has not taken place yet.

Name of the coordinating study entity[1]: _____

Name of (primary) lead investigator[2]: _____

Date: / /

Signature: _____

[1] A legal person, institution or organization which takes responsibility for the design and/or the management of a study. The (primary) lead investigator is the person authorised to represent the coordinating study entity.

[2] A person with the scientific background and experience required for the conduct of a particular pharmacoepidemiological or pharmacovigilance study. The lead investigator is responsible for the conduct of a study at a study site. If a study is conducted at several study sites by a team of investigators, the (primary) lead investigator is the investigator who has overall responsibility for the study across all sites.

## ANNEX 3. DEFINITION OF BIRTH DEFECTS

The PER has adopted the term “birth defect” for an abnormality usually referred to as a “congenital abnormality” and defines birth defect according to the following criteria:

On a case-by-case basis, through evaluator review and agreement from external advisors (if required), any major structural or chromosomal defect diagnosed with signs/symptoms, using the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP) classification of birth defects (CDC MACDP, 1998; British PediatricPaediatric Association [BPA], 1979).

The CDC guidelines disqualify the following as birth defects:

- those findings that are present in infants with outcomes at <36 weeks gestational age or if gestational age is unavailable, weighing <2500 g, and are attributed to prematurity alone, such as patent ductus arteriosus (PDA), patent foramen ovale (PFO), and inguinal hernias.
- infants with only transient or infectious conditions, or biochemical abnormalities, are classified as being without birth defects unless there is a possibility that the condition reflects an unrecognised birth defect.
- birth defects identified in outcomes with a gestational age of <20 weeks.