### 7.5.6. Adverse Events

#### 7.5.6.1. Definitions

**Adverse Event**

According to the International Conference on Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations (CFR) 312.32, IND Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Since bleeding episodes are recorded as an efficacy assessment of fitusiran, these will not be treated as AEs unless they meet any of the SAE criteria listed in Section 7.5.6.1.

**Serious Adverse Event**

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

- Results in death
- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse).
- Bleeding episodes will be recorded for efficacy assessment of fitusiran and will not be treated as AEs unless they meet any of the above criteria for SAEs.

**Adverse Events of Special Interest**

The following events are considered to be AEs of special interest (AESI):

- ALT or AST elevations >3× ULN
- Suspected or confirmed thrombosis
- Severe or serious ISRs, ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections) or, those that lead to temporary dose interruption or permanent discontinuation of fitusiran
- Systemic injection associated reactions (IARs), defined as hypersensitivity reactions which are related or possibly related to IMP.

**Adverse Event Severity**

Adverse events are to be graded according to the categories detailed below:

| | |
|---|---|
| Mild: | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| Moderate: | Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money) |
| Severe: | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an AE |

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

**Relationship of the Adverse Event to Study Treatment**

The relationship of each AE to study treatment should be evaluated by the Investigator using the following criteria:

| | |
|---|---|
| Definitely related: | A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to the medication administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible. |
| Possibly related: | A clinical event, including laboratory test abnormality, with a reasonable time sequence to the medication administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on the drug withdrawal may be lacking or unclear. |
| Unlikely related: | A clinical event, including laboratory test abnormality, with little or no temporal relationship to medication administration, and which other drugs, chemicals, or underlying disease provide plausible explanations. |
| Not related: | A clinical event, including laboratory test abnormality that has no temporal relationship to the medication or has more likely alternative etiology. |

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# SAE/AESI REPORT FORM

MCN # (For PPD Use Only)

**Completed forms should be faxed to**

North America **+1 888 488 9697/ +1 919 654 3849**
Europe, Middle East, and Africa **+44 1223 374102**
Asia Pacific: **+44 1223 374102**

| **Client: Sanofi Genzyme** | **Protocol ID:**<br><br>☐ **ALN-AT3SC-003 (EFC14768)**<br>☐ **ALN-AT3SC-004 (EFC14769)**<br>☐ **ALN-AT3SC-009 (EFC15110)**<br>☐ **LTE15174** | **Country:** |
|---|---|---|
| **Investigator Name:** | **Date Investigator Aware of Event: _____** (DD/MMM/YYYY) | |
| ☐ **Serious Adverse Event (SAE)**<br>*(should only be selected if the event meets any of the serious criteria in section 2)* | ☐ **Adverse Event of Special Interest (AESI)**<br>*(should only be selected if the event meets AESI criteria described in the study protocol*<br>*If the AESI **does** meet serious criteria in section 2 please insure both SAE and AESI are selected)* | |

**Event eCRF Number (per entry into Clinical Database):**_____

☐ **Initial** Date:_____ (DD/MMM/YYYY) ☐**Follow Up** Date: _____ (DD/MMM/YYYY)

**A. Subject Information**

| 1. Site-Subject Number: | 2. Age at Onset: | 3. Race: | 4. Height: | 5. Weight: | 6. Gender |
|---|---|---|---|---|---|
| _____ - _____ | _____<br>Year of Birth<br>_____ | | ☐ cm<br>☐ in | ☐ kg<br>☐ lb | |

7. Is this SAE associated with pregnancy ☐ Yes ☐ No ☐ Unknown
(If yes, please submit pregnancy report form)

**B. Serious Adverse Event /Adverse event of Special Interest**

**1. Serious Adverse Event (SAE)/Adverse event of Special interest (AESI)** **Onset Date** (DD/MMM/YYYY): _____

**Event Term** _____ **Resolution Date**(DD/MMM/YYYY): _____

**1.a. *** Complete this section if SAE/AESI term has changed since the previous report ****

**SAE/AESI previously reported as:** _____

**2. Regulatory Serious Criteria**

**this section should only be completed if the event is a SAE.**

For **SAE** select all that apply

☐ Death

☐ Life-threatening

☐ Inpatient Hospitalization –
- ☐ Initial Hospitalization/prolongation
- ☐ Prolongation of existing hospitalization

Hospitalization Admission Date
(DD/MMM/YYYY): _____

Hospitalization Discharge Date
(DD/MMM/YYYY): _____

☐ Congenital Anomaly/Birth Defect

☐ Important medical event,

☐ Persistent or Significant Disability or Incapacity

# SAE/AESI REPORT FORM

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| 3. Severity | 4. Outcome of Event |
|---|---|
| ☐ Mild<br>☐ Moderate<br>☐ Severe | ☐ Not Recovered/Not Resolved<br>☐ Recovering/Resolving ☐ Recovered/Resolved<br>☐ Resolved *with* sequelae: specify sequelae: _____<br>☐ Fatal ☐ Unknown |

**5a. Suspect Study Drug Relationship**

☐ **Not Related** ☐ **Unlikely Related*** ☐ **Possibly Related** ☐ **Definitely Related***

**Not to be used for LTE15174 (OLE study). ONLY options for OLE study is Not Related and Possibly Related*

**5b. Rationale for Not Related/Unlikely Related Assessment**
(Check all that apply)
- ☐ Event attributed to concomitant medication or disease
- ☐ Event not reasonably temporally associated with study drug administration
- ☐ Event is expected in targeted disease and/or population
- ☐ Negative dechallenge and/or rechallenge
- ☐ other (specify) .....

**5c. Rationale for Possibly/Definitely Related Assessment**
(Check all that apply)
- ☐ temporal relationship of event to study drug exposure
- ☐ event is known to be associated with the study drug or drug class
- ☐ event improved on discontinuation or dose reduction of study drug
- ☐ event reoccurred on rechallenge with study drug
- ☐ biological plausibility
- ☐ other (specify) .....

**C. Study Medication(s)**

| Study Drug | Phase | Therapy Start Date (DD MMM YYYY)<br>Therapy Stop Date (DD MMM YYYY) | Total Monthly Dose including Units | Route and frequency |
|---|---|---|---|---|
| | ☐Lead In<br>☐Blinded<br>☐Open<br>☐N/A | I I<br>I I | | |

Date of last dose prior to event onset

(DD/MMM/YYYY): _____

1. Action Taken with Study Drug:
   - ☐ Dose not Changed
   - ☐ Drug Withdrawn
   - ☐ Not Applicable
   - ☐ Unknown

   ☐ Drug Interrupted: Stop Date: __/___/____(DD/MMM/YYYY);
   Date Restarted: __/___/____(DD/MMM/YYYY);

   ☐ Dose Reduced Date of Reduction __/___/____(DD/MMM/YYYY);
   Dose reduced to (include units) _____

2. Event abated after study drug stopped or dose reduced: ☐ Y ☐ N ☐N/A ☐ Unknown

3. Event reappeared after reintroduction of study drug: ☐ Y ☐ N ☐N/A ☐ Unknown

**D. Concomitant Medication(s)**

| Drug Name (Generic preferred) Including dose/route/frequency | Suspect Drug | Start Date DD MMM YYYY | Stop Date DD MMM YYYY |
|---|---|---|---|
| | ☐ Y ☐ N | | |
| | ☐ Y ☐ N | | |
| | ☐ Y ☐ N | | |

# SAE/AESI REPORT FORM

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**E. Describe Events** (Chronological summary of symptoms, signs and vital signs, diagnosis, treatment given, outcome and autopsy details (If appropriate)

Please also provide any information regarding risk factors of liver injury (alcohol consumption, hepatotoxic agent exposure, travel in the country at risk of infection etc.) if applicable for the event

**F. Relevant Laboratory Tests**

| **Laboratory Tests** (Relevant to SAE/AESI Only) | **Date of Test** DD MMM YY | **Results** (Include Units) | **Baseline** (Include Units) |
|---|---|---|---|
| | / / | | |
| | / / | | |
| | / / | | |
| | / / | | |

**G. Relevant Medical History** (Including pre-existing medical conditions)

**H. Death Information**

**Date of Death: _____ (DD/MMM/YYYY)** **Cause of Death: _____**

Was death certificate completed? ☐ **YES (attach copy)** ☐ **NO** ☐ **Pending**

Was an autopsy performed? ☐ **YES (attach copy)** ☐ **NO** ☐ **Pending**

**I. Prepared By:**

| | |
|---|---|
| Name: | **Title:** ☐ Physician ☐ Nurse ☐ Pharmacist ☐ Other Specify: |
| Telephone #: ( ) | |
| Fax #: ( ) | |

**Investigator Signature: _____ Date: _____** (DD/MMM/YYYY)

***** *Investigator's signature is required* *****