EPIDEMIOLOGY STUDY PROTOCOL

Prevalence of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions

alglucosidase alfa

Study type:	Post Approval Safety Study
Company:	Genzyme, a Sanofi Company
Version Number/Status:	Final V3.0
Study number:	ALGMYC07390

This study will be conducted in accordance with Sanofi standard operating procedures for GPE epidemiologic studies and Sanofi operational quality standards for analyses of pre-existing data and statistical activities

Date: 14-dec-2015 Total number of pages 19

PASS INFORMATION:

Title:	Prevalence of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions
Protocol version identifier	3.0
Date of last version of protocol	27 August 2015
EU PAS register number (if applicable)	ENCEPP/SDPP/10526
Active substance	A16AB07
Medicinal product	Myozyme (alglucosidase alfa)
Product reference	EU/1/06/333/001-003
Procedure number	EMEA/H/C/000636/II/0052
Marketing authorization holder(s)	Genzyme Europe B.V.
Joint PASS	No
Research questions and objective(s):	To determine the prevalence of patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions who undergo immunology testing. The difference in prevalence of testing between the two periods of 3 years before and after the implementation of the revised SIP will be assessed as a measure of effectiveness of risk minimization measures.
Country(-ies) of study	Europe
Author	[redacted]

MARKETING AUTHORIZATION HOLDER(S)

Marketing authorization holder(s)	Genzyme Europe B.V. Gooimeer 10, NL-1411 DD Naarden, The Netherlands
MAH contact person	[redacted] Genzyme Europe B.V. Gooimeer 10, 1411 DD Naarden, The Netherlands

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2 LIST OF ABBREVIATIONS

AR: Adverse Drug Reaction

AE: Adverse Event

EU: European Union

MAH: Marketing Authorization Holder

PRAC: Pharmacovigilance Risk Assessment Committee

SIP: Safety Information Packet

3 RESPONSIBLE PARTIES

Different entities from the MAH organization will be involved in the study:

- The pharmacoepidemiology unit of Global Pharmacovigilance and Epidemiology will be in charge of protocol and reports preparation
- A multidisciplinary research team made of representatives of safety Surveillance and Risk Management, Medical Affairs, Regulatory, Clinical Division will be in charge of study documents review
- The system support unit of Global Pharmacovigilance and Epidemiology will be in charge of data extraction from the pharmacovigilance database
- The Clinical Specialty Laboratory group will be in charge of data extraction from the Clinical Specialty Laboratory database
- The biostatistics group from the clinical division will be in charge of data linkage and data analysis.

4 SYNOPSIS

Title

Prevalence of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions

Version 3.0

[redacted]

Rationale and background

As part of its assessment, PRAC requested revision of the safety information packet (SIP) to improve readability and contents and to assess effectiveness of the revised material in terms of evaluation of the process and evaluation of the outcomes.

This study is focused on evaluation of the outcomes, through the evaluation of the percentage of immunology testing in patients experiencing significant hypersensitivity/anaphylactic reactions.

Research question and objectives

This study aims to determine the prevalence of patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions who undergo immunology testing. The difference in prevalence of testing between the two periods of 3 years before and after the implementation of the revised SIP (version 8.2) will be assessed as a measure of effectiveness of risk minimization measures.

Study design

Cross-sectional study; repeated analyses will be done pre- and post-implementation of the revised SIP using pre-existing data.

Population

- This study will be conducted using existing data sources recording both cases of significant hypersensitivity/anaphylactic reactions in the Genzyme's Pharmacovigilance adverse event database and routine performance of immunology testing in the Genzyme Clinical Specialty Laboratory database since treatment start.

The following population will be considered:

- All patients treated with alglucosidase alfa with a spontaneously reported significant hypersensitivity/anaphylactic reaction during the study period in countries in Europe.

Variables

The outcome will be the history of any immunology testing since treatment start as well as subtypes of testing performed in patients with a reported significant hypersensitivity/anaphylactic reaction:

- alglucosidase alfa IgE antibody
- complement activation
- serum tryptase
- alglucosidase alfa IgG antibody

Data sources

The following data sources will be considered:

- Genzyme's Pharmacovigilance adverse event database,
- Genzyme Clinical Specialty Laboratory database (capturing records and results of immunology testing conducted in these laboratories).

Reports pertaining to the same patients will be linked across databases using date of birth, initials and country of origin.

Study size

All patients available in the study population will be considered for the analysis. No assumption will be made on the expected number of patients.

Data analysis

The primary analysis population will be patients with spontaneously reported significant hypersensitivity/anaphylactic reaction while treated with alglucosidase alfa treatment course in countries in Europe. The analyses will be descriptive and will be made on all patients available in the databases at time of each analysis.

The prevalence of testing will be provided for each period (3-year period before and 3-year period after implementation of the revised SIP). The difference in prevalence rate between two groups will be calculated, with corresponding 95% confidence interval calculated based on normal approximation of two proportions.

The results will be displayed by 3-year period before and after the implementation of revised SIP and by age, gender and country in Europe when appropriate.

Milestones

Annual analyses will be conducted over a 3-year period starting one year after implementation of the revised SIP in Europe. The implementation of the revised SIP may be started from 01 September 2015 after completion of pre-updated SIP data collection.

The first report will be prepared in December 2016, based on data gathered up to one year after implementation of the revised SIP (from 01 October 2015 to 30 September 2016) and will also include results for the 3-year period before implementation of the revised SIP (from 01 September 2012 to 31 August 2015).

The second report prepared in December 2017 will add data gathered in the second year after implementation of the revised SIP (from 01 October 2016 to 30 September 2017) and the final report prepared in December 2018 will include cumulative data for both periods (from 01 September 2012 to 31 August 2015 and from 01 October 2015 to 30 September 2018).

5 AMENDMENTS AND UPDATES

None

6 MILESTONES

Table 1 summarizes the major milestones for this study.

Table 1 - Major milestones for study ALGMYC07390

Milestone	Planned date
Registration in the EU PAS register	3 August 2015
Start of study (start of data collection)	01 October 2015
Interim report 1	December 2016
Interim report 2	December 2017
End of data collection	30 September 2018
Final report of study results	December 2018

Table 2 summarises per country the time schedule of the distribution of the revised SIP in European countries where patients are treated with alglucosidase alfa as of the most recent update of 02 December 2015.

Table 2 - Timelines of distribution of revised SIP by country

Country	effective distribution date
Austria	pending local approval
Belgium	pending local approval
Bulgaria	local approval on 27-oct-2015
Croatia	pending local approval
Cyprus	pending local approval
Czech	pending local approval

Country	effective distribution date
Denmark	07-oct-15
Estonia	23-sept-15
Finland	22-sept-15
France	15-oct-15
Germany	pending local approval
Greece	pending local approval
Hungary	pending local approval
Ireland	30-sept-15
Italy	pending local approval
Netherlands	completed
Poland	14-oct-15
Portugal	pending local approval
Romania	30-sept-15
Slovenia	pending local approval
Spain	pending local approval
Sweden	09-oct-15
UK	30-sept-15
Latvia	14-sept-15
Norway	14-oct-15

7 RATIONALE AND BACKGROUND

As part of its assessment, PRAC requested revision of the SIP to improve readability and contents and to assess effectiveness of the revised material in terms of evaluation of the process and evaluation of the outcomes.

This study is focused on evaluation of the outcomes through the evaluation of the percentage of immunology testing in patients experiencing significant hypersensitivity/anaphylactic reactions.

8 RESEARCH QUESTION AND OBJECTIVES

This study aims to determine the prevalence of patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions who undergo immunology testing. The difference in prevalence of testing between the two periods of 3 years before and after the implementation of the revised SIP (version 8.2) will be assessed as a measure of effectiveness of risk minimization measures.

9 RESEARCH METHODS

9.1 STUDY DESIGN

This study is a cross-sectional study with repeated analyses using pre-existing data covering two periods:

- A 3-year period pre-implementation of the revised SIP (from 01 September 2012 to 31 August 2015)
- A 3-year period post-implementation of the revised SIP (from 01 October 2015 to 30 September 2018)

The implementation of the revised SIP is defined as the date of effective distribution of the revised material in countries in Europe after local approval by competent authorities.

9.2 SETTING

The following data sources will be considered:

- Genzyme's Pharmacovigilance adverse event database,
- Genzyme Clinical Specialty Laboratory database (capturing records and results of immunology testing conducted in these laboratories).

Reports pertaining to the same patients will be linked across databases using date of birth, initials and country of origin.

The Genzyme's Pharmacovigilance adverse event database will be used to identify the population of interest for each study period:

- All patients with a spontaneously reported significant hypersensitivity/anaphylactic reaction occurring during alglucosidase alfa treatment course in countries in Europe.

The following criteria will be used to identify patients with a reported significant hypersensitivity/anaphylactic reaction occurring during alglucosidase alfa treatment course:

- cases identified by the Standardized MedDRA Query "Anaphylactic reaction" and "hypersensitivity".

The Genzyme Clinical Specialty Laboratory database will be used to identify the full history of immunology testing since initiation of treatment with alglucosidase alfa in patients identified from the Genzyme's Pharmacovigilance adverse event database.

9.3 VARIABLES

The following variables will be considered for the analysis.

The characteristics of patients with a reported significant hypersensitivity /anaphylactic reaction (if available):

- age
- gender
- weight
- description of hypersensitivity/anaphylactic reactions
    - nature of event
    - outcome
    - seriousness
    - medically confirmed
    - event date
    - event severity
        - mild, moderate, severe
        - grade 1 to 5 according to NCI Common Terminology Criteria for Adverse Events
- history of hypersensitivity/ anaphylactic reactions
- history of reported drug exposure

The characteristics of alglucosidase alfa treatment course (if available):

- treatment start date
- number of doses received
- treatment dosage received

The history of immunology testing performed since treatment start:

- any immunology testing
- alglucosidase alfa IgE antibody
- complement activation
- serum tryptase
- alglucosidase alfa IgG antibody

Immunology testing results will be generally reported as titers.

9.4 DATA SOURCES

This study is based on secondary analysis of existing data sources.

The following data sources will be considered:

- Genzyme's Pharmacovigilance adverse event database,
- Genzyme Clinical Specialty Laboratory database.

Reports pertaining to the same patients will be linked across databases using date of birth, initials, and country of origin.

The Genzyme's Pharmacovigilance adverse event database will provide information about patients with a reported significant hypersensitivity /anaphylactic reaction.

The Genzyme Clinical Specialty Laboratory database will provide history of records and results of immunology testing conducted in these laboratories for patients treated with alglucosidase alfa.

9.5 STUDY SIZE

All patients available in the study population will be considered for the analysis.

No assumption will be made on the expected number of patients with spontaneously reported significant hypersensitivity/anaphylactic reaction occurring during alglucosidase alfa treatment course in countries in Europe.

The Table 3 provides expected precision (95% confidence intervals) according to different values of expected prevalence of immunology testing. The expected value of prevalence is not known and a range of potential values is presented in the table below.

Table 3 - 95% confidence intervals according to different values of prevalence of immunology testing

	Prevalence				
Number of patients	50%	75%	85%	90%	95%
50	[35.5- 64.5%][a]	[60.7-86.2%][a]	[72.1-93.5%][a]	[78.2-96.7%][a]	[84.8-99.1%][a]
100	[40.2-59.8%]	[66.5-83.5%]	[78.0-92.0%]	[84.1-95.9%]	[90.7-99.3%]
200	[43.1-56.9%]	[69.0-81.0%]	[80.1-89.9%]	[85.8-94.2%]	[92.0-98.0%]
300	[44.3-55.7%]	[70.1-79.9%]	[81.0-89.0%]	[86.6-93.4%]	[92.5-97.5%]

a Exact 95% confidence interval using binomial exact method (Clopper-Pearson exact method)

9.6 DATA MANAGEMENT

For this study, data extractions from Genzyme's Pharmacovigilance adverse event database will be conducted to get reports pertaining to the population of interest.

Data extractions from the Genzyme Clinical Specialty Laboratory database will be conducted on reports pertaining to the population of interest.

These extractions will be combined to serve as analysis data sets for interim and final analyses. The data linkage will be documented.

9.7 DATA ANALYSIS

The analyses will be descriptive and will be made on all patients available in the databases at time of each analysis.

9.7.1 Analysis population:

The primary analysis population will be patients with spontaneously reported significant hypersensitivity/anaphylactic reaction while treated with alglucosidase alfa treatment course in countries in Europe. Patients will be divided by following two groups:

Group 1 (pre-SIP):

- Patients with hypersensitivity/anaphylactic reaction event onset date from 01 September 2012 to 31 August 2015

Group 2 (post-SIP):

- Patients with hypersensitivity/anaphylactic reaction event onset date from 01 October 2015 to 30 September 2018

9.7.2 Determination of patient status on immunology testing:

A patient in Group 1 (or 2) will be considered having undergone any immunology testing (immunology test =Yes) for the respectively period if one of the two conditions is met:

i) a valid test result is available for at least one of the following tests from Genzyme Clinical Specialty Laboratory database
   a. alglucosidase alfa IgE antibody,
   b. alglucosidase alfa IgG antibody,
   c. complement activation,
   d. serum tryptase

ii) the test date is after the alglucosidase alfa treatment start date through the end of the period cutoff (31 August 2015 for Group 1 and 30 September 2018 for Group 2)

Note that patients without a valid test meeting above criteria will be considered without having immunology test performed (immunology test=No). Therefore, there is no missing data for this endpoint.

9.7.3 Demographic and baseline disease characteristics

Patient demographics and baseline disease characteristics will be summarized using descriptive statistics: number of observations (n), mean, median, standard deviation (SD), minimum, and maximum. Categorical variables will be summarized using frequencies and percentages. Denominator will be based on the number of patients in the analysis population as defined in Section 9.7.1.

Following variables will be summarized by Group (1 or 2):

- patient characteristics (age, gender, weight, country/region)
- history of hypersensitivity/anaphylactic reactions

9.7.4 Alglucosidase alfa treatment information and the details on hypersensitivity/anaphylactic reaction event

Following alglucosidase alfa treatment information will be summarized by group as well as the combined analysis population:

- time from treatment initiation to first onset of hypersensitivity/anaphylactic reactions event within the study period
- number of doses received prior to first onset of hypersensitivity/anaphylactic reactions event within the period

The details of the hypersensitivity/anaphylactic reactions event reported in each of the periods will be summarized by intensity, seriousness (SAE or not) of the event, and relationship to alglucosidase alfa treatment, respectively. The summaries will be provided by analysis group (1 and 2). For multiple events occurred in the same study period, patients will be counted only once and only the event with the worst category will be considered for the corresponding

analysis. Corresponding listing will be provided with detailed information collected in the database

9.7.5 Prevalence of immunology testing

- The following summaries will be performed: Number (and %) of patients with any immunology testing among Group 1 and 2 respectively, including 95% confidence interval for the percent for the respective group. The confidence interval will be calculated based on normal approximation for the proportions (exact method may be used if sample size is too small).
- Number (and %) for type of immunology testing performed (alglucosidase alfa IgE, alglucosidase alfa IgG, complement activation, or serum tryptase) within Group 1 and 2 respectively.
- Subgroup analysis as determined by the following covariates:
  - by age group (<18 years and >=18 years respectively)
  - by gender (male, female)
  - by country (or region if sample size is small for certain regions)

In addition, the difference in prevalence rate between two groups will be calculated, with corresponding 95% confidence interval calculated based on normal approximation of two proportions. Exact confidence interval may be used if sample size is too small.

9.8 QUALITY CONTROL

This study will be conducted according to sanofi operational quality standards for analyses of pre-existing data (QOQS-009473) and Statistical activities (QOQS-006704) as well as standard operating procedure for GPE epidemiologic studies (QSOP-001126). Full list of quality documents is provided in Annex 1.

Linkage between Genzyme's Pharmacovigilance adverse event database and clinical specialty laboratory database, as well as the QC process will be described and documented as part of the study file including description of manual checks of all available data sources.

Statistical deliverables as well any data derivation or transformation will be quality controlled according to Sanofi standard operating procedure (QSOP-002240). The method and type of quality control performed for TLFs will be detailed in a Quality Control plan for this study.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The limitations of the current study are related to the characteristics of the data sources. In Genzyme's Pharmacovigilance adverse event database only information reported in documentation of spontaneous reports will be available and missing data may be observed with a different range of frequency for each variable. But all patients' characteristics will be

described when available. High frequency of missing data in some characteristics may limit the possibility to define relevant subgroups of patients with sufficient numbers.

In the Genzyme Clinical Specialty Laboratory database only results of immunology testing conducted in the Clinical Specialty Laboratory will be available. Thus, this may lead to an underestimation of the real prevalence of immunology testing conducted by physicians in the routine practice.

In the absence of a common patient identifier, linkage of these two databases will be conducted by matching of available common patients characteristics from the two data sources but all efforts will be made including manual checks of available data sources to avoid any potential erroneous linking.

9.10 OTHER ASPECTS

Not applicable.

10 PROTECTION OF HUMAN SUBJECTS

As this study would not involve the collection, use or transmittal of individually identifiable data, Institutional Review Board review or approval is not required. This study will follow internal procedures applicable to management of personal data in pharmacovigilance and management of personal data in the Clinical Specialties Laboratories.

11 MANAGEMENT OF REPORTING ADVERSE EVENTS/ADVERSE REACTIONS

This study is based on the secondary use of data, expedited reporting of AE/ADR is not required.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Annual interim reports and a final report will be submitted to EMA.

The first report will be prepared in December 2016, based on data gathered up to one year after implementation of the revised SIP and will also include results for the 3-year period before implementation of the revised SIP.

The second report prepared in December 2017 will add data gathered in the second year after implementation of the revised SIP year and the final report prepared in December 2018 will include cumulative data for both periods.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

1. List of quality documents:

- QOQS-009473 Sanofi Operational Quality Standard for Analyses of Pre-Existing Data
- QOQS-006704 Sanofi Operational Quality Standard for Statistical Activities
- QSOP-001126 Sanofi Standard Operating Procedure for Management of Epidemiological Safety Studies
- QSOP-002240 Sanofi Standard Operating Procedure for Clinical Statistical Activities